1965-03-15

Hydrogenation of 4-methylcinnoline

William E. Maycock
Brigham Young University - Provo

HYDROGENATION OF 4-METHYLCINNOLINE

A Thesis
Submitted to the
Department of Chemistry
Brigham Young University
Provo, Utah

In Partial Fulfillment
of the Requirements for the Degree of
Master of Arts

by

William E. Maycock

September, 1964

This thesis by William E. Maycock is accepted in its present form by the Department of Chemistry of the Brigham Young University as satisfying the thesis requirement for the degree of Master of Arts.

3/15/65
Date

ACKNOWLEDGEMENTS

Sincere appreciation is expressed to Dr. H. Smith Broadbent who directed this work. Appreciation also is expressed to Mr. Richard L. Meibos, Superintendent of Laboratories, for his help with equipment while Dr. Broadbent was on Sabbatical leave.

For various teaching assistantships from Brigham Young University, sincere thanks is given.

Thanks also are due to Mrs. Wanda Snow for typing the Introduction and Literature Review, and Mrs. Luella Wesley who typed the remainder of the thesis. Printing details also were handled by Mrs. Wesley.

This work is dedicated to my parents, for their advice, encouragement, and never-failing faith.

TABLE OF CONTENTS

page

page

NOTE ADDED IN PROOF

Based on hydrogen nuclear magnetic resonance spectroscopy (Besford, Allen, and Bruce, J. Chem. Soc., 1963, 2867), the compound identified in this thesis as 4-methyl-3,4-dihydrocinnoline in reality is the 1,4-dihydro compound having a hydrazone structure. Besford and coworkers studied dihydrocinnoline and its 4-methyl and 4-phenyl derivatives. The reported melting point (63-65°, corrected) of the 4-methyl derivative agrees with that of our compound (61.5-62.5°, uncorrected).

Thus in every case where mentioned in the text, 4-methyl-3,4-dihydrocinnoline should be read as 4-methyl-1,4-dihydrocinnoline.

LIST OF TABLES

page

A. Major Tables (Numbered and Titled).

B. Minor Tables (Not Numbered or Titled)

Subject

LIST OF ILLUSTRATIONS

Note: The spectra of the compounds believed to be 2, 3-dihydroskatole and 4-methyl-3, 4-dihydrocinnoline were not available for publication.

I. INTRODUCTION

Although the cinnoline ring system (1, 2-diazanaphthalene) was discovered in 1883 by von Richter (1), little work was carried out in this field until 1941 (2). Since that time knowledge of the chemistry of the cinnolines has expanded considerably. This expansion, however, has not included the hydrocinnolines.

An interest in the hydrocinnolines followed naturally from work done at this University (3) on the hydroquinoxalines, especially decahydroquinoxaline, which compound was shown to exist in two stereoisomeric forms (3), cis and trans. Similarly, decahydrocinnoline should exhibit stereoisomerism.

The hydrocinnolines reasonably could be expected to show some physiological activity, although none of the hydroquinoxalines or derivatives prepared in these laboratories have shown outstanding pharmacological properties at the present stage of testing (4).

Finally, little is known concerning the chemistry of the hydrocinnolines. In fact, the literature does not record any example of a catalytic hydrogenation of a fully aromatic cinnoline. Only one catalytic reduction has been carried out (5), the substrate being a dihydrocinnoline. Most hydrocinnolines have been made by chemical reduction (5, 6) or, more generally, by ring closure on a cyclohexyl

---

(1) von Richter, Ber., 16, 677 (1883).

(2) Borsche and Herbert, Ann., 546, 293 (1941).

(3) Broadbent, Allred, Pendleton, and Whittle, J. Am. Chem. Soc., 82, 189 (1960).

(4) Broadbent, Unpublished results, Brigham Young University, Provo, Utah, 1960.

(5) Neber, Knoller, Herbst, and Trissler, Ann., 471, 113 (1929).

(6) Busch and Rast, Ber., 30, 521 (1897).

carbonyl compound to give a hydrocinnoline saturated in the homocyclic ring (7, 8, 9). Hydrocinnolines saturated in the hetero ring (retaining the aromatic benzene ring) may be formed by ring closure on a styrene (10, 11, 12).

One problem associated with the catalytic hydrogenation of cinnolines, but not encountered with the related quinoxaline research, was the possibility of cleavage of the nitrogen-nitrogen bond during reduction. This aspect, however, only increased interest in the project.

The research outlined in this thesis consists of the catalytic hydrogenation of 4-methylcinnoline under varying conditions.

4-Methylcinnoline was chosen as the substrate for the following reasons: (1) It is more stable than cinnoline itself, and (2) it is more readily obtained.

Hydrogenations of 4-methylcinnoline were carried out in a Parr High Pressure Reaction Apparatus having a fixed agitation rate of 37 cycles per minute. In a few instances, a Parr Low Pressure Reaction Apparatus was employed, with an agitation rate of approximately 250 cycles per minute.

A variety of catalysts was employed, each under both neutral and acidic conditions. The catalysts thus used were 5% rhodium on alumina, 5% rhodium on activated charcoal, ruthenium oxide, platinum oxide, 5% palladium on activated charcoal, and Raney nickel.

---

(7) Allan and Van Allan, J. Am. Chem. Soc., 73, 5850 (1951).

(8) Horning and Amstutz, J. Org. Chem., 20, 707 (1954).

(9) Baumgarten, Creger, and Villars, J. Am. Chem. Soc., 80, 6609 (1958).

(10) Diels and Alder, Ann., 450, 237 (1926).

(11) Alder and Niklas, Ann., 585, 97 (1954).

(12) Horner and Naumann, Ann., 587, 81 (1954).

The initial hydrogenation pressure usually was 3000 psig., although an initial pressure of 2000 psig. was used several times.

Reaction temperatures ranged from room temperature to 266°C.

Upon completion of a reaction, the reaction mixture was analyzed by physical and chemical methods to determine the products of a reduction such as gas chromatography, infrared and ultraviolet spectrophotometry, physical properties, derivatives, qualitative organic chemistry tests, quantitative elemental analyses, and, in several instances, by syntheses of suspected compounds by alternate, un-ambiguous routes. Attempts at chemical degradation or conversion generally were not successful.

Of the products identified, three have not been reported previously in the literature. These three compounds are 4-methyl-3,4-dihydrocinnoline, 4-methyl-1,2,3,4-tetrahydrocinnoline, and o-amino-β-methylphenethylamine. A fourth compound, octahydroskatole, also has been identified.

II LITERATURE REVIEW

The chemistry of the cinnolines has been reviewed up through 1949 (13), with full coverage of the literature to the end of 1948. This present review covers cinnoline chemistry for the period 1949-1960 (July), with emphasis being placed on the preparation and physical properties of the derivatives of cinnoline. Since 1957 was the last year for which the index to Chemical Abstracts was available, the literature from 1958 to the present was searched by use of Current Chemical Papers, published by the Chemical Society of London.

The review is organized in essentially the same manner as "Beilstein's Handbuch der Organischen Chemie", although no attempt has been made to keep the correlation rigorous. The first section deals with the preparation and properties of the parent heterocycle, cinnoline. The following eight sections treat those functioning classes, in their proper order, which encompass the derivatives of cinnoline. The hydrocinnolines and cinnolines containing additional fused rings are treated separately as the last two sections for proper emphasis and to simplify presentation. The data in each section are presented according to the Beilstein system except where alteration aids presentation.

In a review of this nature, it is neither possible nor practical to discuss each method of preparation which applies to any given cinnoline. Hence, the bulk of each section consists of the tabulated data presented therein. From these tables both the preparation and properties of the numerous cinnolines may be extracted. However, those procedures which are widely applicable are discussed briefly.

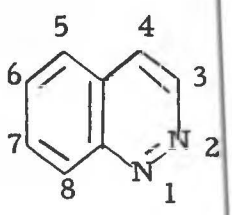
---

(13) Simpson, "Condensed Pyridazine and Pyrazine Rings", Interscience Publishers, Inc., New York, 1953, pp. 3-65, 358-361, 363-366.

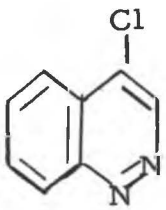
A. Cinnoline

1. Preparation

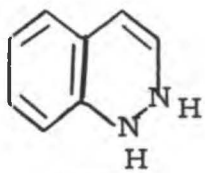
Cinnoline (I), the parent compound, was first obtained (6) by the reduction of 4-chlorocinnoline (II) with iron and 15% sulfuric acid to 1, 2-dihydrocinnoline (III) which was then oxidized with mercuric oxide to cinnoline.



(I)

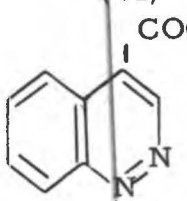


(II)

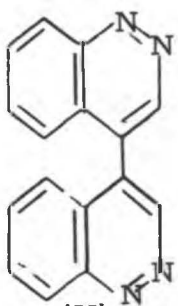


(III)

A more recent procedure (14) and the preferable route consists of synthesizing cinnoline-4-carboxylic acid (IV) which is then decarboxylated in benzophenone at 155-165°. Catalytic reduction (15) of 4-chlorocinnoline, using palladium hydroxide on calcium carbonate with 4-5 atmospheres of hydrogen at room temperature, yields cinnoline and 4, 4-dicinnolyl (V). Cinnoline may also be obtained by the reduction (16) over palladium on charcoal of 3-bromocinnoline (VI) in methanolic potassium hydroxide containing



(IV)



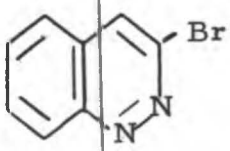
(V)

(14) Jacobs, Winstein, Henderson, and Spaeth, J. Am. Chem. Soc., 68, 1310 (1946).

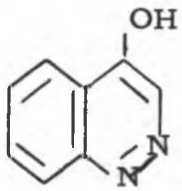
(15) Morley, J. Chem. Soc., 1951, 1971.

(16) Alford and Schofield, J. Chem. Soc., 1953, 1811.

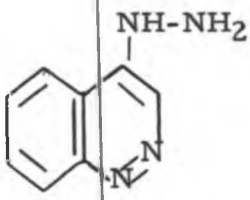
hydrazine hydrate. Lithium aluminum hydride reduction (17) of 4-hydroxycinnoline (VII) in tetrahydrofuran produces cinnoline. Oxidation (18) of 4-cinnolylhydrazine (VIII, prepared from 4-chlorocinnoline) by 10% aqueous copper sulfate gives the parent coumpound, which may also be obtained (19) by the hydrolysis of 4-toluene-p-sulfonylhydrazino cinnoline hydrochloride (IX) in aqueous soldium carbonate at 95° C.



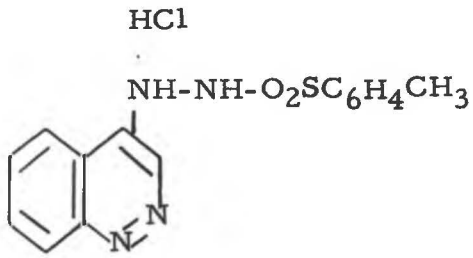
(VI)



(VII)



(VIII)



(IX)

2. Properties

Cinnoline, a pale yellow solid, is a weak base of pKa 2.51 at 21-22° C in 50% aqueous alcohol (20) and 2.70 at 20° in water (21).

---

(17) Atkinson and Sharpe, J. Chem. Soc., 1959, 2858.

(18) Schofield and Swain, J. Chem. Soc., 1950, 392.

(19) Alford and Schofield, J. Chem. Soc., 1953, 609.

(20) Keneford, Morley, Simpson, and Wright, J. Chem. Soc., 1949, 1356.

(21) Albert, Goldacre, and Phillips, J. Chem. Soc., 1948, 2240.

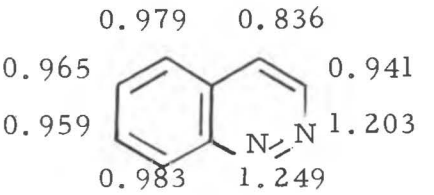
When crystallized from ether with one molecule of solvent, it melts at 24-25° C (6). The solvent-free base melts at 39° C (6) [37-38° C (14), 40-41° C (15)] and boils at 114° C /0.35 mm (15). Although cinnoline liquifies (14) to a green liquid (15) upon standing, apparently no decomposition occurs (15) since a quantitative yield of cinnoline picrate may be obtained from two-month old material. The base forms stable salts, as summarized in Table 1.

Table 1. Cinnoline Salts.

Salt	M. P., °C	Remarks	Referenc
Hydrochloride	156-160		6
	154-156	Sublimes at 110-115°C/3 mm.	14
Hydrochloride monohydrate	82-137	Long, brittle, pale-green needles from ethanol-ether; melt decomposes at 205° C.	15
Picrate	190		6
	196-196.5	Yellow prisms from alcohol	14
	190-191		15
	191-194	Orange prisms from dioxan	16
	190-194	From methanol	17
	191.5-192.5	Khaki leaflets from alcohol	18
	191-193	Large amber crystals from ethanol	19
	196-197		22
Methiodide	168		6
	168-170.5 dec.	Dark reddish-brown crystals	14
	171-173 dec.		22
Chloroplatinate	280 dec.		6
Aurichloride	146		6

(22) Morley and Simpson, J. Chem. Soc., 1949, 1354.

The pi electron densities on each atom of cinnoline have been calculated (23, 24). The data given by Longuet-Higgens and Coulson (24) are presented:



The electric moment of cinnoline has been determined (25) to be 4.14 in benzene at 25°C. The empirical constant, molar refraction, and μ were also reported (25):

MR_D	μ
37.83	4.14

Calculations have been made (26) of the reactivities of the various positions of cinnoline toward electrophilic substitution:

ΔE_3 = -16.8 Kcal./mole $\quad\quad$ $\Delta E_5 = \Delta E_8$ = -12.1

ΔE_4 = -31.5 $\quad\quad$ $\Delta E_6 = \Delta E_7$ = -15.1

The expected order of reactivity therefore was formulated as

$$5 = 8 > 6 = 7 > 3 \gg 4$$

A study (27) of the infrared spectra of eighteen cinnolines indicated that the adsorption band at approximately 6.35 μ was due to

---

(23) Pullman, Rev. Sci., 86, 219 (1948) [C.A., 43, 2095 (1949)].

(24) Longuet-Higgins and Coulson, J. Chem. Soc., 1949, 971.

(25) Rogers and Campbell, J. Am. Chem. Soc., 75, 1209 (1953).

(26) Dewar and Maitlis, J. Chem. Soc., 1957, 2521.

(27) Castle, Cox, and Suttle, J. Am. Pharm. Assoc., 48, 135 (1959) [C.A., 53, 8810 (1959)].

the interaction effects of the ring double bonds -C=C-, -N=N=, and -C=N-, and appeared to be characteristic of the cinnoline ring system.

The ultraviolet absorption spectrum of cinnoline in cyclohexane has been obtained (13, 28). The data are tabulated below:

λ (μ)	E (ref. 13)	E (ref. 28)
390.0	19.5	265
322.5	142	2080
317.0	120	1770
308.5	127	1960
286.0	181	2656
276	187	--
275.5	-	2820

These data (28) have been compared (29) to similar data for naphthalene and phthalazine, and assignments of intensity and order (as $n \rightarrow \pi^*$) made (29) and compared (30) to similar assignments for phthalazine, quinoxaline, 6-chloroquinoxaline, and 6-bromoquinoxaline in various solvents (water, 95% ethanol, and cyclohexane).

B. Cinnolines and Derivative Compounds.

The only synthesis widely applicable to this heterogenous class of cinnolines is the Widman-Stoermer reaction. Although first observed by Widman (31) in 1884 in the preparation of 4-methylcinnoline-4-carboxylic acid, the reaction was not used again until 1909 when Stoermer and Fincke (32) applied the procedure to prepare 4-arylcinnolines.

---

(28) Hearn, Morton, and Simpson, J. Chem. Soc., 1951, 3318.

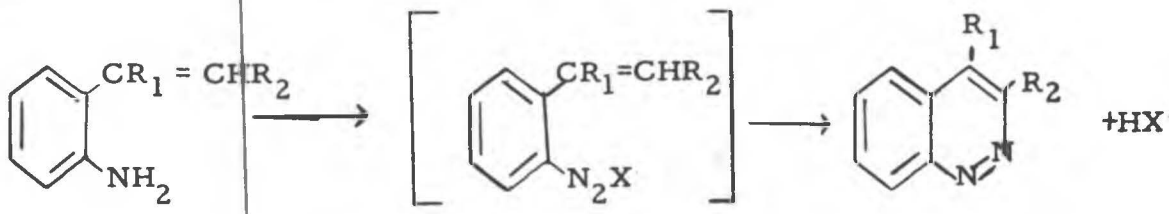
(29) Amstutz, J. Org. Chem., 17, 1508 (1952).

(30) Hirt, King, and Cavagnol, J. Chem. Phys., 25, 574 (1956).

(31) Widman, Ber., 17, 722 (1884).

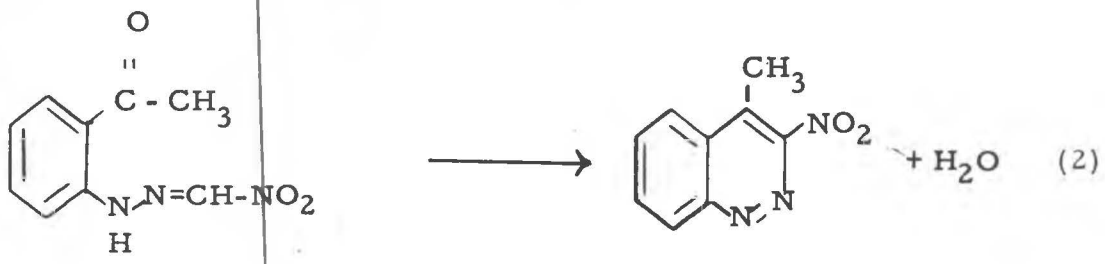
(32) Stoermer and Fincke, Ber., 42, 3115 (1909).

The reaction (equation 1) is based upon the diazotization of o-aminophenylethylenes which undergo ring closure as indicated to



form cinnolines. Investigations of the scope and mechanism of the reaction have been summarized by Simpson (13). The reaction proceeds successfully when R_1 is aryl or methyl and R_2 is alkyl, aryl, or aralkyl, but fails in cases so far investigated when R_1 is hydrogen or carboxyl (R_2 being aryl, 2-pyridyl, or 2-quinolyl). More recently, Nunn and Schofield (33) have studied the synthesis of a number of 4-aryl-3-pyridyl- and -quinolylcinnolines. Their findings indicate that a p-methoxyphenyl group at the potential cinnoline C(4)-position renders cinnoline formation very rapid and independent of pH, provided the latter is not so high as to endanger the stability of the diazonium salt. In contrast the formation of 4-phenyl-3-pyridyl- and -quinolylcinnoline depends considerably on the pH, and yields decrease rapidly with increasing acid concentration.

Baumgarten and his associates (34, 35) recently have observed a reaction which may become widely applicable in the synthesis of cinnolines. The formation of the cinnoline results from the cyclization of nitroformaldehyde o-formyl- or o-acetylphenylhydrazones (see Table 2), illustrated by equation 2.



(2)

(33) Nunn and Schofield, J. Chem. Soc., 1953

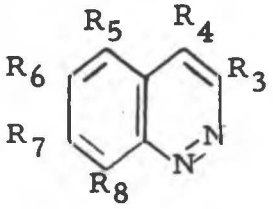
(34) Baumgarten and DeBrunder, J. Am. Chem. Soc., 76, 3489 (1954).

(35) Baumgarten, Pederson, and Hunt, J. Am. Chem. Soc., 80, 1977 (1958).

However, the general applicability of this reaction has not been tested.

Table 2 summarizes those compounds reported since 1949.

Table 2. Cinnolines and Derivative Compounds



where R represents hydrogen unless indicated otherwise

No.	R	Group	M. P., °C	Prep.[a]	%Yield	Remarks	Ref.
1	3	Chloro-	90-91	A, B	75	Needles from ligroin	19, 16
2	4	Chloro-	75-76.5, 76-77	B		Pale yellow needles from Skelly A; unstable	36, 37
3	6	Chloro-	119-120	C		Pale brown, lusterless prisms from ether-ligroin	18
4	7	Chloro-	92-93	D		Fine needles from water	15
5	3 Chloro- 4 Chloro-		128-129, 126-127, 127-128	E	87	Snow-white needles from Skelly C or ether-ligroin	38, 37
6	4 Chloro- 6 Chloro-		111-112	E			37

(36) Castle and Kruse, J. Org. Chem., 17, 1571 (1952).

(37) Schofield and Swain, J. Chem. Soc., 1950, 384.

(38) Baumgarten, J. Am. Chem. Soc., 77, 5109 (1955).

Table 2, continued

No.	R	Group	M. P., °C	Prep.[a]	%Yield	Remarks	Ref.
7	3 4 6	Chloro- Chloro- Chloro-	141-142	E		Pale yellow needles from ether-ligroin	37
8	3	Bromo-	92-93	E	80	From ligroin	19
9	3 Picrate	Bromo-	118-120	F		Yellow prisms	19
10	6	Bromo-	129-130	C		Pale buff-colored needles from ether-ligroin	18
11	3 4	Bromo- Chloro-	149-150, 153-154	E	100	Lemon-yellow blades from acetone	37, 19
12	4 6	Chloro- Bromo-	126-127	E			37
13	3 4 6	Bromo- Chloro- Chloro-	153-154	E			37
14	3 4 6	Chloro- Chloro- Bromo-		G			37
15	3 4 6	Bromo- Chloro- Bromo-	159-160	G			37
16	3	Nitro-	205-206.5, 204-205	H	39-43	Long cream-colored needles from methanol or acetone; light tan solid from dilute acetone.	34, 35
17	5	Nitro-	147-148.5, 151-152	A, I	33	From water; sublimed at 90° C/9.05 mm.; mustard yellow needles	19, 15

Table 2, continued

No.	R	Group	M.P., °C	Prep.[a]	%Yield	Remarks	Ref.
17 continued						from absolute ethanol; stable to 2N and concentrated HCl, 4 N NH_4OH; unstable to 2 N NaOH.	
18	6	Nitro-	205-206	J		Yellow needles from ethanol.	15
19	7	Nitro-	153-154.5	A	51	Light yellow crystals from water	19
20	8	Nitro-	132-132.5, 135-136	A, I	36, 28	Yellow needles from water; long yellow needles from benzene; stability as for 17.	19, 15
21	3 4	Nitro- Chloro-	169-170	E	50-80	Pale yellow needles from Skelly C; unstable for long periods.	38
22	3 6	Nitro- Chloro-	227-228	K	10-17	Pale yellow plates from ethyl acetate.	35
23	3 7	Nitro- Chloro-	165.5-166	K	10-15	Pale yellow needles from ethyl acetate.	35
24	4 5	Chloro- Nitro-	170-171	E		Lemon-yellow crystals from ether ligroin.	39, 19
25	4 6	Chloro- Nitro-		E			19
26	4 7	Chloro- Nitro-	148-149	E		Pale yellow needles from ether ligroin.	39, 19

(39) Schofield and Theobald, J. Chem. Soc., 1949, 2404.

Table 2, continued

No.	R	Group	M.P., °C	Prep.[a]	%Yield	Remarks	Ref.
27	4 8	Chloro- Nitro-	167-169	E		Golden leaflets from ether-ligroin; quickly hydrolyzed when kept.	39, 19
28	3	Methyl-	58.5-61	A		B.p. 106-111°C/0.3-0.4 mm; pale yellow plates from ether-Skelly A.	19
29	3	Methyl-Methiodide	204-204.5	L		Red needles from methanol	16
30	3	Methyl-Picrate	175-176.5	F	86	Khaki prisms from dioxan.	19
31	4	Methyl-		M	74		40
32	4 8	Methyl- Chloro-	126-127, 124-125	M, N		Yellow needles from ligroin	41, 40
33	4 8	Methyl- Chloro-Picrate	177-178, 179-180 dec.	F		Stout green needles from ethanol	41, 40
34	3 4	Nitro- Methyl-	188-189	O	59	Lustrous brown needles from ethanol	34
35	4 8	Methyl- Nitro-	138-139, 137-138 dec.	P	49, 35	Yellow plates from methanol.	41, 40
36	3	Phenyl-	119-120	Q		Red needles from n-hexane and aqueous alcohol.	17

(40) McKenzie and Hamilton, J. Org. Chem., 16, 1414 (1951).

(41) Schofield and Swain, J. Chem. Soc., 1949, 1367.

Table 2, continued

No.	R	Group	M.P., °C	Prep[a]	%Yield	Remarks	Ref.
37	3	Phenyl-Picrate	150-151	F		Yellow	17
38	3 4	Phenyl- Chloro-	119-120	E		Orange microcrystals from ether-ligroin.	42
39	3 1	p-Nitro-phenyl- Oxide	267-268	R	75	Tentative structure.	43
40	4	Benzyl-	104.5	S	43	Nearly colorless crystals from aqueous ethanol.	36
41	4	Styryl-	121.8-122.6	T	62	Green-gold plates from aqueous ethanol.	44
42	4	m-nitro-styryl-Methotoluene-p-sulfonate	N/G	N/G		Compound used as a desensitizing agent in photographic direct positive emulsions.	45
43	6	Phenyl-	111-111.5	U		Pale yellow needles from ligroin.	17
44	6	Phenyl-Picrate	176	F		Deep yellow needles from alcohol or benzene.	17
45	4 6	Chloro- Phenyl-	151-152	E	89	Pale yellow needles from ligroin.	17

(42) Schofield and Swain, J. Chem. Soc., 1949, 2393.

(43) Krohnke and Vogt, Ann., 589, 26 (1954).

(44) Castle and Cox, J. Org. Chem., 18, 1706 (1953).

(45) Kendall, Wood, and Welford (to Ilford, Ltd.) U. S., 2,669,515, Feb. 16, 1954 [C.A., 48, 6892 (1954)].

Table 2, continued

No.	R Group	M.P., °C	Prep.[a]	%Yield	Remarks	Ref.
46	7 Phenyl-	116	U		Very pale yellow needles from aqueous alcohol.	17
47	7 Phenyl- Picrate	175.5-177	F	48	Somewhat gummy brown needles from methanol.	17
48	4 Chloro- 7 Phenyl-	124-125	E	55	Pale yellow needles from ligroin.	17
49	3 Phenyl- 4 Phenyl-	151-152	V		Yellow	7
50	3 Phenyl- 4 Phenyl- Methiodide	246 dec.	L		Black needles (yellow as a powder).	7
51	3 Phenyl- 4 Phenyl- 7 Methyl-	178	W		Yellow	7
52	3 Phenyl- 4 Phenyl- 7 Methyl- Picrate	155	F			7
53	3 Phenyl- 4 Phenyl- 8 Methyl-	158	W		Yellow	7
54	3 Phenyl- 5 Phenyl-	123	X		Tentative structure; nearly colorless.	7
55	3 Phenyl- 5 Phenyl- Picrate	164-165	F		Yellow from alcohol	7
56	3 Phenyl- 5 Phenyl- 6 Methyl-	183	X		Tentative structure; nearly colorless	7

Table 2, continued

No.	R	Group	M.P., °C	Prep.[a]	%Yield	Remarks	Ref.
57	3 5 6	Phenyl- Phenyl- Methyl- Picrate	181-182	F		Yellow from alcohol	7
58	3 5 7	Phenyl- Phenyl- Methyl-	170	X		Tentative structure; nearly colorless	7
59	3 5 7	Phenyl- Phenyl- Methyl- Picrate	194-195	F		Yellow from alcohol	7
60	4	1-[2-(2-Thenyl)-ethenyl]-	113-113.6	T	12	Fine bright yellow crystals from methanol.	44
61	4	2-Thenyl-	85-86	M		Yellow prisms from ether	33
62	4	1-(2-[4-(2-Phenyl)-1,2,3-2H-triazolyl]-ethenyl)-	205.2-205.6	T	8	Bright yellow needles from methanol.	44
63	2	2-Pyridyl-	125-126, 128-129	M		Stout, crisp, almost colorless prisms from methanol or ligroin containing a little ethyl acetate.	46

(46) Schofield, J. Chem. Soc., 1949, 2408.

Table 2, continued

No.	R	Group	M.P., °C	Prep.[a]	%Yield	Remarks	Ref.
64	4	2-Pyridyl-	196-199, 201-203	F		Beautiful, felted, mustard-yellow needles from methanol.	33, 46
65	3 4	Methyl- 2-Pyridyl-	155-156	M		Pale yellow prisms from benzene-ligroin.	33
66	4	3-Pyridyl-	141-142	M		Yellow needles from benzene - Skelly B.	33
67	3 4	Methyl- 3-Pyridyl-	192-193	M		Yellow prisms from ethanol.	33
68	4	4-Pyridyl-Picrate	276-278	M and then F		Yellow prisms from methanol.	33
69	3 4	2-Pyridyl- Phenyl-	145-146	M		Purified by passing over alumina (benzene solvent).	33
70	3 4	2-Pyridyl- Phenyl-Picrate	194-196	F after M		Yellow leaflets from methanol.	46
71	3 4 6	2-Pyridyl- Phenyl- Chloro-	143-144	M		Yellow prisms from aqueous ethanol.	33
72	3 4	2-Pyridyl- 4-Tolyl-	164-165	M		Passed over alumina (benzene solvent), then yellow needles from ethanol.	33
73	3 4	2-Quinolyl- Phenyl-	162-163	M		Yellow prisms from aqueous ethanol.	33

Table 2, continued

No.	R	Group	M.P., °C	Prep.[a]	%Yield	Remarks	Ref.
74	3 4 Pictrate	2-Quinolyl- Phenyl-	219-220	F		Yellow prisms from ethanol.	33
75	3 4 6	2-Quinolyl- Phenyl- Chloro-	205-206	M		Yellow needles from ethanol.	33
76	3 4	2-Quinolyl- 4-Tolyl-	153-154	M		Yellow needles from aqueous ethanol and benzene-ligroin.	33
77	4	4-Cinnolyl-	237-238, 231-232	Y, Z	7.5	Long soft pale needles from aqueous acetic acid; small brittle golden prisms from ethanol.	15

[a] A. By hydrolysis of the appropriate 4-toluene-p-sulfonylhydrazinocinnoline or its hydrochloride salt.

B. By heating the analogous hydroxycinnoline with phosphorous oxychloride and/or phosphorous pentachloride.

C. By oxidation of the appropriate 4-cinnolylhydrazine with 10% aqueous copper sulfate.

D. By catalytic reduction of 4, 7-dichlorocinnoline in methanol with palladium hydroxide on calcium carbonate, 4-5 atmospheres of hydrogen, and at room temperature.

E. By heating the appropriate 4-hydroxycinnoline with phosphorous oxychloride and/or phosphorous pentachloride.

F. By treating the free base with picric acid.

G. By heating 3, 6-dibromo-4-hydroxycinnoline with phosphorous oxychloride and phosphorous pentachloride.

H. By condensing nitroformaldehyde o-formylphenylhydrazone or its acetal.

I. By nitrating cinnoline with conc. sulfuric acid and fuming nitric acd.

J. By oxidation of 6-nitro-4-isopropylidenehydrazinocinnoline as in C.

Table 2, continued

K. By condensing the appropriate nitroformaldehyde chloro-2-formylphenylhydrazone.

L. By treating the free base with methyl iodide in methanol or nitrobenzene.

M. By the Widman-Stoermer reaction.

N. By the Sandmeyer reaction on the analogous 8-amino-compound.

O. By condensing the appropriate nitroformaldehyde o-acetylphenylhydrazone.

P. By nitrating the cinnoline with mixed acids.

Q. By reducing the 4-hydroxy- analog with lithium aluminum hydride in tetrahydrofuran, and then treating the product with red mercuric oxide in benzene.

R. By cyclization of α-amino-β-o-nitrophenyl-p-nitrostyrene with light.

S. By refluxing the corresponding α-(4-cinnolyl)-phenylacetonitrile with 50% aqueous sulfuric acid.

T. By condensing the appropriate aldehyde with 4-methyl-cinnoline.

U. By reducing the 4-hydroxy- analog with lithium aluminum hydride in tetrahydrofuran.

V. By dehydrogenating 3, 4-diphenyl-5, 6, 7, 8-tetrahydro-cinnoline with palladized charcoal at 260° C or in boiling cumene or by selenium at 310-320° C.

W. By dehydrogenating the appropriate 3, 4-diphenyl-5, 6, 7, 8-tetrahydrocinnoline by palladized charcoal at 260° C or in boiling cumene.

X. By dehydrogenating the appropriate 3, 4-diphenyl-5, 6, 7, 8-tetrahydrocinnoline by palladized charcoal at 360-370° C.

Y. By decarboxylating cinnoline-4-carboxylic acid in benzophenone.

Z. By reducing 4-chlorocinnoline as in D.

In the dehydrogenation of the 3, 4-diphenyl-5, 6, 7, 8-tetrahydrocinnolines (7) by palladized charcoal at 260-290° C, 2, 3-diphenylindoles are formed in addition to the diphenylcinnolines. In several instances stable 1:1 molecular complexes are formed, as summarized below:

Cinnoline	Indole	M.P., °C
3, 4-Diphenylcinnoline	2, 3-Diphenylindole	128-129
7-Methyl-3, 4-diphenyl-cinnoline	6-Methyl-2, 3-diphenyl-indole	151
7-Methyl-3, 5-diphenyl-cinnoline	6-Methyl-2, 3-diphenyl-indole	134-135

The structures of the 3, 5-diphenylcinnolines have not been proved, but were suggested because of the frequent 1, 3- shift of phenyl groups in highly arylated compounds (47). In every case the major portion of the reaction is the diarylindole. Indole formation has been observed (48) to be characteristic of 4-arylcinnolines upon reduction with sodium and alcohol.

The basic strength of 4-chlorocinnoline was determined (20) to be 2. 08 in 50% aqueous alcohol at 21-22° C.

The electric moment and related data have been obtained for 4-methylcinnoline:

E_{10}	α'	V_{10}	β'	P_2	MR_D	μ_{obs}	$\mu_{calc.}$
2. 2705	29. 075	1. 4500	-0. 60	462. 9	43. 00	4. 53	4. 49

The values were obtained in benzene at 25° C.

The ultraviolet spectra of a number of cinnolines have been reported. The references for these compounds are tabulated:

Cinnoline	Solvent	Reference
3-Chlorocinnoline		16
6-Bromo-4-phenylcinnoline	Methanol	7
3, 4-Diphenylcinnoline	Methanol	7
3, 5-Diphenylcinnoline	Methanol	7
3, 4-Diphenyl-7-methylcinnoline	Methanol	7
3, 4-Diphenyl-8-methylcinnoline	Methanol	7

---

(47) Allen, Chem. Revs., 37, 233, 263 (1945).

(48) Atkinson and Simpson, J. Chem. Soc., 1947, 1649.

3, 5-Diphenyl-6-methylcinnoline	Methanol	7
3, 5-Diphenyl-7-methylcinnoline	Methanol	7

The heat and entrophy of activation have been determined (15) for the reaction in ethanol of ethoxide ion and 4-chlorocinnoline at 20, 30, and 40° C.

Hydrolysis studies (49) on a number of 4-chlorocinnolines have been carried out, as tabulated below:

Cinnoline	Hydrolysate/Time (hrs.)	Results[a] Initial Material	Results[a] 4-Hydroxy-analog
4-Chlorocinnoline	water/ 1/4	-	+
4, 7-Dichlorocinnoline	water/1	+	+
4, 7-Dichlorocinnoline	0. 02 N HCl/1	-	+
4-Chloro-6-nitrocinnoline	water/ 1/3	-	+
4-Chloro-8-nitro-7-methylcinnoline	N HCl/ 1/2	+	Trace
4-Chloro-8-nitro-7-methylcinnoline	5 N HCl/2	-	+
4-Chloro-5 (or 7)- nitro-8-methylcinnoline	H_2O/1	50%	50%
4-Chloro-5 (or 7)-nitro-8-methylcinnoline	H_2O/3	-	100%
4-Chloro-5 (or 7)-nitro-8-methylcinnoline	0. 02 N HCl/1	-	100%

[a] A - sign indicates the material was not isolated, while a + sign indicates that the material was obtained from the reaction mixture.

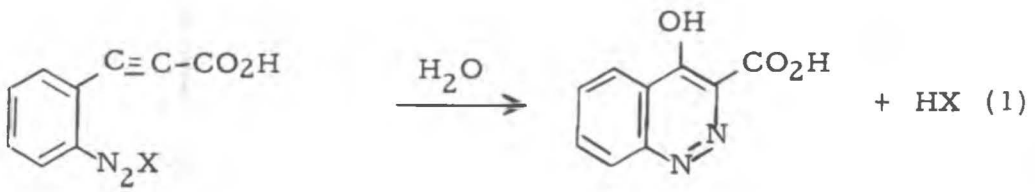
It was shown (49) that there is substantial qualitative agreement between the observed order of reactivity of comparable compounds of cinnoline, quinazoline, and quinoline and the predicted order as deduced from the electron-density calculations of Longuet-Higgins and Coulson (24).

(49) Keneford, Morley, and Simpson, J. Chem. Soc., 1950, 1104.

C. Hydroxycinnolines and Derivatives.

Of the hydroxycinnolines the 4-hydroxy-compounds are by far the most important. Two widely applicable routes are available for their preparation.

Historically, the first is the Richter synthesis, originated in 1883 (1). Improvements and variations have made the reaction a general route for preparing 6-substituted-4-hydroxycinnoline-3-carboxylic acids and 6-substituted-4-hydroxycinnolines. Cinnoline formation results from the cyclization of diazotized o-aminophenylpropiolic acids or o-aminophenylacetylenes. The reaction is illustrated by the original (Equation 1)



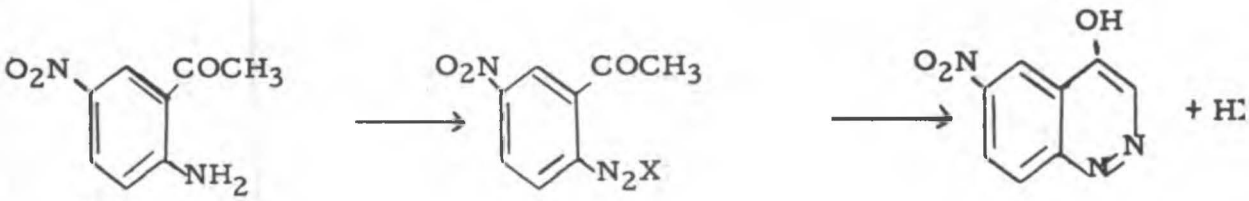
Simpson (13) has reviewed the scope and mechanism of the reaction. The carboxylic acid group may be replaced successfully by hydrogen or by a phenyl group; the synthesis fails when replacement is made by the 2-pyridyl group (50, 51).

The Borsche synthesis is the second and more widely applicable route for the preparation of 4-hydroxycinnolines. In 1941 Borsche and Herbert (2) observed that 5-nitro-2-aminoacetophenone on diazotization undergoes a slow cyclization at room temperature to 6-nitro-4-hydroxycinnoline (equation 2). This reaction has proven to be a valuable general procedure for preparing 3-, 5-, 6-, 7-, and 8-substituted 4-hydroxycinnolines. This reaction has received a good deal of attention, the scope and mechanism having been reviewed by Simpson (13), which source should be consulted for further information.

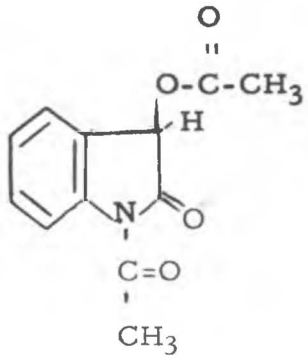
---

(50) Schofield and Simpson, J. Chem. Soc., 1945, 512.

(51) Schofield and Swain, J. Chem. Soc., 1949, 2393.



Although 3-hydroxycinnoline reportedly (5, 52) has been prepared it was not until 1952 (53) that a detailed description became available. The compound was prepared by diazotization and reduction of O, N-diacetyldioxindole (I).



(I)

This same type of reaction also was used to prepare the 6-chloro- and 6-methoxy- analogs (53).

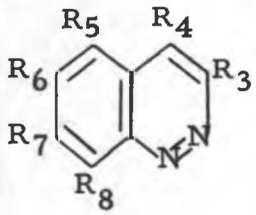
Table 3 lists those hydroxycinnolines and derivatives reported since 1949.

---

(52) Bossel, Inaug.-Diss., Tübingen, May, 1925, pp. 31-33.

(53) Alford and Schofield, J. Chem. Soc., 1952, 2102.

Table 3. Hydroxycinnolines and Derivatives.



where R represents hydrogen unless indicated otherwise.

No.	R	Group	M.P., °C	Prep.[a]	%Yield	Remarks	Ref.
1	3	Hydroxy-	201-203	A, B	62	Bright yellow needles from water then benzene; retains water strongly.	53, 16
2	3	Hydroxy- Methohydroxide anhydro salt	280-283	C		Orange plates from alcohol and chloroform-ligroin.	16
3	3 6	Hydroxy- Chloro-	262-265 (with darkening)	A		Yellow needles from alcohol. Retains water strongly.	53
4	3	Methoxy- Picrate	155-157.5	D		Yellow prisms from alcohol.	16
5	3	Benzoyl-oxy-	148-149	E		White crystals from aqueous alcohol.	53
6	3 4	Chloro- Hydroxy-	278-279	F, G, H	22	From acetic acid	37, 18
7	4 6	Hydroxy- Chloro-	287-288	I, J, K	20		42, 18
8	3 4 6	Chloro- Hydroxy- Chloro-	301-303	F	32		37
9	3 4	Bromo- Hydroxy-	273-274, 275-276	L, M, N	12.5-34, 20	Pale brown or white needles from ethanol.	37, 18

Table 3, continued.

No.	R	Group	M.P., °C	Prep.[a]	%Yield	Remarks	Ref.
10	4 5	Hydroxy- Bromo-		I	20		42
11	4 6	Hydroxy- Bromo-		J			42
12	3 4 6	Bromo- Hydroxy- Bromo-	313-314	O	22	White needles from ethanol.	37
13	3 4 6	Bromo- Hydroxy- Chloro-	308-309	P	19.5	White needles from ethanol.	37
14	3 4 6	Chloro- Hydroxy- Bromo-	306-307	Q	22		37
15	4 8	Hydroxy- Iodo-	261-262	R		Pale yellow leaflets from ethanol.	54
16	3 4	Nitro- Hydroxy-	284.5- 285.5	S	69	Light yellow needles from ethanol.	38
17	4 5	Hydroxy- Nitro-	304-305	R		Colorless needles from alcohol.	39, 19
18	4 6	Hydroxy- Nitro-	231-232	T, R	90	Orange-yellow needles	51, 19
19	4 7	Hydroxy- Nitro-	295-296, 300	R		Pale yellow needles from alcohol	39, 55, 19

(54) Schofield and Theobald, J. Chem. Soc., 1950, 395.

(55) Atkinson, Simpson, and Taylor, J. Chem. Soc., 1954, 1381.

Table 3, continued

No.	R	Group	M.P., °C	Prep[a]	%Yield	Remarks	Ref.
20	4 8	Hydroxy- Nitro-	183-185	R, U	55	Yellow needles.	19, 56
21	4	Methoxy-	125-126 127-128	V			51, 57
22	4 7	Methoxy- Nitro-	200	V		Pale yellow, opaque, flat blades from acetone.	56
23	4	Ethoxy- Picrate	174	V then W			57
24	4	Iso- propoxy- Picrate	163	V then W			57
25	4	Phenoxy-		X			51
26	3 4	Chloro- Phenoxy-	127-128	X		From Skelly C	38
27	3 4 6	Chloro- Phenoxy- Chloro-	107-108	Y	90-95	White or cream-colored needles from ether-ligroin.	37
28	3 4	Bromo- Phenoxy-	143-144	Y	90-95	White or cream-colored needles from ether-ligroin.	37
29	3 4 6	Bromo- Phenoxy- Bromo-	135-136	Y	90-95	White or cream-colored needles from ether ligroin.	37

(56) Atkinson and Taylor, J. Chem. Soc., 1955, 4236.

(57) Adachi, J. Pharm. Soc. Japan, 75, 1426 (1955) [C.A., 50, 10105 (1956)].

Table 3, continued.

No.	R	Group	M.P., °C	Prep[a]	%Yield	Remarks	Ref.
30	3 4 6	Bromo- Phenoxy- Chloro-	113-114	Y	90-95	White or cream-colored needles from ether-ligroin.	37
31	3 4 6	Chloro- Phenoxy- Chloro-	128-129	Y	90-95	White or cream-colored needles from ether-ligroin.	37
32	3 4	Nitro- Phenoxy-	144.5-145	X	21	Pale tan plates from Skelly C.	38
33	4 5	Phenoxy- Nitro-	123	X		Almost colorless needles from Skelly A.	55
34	4 7	Phenoxy- Nitro-	172-173	X		Pale yellow needles from benzene-ligroin.	39
35	4 8	Phenoxy- Nitro-	166-167	X		Pale yellow needles from benzene.	39
36	3 4	Chloro- Acetoxy-	124-125	Z			37
37	4 6	Acetoxy- Chloro-	159-160	Z	90-95	Almost colorless needles from alcohol.	51
38	3 4 6	Chloro- Acetoxy- Chloro-	148-149	Z			37
39	3 4	Bromo- Acetoxy-	139-140	Z			37
40	3 4 6	Bromo- Acetoxy- Bromo-	178-179	Z			37
41	3 4 6	Bromo- Acetoxy- Chloro-	165-166	Z			37

Table 3, continued

No.	R	Group	M.P., °C	Prep.[a]	%Yield	Remarks	Ref.
42	4 5	Acetoxy- Nitro-	185-186	Z		Colorless leaflets from dilute alcohol.	39
43	4 7	Acetoxy- Nitro-	140-141	Z		From dilute alcohol.	39
44	4	Mer- capto-	200-201, 203-205	AA, BB		From acetic acid.	58
45	4	Methyl- mercapto-	98	CC	63-74	Yellow needles from cyclohexane.	58
46	4	5-Thi- uronium chloride	146-148	DD		Assumed intermediate	58
47	4	4-Cinnolyl- mercapto-	181	EE	97	From ethanol.	58
48	4	2-Quin- oxalyl- mercapto-	153-154	FF	Poor	Pale yellow needles from ethanol.	58
49	4 6	Hydroxy- O-methyl- acinitro-	225-226, 225-227 dec.	GG	55	From water or alcohol.	51
50	3 4 6	Methyl- Hydroxy- O-methyl- acinitro-	161-162	GG		Orange flakes from aqueous alcohol.	51
51	3 4 6	Methyl- Methoxy- Nitro-	144-150	V		Golden prismatic needles from methanol; rapidly hydrolyzed to the 4-hydroxy compound by dilute mineral acids.	51

(58) Castle, Ward, White, and Adachi, J. Org. Chem., 25, 570 (1960).

Table 3, continued

No.	R	Group	M.P., °C	Prep[a]	%Yield	Remarks	Ref.
52	3 4 6	Chloro- Hydroxy- Methyl-	298.5-299.5	R		Soft white needles from alcohol.	59
53	3 4 6	Chloro- Acetoxy- Methyl-	186-187	Z			59
54	4 6 7	Hydroxy- Methyl- Methyl-	267-268	R		Buff-colored rhombs from ethanol.	59
55	3 4 6 7	Chloro- Hydroxy- Methyl- Methyl-	314-315 (310)	R		Colorless needles from alcohol.	59
56	4 6 7	Acetoxy- Methyl- Methyl-	151-152	Z		Fawn leaflets from dilute ethanol.	59
57	3 4 6 7	Chloro- Acetoxy- Methyl- Methyl-	196-197	Z		Silky needles from alcohol.	59
58	3 4	Phenyl- Hydroxy-	265-267, 260-261	I, R	64-90	White leaflets from alcohol.	60, 42
59	3 4 6	Phenyl- Hydroxy- Nitro-	347-348	R	50-61	Small yellow needles	60

(59) Schofield, Swain, and Theobald, J. Chem. Soc., 1949, 2399.

(60) Ockenden and Schofield, J. Chem. Soc., 1953, 3706.

Table 3, continued

No.	R	Group	M.P., °C	Prep.[a]	%Yield	Remarks	Ref.
60	3 4 6	Phenyl- Hydroxy- Methyl-	310-312	R	67-86	Cream-colored plates.	60
61	4 6	Hydroxy- Phenyl-	294-296	R	38	Colorless needles from alcohol.	17
62	4 6	Ethoxy- Phenyl-	176	HH		Tentative structure; colorless needles from ligroin or aqueous alcohol.	17
63	4 6	Ethoxy- Phenyl- Picrate	168	II			17
64	4 7	Hydroxy- Phenyl-	323-325	R	37	Colorless needles from methanol or acetic acid.	17
65	3 4	1-Naphthyl- Hydroxy-	285-286	R	77-87	Small plates.	60
66	5	Hydroxy-	285 dec.	JJ		Brownish-yellow cubes from ethanol.	61
67	5	Methoxy-	92-93.5	KK	34	Cream blades from Skelly B.	61
68	4 5	Chloro- Methoxy-	141-142	LL		Needles from Skelly B.	61
69	6	Hydroxy-	300	JJ		Fluffy cream needles from water; material turns blue-black at about 195°.	61

(61) Osborn and Schofield, J. Chem. Soc., 1955, 2100.

Table 3, continued

No.	R	Group	M.P., °C	Prep.[a]	%Yield	Remarks	Ref.
70	6	Methoxy-	87-88	KK		Colorless needles from Skelly B.	61
71	7	Hydroxy-	300	JJ		Needles from water then ethanol.	61
72	7	Methoxy- Monohydrate	109-110 dec.	KK		Needles from Skelly B.	61
73	4 7	Chloro- Methoxy-	178-179	LL		Needles from Skelly B.	61
74	8	Hydroxy-	185-186, 186-187	MM, NN		Long yellow needles from benzene; sublimed at 115-120° C/0.05 mm.	62, 63
75	8	Methoxy-	67-70.5 (sealed tube)	KK		Colorless needles from benzene-ligroin. Quickly liquified, darkened, became green when kept.	62
76	8	Methoxy- Picrate	189-191.5	II		Orange needles.	62
77	4 8	Chloro- Methoxy-	142-143 (slowly darkened)	LL	87	Faint yellow needles from acetone.	62
78	4 8	Methyl- Hydroxy-	177-178.5, 176.5-177.5	MM		Light yellow prisms from benzene; sublimed at 150-160° C/0.1 mm.	62, 63

(62) Alford, Irving, Marsh, and Schofield, J. Chem. Soc., 1952, 3009.

(63) Albert and Hampton, J. Chem. Soc., 1952, 4985.

Table 3, continued

No.	R	Group	M.P., °C	Prep.[a]	%Yield	Remarks	Ref.
79	4 8	Methyl- Methoxy-	130-132, 131-132	OO	72	Yellow prisms from benzene then Skelly D; orange needles from benzene - Skelly A.	62, 63
80	4 8	Phenyl- Hydroxy-	142- 143.5	MM		Fawn-colored needles from benzene-Skelly B.	62
81	4 8	Phenyl- Methoxy-	85-89	OO		Opaque, light yellow plates from chloroform-Skelly B; became sticky in air.	62
82	4 8	Styryl- Hydroxy-	200-201	PP		Yellow needles from benzene then methanol.	63
83	4 8	Styryl- Benzoyl-oxy-	212-213	QQ		Yellow prisms from benzene.	63
84	3 6	Hydroxy- Hydroxy-		RR		Yellow nodules from 5 N HCl. Retains water strongly.	53
85	3 6	Hydroxy- Methoxy-		A		Yellow powder insoluble in most solvents.	53
86	3(6) 6(3)	Hydroxy- Benzoyl-oxy-	233-235 (after darkening)	SS		Fluffy yellow crystals from methanol.	53
87	4 5	Hydroxy- Methoxy-	275 dec.	R		Pale cream needles from water; polymorphic form, m.p. 245 dec., changes into higher melting form upon standing.	61

Table 3, continued

No.	R	Group	M.P., °C	Prep.[a]	%Yield	Remarks	Ref.
88	4 6	Hydroxy- Methoxy-	252	R		Colorless needles from water.	61
89	3 4 6	Phenyl- Hydroxy- Methoxy-	318-319	I		White micro-crystals from dilute acetic acid.	42
90	4 7	Hydroxy- Methoxy-	255-257	R		Needles from water.	61
91	4 8	Hydroxy- Methoxy- Monohydrate	164-165	R	92	White needles from water; dried at 110° C/2 mm.	62
92	4 6 7	Chloro- Methoxy- Methoxy-	195-196	LL		Hair-like, cream-colored crystals from ethanol.	36
93	3 6,7	Nitro- Methyl-enedioxy-	See remarks	TT	12	Cream-colored needles from ethyl acetate; blackened at 250° (not melting), subliming at 255-310° C.	35
94	4 6 7	Hydroxy- Methoxy- Methoxy-	271-272	R	67	White powder.	36
95	4 6 7	Hydroxy- Methoxy- Methoxy-	234 dec.	UU			36
96	4 6 7	Methoxy- Methoxy- Methoxy-	210	V	76	From methanol.	58
97	4 6 7	Ethoxy- Methoxy- Methoxy-	185-187	V		From ethanol.	58

Table 3, continued

No.	R	Group	M.P., °C	Prep.[a]	%Yield	Remarks	Ref.
98	4	Mercapto-	216-217	AA, BB		Yellow powder from acetic acid.	58
	6	Methoxy-					
	7	Methoxy-					
99	4	Methyl-mercapto-	215-217	CC	37	Yellow crystals from benzene.	58
	6	Methoxy-					
	7	Methoxy-					
100	4	5-Thiuronium chloride	175-179	DD			58
	6	Methoxy-					
	7	Methoxy-					
101	4	4-Cinnolyl-	193	EE		From ethanol.	58
	6	Methoxy-					
	7	Methoxy-					
102	4	2-Quinoxalyl-	210	FF		Contains ethanol of recrystallization.	58
	6	Methoxy-					
	7	Methoxy-					
103	4	4-(6, 7-Dimethoxy) cinnolyl-	220-225	VV		From methanol.	58
	6	Methoxy-					
	7	Methoxy-					
104	4	3, 3, 3-Trichloro-2-hydroxy-propyl-	165-166	WW		Glistening silver leaflets from ethanol.	16
105	3	2-Pyridyl-	265-266	XX		Yellow prisms from ethanol.	33
	4	p-Hydroxy-phenyl-					

Table 3, continued

No.	R	Group	M.P., °C	Prep.[a]	%Yield	Remarks	Ref.
106	3	2-Pyridyl-	157-158	OO		Pale yellow tablets from aqueous methanol.	33, 47
	4	p-Methoxy-phenyl-					
107	3	3-Pyridyl-	145-146	OO		Yellow needles from aqueous ethanol.	33
	4	p-Methoxy-phenyl-					
108	3	2-Quinolyl-	151-152	OO		Glistening pale yellow tablets from methanol.	33, 47
	4	p-Methoxy-phenyl-					
109	3	1-(2-o-Hydroxy-phenyl) ethynyl-	224-225	YY		Postulated product; pale green needles from alcohol.	42
	4	Hydroxy-					
110	4	p-Methoxy-styryl-	112.2-112.6	ZZ	42	Golden plates from methanol.	44
111	4	3,4-Di-methoxy-styryl-	193-194	ZZ	10	Very pale yellow needles from ethanol then aqueous ethanol.	44

[a] A. By diazotizing the appropriate O,N-diacetyldioxindole, then reducing the product with stannous chloride in hydrochloric acid.

B. By heating 3-bromocinnoline with sodium in wet methanol in a sealed tube at 110-120° C.

C. By treating the analogous 3-hydroxycinnoline with 2 N sodium hydroxide and dimethyl sulfate.

D. By the procedure outlined in B except with dry methanol.

E. By treating the analogous 3-hydroxycinnoline with benzoyl chloride and sodium hydroxide.

Table 3, continued

F. By chlorination of the 4-hydroxycinnoline using sulfuryl chloride, acetic anhydride, and acetic acid.

G. By treating 3-chloro-4-phenoxycinnoline with ammonium acetate at 160° C.

H. By treating 3, 4-dichlorocinnoline with aqueous ammonia at 150-160° C in a sealed tube.

I. By the Richter synthesis.

J. By decarboxylating the corresponding cinnoline-3-carboxylic acid.

K. By treating 4, 6-dichlorocinnoline with either saturated alcoholic ammonia or aqueous ammonia at 150-160° C in a sealed tube.

L. By bromination with potassium bromide and potassium bromate of the reaction mixture of the Borsche synthesis.

M. By bromination of 4-hydroxycinnoline with bromine in acetic acid at 95° C.

N. By treating 4-chloro-6-bromocinnoline as in F.

O. By treating 6-bromo-4-hydroxycinnoline as in M.

P. By treating 6-chloro-4-hydroxycinnoline as in M.

Q. By treating 6-bromo-4-hydroxycinnoline as in F.

R. By the Borsche reaction.

S. By basic hydrolysis of 4-amino-6-nitrocinnoline.

T. By refluxing 4-hydroxy-6-(o-methylacinitro)cinnoline with 2 N hydrochloric acid.

U. By treating 4-amino-8-nitrocinnoline methiodide with hot water.

V. By treating the analogous 4-chlorocinnoline with the appropriate sodium alkoxide.

W. By treating the free base with picric acid.

X. By treating the analogous 4-chlorocinnoline with phenol and potassium hydroxide at 95° C or with phenol and potassium carbonate or ammonium carbonate at 95, 100, or 120° C.

Y. By treating the analogous 4-hydroxycinnoline with phenol at 180° C.

Z. By treating the analogous 4-hydroxycinnoline with acetic anhydride.

AA. By treating the analogous 4-chlorocinnoline with thiourea in methanol then basic hydrolysis of the product.

BB. By treating the analogous 4-hydroxycinnoline with phosphorous pentasulfide in pyridine.

CC. By treating the analogous 4-mercaptocinnoline with methyl iodide and sodium hydroxide at 25° C.

Table 3, continued

DD. Assumed intermediate (before hydrolysis) of AA.

EE. By refluxing 4-chlorocinnoline and the analogous 4-mercaptocinnoline with sodium methoxide in methanol.

FF. By refluxing the analogous 4-mercaptocinnoline and 2-chloroquinoxaline as in EE.

GG. By treating the analogous 4-hydroxy-6-nitrocinnoline with 2% potassium hydroxide and dimethyl sulfate at 50° C or with methyl toluene-p-sulfonate at 150° C.

HH. By treating the analogous 4-chloro- compound with sodium hydroxide, water, and ethanol.

II. By treating the free base with picric acid.

JJ. By treating the analogous 4-toluene-p-sulfonyl-hydrazino- compound with hydrobromic acid.

KK. By treating the analogous 4-toluene-p-sulfonyl-hydrazino- compound with aqueous sodium carbonate or potassium carbonate.

LL. By treating the 4-hydroxy- analog with phosphorous oxychloride and/or phosphorous pentachloride.

MM. By treating the analogous 8-methoxycinnoline with hydrobromic acid.

NN. By decarboxylating the analogous cinnoline-4-carboxylic acid.

OO. By the Widman-Stoermer synthesis.

PP. By treating the 4-methyl- analog (hydrochloride salt) with benzaldehyde and dry hydrogen chloride at 155-160° C.

QQ. By treating the free base with benzoyl chloride in pyridine.

RR. By treating 6(3)-benzoyloxy-3(6)-hydroxycinnoline with concentrated hydrochloric acid.

SS. By treating 6-methoxy-3-hydroxycinnoline with benzoyl chloride and sodium hydroxide.

TT. By cyclizing nitroformaldehyde 4,5-methylenedioxy-2-formylphenylhydrazone using potassium hydroxide.

UU. By treating the free base with hydrochloric acid.

VV. By treating 4-chloro- and 4-mercapto-6,7-dimethoxy-cinnoline as in EE.

WW. By treating 4-methylcinnoline with chloral in pyridine at 95° C.

XX. By refluxing the 4-p-methoxyphenylcinnoline with hydrobromic acid.

YY. By the tetrazotisation of 2,2'-diaminodiphenyldiacetylene.

ZZ. By condensing 4-methylcinnoline with the appropriate aldehyde using a 1/2-molar equivalent of zinc chloride.

The basic and acid strengths (indicated by pKb and pKa, respectively) of a number of hydroxycinnolines and derivatives have been determined and are tabulated below.

Cinnoline	pKb	Sol.[a]	T. °C	Ref.	pKa	Sol.[a]	T. °C	Ref.
3-Hydroxy-	0.21	A	20	64	8.64	A	20	64
4-Hydroxy-	1.77	B	21-22	20	9.53	B	21	20
	1.66	B	15	20				
	1.72	B	18-19	20				
	-0.35	A	20	64	9.27	A	20	64
4-Methoxy-	2.71	B	21-22	20				
	3.21	A	20	64				
	3.21	A	20	65				
4-Phenoxy-	2.27	B	21-22	20				
4-Phenoxy-6-nitro-	2.49	B	25 ± 2	20				
4-Phenoxy-8-nitro-	3.15	B	25 ± 2	20				
5-Hydroxy-	1.92	A	20	64	7.40	A	20	64
6-Hydroxy-	3.65	A	20	64	7.52	A	20	64
7-Hydroxy-	3.31	A	20	64	7.56	A	20	64
8-Hydroxy-	2.86	C	14 ± 3	62	8.13	C	14 ± 3	62
	2.74	A	20	64	8.20	A	20	64
	2.74	A	20	65	8.20	A	20	65
	2.70	A	20	66	8.20	A	20	66
	1.77	D	20	66	8.84	D	20	66
8-Hydroxy-4-methyl-	3.28	C	14 ± 3	62	8.67	C	14 ± 3	62
	3.18	A	20	65	8.34	A	20	65
	2.59	D	20	66	9.00	D	20	66

[a] A. Water. B. 50% aqueous alcohol. C. Buffered solutions of constant ionic strength 0.3. D. 50% aqueous dioxan.

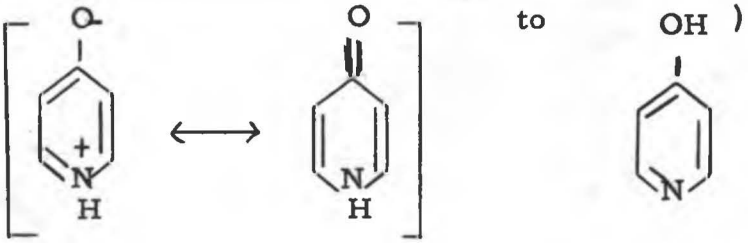
(64) Albert and Phillips, J. Chem. Soc., 1956, 1294.

(65) Albert and Hampton, J. Chem. Soc., 1954, 505.

(66) Irving and Rossotti, J. Chem. Soc., 1954, 2910.

The significance of the relative values of a few of the compounds tabulated has been discussed (64) and generalizations obtained (64). The basic strengths of the 4-hydroxy-, 4-methoxy-, and 4-phenoxycinnolines have been compared (20) to the corresponding quinoline and quinazoline derivatives[1]. Four conclusions were drawn (20): (1) For a given arrangement of substituents, the quinoline is invariably a stronger base than the cinnoline derivative; (2) the difference between the pK value of a quinoline and that of the analogous cinnoline or quinazoline increases as the pK values themselves increase; (3) for the 4-hydroxy-, 4-methoxy-, and 4-phenoxycinnolines the order of basicity is quinoline > quinazoline > cinnoline (this order also applies to 4-chlorocinnoline and cinnoline itself); and (4) the order of effectiveness of the various 4-substituents in promoting basicity is the same in each heterocyclic class; i. e., all amino- derivatives tested 4-methoxy- > 4-phenoxy- > 4-chloro- > 4-hydroxy-.

The tautomeric equilibria between enol and amide in α- and γ-hydroxy- derivatives was shown (64) to favor greatly the amide form. The approximate ratio of amide to enol tautomers (i. e., the ratio of the hybrid



in neutral aqueous solution at 20° C for 4-hydroxycinnoline was found (64) to be 3600.

The bacteriostatic indexes of 8-hydroxy-, 8-hydroxy-4-methyl-, and 8-hydroxy-4-phenylcinnoline have been summarized (62). 8-Hydroxycinnoline was found to have no antibacterial activity (67). Incidentally, this same source (67) apparently gives ionization and stability constants and partition phenomenon; the abstract provided no further information or details.

---

[1]This study also included 4-chlorocinnoline, which is required in the present discussion, and several aminocinnolines and derivatives, which compounds will be treated in the appropriate section.

(67) Albert and Hampton, 2nd Congr. Intern. Biochim., Resumes Communs., (Paris, 1952), 444 [C. A., 49, 4648 (1955)].

The partition coefficients of 8-hydroxycinnoline and 8-hydroxy-4-methylcinnoline with oleyl alcohol and water at 20° and pH 7.3 have been determined (65) to be 5.6 and 16.3, respectively.

Ultraviolet data for a variety of hydroxycinnolines and derivatives are available, as summarized below.

Cinnoline	Solvent	Reference
3-Hydroxy-		16
4-Hydroxy-	Ethanol	28
4-Hydroxy-3, 6-dibromo-	Ethanol	28
4-Hydroxy-6-bromo-3-chloro-	Ethanol	28
4-Hydroxy-3-nitro-		38
4-Hydroxy-6-nitro-	Ethanol	28
4-Hydroxy-6, 7-methylenedioxy-	Ethanol	28
4-Hydroxy-3-methyl-	Ethanol	28
4-Hydroxy-3-methyl-6-nitro-	Ethanol	28
4-Hydroxy-6-methyl-3-chloro-	Ethanol	28
4-Hydroxy-3-ethyl-	Ethanol	28
4-Hydroxy-6, 7-dimethyl-	Ethanol	28
4-Methoxy-	Ethanol	28
4-Methoxy-6-nitro-	Ethanol	28
4-Methoxy-7-nitro-		56
4-Ethoxy-	Ethanol	28
	Cyclohexane	28
4-Phenoxy-	Ethanol	28
	Cyclohexane	28
4-Phenoxy-	Ethanol	28
4-Acetoxy-6-chloro-	Ethanol	28
4-Acetoxy-6-nitro	Ethanol	28
4-Acetoxy-6-methyl-3-chloro-	Ethanol	28
4-Acetoxy-6, 7-dimethyl-3-chloro-	Ethanol	28
8-Hydroxy-	95% Ethanol	62
	0.01 N HCl	62
	0.01 N NaOH	62
8-Hydroxy-4-methyl-		66
8-Methoxy-	95% Ethanol	62
	0.01 N HCl	62
	0.01 N NaOH	62

Cinnoline	Solvent	Reference
8-Methoxy-4-methyl-	95% Ethanol	62
	0.01 N HCl	62
	0.01 N NaOH	62
4-Hydroxy-6-O-methylacinitro-	Ethanol	28
4-Hydroxy-3-methyl-6-O-methylacinitro-	Ethanol	28

The data obtained have been correlated in some instances to structure (28, 62) and chemical properties (28).

Infrared data for 4-hydroxy-3-nitrocinnoline have been obtained (38).

4-Hydroxycinnolines generally exist predominantly in the keto form (28); 4-hydroxycinnoline itself probably is 70% cinnolone (28). Ultraviolet data have been used (66) to make assignments of the more basic nitrogen, which is generally conceded (13) to be N-1.

A number of studies (62, 65, 66, 68, 69) have been made concerning the use of 8-hydroxy- and 8-hydroxy-4-methylcinnoline to a limited extent as analytical reagents for metal ions. These two compounds were usually part of a group related or similar to oxine (8-hydroxyquinazoline), a well-known chelating agent. The metal ions studied were Mg^{++} (66, 69), Zn^{++} (62, 66, 69), Ni^{++} (66, 69), Cu^{++} (62, 65, 66, 69), UO_2^{++} (66, 69), Fe^{+++} (62, 65), Al^{+++} (62), Mn^{++} (62), Co^{++} (62), Fe^{++} (65). Stability constants of the metal-ligand complexes have been measured (62, 65, 66, 69). Irrespective of the nature of the ligand, the stability of several metal-complexes was found (66) always to follow the order $Mg^{++} < Zn^{++} < Ni^{++} < UO_2^{++} < Cu^{++}$. One study (69) with 8-hydroxycinnoline showed the stability of the complex as a function of the stability of the corresponding oxinate.

---

(68) Irving and Rossotti, Analyst, 80, 245 (1955) [C.A., 49, 8728 (1955)].

(69) Rossotti, Rec. trav. chim., 75, 763 (1956).

Hydrolysis studies on a series of 4-phenoxycinnolines have been made (49); the results are tabulated below.

Cinnoline	Hydrolysate/Time (hrs)	Results[a] Initial	4-Hydroxy-compound
4-Phenoxy-	water/ 2	+	-
	0.02 N HCl/ 1/2	-	+
4-Phenoxy-7-chloro-	0.1 N HCl/ 1/2	-	+
4-Phenoxy-6-nitro-	water/ 1	+	-
	0.02 N HCl/ 1	-	+
4-Phenoxy-8-nitro-	0.02 N HCl/ 1	trace	+

[a] A + sign signifies that the indicated material was isolated from the reaction mixture; a - sign signifies the opposite.

Halogen exchange reactions were carried out (37) on a number of halogeno-4-hydroxycinnolines and 4-halogeno- analogs. The conclusions drawn were: (1) Replacement of the 4-hydroxy- group precedes halogen exchange and is a rapid reaction; (2) a mixture of phosphorous oxychloride and phosphorous pentachloride being used, replacement of the bromine at $C_{(6)}$ is relatively rapid, and occurs more readily at the higher of the two temperatures used; (3) by comparison, replacement of a bromine atom at $C_{(3)}$ is relatively slow, appears to be encouraged by the presence of a halogen atom at $C_{(6)}$, and is more rapid at 95° C than at 135° C; (4) replacement of bromine, whether at $C_{(3)}$ or $C_{(6)}$, by using phosphorous pentachloride, proceeds more rapidly at the higher temperature; (5) phosphorous oxychloride, in contrast, produces results similar to those obtained with the mixed chlorides; and (6) generally use of an open vessel, from which bromine may easily escape, facilitates exchange, and the reverse is true for reactions carried out under reflux. [1]

[1] Although portions of this summation dealing with halogenocinnolines could have been discussed in the previous section, it was felt advantagous to present the material as an integrated summary.

D. Carbonyl-substituted Cinnoline Compounds.

Carbonyl-substituted cinnolines may be separated into two groups: (1) Those compounds having a carbonyl- group substituted on the heterocyclic nucleus, and (2) those compounds with the carbonyl- function on a side chain. The first group consists of 4-ketocinnolines and derivatives, with one 3-ketocinnoline having been described (16). The second group is made up entirely of acetylcinnolines and derivatives.

Compounds in group 1 generally are prepared by treating the hydroxycinnoline with basic methyl sulfate (13, 38, 39, 51). The single 3-ketocinnoline (2-methyl-3-ketocinnoline) was prepared by treating 3-hydroxycinnoline with either sodium hydroxide and dimethyl sulfate at 95° C or diazomethane in ether (16). Although a few of the compounds in group 2 were prepared by treating the corresponding acetyl-4-hydroxycinnolines with the appropriate reagents (39), a new general route to 3-acetylcinnolines has been reported by Baumgarten and Anderson (70). The procedure is based upon the cyclization of the appropriate pyruvaldehyde o-formylphenylhydrazone, illustrated by equation 1.

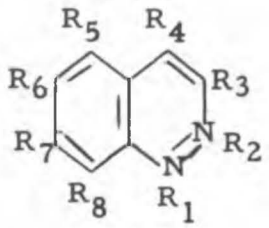
(1)

The carbonyl-substituted cinnoline compounds reported since 1949 are listed in Table 4.

---

(70) Baumgarten and Anderson, J. Am. Chem. Soc., 80, 1981 (1958).

Table 4. Carbonyl-substituted Cinnoline Compounds.



where, except for R_1 and R_2, R represents hydrogen unless indicated otherwise. If nitrogen has no R-group, then it is doubly bonded to an adjacent atom.

No.	R[a]	Group[a]	M. P., °C	Prep.[b]	Remarks	Ref.
1	2 3	Methyl- Keto-	132-134, 135.5- 136.5	A	Golden yellow plates from benzene; glistening yellow plates from acetone.	16
2	1 3 4	Methyl- Nitro- Keto-	232.5	B	41-59% yield. Pale yellow needles from ethanol; darkened rapidly on exposure to light.	38
3	1 4 5	Methyl- Keto- Nitro-	188-189	B	Pale yellow leaflets from ethanol.	39
4	1 4 6	Methyl- Keto- Nitro-	190, 190-191	C, D	4.8% yield. Yellow needles from water.	56 51
5	1 4 7	Methyl- Keto- Nitro-	238	B	Pale orange leaflets from ethanol.	39
6	1 4 8	Methyl- Keto- Nitro-	243-244, 238-239	B, E	Yellow needles from ethanol; glistening yellow plates from methanol.	39 41

Table 4, continued

No.	R[a]	Group[a]	M.P., °C	Prep.[b]	Remarks	Ref.
7	1 3 4 6	Methyl- Methyl- Keto- Nitro-	181-183	B	Massive yellow prismatic needles from alcohol.	51
8	1 4 5 8	Methyl- Keto- Nitro- Methyl-	257-258 dec.	B	Beige-colored prismatic needles from aqueous acetic acid.	51
9	1 4 7 8	Methyl- Keto- Nitro- Methyl-	257-258 dec.	B	Beige-colored prismatic needles from aqueous acetic acid.	51
10	4-Formyl-cinnoline p-dimethyl-aminoaniline anil		196-197	F	Red leaflets from ethanol; stable to 40% hydrochloric acid.	33
11	3	Acetyl-	155-156	G	16-22% yield. Pale yellow needles from Skelly C.	70
12	3 6	Acetyl- Chloro-	206-207	G	18% yield. From Skelly C.	70
13	3 7	Acetyl- Chloro-	211-212	G	39% yield. Pale yellow needles from Skelly C.	70
14	4 7	Chloro- Acetyl-	147-148	H	Pale yellow needles from ether-ligroin.	39
15	4 7	Hydroxy- Acetyl-	242-243	I	Pale yellow prisms from alcohol.	39
16	4 7	Phenoxy- Acetyl-	141-142	J	Colorless leaflets from ether-ligroin.	39

Table 4, continued.

No.	R[a] Group[a]	M.P., °C	Prep.[b]	Remarks	Ref.
17	Methyl 4-hydroxy-7-cinnolyl ketoxime	294-295	K	Buff-colored solid from alcohol.	39

[a] When naming the substituent groups becomes too cumbersome, the complete compound name will be given.

[b] A. By treating 3-hydroxycinnoline with either sodium hydroxide and dimethyl sulfoxide at 95° or diazomethane in ether.

B. By treating the appropriate 4-hydroxycinnoline with potassium hydroxide and dimethyl sulfate at 50° C or 45° C.

C. By treating the 4-amino-6-nitrocinnoline β-metho-salts with hot water or hot alkali.

D. By heating 4-hydroxy-6-(O-methylacinitro) cinnoline with 0.5 N sodium hydroxide.

E. By nitrating 1-methyl-4-cinnolone with mixed acids at 0° C.

F. By condensing 4-methylcinnoline with p-nitrosodimethyl-aniline with sodium carbonate, ethanol, and heat.

G. By the cyclization of the appropriate pyruvaldehyde 1-(o-formylphenyl)hydrazone.

H. By treating the analogous 4-hydroxycinnoline with phosphorous oxychloride at 95° C.

I. By the Borsche synthesis.

J. By treating the analogous 4-hydroxy- compound with phenol and ammonium carbonate at 95° C.

K. By treating 4-hydroxy-7-acetylcinnoline with hydroxyl-amine hydrochloride, water, alcohol, and sodium acetate.

The electric moment and related data have been obtained (25) for 4-acetylcinnoline in benzene at 25° C, as summarized below.

E_{10}	α'	V_{10}	β'	P_2^{∞}	MR_D	μ_{obs}	$\mu_{calc.}$
2.2725	9.30	1.14484	-0.755	177.8	47.93	2.52	3.42

Ultraviolet data are available for a few compounds as indicated.

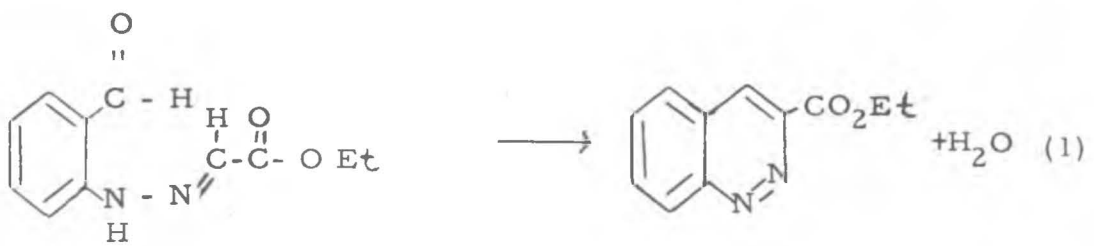
Compound	Reference
3-Keto-2-methylcinnoline	16
4-Keto-1-methylcinnoline	28
4-Keto-1-methyl-6-nitrocinnoline	28
Methyl 6, 7-dimethoxy-1-methyl-4-cinnolon-3-ylacetate	28

The last compound above has not been recorded elsewhere and no further information was available. Hence, this compound does not appear in Table 4.

Treatment of 3-keto-2-methylcinnoline with red phosphorous and hydriodic acid gives oxindole (16).

E. Cinnoline-carboxylic Acids and Derivatives.

Cinnoline-carboxylic acids with the carboxyl group located on the cinnoline nucleus generally have been made by the Borsche, Richter, or Widman-Stoermer reaction, all of which have been discussed previously. A new method (70) for the preparation of 3-ethoxycarbonylcinnolines has been devised by Baumgarten and Anderson, and is a variation of a basic reaction discussed in the preceding section; cyclization of an ethyl glyoxalate o-formylphenylhydrazone yields a 3-ethoxycarbonylcinnoline (equation 1).



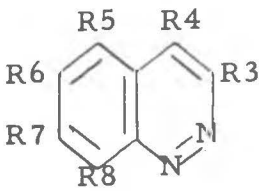
Of the compounds reported since 1949 (Table 5) cinnolines containing a carboxyl- group on a side chain have not been listed, although several esterified derivatives of such compounds have been prepared (71). Almost all of the derivatives of the cinnoline

---

(71) Mizuno, Adachi, and Ikeda, Pharm. Bull. (Japan), 2, 225 (1954) [C. A., 50, 1034 (1956)].

carboxylic acids listed may be considered to be α-substituted acetonitriles.

Table 5. Cinnoline-carboxylic Acids and Derivatives



where R represents hydrogen unless indicated otherwise.

No.	R[a]	Group[a]	M.P., °C	Prep[b]	Remarks	Ref.
1	3	Ethoxy-carbonyl-	97-97.5	A	8-12% yield. Long yellow needles from Skelly C.	70
2	3 6	Ethoxy-carbonyl- Chloro-	152.5-153	A	5% yield. Long yellow needles from Skelly C.	70
3	3 7	Ethoxy-carbonyl- Chloro-	200-201	A	Long, pale yellow needles from Skelly C.	70
4	3 4 6	Carboxy- Hydroxy- Chloro-	263-264 dec.	B	66% yield. Silvery white plates from acetic acid.	42
5	3 4 6	Carboxy- Hydroxy- Bromo-	264 dec.	B	66% yield. White needles from acetic acid.	42
6	4 8	Carboxy- Hydroxy-	200 dec.	C	Red needles from water.	63
7	Ethyl 4-cinnolyl-acetate picrate		110	D	50% yield.	71
8	Ethyl 4-cinnolyl-cyanoacetate		230-233	E	69% yield.	71
9	Diethyl 4-cinnolyl-malonate dipicrate		102-103	F	44.1% yield.	71

No.	R[a] Group[a]	M.P., °C	Prep.[b]	Remarks	Ref.
10	4-cinnolyl-phenylaceta-mide	248-249	G	93% yield. Pale yellow crystals precipitated from hydrochloric acid solution.	36
11	4-cinnolyl-phenylaceto-nitrile	197-198, 197.5-198.5	H	80.5, 94% yield. Golden yellow plates from aqueous ethanol.	71, 36
12	4-cinnolyl-p-fluorophenyl-acetonitrile	170-172.8	H	65% yield. Orange-red needles from benzene.	72
13	4-cinnolyl-o-chlorophenyl-acetonitrile	200.4-201.2	H	60% yield. Small bright yellow needles from aqueous ethanol.	72
14	4-cinnolyl-p-chlorophenyl-acetonitrile	177.6-178.4	H	61% yield. Fibrous orange needles from benzene.	72
15	4-cinnolyl-2,4-dichlorophenyl-acetonitrile	188-188.8	H	52% yield. Stubby golden needles from aqueous ethanol.	72
16	4-cinnolyl-3,4-dichlorophenyl-acetonitrile	263.6-267.6	H	77% yield. Orange-red platelets from ethanol.	72
17	4-cinnolyl-p-bromophenyl-acetonitrile	188.2-188.8	H	71% yield. Orange needles from benzene.	72
18	4-cinnolyl-p-iodophenyl-acetonitrile	185.6-186.4	H	53% yield. Glistening orange-red needles from benzene.	72

(72) Castle and Cox, J. Org. Chem., 19, 1117 (1954).

No.	R[a] Group[a]	M. P., °C	Prep[b]	Remarks	Ref.
19	4-Cinnolyl-m-methoxyphenyl-acetonitrile	194. 5-195	H	55% yield. Deep red plates from aqueous ethanol.	36
20	4-Cinnolyl-p-methoxyphenyl-acetonitrile	183-185	H	66% yield. Orange-red plates from aqueous ethanol.	36
21	4-Cinnolyl-3, 4-dimethoxy-phenylaceto-nitrile	180. 6-181. 2	H	75% yield. Tiny bright orange needles from ethanol.	72
22	6, 7-Dimethoxy-4-cinnolyl-phenylaceta-mide.	234. 5-236. 5	G	18% yield. White opaque crystals from aqueous ethanol.	36
23	6, 7-Dimethoxy-4-cinnolylphenyl-acetonitrile	220-221	H	40% yield. Orange-red plates from aqueous ethanol.	36
24	6, 7-Dimethoxy-4-cinnolyl-p-chlorophenyl-acetonitrile	224. 4-252. 2 dec.	H	39% yield. Orange-red crystals from benzene.	72
25	6, 7-Dimethoxy-4-cinnolyl-3, 4-dichlorophenyl-acetonitrile	275. 2-276. 2 dec.	H	40% yield. Brilliant orange-red needles from ethanol.	72
26	6, 7-Dimethoxy-4-cinnolyl-p-bromophenyl-acetonitrile	241. 4-241. 8 dec.	H	35% yield. Orange-red microcrystalline powder from benzene.	72
27	6, 7-Dimethoxy-4-cinnolyl-p-iodophenyl-acetonitrile	252. 6-253. 0	H	24% yield. Tiny orange-red crystals from benzene.	72

No.	R[a] Group[a]	M.P., °C.	Prep[b]	Remarks	Ref.
28	6, 7-Dimethoxy-4-cinnolyl-m-methoxyphenyl-acetonitrile	222.2-223.2	H	64% yield. Red-gold needles from ethanol.	72
29	6, 7-Dimethoxy-4-cinnolyl-3, 4-dimethoxyphenyl-acetonitrile	250-250.8	H	86% yield. Fine orange needles from ethanol.	72
30	6, 7-Dimethoxy-4-cinnolyl-3, 4-dimethoxy-acetamide	250-252	G	46% yield. Fibrous colorless needles from ethanol.	72
31	4-Cinnolyl-diphenyl-acetonitrile	186.2-186.8	H	20% yield. Pale yellow crystals from aqueous ethanol.	72
32	6, 7-Dimethoxy-4-cinnolyl-diphenyl-acetonitrile	238.6-239.4	H	24% yield. Pale yellow crystals from ethanol.	72
33	4-Cinnolyl-1-naphthyl-acetonitrile	224.0-224.8	H	58% yield. Orange crystals from ethanol.	72
34	6, 7-Dimethoxy-4-cinnolyl-1-naphthyl-acetonitrile	247.2-248.0	H	53% yield. Tiny orange-gold crystals from ethanol.	72
35	4-Cinnolyl-2-naphthyl-acetonitrile	248.2-249.0	H	12% yield. Dark golden needles from aqueous ethanol.	72
36	1-Isopropyl-4, 4-dimethyl-4, 5-dihydro-2-imidazolyl-4-cinnolylacetonitrile	207-208	H	83% yield. Brilliant yellow needles from aqueous ethanol.	72

No.	R[a] Group[a]	M. P., °C	Prep.[b]	Remarks	Ref.
37	1-Isopropyl-4, 4-dimethyl-4, 5-dihydro-2-imidazolyl-6, 7-dimethoxy-4-cinnolyl-acetonitrile	242-243 dec.	H	Bright yellow crystals from chromatogrpahy on alumina and re-crystallization from ethanol.	72

[a]When naming the substituent groups becomes too cumbersome, the complete compound name will be given.

[b]A. By cyclization of the appropriate ethylglyoxalate o-formylphenylhydrazone.

B. By the Richter synthesis.

C. By oxidizing 8-benzoyloxy-4-styrylcinnoline with potassium permanganate in aqueous pyridine, then hydrolyzing the product with hydrochloric acid.

D. By refluxing 4-chlorocinnoline with ethyl acetoacetate in benzene with sodium amide.

E. By refluxing 4-chlorocinnoline with ethyl cyanoacetate as in D.

F. By refluxing 4-chlorocinnoline with diethyl malonate as in D.

G. By treating the corresponding acetonitrile with concentrated sulfuric acid.

H. By treating 4-chlorocinnoline with the appropriate acetonitrile in benzene with sodium amide, or in liquid ammonia with potassium and ferric nitrate.

The electric moment and related data have been obtained (28) for 4-ethoxycarbonylcinnoline:

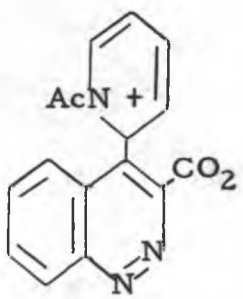
E	α'	V_{10}	β'	P_2^{∞}	MR_D	μobs.	μcalc.
2.2700	18.53	1.14493	-0.85	321.8	54.18	3.62	4.00

A limited amount of ultraviolet data is available as indicated:

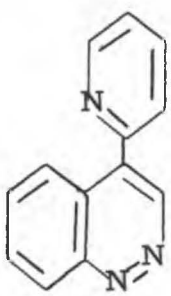
Compound	Solvent	Reference
4-Hydroxycinnoline-3-carboxylic acid	Ethanol	61
4-Hydroxycinnoline-6-methoxy-cinnoline-3-carboxylic acid	Ethanol	61
Methyl 4, 6, 7-trimethoxy-3-cinnolyl-acetate	Ethanol	61

The last compound above has not been reported elsewhere and no other data are available. Hence, this compound does not appear in Table 5.

In 1946 Schofield and Simpson (73) found that treatment of 4-hydroxycinnoline-3-carboxylic acid with a mixture of pyridine and acetic anhydride gave a compound which was considered to be a fully aromatic cinnoline (I). Simpson (13) has reviewed this work in its entirety, but recognized that the series of reactions as formulated by Schofield and Simpson (73) very likely may be in error, since an important degradation product, 4, 2'-pyridylcinnoline (II), obtained from (I) by hot dilute hydrochloric acid, was not identical to 4, 2'-pyridylcinnoline synthesized later by a seemingly independent route (46).



(I)



(II)

Subsequent work by Morley (74) has shown (I) to be an incorrect structure.

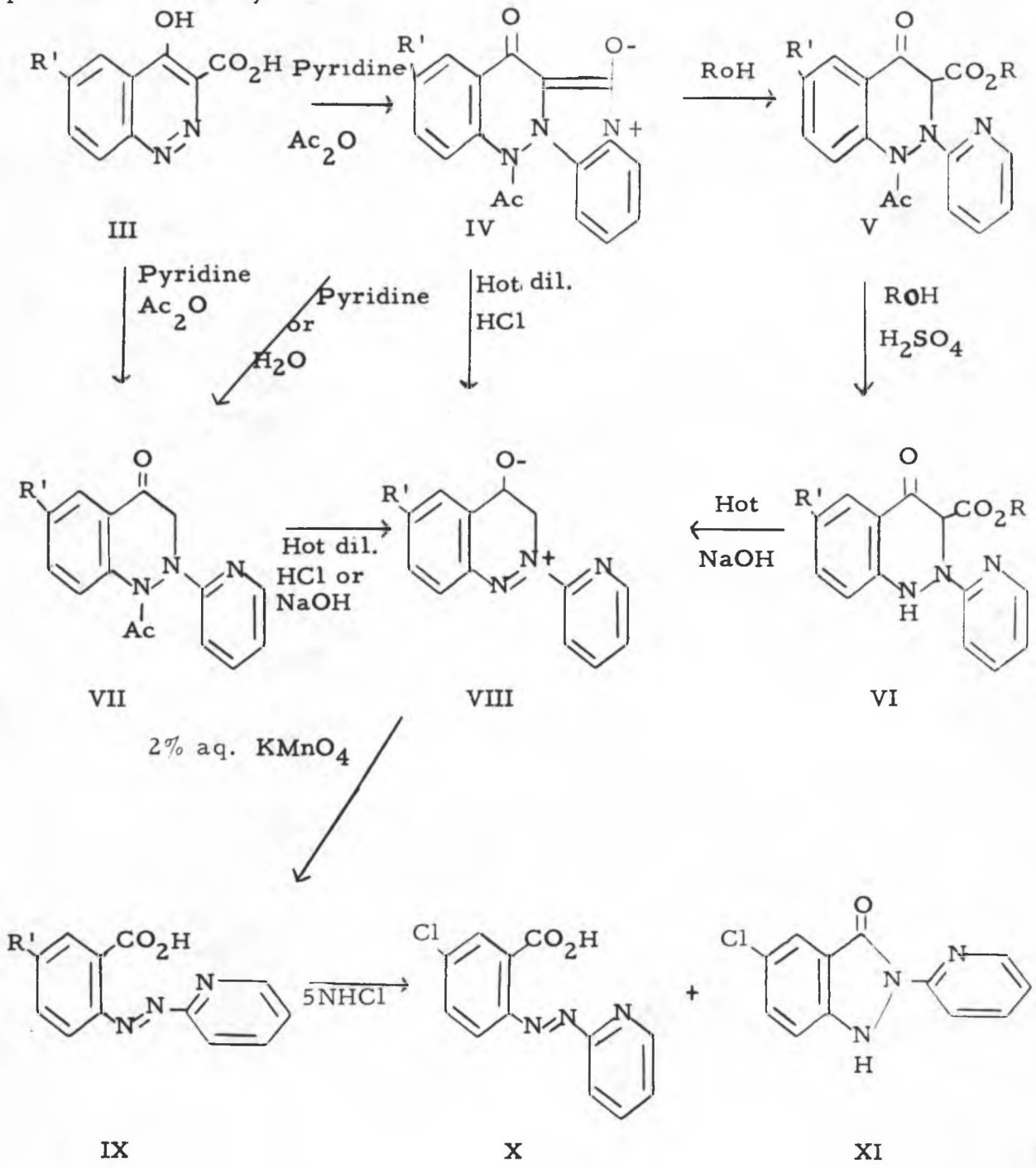
The new reaction scheme is presented (R' = H). Although the scheme includes several compounds which more appropriately could be discussed in other sections, they are treated together at

---

(73) Schofield and Simpson, J. Chem. Soc., 1946, 472.

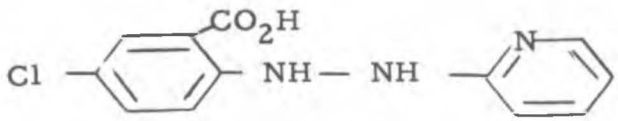
(74) Morley, J. Chem. Soc., 1959, 2280.

this point in view of the uniqueness of the reaction scheme and to preserve continuity.



The scheme was tested by carrying out the pyridine-acetic anhydride reaction on 6-chloro-4-hydroxycinnoline-3-carboxylic acid, yielding IV (R' = Cl). This product was then converted to VIII (R' = Cl), a chloro-acid corresponding to IX (R' = H), but identical with X.

Final proof was accomplished by synthesis. 2-o-Carboxyphenylazopyridine (IX, R' = H) was obtained by condensing o-nitrosobenzoic acid with 2-aminopyridine in 50% aqueous sodium hydroxide. 5-Chloro-2,2'-pyridyl-3-indazolone (XI) was obtained as one product upon condensing 5-chloro-2-hydrazinobenzoic acid with 2-chloropyridine. Reducing the acid (X) catalytically or by stannous chloride or thiol compounds gave 2-(2-carboxy-5-chlorophenylhydrazino)pyridine (XII),



(XII)

the hydrochloride of which, when heated in ethanol at 170-180°, likewise gave the indazole(XI).

Although the assigned structures were incorrect, the physical properties may be found in the original work (73) or in Simpson's review (13). The physical data for the two compounds prepared in testing the reaction scheme are as follows:

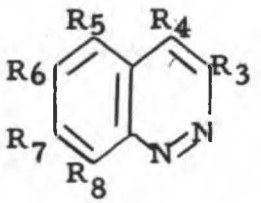
Compound	R'	M. P.	% yield	Remarks
IV	Cl	dec.>240	94	Olive-green crystals, washed with ether, dried at 80° in vacuo.
VIII	Cl	162-163	88	Yellow needles from ethanol (dried at 80°).
VIII Hydrate	Cl	132-133		

F. Aminocinnolines and Derivatives.

Prior to 1949, only one general method was employed to prepare 4-aminocinnolines; this procedure involved treating 4-phenoxycinnolines with an excess of ammonium acetate at elevated temperatures (75, 39). At the present time at least nine methods have been employed to prepare cinnolines having an amino-group located at any one of the six available positions.

This typical example illustrates the wide diversification in the preparative chemistry of the aminocinnolines and derivatives which has taken place during the last decade. In view of the wide range of procedures employed, no attempt will be made to list or discuss any of them. Rather, the preparative methods may be extracted readily from Table 6, which lists those aminocinnolines and derivatives reported in the literature since 1949.

Table 6. Aminocinnolines and Derivatives



where R represents hydrogen unless indicated otherwise.

No.	R[a]	Group[a]	M.P., °C.	Prep[b]	Remarks	Ref.
1	3	Amino-	165-166.5, 163-164.5, 165-166	A, B, C	10-15, 70-83, 20-31% yield. Yellow needles from ethyl acetate or benzene.	16, 34, 35, 70
2	3 6	Amino- Chloro-	215 dec.	C	74-90% yield. Bright yellow needles.	35
3	3 7	Amino- Chloro-	202 dec.	C	70-85% yield. Bright yellow plates.	35 35
4	3	Acetamido-	225-226	D	Colorless crystals.	16
5	3 4	Amino- Methyl-	159.5-160	C	76% yield. Bright yellow needles from benzene.	34

No.	R[a]	Group[a]	M.P., °C	Prep[b]	Remarks	Ref.
6	4	Amino-	N/G	E		51
7	4	Amino-α-Methochloride	261	F	Colorless silky needles from absolute ethanol.	56
8	4	Amino-β-Methochloride	291	F	Massive, colorless prismatic needles from absolute ethanol.	56
9	4	Amino-α-Methiodide	258	G	Yellow prismatic needles from absolute ethanol.	56
10	4	Amino-Methiodide	252-253 dec.	G	35% yield. Greenish-yellow prismatic needles from ethanol.	76
11	3 4	Chloro- Amino-	228-229	H, I	Fine white needles from alcohol.	18
12	4 7	Amino- Chloro-β-Methochloride	320 dec.	N/G	Colorless prismatic needles from water.	56
13	4 7	Amino- Chloro-Methiodide	282-283 dec., 274 slow dec.	G	45% yield. Orange prismatic needles from water.	56, 76
14	3 4	Nitro- Amino-	308-308.5, 305-306	J, K	50-64, 74% yield. Yellow cottony solid from absolute ethanol.	38
15	4 6	Amino- Nitro-	288-290 dec., 297-298	K	86% yield. From water, or precipitated from 30% acetic acid by ammonium hydroxide.	76 77

(76) Keneford, Lourie, Morley, Simpson, Williamson, and Wright, J. Chem. Soc., 1952, 2595.

(77) Lourie, Morley, Simpson, and Walker, (to National Research Development Corp.) Brit. 702, 664, Jan. 20, 1954. [C.A., 50, 5777 (1956)]

No.	R[a]	Group[a]	M.P., °C	Prep[b]	Remarks	Ref.
16	4 Amino- 6 Nitro-	Anhydro base	230-231	L	Golden needles from ethanol.	56
17	4 Amino- 6 Nitro-	α-Methochloride	240 dec.	F		56
18	4 Amino- 6 Nitro-	β-Methochloride	305 dec.	F	Pale yellow needles from water.	56
19	4 Amino- 6 Nitro-	α-Methiodide	222 dec.	G, M, N	Thick red needles from water; deep red prisms from water.	56
20	4 Amino- 6 Nitro-	β-Methiodide	240 dec.	N, G	Golden prismatic needles from water; unstable to hot water.	56
21	4 Amino- 6 Nitro-	1-Methiodide	209-210 dec., 207 dec.	G	40% yield. Rosettes of orange-red needles.	76, 78
22	4 Amino- 6 Nitro-	Methosulfate	234-236	O		78
23	4 Amino- 6 Nitro-	α-Methotoluene-p-sulfonate	254 dec.	P	Golden prismatic needles from water.	56
24	4 Amino- 6 Nitro-	β-Methotoluene-p-sulfonate	268 slow dec.	P	Pale yellow needles from water.	56
25	4 Amino- 7 Nitro-		300-301 dec.	E, M	Yellow leaflets from dilute ethanol.	39

(78) Curd, Hepworth, and Imperial Chemical Industries, Ltd., Brit., 663, 095, Dec. 19, 1951 [C.A., 46, 11250 (1952)].

No.	R[a]	Group[a]	M.P., °C	Prep[b]	Remarks	Ref.
26	4 7	Amino- Nitro- Methiodide	236-238 dec.	G	Orange needles from water.	55
27	4 8	Amino- Nitro-	235-236 dec.	E	Fine yellow needles from dilute ethanol.	39
28	4 8	Amino- Nitro- Methiodide	237-238 dec.	G	Small bronze prisms and soft leafy aggregates of needles from water.	76
29	4	Methyl-amino-	229	Q	Colorless needles from water.	56
30	4	Methyl-amino- Hydrochloride	282	R	Colorless needles from ethanol.	56
31	4 6	Methyl-amino- Nitro-	345, >360	Q	Yellow needles from isopropyl alcohol.	56, 78
32	4 6	Methyl-amino- Nitro- Methiodide	222 dec.	G	Red needles from water.	56
33	4 6	Methyl-amino- Nitro- 1-Methiodide	244 dec.	G		78
34	4	Anilino-	236-237	S	Pale greenish-yellow needles from alcohol.	54
35	3 4	Nitro- Anilino-	187-188	S	63-72% yield. Bright yellow needles.	38
36	4 6	Anilino- Nitro- Methiodide	233-234 dec.	G	Glittering scarlet needles from water.	76

No.	R[a]	Group[a]	M.P., °C	Prep.[b]	Remarks	Ref.
37	4	Acetamido-	264	D	From ethanol.	56
38	4 7	Acetamido- Chloro- Methochloride	275	D		56
39	4 6	Acetamido- Nitro- Methiodide	189-190 dec.	G	Dark red needles from water.	56
40	4 7	Acetamido- Nitro-	235	D	Pale yellow needles from alcohol.	55
41	4 7	Acetamido- Nitro- Methiodide	188-189	G, D	Dark red needles from ethanol.	55, 56
42	4 8	Acetamido- Nitro-	291-292	D	Colorless needles from ethyl methyl ketone.	56
43	3 4 6	Methyl- Amino- Nitro-	320 dec.	K	60-63% yield. Orange-yellow solid.	76
44	3 4 6	Methyl- Amino- Nitro- Methiodide	280-281 dec.	G	50% yield. Deep red prisms or plates from water.	76
45	3 4 8	Methyl- Amino- Nitro- Methiodide	263-264 dec.	G	40% yield. Dark bronze irregular plates from water.	76
46	4 7	Amino- Methyl- Methiodide	287 dec.	G	84% yield. Long reddish-orange prismatic needles from water.	76
47	5	Amino-	160-161	T	Small bright yellow prisms from benzene-cyclohexane; sublimed at 120° C/0.1mm.	61

No.	R[a]	Group[a]	M.P., °C	Prep.[b]	Remarks	Ref.
48	6	Amino-	203-204	T	Deep yellow prisms from benzene.	61
49	7	Amino-	191-192	T	Yellow needles from ethyl acetate; sublimed at 130° C/0.4 mm.	61
50	8	Amino-	89-92	U	Golden-yellow needles from benzene Skelly B.	62
51	8	Amino-Picrate	236-238	V	Jet-black needles from acetic acid.	62
52	8	Acetamido-	173-175, 177-178	W, C	Dense prisms from benzene - Skelly B.	15, 62
53	8	Acetamido-Picrate	238-239 dec.	V	Yellow needles from aqueous ethanol.	15
54	4 8	Methyl- Amino-	133-134, 126-127	C	Orange crystals from benzene then ether - Skelly A; orange prisms from ether-ligroin.	41,
55	4 8	Methyl- 2,2-Dicarbethoxyvinylamino-	155-156	X	78% yield. From ethanol.	40
56	4 5	Phenoxy- Amino-	199-200 dec.	C	Yellow needles from benzene.	55
57	4 7	Hydroxy- Amino-	276-277	C, U	Fawn-colored needles from dilute alcohol.	39
58	4 7	Hydroxy- Acetamido-	>330	Y	Colorless crystals from alcohol.	39
59	4 7	Acetoxy- Acetamido-	>330	D	Very small colorless needles from dilute alcohol.	39

No.	R[a]	Group[a]	M.P., °C	Prep.[b]	Remarks	Ref.
60	4 7	Phenoxy- Amino-	179-180	C	86% yield. Greenish-yellow elongated plates from benzene.	55
61	N^2-Benzoyl-N^1N^3-di-(4-phenoxy-7-cinnolyl)-guanidine		244-245	Z	Colorless needles from Cellosolv (2-ethyoxy-ethanol).	55
62	N^2-Benzoyl-N^1N^3-di(4-phenoxy-7-cinnolyl)-guanidine trihydrochloride		>350	AA	Very low per cent yield. From nitromethane.	55
63	4 8	Hydroxy- Amino-	290-291	C	Lustrous yellow needles from dilute acetic acid.	39
64	4 8	Phenoxy- Amino-	130	C	Separated from benzene-Skelly B in rhombs.	55
65	4 8	Acetoxy- Acetamido-	282-283	D	Tan needles from dilute alcohol.	39
66	3 4	Amino- Amino-	220-220.5	C	76% yield. Pale yellow from water.	38
67	3 4	Amino- Amino-	320-231.5 dec.	C	80% yield. Bright yellow crystals from ethanol.	38
68	4 6	Amino- Amino-	262-264 dec., 260 dec., 266-267, 268-270	C, BB	90, 80% yield. Precipitated by base as soft colorless needles, grey irregular plates.	51, 76, 77, 78
69	4 6	Amino- Amino-Hydrochloride	315-316 dec.	R	Orange prismatic needles.	51

No.	R[a]	Group[a]	M.P., °C	Prep[b]	Remarks	Ref.
70	4 6	Amino- Amino-Methochloride	305 dec., 306	F, C	Yellow needles from water or aqueous acetone; fine needles from water.	56, 76
71	4 6	Amino- Amino-Methobromide	286-287 dec., 284	CC, C	Golden-yellow needles from water.	76, 78
72	4 6	Amino- Amino-Methiodide	273-275 dec., 273-274	C, U	95% yield. Brown prismatic needles from water, yellow needles from water.	76
73	4 6	Amino- Amino-Methothiocyanate	187-188	DD	Golden-yellow needles from water.	76
74	4 6	Methylamino- Amino-	300	BB		78
75	4 6	Methylamino- Amino-1-Methiodide	276-278	BB		78
76	4 6	Anilino- Amino-	259-261 dec.	EE	Yellow gelatinous solid.	76
77	4 6	Anilino- Amino-Hydrochloride	201-302 dec.	BB	Precipitated by acid as glittering rust-colored needles.	76
78	4 6	Anilino- Amino-Methiodide	240-241 dec.	BB	Orange needles from alcohol.	76
79	4 6	Amino- Acetamido	361 dec.	D		78

No.	R[a]	Group[a]	M. P., °C	Prep.[b]	Remarks	Ref.
80	4 6	Anilino- Acetamido-	289-290 dec.	D	Light brown needles from water.	76
81	4 6	Anilino- Acetamido- Methochloride	240-241 dec., 237-238 dec.	FF, GG	Orange-yellow needles.	76
82	4 6	Anilino- Acetamido- Methiodide	267-268 dec.	G	Yellow prismatic needles from water.	76
83	4 6	Acetamido- Acetamido-	272-273 dec.	D	90% yield. Almost colorless fluffy needles from hot water.	51
84	4 6	Acetamido- Acetamido- Methiodide	265 dec.	G	75% yield. Yellow prismatic needles from water.	76
85	4 6	Amino- 4-Amino-2-pyrimidyl-amino-	260	EE		79
86	4 6	Amino- 4-Amino-2-pyrimidyl-amino- Dihydrochloride	360	HH		79
87	4 6	Amino- 4-Amino-2-pyrimidyl-amino- 1, 1'-Dimethiodide	322 dec.	II, N		78, 79

(79) Curd, Hepworth, and Imperial Chemical Industries, Ltd., Brit. 663,096, Dec. 19, 1951 [C. A., 46, 11251 (1952)].

No.	R[a]	Group[a]	M. P., °C	Prep.[b]	Remarks	Ref
88	4 6	Amino- 2-Amino-4-pyrimidyl-amino- 1'-Methiodide hydrate	320 dec.	JJ		79
89	4 6	Amino- 2-Amino-4-pyrimidyl-amino- 1, 1'-Bis(methyl-p-toluenesulfonate)	242-244	KK		79
90	4 6	Amino- 2, 6-Diamino-4-pyrimidyl-amino- 3'-Methiodide hydriodide	342 dec.	LL		78
91	4 6	Amino- 2-Amino-6-methyl-4-pyrimidyl-amino- 1, 1'-Dimethochloride	298 dec.	MM		
92	4 6	Amino- 2-Amino-6-methyl-4-pyrimidyl-amino- Dihydrate	320 dec.	EE		79
93	4 6	Amino- 2-Amino-6-methyl-4-pyrimidyl-amino- Hydrochloride hydrate	>370	HH		79

No.	R[a]	Group[a]	M.P., °C	Prep.[b]	Remarks	Ref.
94	4 6	Amino- 2-Amino-6-methyl-4-pyrimidyl-amino- 1'-Methiodide	320 dec.	EE		78
95	4 6	Amino- 2-Amino-6-methyl-4-pyrimidyl-amino- 1'-Methiodide hydriodide dihydrate	296-297	NN, OO		78
96	4 6	Amino- 2-Amino-6-methyl-4-pyrimidyl-amino- 3'-Methiodide hydriodide	172-174 dec.	PP		78
97	4 6	Amino- 2-Amino-6-methyl-4-pyrimidyl-amino- 1, 1'-Dimethiodide	305 dec.	QQ, RR	Yellow.	78, 79
98	4 6	Amino- 2-Methyl-amino-4-pyrimidyl-amino- 1, 1'-Dimethiodide	274-278	SS		78
99	4 6	Amino- 2-Methyl-amino-6-methyl-4-pyrimidyl-amino-	310 dec.	OO		78

No.	R[a]	Group[a]	M.P., °C	Prep.[b]	Remarks	Ref.
99 continued						
		1,1'-Dimethiodide				
100	4 6	Amino- 2-Methyl-amino-6-ethyl-4-pyrimidyl-amino- 1,1'-Dimethiodide	320 dec.	TT		78
101	4 6	Amino- 2-Isopropyl-amino-6-methyl-4-pyrimidyl-amino- 1'-Methiodide		EE		78
102	4 6	Amino 2-Isopropyl-amino-6-methyl-4-pyrimidyl-amino- 1'-Methiodide hydriodide	287 dec.	UU		78
103	4 6	Amino- 2-Isopropyl-amino-6-methyl-4-pyrimidyl-amino- 1,1'-Dimethiodide	320 dec.	VV, N		78, 79
104	4 6	Amino- 2,3-Dihydro-2-imino-3,6-bis(hydroxy-methyl)-4-pyrimidyl-amino-	308 dec.	PP		78

No.	R[a]	Group[a]	M.P., °C	Prep[b]	Remarks	Ref.
105	4 6	Methyl-amino- 2-Methyl-amino-6-methyl-4-pyrimidyl-amino- 1'-Methiodide trihydrate	296 dec.	EE		78
106	4 6	Methyl-amino- 2-Methyl-amino-6-methyl-4-pyrimidyl-amino- 1'-Methiodide hydrochloride	288-290 dec.	WW		78
107	4 6	Methyl-amino- 2-Methyl-amino-6-methyl-4-pyrimidyl-amino- 1, 1'-Dimethiodide	272-274	XX, YY		78, 79
108		N^1N^3-Bis(4-amino-6-cinnolyl) urea dimethochloride	295-297 dec.	ZZ	Small yellow needles from aqueous acetone.	77, 80
109		N^1N^3-Bis(4-amino-6-cinnolyl) urea dimethochloride	245-270 (dec. 240-245), 240-245	AAA	Product evolves hydrogen sulfide in warm water.	77, 80

(80) Morley and Simpson, J. Chem. Soc., 1952, 2617.

No.	R[a] Group[a]	M.P., °C	Prep[b]	Remarks	Re
109 continued		dec., melted at 270			
110	N^1N^3-Bis(4-amino-6-cinnolyl)thiourea dimethochloride	See remarks	BBB	Small yellow needles; effervessed at 205° C; melted gradually up to 280° C.	80
111	N^1N^3-Bis(4-amino-6-cinnolyl)-guanidine	245-250 dec., dec. 250	CCC, DDD	Yellow, precipitated by base; gelatinous mass of yellow needles.	77 80 55
112	N^1N^3-Bis(4-amino-6-cinnolyl)-guanidine trihydrochloride	335 dec.	R	Colorless from aqueous acetone	77 80
113	N^1N^3-Bis(4-amino-6-cinnolyl)-guanidine dimethiodide	270 dec.	G	Small yellow needles from water.	77 80
114	3 Methyl-4 Amino-6 Amino-	270 dec., 272-274	BB	Precipitated by base.	76, 78
115	3 Methyl-4 Amino-6 Amino- Dihydrochloride	325 dec.	R	Almost colorless prismatic needles.	76
116	3 Methyl-4 Amino-6 Amino- Methochloride	314-315 dec.	F	Long golden-yellow needles.	76

No.	R[a]	Group[a]	M.P., °C	Prep.[b]	Remarks	Ref.
117	3 4 6	Methyl- Amino- Amino- Methiodide	282-283 dec., 283-284 dec.	U, C	87% yield. Long bronze-colored needles from water, long golden needles.	76
118	3 4 6	Methyl- Acetamido- Acetamido-	297-298 dec.	D	100% yield. Colorless needles from acetone.	76
119	3 4 6	Methyl- Acetamido- Acetamido- Methiodide	243-244 dec.	G	53% yield. Stout orange-red prismatic needles from ethanol.	76
120	3 4 6	Methyl- Amino- 2-Amino-6-methyl-4-pyrimidyl-amino- 1'-Methiodide dihydrate	270 dec.	EE		78
121	3 4 6	Methyl- Amino- 2-Amino-6-methyl-4-pyrimidyl-amino- 1'-Methiodide hydroxide	263-265 dec.	OO		78
122	3 4 6	Methyl- Amino- 2-Amino-6-methyl-4-pyrimidyl-amino- 1,1'-Dimethiodide dihydrate	284 dec.	YY		79

No.	R[a] Group[a]	M.P., °C	Prep.[b]	Remarks	Ref.
123	N^1N^3-Bis(4-amino-3-methyl-6-cinnolyl) urea dimethochloride	288-290	ZZ	Small yellow needles from water.	80
124	N^1N^3-Bis(4-amino-3-methyl-6-cinnolyl)-thiourea		EE	Yellow slightly gelatinous mass.	80
125	N^1N^3-Bis(4-amino-3-methyl-6-cinnolyl)-thiourea dihydrochloride	290 dec.	AAA	Slightly gelatinous mass of yellow needles; precipitated from aqueous acetic acid by hydrochloric acid.	80
126	N^1N^3-Bis(4-amino-3-methyl-6-cinnolyl)-thiourea dimethochloride	313-314 dec.	AAA	Small yellow needles from water.	80
127	N^1N^3-Bis(4-amino-3-methyl-6-cinnolyl)-guanidine	240-270 dec.	CCC	81% yield. Pale yellow needles precipitated from aqueous ammonia-ethanol.	80
128	N^1N^3-Bis(4-amino-3-methyl-6-cinnolyl)-guanidine trihydrochloride	315 dec.	R	Colorless needles.	80
129	N^1N^3-Bis(4-amino-3-methyl-6-	See remarks	N/G	Small yellow needles; effervesced at 251-253° C. Decomposed up to	80

No.	R[a]	Group[a]	M.P., °C	Prep.[b]	Remarks	Ref.
129 continued						
	cinnolyl)-guanidine				280° C.	
130	4 7	Amino- Amino-	250 dec.	E	76% yield. Long very pale yellow needles from water.	55
131	4 7	Amino- Amino- Methiodide	262-263	C	Long yellow needles from ethanol.	55
132	4 7	Acetamido- Acetamido-	312 dec. (300)	C and combined	Very small colorless needles from dilute ethanol.	39
133	N^1N^3-Bis(4-amino-7-cinnolyl)-thiourea		256-257 dec.	EEE	Yellow needles.	55
134	N^1N^3-Bis(4-amino-7-cinnolyl)-guanidine		238-240			55
135	N^1N^3-Bis(4-amino-7-cinnolyl)-guanidine trihydrochloride		330 dec.	CCC	Colorless salt.	55
136	4 8	Amino- Amino-	167-168	C	Buff-colored solid from ether-ligroin.	39
137	4 8	Acetamido- Acetamido-	299-300	D	Pale greenish-yellow needles from dilute ethanol.	39
138	4 7 8 Methiodide	Amino- Methyl- Amino-	338 dec.	C	Small red needles from water.	76

139	4	p-Amino-benzyl-	176-177	FFF	64% yield. Glistening needles from benzene.	72
140	4 6 7	p-Amino-benzyl- Methoxy- Methoxy-	175.8-177	FFF	69% yield. Pale yellow crystals from benzene.	72
141	4-Cinnolyl-p-aminophenyl-acetonitrile		236.4-237.4	GGG	71% yield. Deep red needles from ethanol.	72
142	6,7-Dimethoxy-4-cinnolyl-p-aminophenyl-acetonitrile			GGG	Deep red needles from aqueous ethanol.	72

---

[a]When naming the substituent groups becomes too cumbersome, the complete compound name will be given.

[b]A. By treating the 3-bromocinnoline with copper sulfate and aqueous ammonia.

B. By treating the 3-acetylcinnoline with sodium azide and sulfuric acid.

C. By reducing the analogous nitro- or nitro-4-amino-compound with iron powder or stannous chloride or zinc dust.

D. By treating the analogous amino- compound with acetic anhydride or with acetyl chloride.

E. By treating the 4-phenoxy- analog with ammonium acetate.

F. By treating the analogous methiodide salt with silver chloride.

G. By treating the base with methyl iodide in ethanol, methanol, or without a solvent, or by treating the methosulfate with sodium iodide.

H. By treating 3-chloro-4-hydroxycinnoline with ammonia.

I. By treating 3,4-dichlorocinnoline with either saturated alcoholic ammonia or aqueous ammonia in a sealed tube at 150-160° C.

J. By treating 3-nitrocinnoline with ammonium hydroxide, ethanol, and methanolic potassium hydroxide at 50° C.

K. By treating the 4-chloro- analog with ammonium carbonate and phenol at 90° C or dry ammonia and phenol at 135-145° C.

L. By treating β-4-amino-6-nitrocinnolinium salts with cold alkali.

M. By hydrolyzing the corresponding 4-acetamido- compound with N hydrochloric acid, then treating the product with potassium iodide, or by treatment with boiling water.

N. By treating the corresponding methotoluene-p-sulfonate with potassium or sodium iodide.

O. By treating the base with dimethylsulfate in nitro-benzene.

P. By treating the cinnoline with methyl toluene-p-sulfonate.

Q. By treating the analogous 4-chlorocinnoline with phenol and methylamine at 140° C, or by treating the analogous 4-phenoxy-compound with phenol, methylamine hydrochloride, and sodium hydroxide at 180° C.

R. By treating the base with hydrochloric acid.

S. By treating the 4-chloro- analog with aniline, acetone, and hydrochloric acid, or by treating just with aniline.

T. By treating the analogous hydroxycinnoline with sodium bisulfite, ammonia, and water in a sealed tube at 100°.

U. By treating the corresponding acetamidocinnoline with hydrochloric acid.

V. By treating the base with picric acid.

W. By treating the hydroxycinnoline with aqueous ammonia and ammonium sulfite in a sealed tube at 100-120° C, then treating the product with acetic anhydride.

X. By treating the analogous 8-aminocinnoline with diethyl ethoxymethylenemalonate in benzene at 40-50° and dry air at 20-50 mm.

Y. By treating the 7-acetyl- analog with sodium azide, sulfuric acid, and chloroform.

Z. By passing ammonia through a nitromethane suspension of the trihydrochloride.

AA. By treating 7-amino-4-phenoxycinnoline in nitromethane with dichloromethylenebenzamide.

BB. By reducing the 6-nitro-analog over Raney nickel or with iron powder and hydrochloric acid, or stannous chloride in hydrochloric acid.

CC. By refluxing the corresponding methiodide with silver bromide, then adding sodium bromide.

DD. By treating the corresponding methobromide with ammonium thiocyanate.

EE. By treating the hydrochloride salt or hydriodide salt with base, and, in some instances, sodium iodide.

FF. By recrystallizing the corresponding methiodide from 2 N hydrochloric acid.

GG. By treating the analogous amino-compound as in D, then adding 2 N hydrochloric acid.

HH. By treating the appropriate 4, 6-diaminocinnoline with the appropriate 2-chloropyrimidine in aqueous hydrochloric acid.

II. By treating the appropriate 4, 6-diaminocinnoline methiodide with the appropriate 2-chloropyrimidine 1-methiodide, followed by treatment with sodium iodide.

JJ. By treating the appropriate 4, 6-diaminocinnoline 1-methiodide with the appropriate 4-chloropyrimidine.

KK. By treating the dry base with methyl p-toluenesulfonate in nitrobenzene.

LL. By treating the appropriate 4, 6-diaminocinnoline with the appropriate 4-chloropyrimidine 3-methiodide, then adding sodium iodide.

MM. By the procedure outlined in II, using the analogous methochlorides and sodium chloride.

NN. By refluxing 6-acetamido-4-aminocinnoline and 4-chloro-2-amino-6-methylpyrimidine 1-methochloride in aqueous hydrochloric acid and adding sodium iodide.

OO. By treating the appropriate 4, 6-diaminocinnoline with the appropriate 4-chloropyrimidine 1-methiodide and then adding sodium iodide in some instances.

PP. By the procedure outlined in LL using the appropriate 4-iodopyrimidine in place of the 4-chloro-analog.

QQ. By treating the appropriate 4, 6-diaminocinnoline methiodide with the appropriate 4-chloropyrimidine in aqueous hydrochloric acid and adding sodium iodide.

RR. By treating the dried analogous 1'-methiodide with dimethylsulfate or by similarly treating the dried free base and adding sodium iodide.

SS. By treating the appropriate 4, 6-diaminocinnoline methiodide with the appropriate 4-methylmercaptopyrimidine 1-methiodide and adding sodium iodide.

TT. By treating the appropriate 4, 6-diaminocinnoline methiodide with the appropriate 4-chloropyrimidine 1-methiodide.

UU. By treating the appropriate 4, 6-diaminocinnoline with the appropriate 4-chloropyrimidine (abstract appears to be in error regarding preparation of this compound).

VV. By the procedure outlined in TT, using the analogous 4-bromopyrimidine in place of the 4-chloro- compound.

WW. By treating the 4-methylamino-6-aminocinnoline as in TT.

XX. By treating 4-methylamino-6-aminocinnoline methiodide as in TT.

YY. By treating the dried 1'-methiodide analog with dimethyl sulfate.

ZZ. By treating the 4, 6-diaminocinnoline methiodide with carbonyl chloride in 50% acetone, or with carbonyl chloride and aqueous sodium acetate.

AAA. By treating the 4, 6-diaminocinnoline or the hydrochloride salt or the methochloride with thiocarbonyl chloride in 50% acetone.

BBB. By treating the diaminocinnoline methiodide as in AAA.

CCC. By treating the analogous thiourea dihydrochloride with yellow mercuric oxide and methanolic ammonia, then with 0.5 N hydrochloric acid, then with ammonium hydrogen sulfide, or by using sodium hydroxide in place of the last two reagents.

DDD. By treating the 4,6-diaminocinnoline with dichloromethylenebenzamide followed by potassium hydroxide.

EEE. By treating 7-amino-4-phenoxycinnoline with thiocarbonyl chloride in 50% acetone.

FFF. By treating the analogous acetonitrile with 50% sulfuric acid.

GGG. By treating the appropriate 4-chlorocinnoline with the appropriate phenylacetonitrile using liquid ammonia, potassium, and ferric nitrate.

A limited amount of pk data is available, as summarized below.

Cinnoline	pka	Solvent[a]	T. °C.	Ref.
4-Amino-	6.26	A	25	20
	6.25	A	24-25	81
4-Amino-6-chloro-	5.4	A	28	81
4-Amino-6-nitro-	5.08	A	25	20
	5.0	A	24-25	81
4-Anilino-	5.31	A	21-22	20
4,6-Diamino-	6.86	A	25±2	20

[a]A. 50% aqueous alcohol.

The conclusions drawn on page 40 concerning the pk values of various hydroxycinnolines and derivatives apply here, also. The order of effectiveness of the amino- compounds tested as indicated in the fourth conclusion is 4-amino- > 4-anilino- > 6-nitro-4-amino- (20).

Trypanocidal activity has been observed in various compounds belonging to the biscinnolylguanidine quaternary salts. The most

---

(81) Morley and Simpson, J. Chem. Soc., 1949, 1014

active of this type of compound, tested against Trypanosoma congolense infections in mice, was N^1N^3-bis(4-amino-6-cinnolyl)guanidine dimethiodide (82). The LD_{50} in mice (subcutaneous) was 1.30-2.20 mg. (77). The curative dose was 0.062-0.095 mg. (40). The theraputic index LD_{10}/CD_{90} did not differ significantly from that of antyricide methyl sulfate (82). This compound also has been tested (83) against a syringe-transmitted strain of T. congolense and had appreciable curative action. The maximum permissable dose for cattle was 2 mg/kg and >5 mg/kg was lethal (83). The salt was not effective against two strains of T. vivax (83).

The following table lists the ultraviolet data available:

Compound	Solvent	Ref.
3-Aminocinnoline		71
4-Aminocinnoline	Ethanol	28
4-Amino-7-chlorocinnoline α-methiodide		56
4-Amino-7-chlorocinnoline β-methiodide		56
4-Amino-6-nitrocinnoline	Ethanol	28
4-Amino-6-nitrocinnoline α-methiodide		56
4-Amino-6-nitrocinnoline β-methiodide		56
4-Anilinocinnoline	Ethanol	28
4-Anilino-6-nitrocinnoline	Ethanol	28
4-Acetamidocinnoline	Ethanol	28
4-Acetamido-6-nitrocinnoline	Ethanol	28

The ultraviolet data (28) indicate that 4-amino- and 4-anilinocinnolines exist in the imino- form; 4-acetamidocinnolines, however, do not (28).

4-Acetamido-8-nitrocinnoline could not be quaternized by heating with methyl iodide in ethanol (56). The methiodide salt of 4-amino-8-nitrocinnoline was more stable to hot water than the free base (56), the attempted quaternization of which with methyl iodide in ethanol resulted in the formation of 4-hydroxy-8-nitrocinnoline (56). 4-Aminocinnolines with methyl iodide in alcohol yield mixtures

---

(82) Lourie, Morley, Simpson, and Walker, Brit. J. Pharmacol. 6, 643 (1951) [C. A., 46, 2695 (1951)].

(83) Chandler, Brit. J. Pharmacol., 12, 44 (1957) [C. A., 51, 10753 (1957)].

of two series of quaternary salts in which only the ring nitrogen atoms are involved (56). Studies connected with the ultraviolet absorption spectra of these salts have permitted classification (56) of the salts as α- and β- those exhibiting a double and a single peak, respectively, in the 3000-4000 Å band. Only the α- salts would undergo acetylation. Proof has been cited (56) that the α- salts are N- (1) quaternized. The β- salts are believed to be N- (2) quaternized, but not proved as yet (56).

Attempted coupling of 4-amino-, 4-amino-6-chloro-, and 4-amino-6-nitrocinnoline with 4-chloro-6-nitro- or 4-chloro-7-nitroquinazoline in 30% aqueous acetone with 2-3 drops of concentrated hydrochloric acid failed (81).

Various halogeno-aminocinnolines and derivatives were involved in hydrolysis studies, as indicated below.

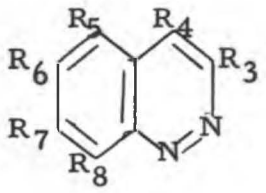
Cinnoline	Hydrolysate/Time (Hrs.)	Results	Ref.
4-Amino-7-chloro-	5 N HCl/3	No reaction	49
4-N, N-Dibutylamino-ethylamino-7-chloro-	N HCl/2	No reaction	49
4-N, N-Dimethylamino-ethylamino-7-chloro-	5 N HCl/2	No reaction	49
4-N, N-Diethylamino-ethylamino-7-chloro-	5 N HCl/2	No reaction	49
4-Acetamido-	5 N HCl/$\frac{1}{2}$	Hydrolysis to 4-amino-cinnoline	49

The remarks on page 22 concerning hydrolysis studies of halogenocinnol and derivatives apply here also.

G. Hydroxylaminocinnolines and Derivatives.

Only two compounds of this type have been reported in the literature since 1949. Since Table 7 lists all pertinent information concerning them, no discussion is required at this point.

Table 7. Hydroxylaminocinnolines and Derivatives



where R represents hydrogen unless indicated otherwise.

No.	R[a]	Group[a]	M. P., °C	Prep.[b]	Remarks	Ref.
1	4 7	Hydroxyl-amino- Acetamido-	229-230	A	Pale yellow needles from alcohol.	39
2	Methyl 4-hydroxylamino-7-cinnolyl-ketoxime		264-265 dec.	B	Pale yellow crystals from alcohol.	39

[a]When naming the substituent groups becomes too cumbersome, the complete compound name will be given.

[b]A. By treating methyl 4-hydroxylamino-7-cinnolyl ketoxime with acetic acid and acetic anhydride.

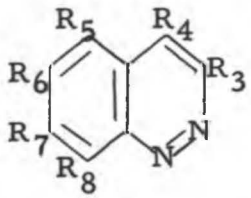
B. By treating 4-phenoxy-7-acetylcinnoline with hydroxylamine hydrochloride, sodium acetate, alcohol, and water.

H. Hydrazinocinnolines and Derivatives.

This general group of compounds is restricted to the cinnolines substituted at position 4. In addition, only one general method of preparation has been employed; namely, replacement of chlorine by hydrazine, a substituted hydrazine, or a hydrazide.

The hydrazinocinnolines and derivatives reported since 1949 are listed in Table 8.

Table 8. Hydrazinocinnolines and Derivatives



where R represents hydrogen unless indicated otherwise.

No.	R[a]	Group[a]	M.P., °C	Prep[b]	Remarks	Ref.
1	4	Hydrazino-	290-291, 293-294 dec., 226-227 dec., 301 dec., 229 dec.	A, B, C	90, 91% yield. The compound exists in two forms; the higher melting is red or deep orange; the lower, yellow or orange, and obtained from the red by refluxing in ethanol.	48, 11
2	4	Hydrazino- Hydrochloride	244-245	D	Very small white crystals.	18
3	3 4	Chloro- Hydrazino-	>300	E	Orange leaflets; deep red at 200-220° C.	18
4	4 6	Hydrazino- Chloro-	>320	E	Orange-yellow crystals from alcohol; deep red at 220° C.	18
5	4 6	Hydrazino- Bromo-	>300	E	Orange microcrystals; deep red at 220° C. precipitated from hydrochloric acid solution by ammonia.	18
6	4 6	Hydrazino- Nitro-	>330	E	Maroon solid.	15

No.	R[a]	Group[a]	M.P., °C	Prep.[b]	Remarks	Ref.
7	4 6	Hydrazino- Nitro- Hydrochloride	215 dec.	E	Golden-colored needles.	15
8	4	Hydrazino- Monoformyl derivative	229-230	F	Yellow plates from hot water.	18
9	4 6	Isopropylidenehydrazino- Nitro-	179-180	G	Orange hair-like needles from aqueous acetone; occasionally maroon needles.	15
10	4	Hydrazino- Diacetyl derivative	208-209	H	White crystals from alcohol.	18
11	4	Phenylhydrazino-	238 dec.	I	Yellow rhombs from alcohol.	18
12	3 4	Chloro- Phenylhydrazino-	134-135	I	Lustreless brown leaflets from dilute alcohol.	18
13	Benzaldehyde 4-cinnolylhydrazone		307	J		11
14	4	Toluene-p-sulfonylhydrazino- Hydrochloride	224-226	K	59% yield. Crimson needles from acetic acid.	19
15	3 4	Chloro- Toluene-p-sulfonylhydrazino-	167-169	K	98% yield. Almost colorless crystals from acetic acid.	19
16	3 4	Bromo- Toluene-p-sulfonylhydrazino-	187-189	K	Pink solid.	19

No.	R[a]	Group[a]	M. P., °C	Prep[b]	Remarks	Ref.
17	4	Toluene-p-sulfonyl-hydrazino-		K	No data given.	19
	5	Nitro-				
18	4	Toluene-p-sulfonyl-hydrazino-	190-192	K	Red prisms from chloroform.	19
	6	Nitro-				
19	4	Toluene-p-sulfonyl-hydrazino-	195-196 dec.	K	98% yield. Orange crystals from acetic acid.	19
	7	Nitro-				
20	4	Toluene-p-sulfonyl-hydrazino-	195-196 dec.	K	Brown needles from acetic acid.	19
	8	Nitro-				
21	Phenanthraquinone mono-4-cinnolylhydrazone		267-268	L	Glistening red microcrystals from alcohol.	18
22	3	Methyl-	186-187 dec.	K	92% yield. Pink rosettes from acetic acid.	19
	4	Toluene-p-sulfonyl-hydrazino-				
23	4	Toluene-p-sulfonyl-hydrazino-	221 dec.	K	Yellow prisms from ethanol.	61
	5	Methoxy-				
24	4	Toluene-p-sulfonyl-hydrazino-	199-201 dec.	K	Cream flocks from ethanol.	61
	6	Methoxy-				

No.	R[a]	Group[a]	M. P., °C	Prep.[b]	Remarks	Ref.
25	4	Toluene-p-sulfonyl-hydrazino-	169-172 dec.	K	Small bright red crystals from ethanol-ether.	61
	7	Methoxy-				
26	4	Toluene-p-sulfonyl-hydrazino-	169-172 dec.	K	96% yield. Yellowish-orange crystals from acetic acid - chloroform.	62
	8	Methoxy-				

[a]When naming attached radicals or groups becomes too cumbersome, the compound name will be given in place of the usual listing of R and Group.

[b]A. By treating the 4-chloro- analog with hydrazine hydrate in a sealed tube at 150-160°.

B. By treating the 4-chloro- analog with ethanolic hydrazine at room temperature.

C. By treating 1,2-dihydro-4-hydrazinocinnoline (reagents or conditions not given).

D. By treating the base, both high- and low-melting forms, with hot hydrochloric acid.

E. By treating the appropriate halogeno-4-chlorocinnoline with ethanolic hydrazine.

F. By treating both the low- and high-melting forms of 4-hydrazinocinnoline with hot formic acid, anhydrous.

G. By treating 4-hydrazino-6-nitrocinnoline with acetone.

H. By treating boththe low- and high-melting forms of 4-hydrazinocinnoline with boiling acetic anhydride.

I. By treating the appropriate 4-chlorocinnoline with phenylhydrazine in alcohol.

J. By heating either the high- or low-melting forms of 4-hydrazinocinnoline with benzaldehyde in 50% acetic acid.

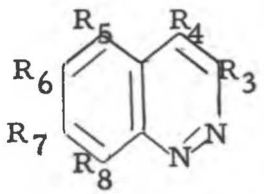
K. By treating the appropriate 4-chlorocinnoline with a chloroform solution of toluene p-sulfonylhydrazide.

L. By treating both the low- and high-melting forms of 4-hydrazinocinnoline with phenanthraquinone in boiling acetic acid.

I. Azocinnolines and Derivatives.

The azocinnolines and derivatives are restricted to those compounds with the azo- substituent located at position 6. The compounds included in this section were obtained by the following general procedure (77, 84, 85): The Borsche synthesis was employed to prepare the 4-hydroxy- analog. Alterations of the hydroxy- group were then carried out to prepare other 4-substituted compounds. The details of the reactions involved are included in Table 9, which lists the azocinnolines and derivatives reported since 1949.

Table 9. Azocinnolines and Derivatives



where R represents hydrogen unless indicated otherwise.

No.	R[a]	Group[a]	M.P., °C.	Prep[b]	Remarks	Ref.
1	4 6	Chloro- Phenylazo-	161-162	A	From ethyl acetate.	84
2	4 6	Hydroxy- Phenylazo-	298-300	B	60% yield. Yellow needles from acetic acid.	84
3	4 6	Acetoxy- Phenylazo-	179-180	C	From benzene, acetic acid, ethanol, or ethyl acetate.	84
4	4 6	Phenoxy- Phenylazo-	167-179, 164-167	D	75% yield. Red needles from ethyl acetate.	84
5	4 6	Amino- Phenylazo-	300-301 dec.	E	85% yield. Small golden needles from 2-ethoxyethanol.	84

(84) McIntyre and Simpson, J. Chem. Soc., 1953, 2606.

(85) McIntyre and Simpson, J. Chem. Soc., 1952, 2615.

No.	R[a]	Group[a]	M.P., °C.	Prep.[b]	Remarks	Ref.
6	4 6	Amino- Phenylazo- Hydrochloride	275-280 dec.	F	Golden fibrous needles.	84
7	4 6	Amino- Phenylazo- Methochloride	250-255, 252-254	G	Fibrous yellow needles from aqueous acetone then dilute hydrochloric acid.	84
8	4 6	Amino- Phenylazo- Methiodide	243-246 dec., 251-253 dec., 253-255 dec.	H, I	87, 58% yield.	84
9	4 6	Acetamido- Phenylazo-	271-275 dec.	J	84% yield. Dark red leaflets from 2-ethoxy-ethanol.	84
10	4 6	Acetamido- Phenylazo- Methiodide	195-197	K	Small red needles from water.	84
11	4 6	Acetamido- Phenylazo- Methotoluene- p-sulfonate	188-192	L	96% yield. Reddish needles from alcohol-ether.	84
12	4 6	Chloro- m-Acetyl- phenylazo-	194-196	A	Orange needles from benzene.	84
13	4 6	Hydroxy- m-Acetyl- phenylazo-	279-280 dec.	B	50% yield. Red needles from acetic acid.	84
14	4 6	Acetoxy- m-Acetyl- phenylazo-	178-180	C	Yellow needles from ethyl acetate.	84

No.	R[a] Group[a]	M. P., °C	Prep[b]	Remarks	Ref.
15	4, 4'-Dichloro-6, 6'-azo-cinnoline	>300, >320	A	Insoluble in organic solvents; precipitated by ligroin.	84, 77
16	4, 4'-Di-hydroxy-6, 6'-azocinnoline	>320	B	52% yield. Too insoluble to be recrystallized.	84, 77
17	4, 4'-Di-phenoxy-6, 6'-azocinnoline	254-258 dec.	D	48% yield. Orange-red needles from benzene.	84, 77
18	4, 4'-Diamino-6, 6'-azo-cinnoline	>320	M	83% yield from No. 17. Fine red needles, insoluble in organic solvents.	84, 77
19	4, 4'-Diamino-6, 6'-azo-cinnoline Dihydro-chloride	>320	E	Fine red needles from acetic acid or aqueous acetic acid - hydrochloric acid.	84, 77
20	4, 4'-Diamino-6, 6'-azo-cinnoline α-Dimetho-chloride trihydrate	279-281 dec., 282-285 dec.	N	Golden brown needles.	84, 77
21	4, 4'-Diamino-6, 6'-azo-cinnoline β-Dimetho-chloride Hemihydrate	312-314 dec.	N	Purplish needles from water.	84, 77
22	4, 4'-Diamino-6, 6'-azo-cinnoline Dimethiodide	284-288	H	98% yield. Amorphous dark red solid; could not be recrystallized.	84, 77

No.	R[a] Group[a]	M.P., °C	Prep[b]	Remarks	Ref.
23	4,4'-Bis-(methylamino)-6,6'-azo-cinnoline	>320	M	Scarlet solid; insoluble in water and common organic solvents.	77, 85
24	4,4'-Bis-(methylamino)-6,6'-azo-cinnoline Dihydrochloride	>320	O	71% yield. Small orange-red needles from dilute acid.	77, 85
25	4,4'-Bis-(methylamino)-6,6'-azo-cinnoline α-Dimetho-chloride	269-300 dec., 295-300	N	27% yield. Fine brown needles from 5 N hydro-chloric acid - acetone.	77, 85
26	4,4'-Bis-(methylamino)-6,6'-azo-cinnoline β-Dimetho-chloride	291-294 dec.	N	50% yield. Minute brown-red needles from water.	77, 85
27	4,4'-Bis-(methylamino)-6,6'-azo-cinnoline Dimethiodide	274-278	H	100% yield.	77, 85
28	4,4'-Diacet-amido-6,6'-azocinnoline	231-239 dec.	J	89% yield. Ocher solid; not recrystallizable.	84, 77
29	4,4'-Diacet-amido-6,6'-azocinnoline Dimethiodide	284-287 dec.	K	Violet.	77

No.	R[a] Group[a]	M.P., °C	Prep.[b]	Remarks	Ref.
30	4,4'-Diacetamido-6,6'-azocinnoline Dimethotoluene-p-sulfonate		L	99% yield. No other data given.	84, 77
31	1,8-Azo-1,4-dihydro-4-cinnolone	159-160 dec.	P	Buff-colored leaflets from dilute ethanol.	39

[a]When naming the substituent groups becomes too cumbersome, the complete compound name will be given.

[b]A. By heating the 4-hydroxy- or 4,4'-dihydroxy- analog with phosphorous pentachloride and phosphorous oxychloride or with phosphorous oxychloride in dimethylaniline.

B. By the Borsche synthesis on the appropriate 3-acetyl-4-aminoazobenzene.

C. By treating the appropriate hydroxy- compound with acetic anhydride.

D. By treating the appropriate chloro- or dichloro- analog with phenol and ammonium carbonate, phenol and dry ammonia at 120° C, or phenol and potassium hydroxide at 90° C.

E. By treating the appropriate phenoxy- or diphenoxy- compound with dry ammonia, ammonium chloride, and phenol.

F. By treating the base with hydrochloric acid.

G. By refluxing the corresponding methiodide with aqueous silver chloride.

H. By refluxing the base with methyl iodide in ethanol or by treating the base with methyl iodide and phenol at 100° C.

I. By refluxing the analogous acetamido- compound with hydrochloric acid.

J. By treating the appropriate amino- compound with acetic anhydride.

K. By treating the analogous methotoluene-p-sulfonate with aqueous potassium iodide, or sodium iodide.

L. By treating the base with methyl toluene-p-sulfonate at 110° C.

M. By treating the dihydrochloride salt with base.

N. By treating the corresponding dimethiodide with hydrochloric acid and silver chloride, from the analogous diacetamido-dimethiodide by treating in a similar manner, or by treating the methotoluene-p-sulfonate with hydrochloric acid.

O. By treating the analogous diphenoxy- compound with dry methylamine, phenol, and ammonium chloride.

P. By diazotization of 8-amino-4-hydroxycinnoline.

The α-dimethochloride of 4, 4'-bis(methylamino)-6, 6'-azocinnoline cures T. congolense, but the β-salt, although effective, does not (85). The α- and β-forms have been shown (84) not to be the same entity. The α-form is a trihydrate, while the β-salt is a hemihydrate. The exact structural differences have not been established (84).

J. Hydrocinnolines and Derivatives.

The first and simplest member of this group, 1, 2-dihydrocinnoline, was prepared by Busch and Rast (6) by the reduction of 4-chlorocinnoline with iron and 15% sulfuric acid. A few years later a compound was described (86, 87) as 1-ethyl-1, 2, 3, 4-tetrahydrocinnoline, prepared by the reaction of diethylzinc with either benzenediazonium chloride (86) or phenylazoethane (87). The fact that this compound is insoluble in 2% hydrochloric acid seems to be contrary (13) to the structure proposed.

Boiling the phenylhydrazone of diphenylhydroxyacetaldehyde with 1 N sulfuric acid gave 4, 4-diphenyl-1, 4(3, 4)-dihydrocinnoline (88). Although a 3-hydroxy-1, 2-dihydrocinnoline is reported in the literature (5) details of its preparation (52) are not accessible.

---

(86) Tichwinski, J. Russ. Phys. Chem., 36, 1052 (1904) [C. Z., I, 79 (1905)].

(87) Tichwinski, J. Russ. Phys. Chem., 36, 1056 (1904) [C. Z., I, 80 (1905)].

(88) Zerner, Monafsh., 34, 1609 (1913).

The addition of 2 moles of dimethyl azodicarboxylate to styrene gave 1,2,N^1,N^2-tetrakis(methoxycarbonyl)-1,2,3,4-tetrahydrocinnoline (10). Treatment by hot 33% potassium hydroxide removed the groups at positions 1 and 2.

2-Phenyl-3-keto-2,3,5,6,7,8-hexahydrocinnoline was prepared (89) by condensing phenylhydrazine with ethyl 2-ketocyclohexylglyoxylate in a mixture of ethanol and acetic acid.

Then in 1929 4-phenyl-1,2,3,4-tetrahydrocinnoline was prepared (5) by the catalytic reduction of the 1,2-dihydro- analog, which was prepared from 4-phenylcinnoline by refluxing with zinc dust and ammoniacal alcohol (5).

A hexahydrocinnoline has been described (90) as 1-phenyl-3-methyl-1,4,5,6,7,8-hexahydrocinnoline, but the structure is open to question (13). The compound was prepared by treating 2-acetonyl-cyclohexanone with phenylhydrazine.

Renewed interest in the hydrocinnolines did not come until 1945. All of the compounds prepared contain oxygenated rings. 1-Methyl-4-keto-1,2-dihydrocinnolines were obtained (50, 91, 92, 41, 39, 49) by methylation of 4-hydroxycinnolines with methyl sulfate and alkali. Under the proper methylating conditions, methyl 4-keto-4,6-dihydrocinnolyl-6-nitronates were formed (50, 49). By coupling diazotized arylamines with m-hydroxyphenylacetic acid in alkaline solution, followed by cyclization of the resulting azo-compounds with hot acetic anhydride and a trace of sulfuric acid, 3-acetoxy-2-aryl-6-keto-2,6-dihydrocinnolines were obtained (92).

Since 1949 the preparative chemistry of the hydrocinnolines has expanded somewhat. However, as stated in the introduction, very few of these new compounds were prepared by reductive procedures

---

(89) Von Auwers, Ann., 453, 211 (1927).

(90) Ebel, Huber, and Brunner, Helv. chim. Acta, 12, 16 (1929).

(91) Simpson, J. Chem. Soc., 1947, 1653.

(92) Kornfeld, J. Am. Chem. Soc., 70, 1373, (1948).

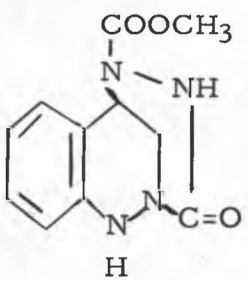
on more highly unsaturated cinnolines. The statement in the introduction which states that the literature does not record any example of a catalytic hydrogenation of a fully aromatic cinnoline is not strictly true. 3,4-Diphenylcinnoline and the 7-methyl- analog have been converted to the dihydro- compounds in alcoholic solution in the presence of Adam's platinum catalyst at either room temperature or 70° C (7).

Table 10 lists the hydrocinnolines and derivatives reported since 1949.

Table 10. Hydrocinnolines and Derivatives

The complete compound name is given in each case.

No.	Compound	M. P. °C	Prep.[a]	Remarks	Ref.
1	1,2-Dihydro-4-hydrazino-cinnoline		A	No details given.	11
2	1,4-Dihydro-3,4-diphenyl-cinnoline	129-130	B		7
3	1,4-Dihydro-3,4-diphenyl-7-methyl-cinnoline	150	B, C		7
4	1,2,6,7-tetra-hydro-1(2), 3,4-triphenyl-cinnoline	250-251	D	80-90% yield. Colorless from toluene-ligroin; location of N-phenyl group not proved.	7
5	1,2-Bis(ethoxy-carbonyl)-1,2,3,4-tetrahydrocinnoline		E	No details given.	12
6	1,2,3,4-Tetra-hydro-2-methyl-3-keto-cinnoline	91-92.5	F	Light yellow crystals from benzene-ligroin.	71

No.	Compound	M.P., °C	Prep.[a]	Remarks	Ref.
7	1,2-Bis(methoxycarbonyl)-1,2,3,4-tetrahydro-3-ketocinnoline	206	G		11
8	1H-3-keto-5-methoxycarbonyl-3,4,5,6-tetrahydro-2,6-methano-1,2,4,5-benzotetracine	197	H		11
					
9	4-Hydrazino-N^1-methoxycarbonyl-1,2,N^2-tris(acetamido)-1,2,3,4-tetrahydrocinnoline	208	I		11
10	4-Hydrazino-1,2,N^1 N^2-tetrakis(methoxycarbonyl)-1,2,3,4-tetrahydrocinnoline	178	J		11
11	4-Hydrazino-1,2,N^1N^2-tetrakis(ethoxycarbonyl)-1,2,3,4-tetrahydrocinnoline		K	No details given.	12
12	4-Hydrazino-tetrakis-(methoxycarbonyl)-4-	175	L		11

No.	Compound	M.P., °C	Prep.[a]	Remarks	Ref.
12 continued	phenyl-1,2,3,4-tetrahydrocinnoline				
13	4-Hydrazino-1,2,N^1N^2-tetrakis (methoxycarbonyl)-4-methoxy-1,2,3,4-tetrahydrocinnoline	167	M		11
14	5,6,7,8-Tetrahydrocinnoline		N	Poor yield. Oil; not too stable, becoming violet colored upon standing.	8
15	5,6,7,8-Tetrahydrocinnoline	156-157	O		8
16	3-Chloro-5,6,7,8-tetrahydrocinnoline	29-29.5	P	Boils at 123-127° C/ 0.5 mm. or 135-137°C/ 2mm; from Skelly B; colorless oil, turned red upon standing.	9, 8
17	3-Iodo-5,6,7,8-tetrahydrocinnoline	181-183 dec.	N	75% yield.	8
18	2-Phenyl-5,6,7,8-tetrahydrocinnoline	52-53	Q	From water.	9
19	2-Phenyl-5,6,7,8-tetrahydrocinnoline Hydrochloride	175-177	R	From ether.	9
20	3-Methyl-5,6,7,8-tetrahydrocinnoline	53.5-54.5	S	56% yield.	9

No.	Compound	M.P., °C	Prep.[a]	Remarks	Ref.
21	3-Methyl-5,6,7,8-tetrahydrocinnoline Picrate	139.5-141.5	O	From ethanol.	9
22	3-Phenyl-5,6,7,8-tetrahydrocinnoline	86-87.5	T	From Skelly B	9
23	3-Phenyl-5,6,7,8-tetrahydrocinnoline Picrate	174-175 dec.	O	From ethanol.	9
24	3,4-Diphenyl-5,6,7,8-tetrahydrocinnoline	173	U	82% yield. Colorless from toluene-ligroin.	7
25	3,4-Diphenyl-5,6,7,8-tetrahydrocinnoline Methoperchlorate	205-206	V	Yellow needles from methanol.	7
26	3,4-Diphenyl-5,6,7,8-tetrahydrocinnoline Picrate	165	O	Yellow needles from alcohol.	7
27	3,4-Diphenyl-6-methyl-5,6,7,8-tetrahydrocinnoline	192	U	80-90% yield. Colorless from toluene-ligroin.	7
28	3,4-Diphenyl-6-methyl-5,6,7,8-tetrahydrocinnoline Picrate	167	O	Yellow needles from alcohol.	7
29	3,4-Diphenyl-7-methyl-5,6,7,8-tetrahydrocinnoline	170	U	80-90% yield. Colorless from toluene-ligroin.	7

No.	Compound	M.P., °C	Prep.[a]	Remarks	Ref.
30	3,4-Diphenyl-7-methyl-5,6,7,8-tetrahydrocinnoline Methiodide	238	W	Black needles; yellow when crushed.	7
31	3,4-Diphenyl-7-methyl-5,6,7,8-tetrahydrocinnoline Methoperchlorate	208-209	V	Yellow needles from methanol.	7
32	3,4-Diphenyl-7-methyl-5,6,7,8-tetrahydrocinnoline Picrate	174	O	Yellow needles from alcohol.	7
33	3,4-Diphenyl-8-methyl-5,6,7,8-tetrahydrocinnoline	147	U	80-90% yield. Colorless from toluene-ligroin.	7
34	3,4-Diphenyl-8-methyl-5,6,7,8-tetrahydrocinnoline Methoperchlorate	207-210 dec.	V	Yellow needles from methanol.	7
35	3,4-Diphenyl-8-methyl-5,6,7,8-tetrahydrocinnoline Picrate	182	O	Yellow needles from alcohol.	7
36	3,4-Diphenyl-6-isopropyl-5,6,7,8-tetrahydrocinnoline	146	U	80-90% yield. Colorless from toluene-ligroin.	7

No.	Compound	M.P., °C	Prep[a]	Remarks	Ref.
37	3,4-Diphenyl-6-s-butyl-5,6,7,8-tetrahydrocinnoline	110-111	U	80-90% yield. Colorless from toluene-ligroin.	7
38	3-Methoxy-5,6,7,8-tetrahydrocinnoline	17-18	X	From Skelly B.	9
39	3-Methoxy-5,6,7,8-tetrahydrocinnoline Hydrochloride	187-192	R	Poor derivative.	9
40	3-Methoxy-5,6,7,8-tetrahydrocinnoline Picrate	161-163	O	From ethanol.	9
41	2,3,5,6,7,8-Hexahydro-3-keto-cinnoline	192-194, 194.5-196.5	Y	From water.	8, 9
42	2,3,5,6,7,8-Hexahydro-3-keto-cinnoline Hydrobromide	193-199, 193-197	Z	82% yield.	8, 9
43	2,3,5,6,7,8-Hexahydro-2-p-tolyl-3-keto-4,7-dimethyl-cinnoline	125-126	AA	Pale yellow cubes from ether.	93
44	2,3,5,6,7,8-Hexahydro-		BB	No data given.	94

(93) Woodward and Eastman, J. Am. Chem. Soc., 72, 399 (1950).

(94) Schmidt and Druey, Helv. chim. Acta, 37, 134 (1954).

No.	Compound	M.P., °C	Prep.[a]	Remarks	Ref.
44 continued	3-keto-4-hydroxy-cinnoline				

[a]A. By heating 4-hydrazino-1,2,N^1N^2-tetrakis(methoxycarbonyl)-4-methoxy-1,2,3,4-tetrahydrocinnoline with hydrazine hydrate.

B. By reducing the analogous 3,4-diphenylcinnoline in ethanol with Adam's platinum catalyst at 70°C.

C. By hydrogenating the analogous 5,6,7,8-tetrahydro- compound.

D. By reacting 2-(hydroxydesyl)cyclohexanone, hydrazine, hydrate, and phenylhydrazine.

E. By condensing styrene with diethyl azodicarboxylate.

F. By refluxing the 2,3-dihydro- analog with alcohol, zinc dust, and aqueous ammonia.

G. By treating the compound in A. with 2 N hydrochloric acid at 70°C.

H. By treating the compound in A. with aqueous potassium hydroxide.

I. By treating Compound No. 8 with boiling acetic anhydride.

J. By condensing styrene with dimethyl hydrazinedicarboxylate.

K. By condensing styrene with diethyl hydrazinedicarboxylate.

L. By condensing α-phenylstyrene with dimethyl hydrazinedicarboxylate at 70-80°C.

M. By treating α-methoxy-β-[N^1N^2-bis(methoxycarbonyl)-hydrazino]styrene with 80% acetic acid.

N. By refluxing the 3-chloro-analog with red phosphorous and constant-boiling hydriotic acid.

O. By treating the base with picric acid.

P. By heating at 80° 2,3,5,6,7,8-hexahydro-3-ketocinnoline or the hydrobromide with phosphorous oxychloride.

Q. By condensing benzamidine hydrochloride and hydroxymethylenecyclohexanone in absolute ethanol with piperidine as catalyst.

R. By treating the base with hydrochloric acid.

S. By treating α-(2-oxocyclohexyl)acetone with hydrazine hydrate (acetic acid-catalyzed), then reducing the product with palladium on charcoal in boiling cyclohexene.

T. By treating α-(2-oxocyclohexyl)acetophenone as in S.

U. By condensing the appropriate 2-(hydroxydesyl)cyclohexanone with hydrazine hydrate in refluxing toluene.

V. By treating the methiodide (which was not isolated) with sodium perchlorate.

W. By treating the base with methyl iodide in nitrobenzene.

X. By treating the analogous 3-chloro-compound with sodium methoxide in methanol.

Y. By treating the hydrochloride or hydrobromide with base.

Z. By treating 2, 3, 4, 4a, 5, 6, 7, 8-octahydro-3-ketocinnoline with bromine and acetic acid.

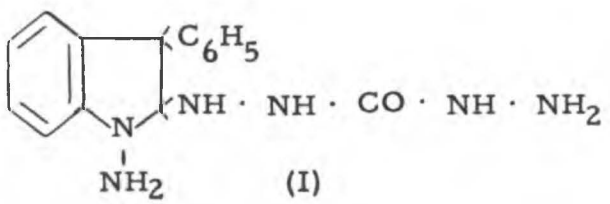
AA. By boiling the autoxidation product of menthofuran with p-tolylhydrazine in ether.

BB. By treating 1, 2-cyclohexadione and cyanoacetylhydrazide together in ethanol with sodium at 90°.

References to the ultraviolet data available on hydrocinnolines are listed below.

Cinnoline	Solvent	Ref.
1, 4-Dihydro-3, 4-diphenylcinnoline	Methanol	7
1, 4-Dihydro-3, 4-diphenyl-7-methylcinnoline	Methanol	7
5, 6, 7, 8-Tetrahydrocinnoline	Isooctane	95
	95% Ethanol	95
	Water	95
	Sulfuric acid	95
6-Chloro-5, 6, 7, 8-tetrahydrocinnoline	Isooctane	95
3, 6-Dichloro-5, 6, 7, 8-tetrahydrocinnoline	Isooctane	95
3, 4-Diphenyl-5, 6, 7, 8-tetrahydrocinnoline	Methanol	7
3, 4-Diphenyl-7-methyl-5, 6, 7, 8-tetrahydrocinnoline methiodide	Methanol	7
1(2), 3, 4-Triphenyl-1, 2, 3, 4-tetrahydrocinnoline	Dioxan	7

Treatment of 1, 2, N^1N^2-tetrakis(methoxycarbonyl)-4-phenyl-1, 2, 3, 4-tetrahydrocinnoline with hydrazine hydrate (11) yields either N-amino-3-phenylindole or an analogous 2, 3-dihydro- compound (I).



(I)

(95) Horning and Amstutz, J. Org. Chem., 20, 1069 (1955).

K. Cinnolines Containing Additional Fused Rings.

Table 11 lists the compounds of this group reported since 1949. In view of the diverse nature of these compounds, no attempt will be made to discuss any of them at this point.

Table 11. Cinnolines Containing Additional Fused Rings.

The complete compound name is given in each case. Naming and numbering follow Ring Index recommendations.

No.	Compound	M.P., °C	Prep.[a]	Remarks	Ref.
1	4-Hydroxy-7,8-dihydro-6H-cyclopenta[g]-cinnoline	271-272	A	Colorless prisms from alcohol.	59
2	4-Acetoxy-7,8-dihydro-6H-cyclopenta[g]-cinnoline	112-113	B	Pinkish needles from dilute alcohol.	59
3	3-Chloro-4-hydroxy-7,8-dihydro-6H-cyclopenta[g]-cinnoline	>340	A	Colorless leaflets from alcohol.	59
4	3-Chloro-4-acetoxy-7,8-dihydro-6H-cyclopenta[g]-cinnoline	159-160	B	Colorless needles from dilute alcohol.	59
5	4-Hydroxy-8,9-dihydro-7H-cyclopenta[h]-cinnoline	246-247	A	Colorless needles from dilute alcohol.	59
6	Benzo[c]-cinnoline	156	C, D	92% yield. Pale yellow blades from benzene.	96

(96) Badger, Seidler, and Thomson, J. Chem. Soc., 1951, 3207.

No.	Compound	M.P., °C	Prep[a]	Remarks	Ref.
7	3,8-Dichloro-benzo[c]-cinnoline	259-260	C	Small pale yellow crystals from alcohol.	97
8	1-Nitro-benzo[c]-cinnoline	160-161	E	Extracted with Skelly B, recrystallized from ethanol; proof given for structure.	97
9	3,8-Dichloro-benzo[c]-cinnoline-5-oxide	244-245	F	Pale yellow needles from benzene then alcohol.	97
10	1-Amino-benzo[c]-cinnoline	155-157 (crude)	G	81% yield. Apparently not purified.	98
11	1-Benzene-sulfonamido-benzo[c]-cinnoline	211-213	H	23.6% yield. From ethanol.	98
12	3,8-Diamino-benzo[c]-cinnoline	265	D	From benzene.	99
13	1,2,3,4-Tetra-hydrobenzo-[c]cinnoline	98	I	15% yield. Yellow prisms from ligroin.	100

(97) Calderbank and LeFèvre, J. Chem. Soc., 1951, 649.

(98) Smith, Jr., and Ruby, J. Am. Chem. Soc., 76, 5807 (1954).

(99) Braithwaite, Holt, and Hughes, J. Chem. Soc., 1958, 4073.

(100) Moore, Nature, 163, 918 (1949).

No.	Compound	M. P., °C	Prep.[a]	Remarks	Ref.
14	4-Hydroxy-6, 7, 8, 9-tetrahydrobenzo-[g]-cinnoline	262-263	J	Small white rhombs from methanol.	59
15	3-Chloro-4-hydroxy-6, 7, 8, 9-tetrahydrobenzo-[g]cinnoline	288-289	J	Colorless crystals from alcohol.	59
16	3-Chloro-4-acetoxy-6, 7, 8, 9-tetrahydrobenzo-[g]cinnoline	148-149	B	Colorless needles from alcohol.	59
17	4-Hydroxy-7, 8, 9, 10-tetrahydrobenzo-[h]cinnoline	276-277	J	Pale buff microcrystals from dilute methanol.	59
18	1, 10-Dimethylbenzo[c]-cinnoline	135-136	C	Colorless crystals from alcohol.	97
19	1, 10-Dimethylbenzo[c]-cinnoline-5-oxide	153	F		101
20	2, 9-Dimethylbenzo[c]-cinnoline	184, 185, 186	K	Needles from acetone or benzene.	99
21	3, 8-Dichloro-2, 9-dimethylbenzo[c]-cinnoline	277, 279	L	Yellow base from benzene or acetone.	99

(101) Sako, Bull. Chem. Soc. Japan, 9, 393, (1934)[C. A., 29, 1083 (1935)].

No.	Compound	M.P., °C	Prep.[a]	Remarks	Ref.
22	3,8-Dibromo-2,9-dimethylbenzo[c]cinnoline	280	M	Yellow needles from benzene.	99
23	3,8-Dichloro-2,9-dimethylbenzo[c]cinnoline-5-oxide	275 dec.	N	Light yellow powder from dimethyl formamide.	99
24	3,8-Dibromo-2,9-dimethylbenzo[c]cinnoline-5-oxide	284 dec., 286 dec.	O	Pale yellow needles from dimethyl formamide.	99
25	3,8-Diiodo-2,9-dimethylbenzo[c]cinnoline-5-oxide	212-215 dec.	P		99
26	3,8-Diiodo-2,9-dimethylbenzo[c]cinnoline-5-oxide with acetone of crystallization	242-246 dec.	Q	Material could not be freed of solvent due to thermal instability; unstable in light.	99
27	2,9-Dimethyl-3,8-diaminobenzo[c]cinnoline	272-274 dec.	R	From benzene.	99
28	2,4-Dimethyl-1,2,3,4-tetrahydrobenzo[c]cinnoline	111	I	85% yield. Yellow needles from ligroin.	100
29	3,4-Diphenylbenzo[h]cinnoline	182	S		7

No.	Compound	M. P., °C	Prep.[a]	Remarks	Ref.
30	3, 4-Diphenyl-benzo[h]-cinnoline Picrate	174	T		7
31	3, 4-Diphenyl-5, 6-dihydro-benzo[h]-cinnoline	230	U		7
32	3, 4-Diphenyl-5, 6-dihydro-benzo[h]-cinnoline	188	T		7
33	4-Methyl-7-hydroxy-pyrido[3, 2-h]-cinnoline	325-326	V	93% yield. Light tan amorphous powder from ethanol.	40
34	4-Methyl-7-hydroxy-pyrido[3, 2-h]-cinnoline-8-carboxylic acid	313-314 dec.	W	100% yield. White precipitate by adding acid to the reaction mixture.	40
35	4-Methyl-7-hydroxy-8-ethoxycarbonylpyrido-[3, 2-h]cinnoline	257-258	X	31% yield. Yellow needles from 95% ethanol.	40
36	Dibenzo[c, f]-cinnoline	156.5-157.5	Y	Purified by chromatography on alumina, then yellow leaflets from benzene-hexane.	102
37	3-Keto-4-cyano-2, 3-	290	Z	From ethanol.	94

(102) Badger and Walker, J. Chem. Soc., 1956, 122.

No.	Compound	M.P., °C	Prep[a]	Remarks	Ref.
37 continued	dihydro-dibenzo[f,h]-cinnoline				
38	Dibenzo[5,6-7,8]quinoxalino-[2,3-c]cinnoline	315-316	AA	50-72% yield. Bright yellow needles from pyridine.	38

[a]A. By diazotization of the appropriate acetylaminoindane.

B. By treating the base with acetic anhydride.

C. By reducing the 5-oxide with zinc dust in acetic acid, with lithium aluminum hydride in benzene-ether, or with stannous chloride in hydrochloric acid.

D. By reducing the appropriate 2,2'-dinitrobiphenyl with lithium aluminum hydride in benzene-ether.

E. By nitrating with mixed acids the parent heterocycle.

F. By reducing the appropriate 2,2'-dinitrobiphenyl with alcoholic sodium sulfide nonahydrate at 100° C.

G. By reducing the nitro-analog in methanol over nickel with 3 atmospheres of hydrogen.

H. By treating the base with benzenesulfonyl chloride in pyridine.

I. By treating the appropriate 1,2-cyclohexadione-1-phenyl-hydrazone with sulfuric acid.

J. By diazotization of the appropriate acetylaminotetralin.

K. By reducing 4,4'-diiodo- or 4,4'-dibromo-3,3'-dimethyl-6,6'-dinitrobiphenyl as in D or with sodium amalgam in dry methanol.

L. By reducing the 4,4'-dichloro- analog of K with either sodium amalgam in methanol or with zinc dust and 40% potassium hydroxide in hot ethanol.

M. By reducing the 4,4'-dibromo- analog of K as in K.

N. By reducing the 4,4'-dichloro- analog of K with sodium sulfide in boiling 90% ethanol.

O. By reducing the 4,4'-dibromo-analog of K as in N or with sodium amalgam in dry methanol.

P. By reducing the 4,4'-diiodo- analog of K as in N with added sodium hydroxide.

Q. By the procedure in P except that no base was added.

R. By reducing the appropriate 6,6'-dinitro-o-tolidine as in D.

S. By dehydrogenating the analogous dihydro- compound using palladized charcoal or chromium trioxide.

T. By treating the base with picric acid.

U. By treating the diketone formed from α-tetralone, 1-naphthalon-2-yl-β-hydroxy-β-phenylacetophenone, with hydrazine.

V. By decarboxylating the 8-carboxylic acid analog in benzophenone at 265-275° C under a nitrogen atmosphere.

W. By treating the analogous ethoxycarbonyl- compound with 2% aqueous sodium hydroxide under reflux.

X. By treating 8-(2, 2-diethoxycarbonylvinylamino)-4-methylcinnoline with diphenyl ether at 245° C.

Y. By cyclizing 1-o-aminophenyl-2-naphthylamine with ammonium persulfate and sulfuric acid at 0° C.

Z. By condensing 9, 10-phenanthraquinone with cyanoacetylhydrazide using anhydrous ethanol and boiling three hours.

AA. By condensing 9, 10-phenanthraquinone with 3, 4-diaminocinnoline at 100° C with acetic acid or potassium acetate and acetic acid.

The dipoles of various fused-ring cinnolines have been obtained, as summarized:

Cinnoline	Dipole	Ref.
Benzo[c]cinnoline	3.90	78
Benzo[c]cinnoline-5-oxide	5.20	78
3, 8-Dichlorobenzo[c]cinnoline-5-oxide	5.1	77
X-Nitrobenzo[c]cinnoline-5-oxide	5.6	77
X-Bromobenzo[c]cinnoline-5-oxide	5.3	77

The above data were used (77) as evidence that the x-nitro- and x-bromo- compounds were 3-nitro- and 3-bromo-, respectively. The x-nitro- compound was obtained by nitration of the benzo[c]cinnoline-5-oxide (103) and was considered to be the 2-nitro- compound (103)

The reactivities toward electrophilic substitution of the various positions of benzo[c]-cinnoline have been calculated (36):

---

(103) King and King, J. Chem. Soc., 1945, 824.

ΔE_1 = 10.0 kcal/mole ΔE_3 = -11.3

ΔE_2 = -17.0 ΔE_4 = -14.8

The expected order of reactivity was therefore given (36) as 1 > 3 > 4 > 2.

The following references to the ultraviolet data have been obtained:

Compound	Solvent	Ref.
Benzo[c]cinnoline		104
	Ethanol	102
	Cyclohexane	102
Benzo[c]cinnoline-5-oxide		104
3,8-Dichlorobenzo[c]cinnoline-5-oxide		97
X-Nitrobenzo[c]cinnoline-5-oxide		97
X-Bromobenzo[c]cinnoline-5-oxide		97
Dibenzo[c,f]cinnoline		97
4-Methyl-7-hydroxy-8-ethoxycarbonylpyrido-[3,2-h]cinnoline	Ethanol	40

Hydrogenation with nickel at 70 atmospheres of hydrogen at 70° in ethanol of 1-Benzenesulfonamidobenzo[c]cinnoline gave 2-benzenesulfonamido-6,6'-diaminobiphenyl (98).

---

(104) Badger, Pearce, and Pettit, J. Chem. Soc., 1951, 3199.

III. EXPERIMENTAL

High-pressure reductions were carried out in a Parr Instrument Company No. 4011-H High-Pressure Reaction Apparatus (Parr High Reactor), having a fixed agitation rate of 37 cycles per minute. Low-pressure reductions were accomplished in a Parr Instrument Company Series 3910 Low-Pressure Shaker-Type Apparatus (Parr Low Reactor).

Melting points usually were taken with a Fisher-Johns Melting Point Apparatus. For those compounds (notably picrates and picrolonates) which tended to sublime, capillary melting points were taken in an electrically-heated, circulating oil-bath. All melting and boiling points are reported uncorrected.

Analyses were performed by the microanalytical laboratories of Schering Corporation, Bloomfield, New Jersey, and the University of Melbourne, Australia.

A. Preparation of Catalysts.

1. Commercially-Obtained Catalysts.

With one exception, all catalysts used were commercial preparations obtained from Baker and Co., Inc., Newark, New Jersey. These catalysts were 5% rhodium on alumina, ruthenium oxide, platinum oxide, 5% palladium on activated charcoal, and 5% rhodium on activated charcoal.

2. Preparation of Raney Nickel W-2.

The method of Mozingo (105) was used. The preparation utilized 300 g. of Raney nickel-aluminum alloy. The catalyst was stored under absolute ethanol.

B. Preparation of 4-Methylcinnoline.

This preparation followed the procedure of Jacobs, et.al. (106)

---

(105) Mozingo, Org. Syn., Coll. Vol., III, 181 (1955)

(106) Jacobs, Winstein, Henderson, and Spaeth, J. Am. Chem. Soc., 68, 1310 (1946)

1. Preparation of 2-(o-Aminophenyl)propene.

Methylmagnesium bromide was prepared from 243 g. (10 g.-atoms) of magnesium turnings in 1.5 liters of anhydrous ether, and gaseous methyl bromide. Under nitrogen atmosphere and at 0° the Grignard reagent was treated dropwise, during 2 hours, with 250 g. (1.65 moles) of methyl anthranilate in 1 liter of anhydrous ether. A Hershberg-type tantalum wire stirrer was used. The reactant mixture was allowed to come to room temperature and then refluxed for 5.5 hours. The mixture was cooled and poured into a mixture of 1200 g. of ammonium chloride and ice. Additional ice was added as required to prevent overheating. Basic magnesium salts were partly neutralized by adding 700 ml. of 6 N aqueous hydrochloric acid. The mixture was extracted with ether until no additional color was removed. The combined extracts were concentrated to 3 liters, dried over anhydrous potassium carbonate, and the remaining ether distilled under reduced pressure. The crude dimethyl-(o-aminophenyl)carbinol was dissolved in 1 liter of toluene containing 0.1 g. of iodine and refluxed for 72 hours. Use of a combination distillation-reflux condenser permitted collection of 28.5 ml. of water (95% of the theoretical amount). Toluene was removed under reduced pressure and the residue vacuum-distilled through a Claissen-type Vigreaux column. The yield of 2-(o-aminophenyl)propene, b.p. 87-91°/1-2 mm. [lit. (106) b.p., 83.5-87.5°/1-2 mm.], was 192 g. (86%).

2. Preparation of 4-Methylcinnoline.

A solution of 189 g. (1.41 moles) of 2-(o-aminophenyl)propene in 950 ml. of water and 105 ml. (3.8 equivalents) of concentrated sulfuric acid was diazotized at 0-5° by the dropwise addition of 97.5 g. (1.42 moles) of sodium nitrite in 210 ml. of water. The addition required 2 hours. A small excess of nitrous acid was detected with potassium iodide-starch test paper. The diazotized solution was diluted to 12 liters with ice and water and stored in the dark for 3.5 days. After making basic with 160 g. of sodium hydroxide in 160 ml. of water, the solution was extracted continuously with benzene for 10-12 hours in 3-liter batches using an apparatus described by Wilson (107). The benzene was distilled at atmospheric pressure. The residue was vacuum-distilled, giving 164 g. (84%) of 4-methylcinnoline which was recrystallized from n-heptane or Skelly Solve B.

---

(107) Wilson, Org. Syn., Coll. Vol. I, 277 (1941)

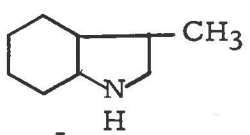
The recrystallized product, m.p. 72-72.5°, originally pale yellow, turned blue to blue-green upon standing uncovered overnight. The blue crystals melted at 71-72°. A mixture of the blue solid and a sample of 4-methylcinnoline (orange crystals, m.p. 74-75°) received from Dr. H. Smith Broadbent, prepared in a similar fashion (108), melted at 72-72.5°. The unusual color change has not been explained.

C. High-Pressure Hydrogenation of 4-Methylcinnoline Using 5% Rhodium on Alumina Catalyst.

1. High-Pressure Hydrogenation of 4-Methylcinnoline in Neutral Solution Using 5% Rhodium on Alumina. First Hydrogenation.

A 500-ml. glass reactor liner was charged with 20 g. (0.14 mole) of 4-methylcinnoline, 150 ml. of absolute ethanol, and 0.5 g. of 5% rhodium on alumina. Reduction was carried out in the Parr High Reactor with a hydrogen pressure of 2000 psig, the temperature gradually being increased to 200° over a 6-day period. Upon cooling to room temperature a 600-psi pressure drop was observed, equivalent to 4.3 molar equivalents of hydrogen absorbed. The vented gas had an ammonia-like odor. The catalyst was removed by suction filtration and the solvent stripped under reduced pressure. The remaining liquid was vacuum-distilled at 0.4-0.6 mm. pressure through a 20-cm. Vigreaux column. Four fractions were taken: (1) 1.4 g., b.p. up to 30°, n_D^{20}, 1.3703; (2) 0.3 g., b.p. 30-32°, n_D^{20} 1.4709; (3) 8.1 g., b.p. 32°, n_D^{20} 1.4802; (4) 1.9 g., b.p. 32-80°, n_D^{20} 1.4893. Total recovery of material was 11.7 g. or 59%.

The first two fractions were shown by gas chromatography on a 5-foot silicone column* to be mainly ethanol. Fraction 3, ca. 90% pure, was identified as a mixture of stereoisomers of octahydroskatole



I.

* The instrument used for all gas chromatography was an Aerograph Master Model A-100, Silkens Instrument and research, Inc., Berkeley, California, with a Model G-10 recorder, Varian Associates, Palo Alto, California.

(108) Private communication.

by comparison with an authentic sample obtained from the hydrogenation of skatole (see Section III. L. 3.). A gas chromatogram of fraction 3 was obtained using a 5-foot column packed with silicone on Fluoropak 80. Column temperature was 198°. Retention time was 5.9 min. Upon redistilling fraction 3 at 44-45°/0.7 mm., n_D^{20} 1.4775, a purity of 99% was indicated by gas chromatography.

Anal. Calcd. for $C_9H_{17}N$: C, 77.63; H, 12.31; N, 10.06

Found: C, 79.95; H, 9.70; N, 10.16; Total, 99.81

In the Hinsberg reaction*, I. gave an oil insoluble in water and dilute acid. A similar result was obtained upon directly mixing benzenesulfonyl chloride and I. The nickel chloride, carbon disulfide, and ammonium hydroxide test for secondary amines was negative.

---

* Unless otherwise noted, Shriner, Fuson, and Curtin, "The Systematic Identification of Organic Compounds", 4th Ed., John Wiley and Sons, Inc., New York, 1946, was used for all qualitative and classification tests, and for the preparation of derivatives.

The hydrochloride of I. was prepared but liquified immediately. Attempts to prepare the following derivatives also were unsuccessful: acetamide, benzamide, methanesulfonamide, oxalate, p-toluenesulfonamide, benzylsulfonamide, and phenylthiourea. Repeated attempts to prepare the picrate resulted in the isolation of a solid which decomposed upon attempting to recrystallize it from ethanol. The water-washed solid melted at 145.5-155°. The picrolonate of octahydroskatole was successfully prepared and melted at 226-228°.

Acetylation of I. was attempted using 0.2 ml. of 70% perchloric acid as catalyst. Nothing was isolated. The octahydroskatole was redistilled at 28-32°/0.10-0.13 mm., n_D^{20} 1.4804. Following a procedure for acetylating weakly basic amines (109), a mixture of 0.5 g. of I., 3-4 ml. of acetic anhydride, and 2 drops of concentrated sulfuric acid was allowed to stand 3 days. The mixture was poured into 50 ml. of water. No solid separated. Evaporation of the water left a brown tarry material. Trituration with ether left a brown, tacky tar. The ether was evaporated, leaving a yellow liquid with a fruity odor. The infrared spectrum* of this material

---

* Beckman IR-5 Infrared Recording Spectrophotometer; this excellent instrument greatly aided the project.

---

(109) Stacy and Bresson, J. Org. Chem., 24, 1892 (1959)

had a secondary amide carbonyl peak at 6.05 μ. Two peaks, assumed to be N-H absorption bands, were observed at 2.85 μ and 3.05 μ. The liquid was taken up in ether, washed with 1 N aqueous hydrochloric acid, dilute aqueous sodium bicarbonate, and water. The ether was dried over anhydrous sodium sulfate. The infrared spectrum of the residue remaining after evaporation of the ether showed one N-H peak at 3.07 μ. No solid could be obtained.

2. High-Pressure Hydrogenation of 4-Methylcinnoline in Neutral Solution Using 5% Rhodium on Alumina. Second Hydrogenation.

A second hydrogenation was carried out, the reactant mixture consisting of 14.4 g. (0.1 mole) of 4-methylcinnoline, 50 ml. of absolute ethanol, and 0.5 g. of 5% rhodium on alumina. The initial hydrogen pressure was 2000 psig and the maximum temperature was 132°. Reduction appeared to be complete in ca. 5 hours*, during which period the temperature increased from 111° to 132°. Upon allowing the reactor to cool, a pressure drop of 340 psi was observed, corresponding to 3.4 molar equivalents of hydrogen absorbed. The vent gas had the ammonia-like odor observed in

---

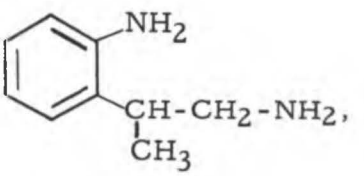
* Completeness of reaction was determined by the ratio of the change in gauge pressure (ΔGP) to the change in the theoretical pressure assuming no reaction (Δ NRP). When this ratio (Δ GP/ ΔNRP) became positive (or 0 in the event of constant temperature) and relatively constant, reduction was assumed to be complete.

---

the previous reduction (section III. C. 1.). The catalyst was removed and the filtrate diluted with water to ca. 800 ml. The solution was made strongly basic with 40% aqueous sodium hydroxide and extracted with ether. The combined ether extracts were washed once with water and dried over sodium sulfate. The ether was evaporated under reduced pressure and the residue vacuum-distilled through a 45-cm., vacuum-jacketed, electrically-heated Vigreaux column. One fraction was taken: 7.0 g., b.p. 120-127°/ 5 mm., n_D^{20} 1.5807. The kettle residue weighed 2.0 g. Material recovery was 62%. An infrared spectrum of the distillate was obtained.

The following derivatives were prepared: picrate, m.p. 182.5-183.5°; hydrochloride, m.p. 193-220° (recrystallized once from ethyl acetate-ethanol); picrolonate, m.p. 210-214° with some decomposition. A Volhard titration of the hydrochloride gave 31.10% chlorine (calcd. for $C_9H_{16}Cl_2N_2$, 31.77%). The free base was

assigned the structure



II.

o-amino- β -methylphenethylamine or 2-(2-aminophenyl)propylamine, pending synthesis of the compound by an unambiguous route.

A 1.5-g. sample of o-amino- β -methylphenethylamine (II) was diazotized by the procedure outlined for the preparation of 4-methylcinnoline (106). The reactant mixture was diluted to 150-200 ml. with ice and water and stored in the dark for 3 days. The mixture was made basic, then continuously extracted with benzene. Evaporation of the benzene left a dark brown-orange oil. The infrared spectrum of the material had no N-H or O-H bands and showed no resemblance to the spectrum of 4-methylcinnoline. The oil could not be purified.

3. High-Pressure Hydrogenation of 4-Methylcinnoline In Neutral Solution Using 5% Rhodium on Alumina. Third Hydrogenation

A third reduction was carried out. A mixture of 14.4 g. (0.1 mole) of 4-methylcinnoline, 50 ml. of absolute ethanol, and 0.5 g. of 5% rhodium on alumina was hydrogenated under an initial hydrogen pressure of 2000 psig. The temperature was maintained at 200-232° for 8 hours. The ratio Δ GP/ Δ NRP was essentially constant for the last 5 hours. Upon cooling to room temperature the gauge pressure was 1500 psi, indicating 5.0 molar equivalents of hydrogen were absorbed. The vent gas exhibited the now-familiar ammonia-like odor. The reactant mixture was filtered and the filtrate treated as described in the previous reduction (Section III. C. 2.). After evaporating the ether the remaining liquid was vacuum-distilled. Four fractions were taken: (1) 0.4 g., b.p. 80-119°/15 mm., n_D^{20} 1.4794; (2) 5.5 g., b.p. 121-144°/15 mm., n_D^{20} 1.4811; 0.9 g., b.p. 112-119°/5 mm., n_D^{20} 1.5174; (4) 1.9 g., b.p. 120-128°/5 mm., n_D^{20} 1.5630. Material recovery was 60%.

The infrared spectra of the four fractions identified fractions 1 and 2 as octahydroskatole (I) and fraction 4 as impure II. The third fraction appeared to be unique; it has not been identified.

An analytical sample of I was obtained by redistillation of fraction 2, b.p. 115°/15 mm.; density at 25°, 0.9306.

Anal. Calcd. for $C_9H_{17}N$: C, 77.63; H, 12.31; N, 10.06

Found: C, 76.58; H, 11.80; N, 10.35; Total, 98.73.

An attempt to prepare the hydrochloride of II (fraction 4) resulted in a small amount of solid which was washed with ether; the material melted at 198-208°. The picrate was prepared (m.p. 183-184° after washing with ethanol).

4. High-Pressure Hydrogenation of 4-Methylcinnoline In Acidic Solution Using 5% Rhodium on Alumina.

First Hydrogenation

4-Methylcinnoline, 14.4 g. (0.1 mole) in 50 ml. of absolute ethanol containing 8.4 ml. (0.1 mole) of concentrated hydrochloric acid and 0.5 g. of 5% rhodium on alumina, was reduced in the Parr High Reactor. The initial hydrogen pressure was 3000 psig. The temperature was maintained at 110° for 22 hours. Upon cooling to room temperature the gauge pressure was 2600 psi, equivalent to 4.0 molar equivalents of hydrogen absorbed. The filtered reactant mixture was evaporated to dryness under reduced pressure, leaving 8.8 g. of solid, a recovery of 49%. The material was recrystallized four times from ethanol, m.p. 165.5-166.5°.

Anal. Calcd. for $C_9H_{15}ClN_2$: C, 57.90; H, 8.10; Cl, 18.99; N, 15.01

Found: C, 58.15; H, 8.21; N, 15.33; Cl, 19.00.*

---

* The average of 2 runs; chlorine by Volhard

The free base was obtained by treating an aqueous solution of the above solid with base and extracting with ether. The combined ether extracts were dried over sodium sulfate and the ether evaporated. The residue was vacuum-distilled, giving 2.0 g. of distillate, b.p. 92-93°/0.7 mm. An infrared spectrum identified the material as o-amino-β-methylphenethylamine (II).

Anal. Calcd. for $C_9H_{14}N_2$: C, 71.96; H, 9.39; N, 18.65

Found: C, 70.86; H, 9.39; N, 18.62; Total, 98.87.*

---

* The average of 2 runs.

The picrate of II was prepared and recrystallized once from ethanol (m.p. 179.5-181.5°). The picrolonate was similarly obtained (m.p. 214-217°). The phenylthiourea was obtained in poor purity only after considerable manipulation (m.p. 112-117°).

5. High-Pressure Hydrogenation of 4-Methylcinnoline In Acidic Solution Using 5% Rhodium on Alumina. Second Hydrogenation.

A second hydrogenation was carried out, using 14.4 g. (0.1 mole) of 4-methylcinnoline, 50 ml. of absolute ethanol containing 8.4 ml. (0.1 mole) of concentrated hydrochloric acid, and 0.5 g. of 5% rhodium on alumina. The reaction was maintained at 104-117° for 21 hours. At ambient temperature the final pressure was 2100 psig, corresponding to 9.0 molar equivalents of hydrogen absorbed. The reactant mixture was filtered; the filtrate was diluted to 700 ml. with water and made basic with 40% aqueous sodium hydroxide. The mixture was extracted with ether and the combined extracts dried over sodium sulfate and potassium carbonate. The ether was evaporated and the residue vacuum-distilled. Two fractions were taken: (1) 0.5 g., b.p. 78-84°/15 mm., n_D^{20} 1.4834; (2) 4.4 g., b.p. 127-131°/5 mm., n_D^{20} 1.5752. Infrared spectra of both fractions were obtained. Material recovery was only 34%, apparently because of physical loss in the extraction and drying steps of the work-up.

Two derivatives of fraction 2 were prepared: (1) hydrochloride, m.p. 198-210° (recrystallized once from ethyl acetate-ethanol); (2) picrate, m.p. 181-182° (recrystallized once from ethanol). These derivatives and the infrared spectrum identified fraction 2 as o-amino-β-methylphenethylamine (II). The first fraction was identified as octahydroskatole (I) by infrared absorption data.

D. High-Pressure Hydrogenation of 4-Methylcinnoline Using Ruthenium Oxide Catalyst.

1. High-Pressure Hydrogenation of 4-Methylcinnoline In Neutral Solution Using Ruthenium Oxide. First Hydrogenation.

A 500-ml. glass reactor liner was charged with 14.4 g. (0.1 mole) of 4-methylcinnoline, 50 ml. of absolute ethanol, and 0.1 g. of ruthenium oxide. The hydrogenation was carried out at a hydrogen pressure of 3000 psig in the Parr High Reactor at 132° for ca. 14 hours. At room temperature the final gauge pressure was 2480 psi, the drop corresponding to 5.2 molar equivalents of hydrogen absorbed. A sample of the filtered ethanolic

reactant solution was chromatographed in the vapor phase on a 5-foot silicone column at 158-161°. Maximum sensitivity at a filament current of 150 ma. was employed. The chromatogram indicated that essentially one compound had been formed. The ethanol was stripped off and the residue vacuum-distilled. Three fractions were taken: (1) 1.5 g., b.p. 43-44°/1.25 mm.; (2) 12.6 g., b.p. 45-47°/1.1 mm.; (3) 1.8 g., b.p. 48-54°/1.1 mm. Gas chromatography showed the first fraction to be solvent. Hence material recovery was 100%.

Fraction 2 was shown by gas chromatography to be the product observed in the initial chromatogram. The material was redistilled (b.p. 30-32°/0.1 mm., n_D^{20} 1.4737). A second redistillation was done (b.p. 25-28°/0.1 mm.) to obtain a constant boiling sample (b.p. 28°/0.1 mm., n_D^{20} 1.4718). The distillate was chromatographed under the same conditions employed for octahydroskatole (I).* Although the chromatogram of the constant-boiling sample was similar to that of I, sufficient differences existed to indicate two different compounds were involved.

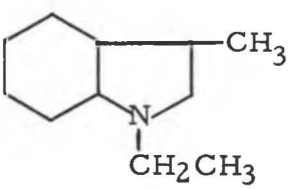
---

* Refer to Page 111.

Although similar, the infrared spectrum of the material was not identical with that of I, which showed much stronger N-H absorption.

The hydrochloride of the distillate could not be obtained; although a solid hydrochloride formed, it liquified almost immediately. The picrolonate was prepared (m.p. 227-230°). The picrolonate of the constant-boiling sample melted at 228-229°.

The free base was identified as 1-ethyloctahydroskatole,



III.

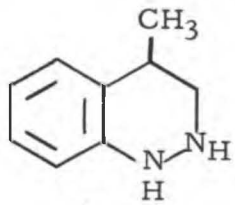
by comparison with an authentic sample (see section III. L. 2.).

2. High-Pressure Hydrogenation of 4-Methylcinnoline In Neutral Solution Using Ruthenium Oxide. Second Hydrogenation

The hydrogenation was repeated at ca. 100° and an initial hydrogen pressure of 3000 psig. for approximately 10 hours; the reactant mixture consisted of 14.4 g. (0.1 mole) of 4-methylcinnoline, 50 ml. of absolute ethanol, and 0.1 g. ruthenium oxide.

The final pressure at room temperature was 2650 psig, corresponding to 3.5 molar equivalents of hydrogen absorbed. The filtered reactant mixture was diluted with water, made basic, and extracted with ether. The ether was dried and evaporated. The remaining liquid was vacuum-distilled. Only one fraction was obtained: 12.4 g., b.p. 120-123°/5 mm., n_D^{20} 1.5970. Material recovery was 86%. Upon standing, the distillate partly solidified.

The hydrochloride and picrate of the material could not be obtained. The compound was identified as 4-methyl-1,2,3,4-tetrahydrocinnoline (IV) by infrared absorption data and elemental analysis.



IV.

Anal. Calcd. for $C_9H_{12}N_2$: C, 72.93; H, 8.16; N, 18.90

Found: C, 73.19; H, 7.41; N, 18.80; Total, 99.40

3. High-Pressure Hydrogenation of 4-Methylcinnoline In Neutral Solution Using Ruthenium Oxide. Third Hydrogenation.

A third hydrogenation was carried out, using 14.4 g. (0.1 mole) of 4-methylcinnoline, 50 ml. of absolute ethanol, and 0.1 g. of ruthenium oxide. Initial hydrogen pressure was 3000 psig. The reactor was maintained at ca. 230° for 17 hours. At ambient temperature the pressure drop was 940 psi, equivalent to 9.4 molar equivalents of hydrogen absorbed. The vent gas had a very strong ammonia-like odor. The filtered reactant mixture was treated as described in the previous reduction (section III. D. 2.). The dried ether solution was concentrated and the residue vacuum-distilled. A single fraction was taken: 12.0 g., b.p. 81-87°/15 mm., n_D^{20} 1.4714. Recovery of material was 83%. The fraction was redistilled to obtain an analytical sample (b.p. 84-85°/15 mm.).

An infrared spectrum of the material identified it as 1-ethyloctahydroskatole (III). An attempt to prepare the methiodide resulted in a small amount of white crystals which was recrystallized once from acetone-ether. Two crops of faintly yellow crystals were obtained (m.p. 234-236.5° and 223-225°, respectively). Both crops turned yellow upon standing, the second more so than the first.

Anal. Calcd. for $C_{11}H_{21}N$: C, 78.97; H, 12.65; N, 8.37

Found: C, 78.08; H, 12.36

4. High-Pressure Hydrogenation of 4-Methylcinnoline In Acidic Solution Using Ruthenium Oxide.

A 500-ml. glass reactor liner was charged with 14.4 g. (0.1 mole) of 4-methylcinnoline, 50 ml. of absolute ethanol, 8.4 ml. (0.1 mole) of concentrated hydrochloric acid, and 0.1 g. ruthenium oxide. The reduction was carried out in the Parr High Reactor at a hydrogen pressure of 3000 psig. Over a 16-hour period the temperature was increased from 104° to 164°. Upon cooling to room temperature the final pressure was 2350 psig, corresponding to 6.5 molar equivalents of hydrogen absorbed. Concentration of the filtered reactant mixture caused crystals of ammonium chloride to precipitate. The concentrated filtrate was diluted with water, made basic, and extracted with ether. The ether extracts were combined and dried over anhydrous sodium sulfate. The ether was evaporated and the residue vacuum-distilled. Two fractions were taken: (1) 6.8 g., b.p. 69-63°/4.5-2.5 mm.; (2) 2.9 g., b.p. 70-115°/2.0-1.6 mm. About 3 g. of material remained undistilled. Including the residue the material recovered was 12.7 g. or 88%.

The first fraction was redistilled to give a single fraction, 1a: 5.4 g., b.p. 31-32°/0.2 mm., n_D^{20} 1.4827. The second fraction also was redistilled; two fractions were taken: (2a) 0.3 g., b.p. 30-64°/0.25 mm., n_D^{20} 1.4842; (2b) 1.1 g., b.p. 67-72°/0.25 mm., n_D^{20} 1.5121. Infrared spectra identified fractions 1a and 2a as octahydroskatole (I). Fraction 2b appeared to be the unknown compound isolated previously (see section III. C. 3., page 113).

E. High-Pressure Hydrogenation of 4-Methylcinnoline Using Platinum Oxide Catalyst.

1. High-Pressure Hydrogenation of 4-Methylcinnoline In Neutral Solution Using Platinum Oxide. First Hydrogenation.

The reduction was carried out in the Parr High Reactor, using a 500-ml. glass reactor liner. The reactant mixture consisted of 14.4 g. (0.1 mole) of 4-methylcinnoline, 50 ml. of absolute ethanol, and 0.1 g. of platinum oxide. The initial hydrogen pressure was 3000 psig. The temperature was raised gradually from 104° to 260° over a 26-hour period. The final pressure at ambient temperature was 2700 psig, corresponding to 3.0 molar equivalents of hydrogen absorbed. The

usual ammonia-like odor was observed in the vent gas. The reactant mixture was filtered and the solvent evaporated under reduced pressure. The residue was vacuum-distilled. A single fraction was taken: 8.0 g., b.p. 90°/0.3 mm (56% recovery). The material was redistilled in order to obtain an analytical sample (b.p. 83-84°/0.15-0.2 mm.).

Anal. Calcd. for $C_9H_{14}N_2$: C, 71.96; H, 9.39; N, 18.65

Found*: C, 72.21; H, 8.69; N, 16.29; Total, 97.19

An infrared spectrum of the material showed it to be o-amino-β-methylphenethylamine (II).

---

* The average of two runs.

The hydrochloride of II was prepared and recrystallized once from ethyl acetate-ethanol (m.p. 208-213°); the solid appeared to be wet. Additional salt was prepared, recrystallized twice, and dried over phosphorus pentoxide in vacuo at 56°.† (m.p. 225-230°, still melting as though it were wet). An infrared spectrum of the salt was obtained.

---

† The drying procedure was standard for all solids submitted for elemental analysis.

Anal. Calcd. for $C_9H_{16}Cl_2N_2$: N, 12.56; Cl, 31.77

Found: N, 12.30; Cl, 31.34 (31.30*)

---

* By Volhard, the average of two runs.

Additional derivatives of II were prepared: picrate, m.p. 183-184° (recrystallized twice from ethanol); picrolonate, m.p. 206-209°; styphnate, m.p. 202-204°; phenylthiourea (after two attempts and in poor yield), m.p. 151-154°. Varous attempts to prepare the acetamide were unsuccessful; although attempts to prepare this derivative from II and acetyl chloride in tetrahydrofuran resulted in the formation of triethylamine hydrochloride, the acetamide could not be isolated.

A sample of II was diazotized at 0° and the resultant mixture poured into 50% aqueous sulfuric acid. The mixture then was steam-distilled in a Wallenberger apparatus (110). The yellow distillate was single phase and possessed a phenolic odor. Distillation was continued until the distillate was essentially odorless and colorless. The distillate was saturated with sodium chloride, extracted with ether, and the ether dried over sodium sulfate. Evaporation of the ether left only a trace of an oil.

The diazotization was repeated in concentrated hydrochloric acid and the reaction mixture poured into hot 50% aqueous sulfuric acid. The resultant mixture was steam-distilled as before. The distillate was extracted with ether; the ether solution was washed with water, dried over Drierite, and evaporated. Again, only a trace of liquid remained. The acidic solution remaining from the steam-distillation was neutralized to pH 6.4 with 40% aqueous sodium hydroxide and steam-distilled. The distillate was extracted with ether and the ether washed with water and dried over Drierite. Evaporation of the ether left an oil, ca. 0.3 g. The material solidified upon standing and was recrystallized twice from Skelly Solve B (m.p. 68-70°). Infrared and ultraviolet spectra identified the material as 4-methylcinnoline.

2. High-Pressure Hydrogenation of 4-Methylcinnoline In Neutral Solution Using Platinum Oxide. Second Hydrogenation.

A second hydrogenation was carried out, using 28.8 g. (0.2 mole) of 4-methylcinnoline, 50 ml. of absolute ethanol, and 0.2 g. of platinum oxide. Initial hydrogen pressure was 3000 psig. Over a period of 8 hours the maximum temperature reached was 262°. The pressure drop at ambient temperature was 600 psi., equivalent to 6.0 molar equivalents of hydrogen absorbed. The reactant mixture was filtered and the solvent distilled at atmospheric pressure. The remaining material was vacuum-distilled. One fraction was taken: 24.1 g., b.p. 73-81°/0.1 mm. The distillate solidified in the receiver. Material recovery was 84%. An infrared spectrum was obtained.

An attempt to sublime a portion of the solidified distillate was unsuccessful. The material was recrystallized twice from Skelly Solve B (m.p. 61.5-62.5°).

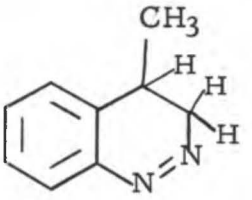
---

(110) Wallenberger, O'Connor, and Moriconi, J. Chem. Ed., 36, 251 (1959).

Anal. Calcd. for $C_9H_{10}N_2$: C, 73.94; H, 6.90; 19.16

Found: C, 71.82; H, 6.26; N, 18.16; Total 96.24

The distillate was identified as 4-methyl-3,4-dihydrocinnoline (V) by comparison with the compound obtained under mild conditions.*



V.

---

* Section III. I.

The distillate was taken up in ether and extracted with 20% aqueous sodium hydroxide. The ether solution was washed with water and dried over potassium hydroxide. The ether was evaporated and the residue vacuum-distilled. The distillate, b.p. 77-78°/0.3 mm., solidified in the condenser and the distillation had to be discontinued. Attempts to recrystallize the material from Skelly Solve B were discouraging. Solubility was limited and purity decreased sharply with each successive crop.

Attempts to prepare the hydrochloride were unsuccessful. The picrate was obtained only with difficulty and in poor yield. Red and yellow granules melting at 97-102° were obtained.

3. High-Pressure Hydrogenation of 4-Methylcinnoline In Acidic Solution Using Platinum Oxide.

4-Methylcinnoline, 14.4 g. (0.1 mole), in 50 ml. of absolute ethanol containing 8.4 ml. (0.1 mole) of concentrated hydrochloric acid and 0.1 g. of platinum oxide, was reduced in the Parr High Reactor at an initial hydrogen pressure of 3000 psig. The temperature was increased to 266° over a 24-hour period. After cooling to room temperature the pressure drop was 400 psig., corresponding to 4.0 molar equivalents of hydrogen absorbed. The filtered reactant mixture was neutralized with 10% aqueous sodium hydroxide, mixed with a saturated solution of sodium chloride, and extracted with ether. The combined ether extracts were washed with water and dried over anhydrous sodium sulfate. The ether was distilled under reduced pressure, and the residue

vacuum-distilled. Two fractions were taken: (1) 4.8 g., b.p. 50-62°/0.4 mm.; (2) 2.3 g., b.p. 62-94°/0.4 mm. The black, tarry residue amounted to ca. 5 g. Total material recovery was 12.1 g. or 84%.

The first fraction was redistilled to give three fractions: (1a) 1.0 g., b.p. 43°/0.1 mm., n_D^{20} 1.5284; (1b) 0.5 g., b.p. 47-38°/0.1 mm.*, n_D^{20} 1.5442; (1c) 2.5 g., b.p. 43-40°/0.1 mm.*, n_D^{20} 1.5541. The second fraction was redistilled also. Two fractions were taken, the second one solidifying in the condenser: (2a) 0.5 g., b.p. 68-72°/0.7 mm.; (2b) b.p. 104-107°/1.5-2.2 mm. Fraction 2a was used as an analytical sample. Infrared spectra were obtained.

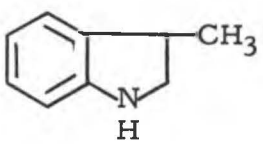
Anal. Calcd. for $C_9H_{11}N$: C, 81.16; H, 8.32; N, 10.52

Found: C, 81.09; H, 8.46; N, 10.50;
Total, 100.05

---

* Curiously, head temperature became lower as the distillation progressed.

Based on the analytical data, fraction 2a tentatively was identified as 2,3-dihydroskatole (VI),



VI.

Since the infrared spectra of all fractions were very similar, VI was assumed to be the only compound involved.

The picrate of fraction 1c was prepared and recrystallized once from ethanol (m.p. 159-163°). The pricolonates of fractions 1a and 1c also were prepared (m.p. 230-232° and 228-230°, respectively).

F. High-Pressure Hydrogenation of 4-Methylcinnoline Using 5% Palladium on Activated Charcoal Catalyst

1. High-Pressure Hydrogen of 4-Methylcinnoline In Neutral Solution Using 5% Palladium on Activated Charcoal

A 500-ml. glass reactor liner was charged with 14.4 g. (0.1 mole) of 4-methylcinnoline, 50 ml. of absolute alcohol,

and 0.5 g. of 5% palladium on activated charcoal. The Parr High Reactor was used. Initial hydrogen pressure was 3000 psig. The reaction was maintained at 200-263° for 6 hours. The pressure drop at room temperature was 650 psi., equivalent to 6.5 molar equivalents of hydrogen absorbed. The vent-gas had an ammoniacal odor. The reactant mixture was filtered and the solvent distilled under reduced pressure. The residual liquid was vacuum-distilled. Four fractions were taken: (1) 1.7 g. b.p. 32-34°/0.2 mm., n_D^{20} 1.4873; (2) 1.0 g., 65-72°/0.2 mm., n_D^{20} 1.4993; (3) 4.2 g., 73-78°/0.2 mm., n_D^{20} 1.5258; (4) 4.8 g., 81-87°/0.2 mm., n_D^{20} 1.5678. The recovery of material represented 81% of the original amount.

Fractions 3 and 4 were identified as o-amino-β-methylphenethylamine (II) by their infrared spectra. Similarly, fractions 1 and 2 were mainly octahydroskatole (I); fraction 2 contained some II.

Fraction 3 was chromatographed (GLPC) at 220° on a 5-foot silicone on Fluoropak 80 column with a filament current of 194 ma. Two main peaks were obtained as summarized below:

Peak	Retention Time	Relative Area[b]
First	4.4 units	10%
Second[a]	8.8	50%
	10.3	40%

[a] Two maxima were present.

[b] Assuming a separate compound for each maximum.

Several derivatives of various fractions were prepared as tabulated below:

Fraction	Derivative	Recrystallization Solvent	M.P., °C.
1	Picrolonate	Ethanol	227-228.5
3	Picrolonate	Ethanol	267-273 dec.
4	Picrate	Ethanol	183-184
4[a]	Hydrochloride	Ethylacetate-ethanol	163-163.5

[a] Combined with other fractions (from other hydrogenations) having identical infrared spectra.

Analyses were obtained on the last two derivatives.

Anal. Calcd. for $C_{15}H_{17}N_5O_7$: C, 47.49; H, 4.52; N, 18.46; O, 29.52

Found: C, 47.63; H, 4.52; N, 19.29; O, 29.0; Total, 100.44

Anal. Calcd. for $C_9H_{15}ClN_2$: C, 57.90; H, 8.09; Cl, 18.99; N, 15.01

Found: C, 57.50; H, 8.08; Cl, 19.1; N, 14.44; Total, 99.12

A portion of the hydrochloride of II was diazotized in concentrated hydrochloric acid and the mixture poured into hot 50% aqueous sulfuric acid. The resultant mixture was diluted with water, made basic with 40% aqueous sodium hydroxide, and extracted continuously with benzene for 23 hours. The benzene was evaporated, leaving ca. 1.0 g. of a red-brown, oily material, which was extracted with boiling Skelly Solve B. After decanting, concentrating and cooling, this extract yielded ca. 0.1 g. of tan solid (m.p. 121-124°). The tarry, insoluble residue could not be worked up. Bromination of the tar resulted in another tar.

The diazotization was repeated, using the same procedure outlined for the preparation of 4-methylcinnoline (106). Thus 2 g. of the hydrochloride was dissolved in 12.2 ml. of water containing 1.4 ml. of concentrated sulfuric acid. A solution of sodium nitrite, 1.2 g. in 2.8 ml. of water, was added dropwise at 0° until an excess of nitrous acid was present, which required almost all of the nitrite solution. The reactant mixture was diluted to 180-200 ml. with ice and water and allowed to stand 3 days in the dark. The solution was neutralized with base and extracted continuously with benzene. The benzene was evaporated, leaving a yellow-brown solid (1.5 g., m.p. 124.5-126.5°) which gave a positive test for nitrogen. A sample was recrystallized twice from Skelly Solve B (m.p. 127.5-128.5°).

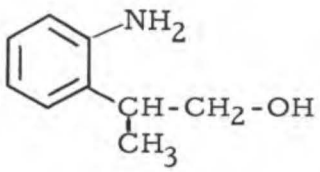
Anal. Calcd. for $C_9H_{13}NO$: C, 71.49; H, 8.67; N, 9.26; O, 10.58

Found: C, 71.70; H, 8.57; N, 9.22; O*, 10.51

---

* By difference.

Based on the analytical data, the compound was assigned the structure,



2-(o-aminophenyl)-1-propanol.

2. High-Pressure Hydrogenation of 4-Methylcinnoline In Acidic Solution Using 5% Palladium on Activated Charcoal.

A 500-ml. glass reactor liner was charged with 14.4 g. (0.1 mole) of 4-methylcinnoline, 50 ml. of absolute ethanol, 8.4 ml. (0.1 mole) of concentrated hydrochloric acid and 0.5 g. of 5% palladium on activated charcoal. Reduction was carried out in the Parr High Reactor at 3000 psig. hydrogen pressure. The temperature was increased from 100° to 222° over a 4-hour period. The pressure drop of 450 psi. was equivalent to 4.5 molar equivalents of hydrogen absorbed. The filtered reactant mixture was diluted with water, made basic with 40% aqueous sodium hydroxide, and extracted with ether. The combined ether extracts were washed with water and dried over anhydrous sodium sulfate. The ether was evaporated and the residue vacuum-distilled. Two fractions were taken: (1) 1.7 g., b.p. 69-92°/0.3 mm., n_D^{20} 1.5750. Recovery was 9.3 g. or 65%.

The two fractions were identified by their infrared spectra as octahydroskatole (I) and o-amino-β-methylphenethylamine (II), respectively. The picrolonate of fraction 1 was prepared and recrystallized twice from ethanol (m.p. 229-231°). Similarly, the picrate of fraction 2 was prepared (m.p. 181.5-182.5°).

G. High-Pressure Hydrogenation of 4-Methylcinnoline Using 5% Rhodium on Activated Charcoal Catalyst.

1. High-Pressure Hydrogenation of 4-Methylcinnoline In Neutral Solution Using 5% Rhodium on Activated Charcoal.

The reduction was carried out in the Parr High Reactor. The reactant mixture consisted of 14.4 g. (0.1 mole) of 4-methylcinnoline, 50 ml. of absolute ethanol, and 0.5 g. of 5% rhodium

on activated charcoal. The initial hydrogen pressure was 3000 psig. The temperature was increased from 96° to 242° over a 7-hour period, the ratio $\Delta GP/\Delta NRP$ becoming constant. The pressure at room temperature was 2400 psig., corresponding to 6.0 molar equivalents of hydrogen absorbed. The reactant mixture was filtered and the solvent distilled. The residue was vacuum-distilled, giving 3 fractions: (1) 2.0 g., b.p. 30-32°/0.4 mm. n_D^{20} 1.4812; (2) 1.0 g., b.p. 75-87°/0.4 mm., n_D^{20} 1.5033; (3) 9.2 g., b.p. 88-92°/0.4 mm., n_D^{20} 1.5720. Material recovery was 85%.

Fractions 1 and 3 were identified by their infrared spectra as octahydroskatole (I) and o-amino-β-methylphenethylamine (II), respectively. Fraction 2 was a mixture of I and II. The picrate of fraction 3 was prepared and recrystallized twice from ethanol (m.p. 181.5-182.5°). The picrolonate of fraction 1 also was prepared (m.p. 226-229°). The second fraction would not form a crystalline picrolonate.

2. High-Pressure Hydrogenation of 4-Methylcinnoline In Acidic Solution Using 5% Rhodium on Activated Charcoal.

The hydrogenation was done in the Parr High Reactor. The reactant mixture consisted of 14.4 g. (0.1 mole) of 4-methylcinnoline, 50 ml. of absolute ethanol, 8.4 ml. (0.1 mole) of concentrated hydrochloric acid, and 0.5 g. of 5% rhodium on activated charcoal. The initial hydrogen pressure was 3000 psig. The temperature was increased from 97° to 232° over a 7-hour period, the ratio $\Delta GP/\Delta NRP$ becoming constant. The pressure drop at room temperature was 610 psi., equivalent to 6.1 molar equivalents of hydrogen absorbed. The reactant mixture was filtered, diluted with water, made basic, extracted with ether, and the ether washed with water. After drying over anhydrous sodium sulfate the ether was evaporated. The remaining liquid was vacuum-distilled. Two fractions were taken: (1) 8.7 g., b.p. 35-38°/0.6 mm., n_D^{20} 1.4820; (2) 2.0 g., b.p. 95-100°/0.6 mm., n_D^{20} 1.5478. Recovery was 74%.

The infrared spectra of the two fractions identified them as octahydroskatole (I) and o-amino-β-methylphenethylamine (II), respectively. The picrate of fraction 2 was prepared (m.p. 181-182°). Attempts to prepare the phenylthiourea and picrolonate of fraction 2 were unsuccessful. The picrolonate of fraction 1 was prepared (m.p. 228-229°).

The second fraction was chromatographed (GLPC) at 220° on a 5-foot silicone on Fluoropak 80 column (filament current, 194 ma.). Two peaks were obtained. The retention

time for the first peak was 4.3 min. The retention time of the second peak was 11.0 min., with a slight shoulder at 8.7 min. The relative areas of the two bands were approximately 20% and 80%, respectively.

H. Low-Pressure Hydrogenation of 4-Methylcinnoline In Acidic Solution Using Platinum Oxide Catalyst.

The Parr Low Reactor was employed. The reactant mixture consisted of 14.4 g. (0.1 mole) of 4-methylcinnoline, 100 ml. of absolute ethanol, 8.4 ml. (0.1 mole) of concentrated hydrochloric acid, and 0.1 g. of platinum oxide. The reduction at 60 psig. hydrogen pressure was carried out at room temperature. After 24 hours reaction was complete, the final pressure being 42.5 psig. The pressure drop of 17.5 psi. was equivalent to 2.1 molar equivalents of hydrogen absorbed. The filtered reactant mixture was diluted with water, made basic, extracted with ether, and the ether dried. The ether was evaporated and the liquid residue vacuum-distilled. A single fraction was taken: 11.2 g., b.p. 124-128°/5 mm., n_D^{28} 1.5927. Kettle residue was ca. 1 g. Recovery was 85%.

Anal. Calcd. for $C_9H_{12}N_2$: C, 72.94; H, 8.16

Found: C, 71.07; H, 8.18.

The infrared spectrum of the material was identical with that of 4-methyl-1,2,3,4-tetrahydrocinnoline (IV) prepared by Dr. H. Smith Broadbent (108).

The hydrochloride of IV was prepared and recrystallized once from ethyl acetate-ethanol (m.p. 164-166°). The phenylthiourea also was prepared (m.p. 203-5.205°). The picrolonate could not be obtained.

Various derivatives of IV were prepared from an authentic sample prepared by Dr. H. Smith Broadbent: hydrochloride, m.p. 151.5-153.5° (recrystallized once from ethyl acetate-ethanol); phenylthiourea, m.p. 204.5-206° (recrystallized once from ethanol); picrolonate, m.p. 154-155°.

I. Low-Pressure Hydrogenation of 4-Methylcinnoline In Acidic Solution Using 5% Rhodium on Alumina Catalyst.

The reduction was carried out in the Parr Low Reactor. The reactant mixture consisted of 14.4 g. (0.1 mole) 4-methylcinnoline, 100 ml. glacial acetic acid, and 0.5 g. 5% rhodium on alumina. The initial hydrogen pressure was 60

psig. The reduction was carried out at room temperature over an 11-hour period. The observed pressure drop was 8.5 psig., equivalent to 1.0 molar equivalent of hydrogen absorbed. The filtered reactant mixture was diluted with water and made basic with 40% aqueous sodium hydroxide. A grey-brown solid immediately precipitated. The solid was filtered and dried (m.p. 60-62°). The material weighed 14.5 g., indicating quantitative recovery.

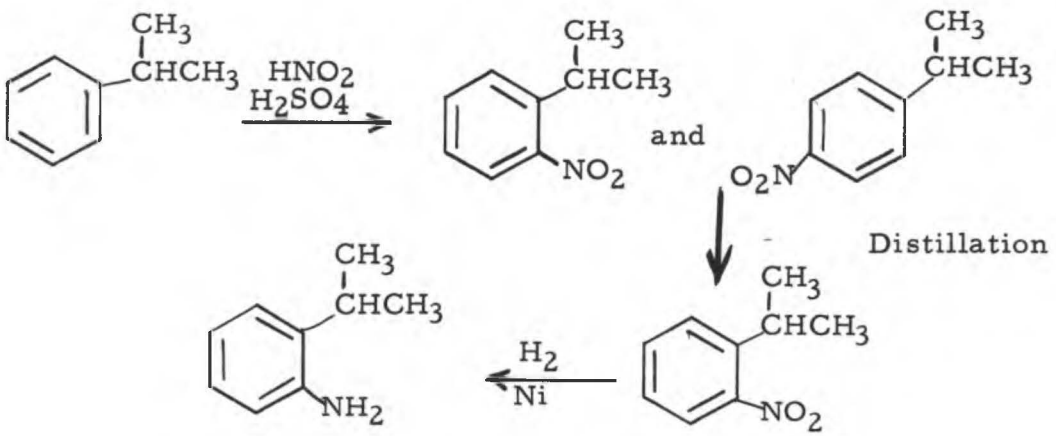
The material was identified as 4-methyl-3,4-dihydrocinnoline (V), based on hydrogen take-up and infrared absorption data.

The 4-methyl-3,4-dihydrocinnoline was recrystallized from water, although solubility was low (m.p. 60-60.5°). The picrate was prepared (m.p. 102° dec.). The hydrochloride also was prepared (m.p. 95-99° dec.) Both the free base and its hydrochloride appeared to deteriorate upon standing.

A sample of the hydrochloride was titrated by the Volhard procedure, giving 18.72% chlorine (calcd., 19.41%).

J. Synthesis of o-Cumidine.

A literature survey indicated that cumeme could be nitrated to give a 30% yield of the o-isomer (111). Furthermore, the o- and p-isomers can be separated by distillation at reduced pressure(112). Accordingly, the following reaction scheme was chosen for the preparation of o-cumidine:



(111) Brown and Bonner, J. Am. Chem. Soc., 76, 605 (1954).

(112) Sterling and Bogert, J. Am. Chem., 4, 20 (1939).

1. Nitration of Cumene (113).

A 500-ml., 3-necked, r.b. flask was fitted with stirrer, condenser, and pressure-equalizing dropping funnel and charged with 120 g. (1 mole) of cumene. The nitration mixture, consisting of 90 g. (1 mole) of concentrated nitric acid, 264 g. of concentrated sulfuric acid, and 49 g. of water, was added to the vigorously stirred cumene at 25-30°. The addition required 4.5 hours. The reactant mixture was stirred an additional 1.5 hours at 25-30° and then 1 hour at 40°. The reactant mixture was poured over 500 g. of ice and the nitration products extracted with benzene. The combined benzene extracts were washed with 5% aqueous sodium bicarbonate and then with water. The benzene solution was dried over anhydrous sodium sulfate. The benzene was evaporated and the residue vacuum distilled. Three fractions were taken: (1) 2.3 g., b.p. 32-43°/12-13 mm., n_D^{20} 1.4900; (2) 52.9 g., b.p. 119-122°/12-13 mm., n_D^{20} 1.5282; (3) 76.4 g., b.p. 126-131°/12-13 mm., n_D^{20} 1.5337. Fraction 1 was unchanged cumene. The last two fractions were o- and p-nitrocumene, respectively. The following data are recorded in the literature as indicated:

Compound	B.p., °C/mm.	n_D^t	Ref.
o-Nitrocumene	115/13	1.5248^{20}	111
		1.5259^{20}	114
	117-119/12	1.5237^{20}	112
p-Nitrocumene	134/13	1.5369^{20}	111
		1.5367	114
	128/12		112

The refractive indices of fractions 2 and 3 show that poor separation was obtained. Hence, the second fraction was redistilled at 115-119°/12-13 mm., n_D^{20} 1.5258.

The yield of mononitration products was 78%. The yield of crude o-nitrocumene was 32% and that of crude p-isomer, 46%.

---

(113) Nelson and Brown, J. Am. Chem. Soc., 73, 5605 (1951)

(114) Brown and Reagan, , J. Am. Chem. Soc., 69, 1032 (1947)

2. Reduction of o-Nitrocumene.

The reduction was carried out in the Parr Low Reactor. The 500-ml reaction bottle was charged with 18.1 g. (0.11 mole) of o-nitrocumene, 120 ml. of absolute ethanol, and 4-6 g. of Raney nickel W-2 catalyst. The initial hydrogen pressure was 60 psig. The reaction was carried out at room temperature. After 13 hours the observed pressure drop was 10 psi; hence a small amount of platinum oxide catalyst was added and the system recharged to 50 psig. After 3 hours the gauge pressure was 30 psi. (the theoretical pressure drop was 28 psi.). Hence, the reduction was stopped. The reactant mixture was filtered. The filtrate was diluted with water, made basic with 40% aqueous sodium hydroxide, and extracted with ether. The combined ether extracts were dried over anhydrous sodium sulfate and the ether evaporated. The residue was vacuum distilled. A single fraction was taken: b.p. 110-117°/24-25 mm.; n_D^{25} 1.5423; n_D^{20} 1.5451. The infrared spectrum of the material showed strong N-H absorption. A portion of the material was redistilled at 117°/24-25 mm., n_D^{25} 1.5438; the material was submitted for analysis. Attempts to prepare the picrate and acetanilide of the material were unsuccessful.

Anal. Calcd. for $C_9H_{13}N$: C, 80.00; H, 9.64

Found: C, 79.5; H, 9.6.

The analytical data were only approximate since most of the material apparently was lost during shipment to the analytical laboratory.

In order to be certain that reduction of the benzene ring had not occurred, the reduction was repeated. The charge consisted of 18.1 g. (0.11 mole) o-nitrocumene, 100 ml. absolute ethanol, and 4-6 g. Raney nickel W-2 catalyst. The initial hydrogen pressure was 60 psig. After 4.5 hours at room temperature, no pressure drop was observed. Hence, an additional 6-8 g. of the nickel catalyst was added and the reactor recharged to 60 psig. After 33 hours the pressure had leveled off at 29 psig. The reactant mixture was filtered and the filtrate treated as before. The ether was evaporated and the residue vacuum-distilled. All of the material was not distilled; a constant-boiling sample was collected: 9.0 g., b.p. 120-121°/24-25 mm., n_D^{20} 1.5437. The infrared spectrum was identical with that of the material isolated in the first reduction. The picrate of the distillate could not be obtained. The hydrochloride was prepared, m.p. 254-257° (sealed tube). The literature value is 182° [recrystallized from water (115)]. The density of the distillate was determined to be

---

(115) v. Braun, Bayer, and Blessing, Ber., 57B, 397 (1924) [C.A., 18, 2162 (1924)]

$0.9444^{29.5}$ and $0.9478^{29.5}$ (two runs) [literature value (115), 0.9760^{12}].

Thus, the products from both reductions were identical and considered to be o-cumidine.

K. Synthesis of 2-Isopropylcyclohexylamine.

In view of the small amount of material to be reduced, the autoclave used was a Magnadash apparatus, agitated by a magnetically-actuated stirrer. The charge consisted of 6.2 g. (0.046 mole) of o-cumidine, 50 ml. of absolute ethanol, and 0.1 g. of ruthenium oxide catalyst. The initial hydrogen pressure was 3000 psig. The reaction was maintained at 100-132° for 6 hours. At ambient temperature the pressure drop was 300 psi. (the theoretical drop was 240 psi.). The filtered reactant mixture was diluted to 700 ml. with water, made basic with 40% aqueous sodium hydroxide, and extracted with ether. The combined ether extracts were dried over anhydrous potassium carbonate. The ether was evaporated and the residue vacuum distilled. One fraction was taken: 4 g., b.p. 79-80°/15 mm., n_D^{20} 1.4620 [lit. (116) b.p. 68°/15 mm.].

The infrared spectrum of the distillate exhibited two N-H bands at 2.92 and 3.00 μ. The density of the distillate was 0.8590^{32} [lit. value (116) 0.8790^{17}]. The compound was assumed to be 2-isopropylcyclohexylamine.

L. Synthesis of Skatole and Related Compounds.

1. Preparation of Skatole (Attempted).

Two independent procedures were tried, both of which failed. The first procedure was that of Cornforth and Robinson (117) and involved the methylation of indole with methanolic sodium methoxide in an autoclave at 210-220°. The second method was the Fischer indole synthesis as outlined by Atkinson, Simpson, and Taylor (118). The intermediate propianaldehyde phenylhydrazone was prepared in 86% yield.

A commercial sample of skatole was later obtained.

---

(116) v. Braun and Bayer, Ber., 58B, 387 (1925) [C.A., 19, 1862 (1925)].

(117) Cornforth and Robinson, J. Chem. Soc., 1942, 680.

(118) Atkinson, Simpson, and Tayler, J. Chem. Soc., 1954, 165.

2. Preparation of 1-Ethyloctahydroskatole.

The procedure of Adkins and Coonradt (119) was followed except that ethanol was used as solvent in place of dioxane. The Parr High Reactor 500-ml. glass liner was charged with 7.4 g. (0.056 mole) of skatole, 70 ml. of absolute ethanol, and ca. 4 g. of Raney nickel W-2 catalyst. The reduction was carried out at 3800 psig. hydrogen pressure and 209-236° over a 2-hour period. The pressure drop at ambient temperature was 700 psi. The theoretical drop was 500 psi. The reactant mixture was filtered, diluted with water, made basic, and extracted with ether. The combined ether extracts were dried over anhydrous potassium carbonate. The ether was evaporated and the residue vacuum-distilled. One fraction was obtained: 5.7 g., b.p. 115-127°/15 mm., n_D^{20} 1.4668.

The infrared spectrum of the fraction showed no N-H absorption. The methiodide of the distillate was prepared, m.p. 202-205° [lit. m.p. 197° (116)]. After one recrystallization from acetone-ether, the first crop of crystals melted at 206.5-208.5°; four successive crops melted progressively lower in ca. 6° decrements. The compound obtained above was assumed to be 1-ethyloctahydroskatole on the basis of method of preparation and infrared absorption data.

3. Preparation of Octahydroskatole.

The reduction was carried out in the Parr High Reactor. The charge consisted of 5 g. (0.038 mole) of skatole, 30 ml. of dioxane, and 3-4 g. of Raney nickel W-2 catalyst. The initial hydrogen pressure was 3800 psig. The reaction was maintained at 204-227° for ca. 3 hours. The final pressure at room temperature was 3550 psig. The theoretical pressure drop was 296 psi. The filtered reactant mixture was diluted with water, made basic, and extracted with ether. The combined ether extracts were dried over anhydrous potassium carbonate and the ether evaporated. The residue was vacuum-distilled. One fraction was collected: 3.6 g., b.p. 84-88°/15 mm. The material was redistilled: 2.7 g., b.p. 81-85°/15 mm., n_D^{20} 1.4758. [lit. (116) b.p., 75°/15 mm.]

The distillate was assumed to be octahydroskatole on the basis of method of preparation and infrared absorption data.

---

(119) Adkins and Coonradt, J. Am. Chem. Soc., 63, 1563, (1941)

M. Determination of pka Values.

The procedure employed was simple: the amine was titrated in 66% aqueous dimethylformamide (DMF), using 0.1043 N hydrochloric acid. Measurements of pH were made with a Photovolt Model 110 meter, serial 20234. A Magnestir was employed for efficient mixing and was shut off during readings. The data obtained were plotted and the pka value(s) determined from the titration curve. For the purpose of this thesis it was not considered necessary to tabulate the data nor to reproduce the graphs.

Before titrating octahydroskatole (I) and o-amino-β-methylphenethylamine (II), two known compounds were run in order to test the procedure.

1. Titration of Aniline.

A solution of aniline, 0.3402 g. (3.65 meg.) in 40 ml. of 66% aqueous DMF, was titrated with 0.1043 N hydrochloric acid. A graph was prepared from the recorded data. The pKa was determined to be 4.58 [lit. (120) value, 4.58].

2. Titration of Phenethylamine.

Phenethylamine, 0.4675 g. (3.86 meg.), was dissolved in 100 ml. of 66% aqueous DMF and titrated with the standard acid. The data were plotted as before. End-point inflection was excellent. The pK_a was estimated to be 9.24 [lit. (120) value, 9.83].

These two trial runs demonstrated the validity of the procedure.

3. Titration of Octahydroskatole

A solution of octahydroskatole (I), 0.4052 g. in 100 ml. of 66% aqueous DMF, was titrated with 0.1043 N hydrochloric acid. The data were plotted. Excellent end-point inflection was obtained, from which an end-point volume of 25.8 ml. of acid was estimated. Using one-half of this value, a pK_a of 10.09 was read from the graph. Using the straight-line portion of the titration curve, the pK_a was estimated as 10.14. The end-point volume of 25.8 ml. corresponds to an equivalent weight of 151 g./eg. (Theoretical equivalent weight, 139 g./eg.).

---

(120) Wenzig, Ann., 239, 242 (1887)

4. Titration of o-Amino-β-methylphenethylamine.

A solution of 0.2551 g. of o-amino-β-methylphenethylamine (II) in 100 ml. of 66% aqueous DMF was titrated. The data were plotted. Only one endpoint inflection was obtained; the volume of acid required was estimated as 9.95 ml. Assuming that the end-point inflection represented neutralization of the more basic of the two basic centers, complete neutralization would require 19.9 ml. of acid. The pK_a values were estimated by reading from the graph the pH values at acid volumes lying midway between 0 and 9.95 ml., and 9.95 ml. and 19.9 ml. These values were 8.92 and 3.68, respectively. The preceding assumption requires a molecular weight of 244 g./mole.

N. Nonaqueous Titrations.

1. Standardization of Perchloric Acid.

The procedure of Fritz (121) was followed. The perchloric acid solution was prepared by adding 12 ml. of 72% perchloric acid and 30 ml. of acetic anhydride to 300 ml. of glacial acetic acid and diluting the resultant solution to 1400 ml. with additional acetic acid. The solution was allowed to stand overnight.

The perchloric acid solution was standardized by titrating against potassium acid phthalate. The phthalate was dissolved in 60 ml. of warm acetic acid. To the cooled solution was added 2 drops of 0.2% methyl violet in chlorobenzene. Titration was to the first disappearance of the violet tinge. The end-point was exceptionally sharp and easily overshot. The average of the three runs was 0.0976 N. This standardized perchloric acid solution was then used in each titration, following the procedure of Fritz (121).

2. Titration of Aniline In Acetic Acid.

The amine was dissolved in 50 ml. of acetic acid and several drops of the methyl violet indicator solution added. The titration was carried out to the first disappearance of violet. The titration gave an equivalent weight for aniline of 94.52 g/eg. The theoretical value for aniline is 93.12 g/eg.

---

(121) Fritz, "Acid-Base Titrations in Non-Aqueous Solvents," G. Fredrick Smith Chemical Company, Columbus, Ohio, 1952.

3. Titration of Aniline In Chlorobenzene.

The base was dissolved in 50 ml. of chlorobenzene, indicator added, and titrated to the first loss of violet. An equivalent weight of 95.77 g./eg. was calculated. The titration was continued, with a second end-point being taken as the first appearance of green. The equivalent weight was reduced to 92.63 g./eg. Carrying the titration to the first appearance of green gave the better value (theoretical value, 93.12 g./eg.). In general, color transitions were much sharper in chlorobenzene than in acetic acid. However, when carried to the first loss of violet as recommended, the titration in acetic acid was more accurate.

4. Titration of Phenethylamine In Chlorobenzene.

The amine was dissolved in 50 ml. of chlorobenzene, indicator added, and the titration carried to the first loss of violet. An equivalent weight of 120.6 g./eg. was obtained. The calculated value is 121.2 g./eg. On the basis of the preceding titrations, octahydroskatole (I) and o-amino-β-methylphenethylamine (II) were titrated in chlorobenzene.

5. Titration of Octahydroskatole in Chlorobenzene.

Titration of octahydroskatole in chlorobenzene gave an equivalent weight of 140.5 g./eg. (the average of two runs). The theoretical value is 139 g./eg.

6. Titration of o-Amino-β-methylphenethylamine In Chlorobenzene.

This compound was titrated as outlined previously and an equivalent weight of 127.0 g./eg. (the average of two runs) was calculated. Since this compound is dibasic, the molecular weight must be 254 g./mole.

7. Titration of 1-Ethyloctahydroskatole In Chlorobenzene.

The material was dissolved in chlorobenzene and titrated with perchloric acid. The equivalent weight of 153.6 g./eg. (the average of two runs) was calculated. The theoretical value is 167 g./eg.

IV. DISCUSSION

Seven different compounds have been obtained in the hydrogenation of 4-methylcinnoline under various conditions. Six of these have been assigned structures. The results of the hydrogenations are summarized in Table 12 (yields are given as weight-per cent since in several cases yields based on structure cannot be calculated).

Table 12.

Summary of Results of the Hydrogenation of 4-Methylcinnoline Under Various Conditions.

Catalyst	Initial Pressure, Psig.	Temp. Range, °C	Reaction Time Hrs.	Solvent	Products	Yield Grams	Yield Wt.-%
Rh/Al_2O_3[a]	60	Ambient	11	HOAc	V[b]	14.5	100
	2000	111-132	5	EtOH	II[c]	7.0	49
Rh/Al_2O_3	2000	25-200	104	EtOH	I[d]	8.1	56
		200-232	8	EtOH	I	5.9	41
					II	1.9	13
					Unknown	0.9	6
	3000	110	22	EtOH-HCl[e]	II	8.8	5.
		104-117	21	EtOH-HCl	II	4.4	31
					I	0.5	3
RuO_2[f]	3000	ca. 100	10	EtOH	IV[g]	12.4	86
		132	14	EtOH	III[h]	12.6	88
		104-164	16	EtOH-HCl	I	6.8	47
					Unknown	2.9	20
		ca. 230	17	EtOH	III	12.0	83
Pd/C[i]	3000	100-222	4	EtOH-HCl	II	7.6	53
					I	1.7	12
		200-263	6	EtOH	II	9.0	63
					I	2.7	19

Catalyst	Initial Pressure, Psig.	Temp. Range, °C	Reaction Time Hrs.	Solvent	Products	Yield Grams	Yield Wt.-%
Rh/c[j]	3000	97-232	7	EtOH-HCl	I	8.7	60
					II	2.0	14
		96-242	7	EtOH	II	9.2	64
					I	2.0	14
PtO_2[k]	60	Ambient	24	EtOH-HCl	IV	11.2	78
	3000	104-260	26	EtOH	II	8.0	56
		25-262	8	EtOH	V	24.1	84
		25-266	24	EtOH-HCl	VI[l]	7.1	49

a 5% Rhodium on alumina.
b 4-Methyl-3,4-dihydrocinnoline.
c o-Amino-β-methylphenethylamine.
d Octahydroskatole.
e 0.1 Mole hydrochloric acid/0.1 mole substrate.
f Ruthenium oxide.
g 4-Methyl-1,2,3,4-tetrahydrocinnoline.
h 1-Ethyloctahydroskatole.
i 5% Palladium on activated charcoal.
j 5% Rhodium on activated charcoal.
k Platinum oxide.
l 2,3-Dihydroskatole.

A. Catalysts.

Exact comparisons of the various catalysts are not possible. Several contributing factors are the poor material recoveries usually obtained, the lack of standard conditions, and the poor control over all reaction variables. However, definite trends are evident which permit some generalizations.

1. 5% Rhodium on Alumina.

In neutral ethanolic solutions, low-temperature hydrogenations ($\sim 132°$) favored o-amino-β-methylphenethylamine (II) formation, while higher temperatures ($> 200°$) gave mainly octahydroskatole (I).

Low-temperature reductions in acidic ethanolic solution also favored formation of II. The effect of high temperatures at low pressures was not determined.

2. Ruthenium Oxide.

Hydrogenations in neutral ethanolic solution gave 1-ethyloctahydroskatole (III), independent of the reaction temperature. In acidic solution, the main product was octahydroskatole (I), with formation of 20% of an unknown compound. The formation of 4-methyl-1,2,3,4-tetrahydrocinnoline (IV) in a low-temperature run in neutral solution probably was due to reactor leakage of hydrogen during the reaction; the resultant pressure drop may have been sufficient to prevent further reaction.

3. 5% Palladium on Activated Charcoal.

o-Amino-β-methylphenethylamine (II) along with lesser amounts of octahydroskatole (I) was the main product, in both neutral and acidic ethanolic solutions. All runs were at high temperatures ($> 200°$).

4. 5% Rhodium on Activated Carbon.

In neutral ethanolic solution the main product was o-amino-β-methylphenethylamine (II). In acidic solution the main product was octahydroskatole (I). All runs were at high temperatures.

5. Platinum Oxide.

The results with this catalyst were the same as in the preceding section (IV.A.4.). In one instance (neutral ethanolic solution), 4-methyl-3,4-dihydrocinnoline (V) was obtained. This probably was the result of hydrogen leakage during the reaction.

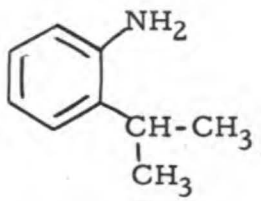
6. General.

Of all the catalysts, only the results with 5% palladium on activated charcoal were independent of the pH. The results with ruthenium oxide also were pH-independent in that o-amino-β-methylphenethylamine (II) was never isolated. However, in neutral ethanolic solution 1-ethyloctahydroskatole was the main product.

Both 5% rhodium on activated charcoal and platinum oxide gave II. in neutral solution and octahydroskatole (I) in acidic solution. The results with 5% rhodium on alumina were the reverse, except for one low-temperature run in neutral solution which gave II.

B. Octahydroskatole.

Based upon the first analytical data obtained, the empirical formula $C_9H_{13}N$ was calculated and the structure of o-cumidine,



tentatively assigned in preference to 2-phenyl-n-propylamine.

Difficulties soon were encountered. The infrared spectrum of the material was found to lack aromatic character. The material gave a negative test for primary amines, using nickel chloride and 5-nitrosalicylaldehyde. However, a test for secondary amines* (sodium nitroprusside and acetaldehyde) was positive, while another test (nickel chloride, carbon disulfide, and ammonium hydroxide) was negative.

An attempt to prepare the 3-nitrophthalimide (122) of the compound resulted in a grey solid after two recrystallizations from benzene-ethanol (m.p. 188-188.5°). The analytical data required

---

* F. Feigl, "Spot Tests In Organic Analysis," 5th English Ed., Elsevier Publishing Company, Amsterdam, 1956, pp. 260-262.

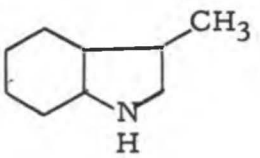
---

(122) J. W. Alexander and S M. McElvain, J. Am. Chem. Soc., 60, 2285 (1938)

an empirical formula of $C_{17.78}H_{21.20}N_{2.00}O_{5.06}$, which indicates formation of a phthalamic acid. Titration of this derivative with standard base gave a neutralization equivalent of 338. Thus a secondary amine with a molecular weight of 145 was suggested.

Additional analytical data led to an empirical formula of $C_{8.62}H_{15.82}N_{1.00}$ for the material. This formula required non-aromaticity but was not compatible with 2-isopropylcyclohexylamine.

A study of the literature suggested a plausible explanation. Atkinson and Simpson (123) obtained skatole in 65% yield upon reducing 4-methylcinnoline or 7-chloro- and 6-chloro-4-methylcinnoline with sodium in ethanol. Thus our compound conceivably could be octahydroskatole:



However, o-cumidine and 2-isopropylcyclohexylamine cannot be ruled out because the reduction of skatole over nickel at 250° in decalin is reported to give the cyclohexylamine (116).

Titration of our compound in 66% aqueous dimethylformamide gave a pK_a of 10.14, thus eliminating o-cumidine as a possibility. These data indicated an equivalent weight of 151. A non-aqueous titration in chlorobenzene, using perchloric acid in acetic acid, gave an equivalent weight of 140.5.

Although all of the possible compounds were known, reported derivatives of the compound either could not be obtained or were isolated in low purity.

This material was finally proved to be octahydroskatole when compared with an authentic sample obtained by the hydrogenation of skatole over Raney nickel.

C. o-Amino-β-methylphenethylamine.

Since two basic centers were present in this compound as shown by elemental analyses and Volhard titrations of the hydrochloride, the most logical possibility for its structure was that

---

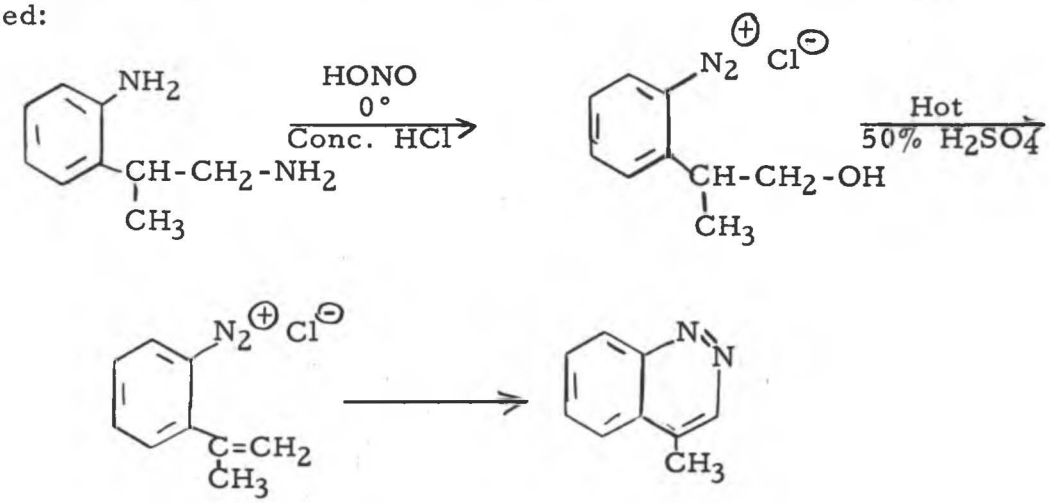
(123) C. M. Atkins and J. C. E. Simpson, J. Chem. Soc., 1947, 1649

of o-amino-β-methylphenethylamine, a new composition of matter.

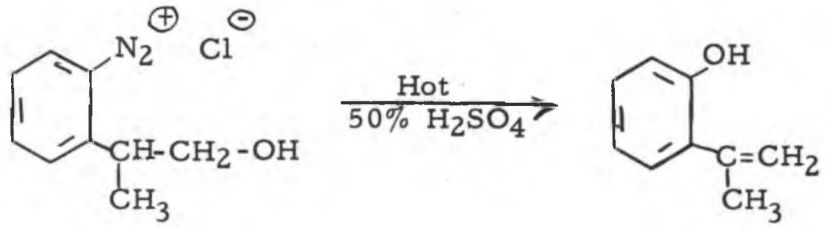
Although elemental analyses of the free base usually were poor, analyses of the hydrochloride and picrate agreed reasonably well with the calculated values. Volhard titrations of the dihydrochloride and monohydrochloride (obtained directly from the reaction mixture of a run in acidic solution) gave excellent chlorine values.

The infrared spectrum of the free base possessed aromatic character and had two N-H bands at 2.96 μ and 3.10 μ.

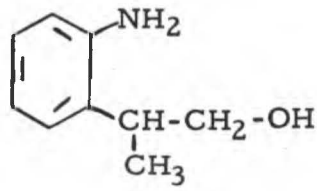
Diazotization of the compound in concentrated hydrochloric acid gave 4-methylcinnoline, identified by melting point, infrared and ultraviolet spectra. The following reaction scheme was postulated:



o-Isopropenylphenol could be expected to form to some extent:



Diazotization of o-amino-β-methylphenethylamine (II) as in the preparation of 4-methylcinnoline also gave a solid, m.p. 127.5-128.5°. From the elemental analysis, the formula $C_{9.06}H_{13.0}N_{1.00}O_{1.00}$ was calculated. The structure



fits the data very well. This compound has not been reported in the literature.

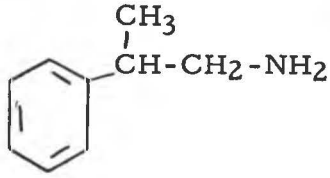
The pK_a determination and non-aqueous titration (in chlorobenzene with perchloric acid) of II gave equivalent weights of 122 g./eg. and 127 g./eg.) respectively. The calculated equivalent weight of II is 75 g./eg. The pK_a titration gave only one inflection, from which pK_a's of 8.92 and 3.68 were estimated.

Final proof of structure will require synthesis of o-amino-β-methylphenethylamine (II) by an unambiguous route.

D. Unknown Compound.

Although isolated on two different occasions, this compound was obtained in the smallest total amount, 3.8 g., of the 7 product compounds.

The infrared spectrum of the material is unique, but similar to that of o-amino-β-methylphenethylamine (II). The refractive index was found to be 1.5174^{20} and 1.5121^{20}. Nothing else is known. Possibly the material is not a separate entity but a mixture of octahydroskatole (I) and II. Interestingly, the refractive index is close to that of β-methylphenethylamine, 1.5255^{20} (124).



E. 1-Ethyloctahydroskatole.

This material was obtained only from the hydrogenation of 4-methylcinnoline with ruthenium oxide in neutral ethanolic solution. The infrared spectrum of the compound was quite

---

(124) Weston, Ruddy, and Suter, J. Am. Chem. Soc., 65, 675 (1943)

similar to that of octahydroskatole (I), except for the notable lack of a pronounced N-H absorption. Also, I has a slightly higher refractive index.

The picrolonate of the compound has a melting point range similar to those of the picrolonates of I and o-amino-β-methylphenethylamine (II).

Since the hydrogenation of indole over nickel at 170° and 80 atm. (or 150-160° and 90-100 atm) in methanol or ethanol yielded 1-methyl- or 1-ethyloctahydroindole (125), our compound probably is 1-ethyloctahydroskatole (III).

The analytical data for III were of little value since nitrogen was not determined. Although the formula $C_{9.26}H_{18.03}N_{1.00}$ was calculated, the carbon-to-hydrogen ratio is the same for the analytical data, I, and III: 0.526, 0.528, and 0.526, respectively. Thus without nitrogen data the reliability of the analysis could not be estimated.

The structure subsequently was proved by preparing III by the hydrogenation of skatole over Raney nickel in ethanol.

F. 4-Methyl-3,4-dihydrocinnoline.

When this compound was first isolated with platinum oxide in neutral solution, it presented an enigma; o-amino-β-methylphenethylamine (II) had been expected. However, the material obtained showed no infrared N-H absorption bands and solidified upon standing (m.p 61.5-62.5°, after two recrystallizations from Skelly Solve B). Although the analytical data were poor, the formula $C_{9.20}H_{9.54}N_{2.00}$ was calculated. A picrate was prepared in poor yield (m.p. 97-102° with decomposition). Obviously II was not obtained, in spite of the apparent hydrogen absorption of 3.0 molar equivalents.

The problem was resolved with the low-pressure hydrogenation of 4-methylcinnoline over 5% rhodium on alumina in acetic acid. In this reaction 1.0 molar equivalent of hydrogen was absorbed. The solid product was recrystallized from water (m.p. 60-60.5°). The picrate (m.p. 102° with decomposition) and hydrochloride (95-99° with decomposition) were prepared. The infrared spectrum of the base was identical with that of the material first obtained.

---

(125) King, Barltrop, and Walley, J. Chem. Soc., 1945, 277

Based on hydrogen up-take, the material must be a methyl-dihydrocinnoline. Since the infrared spectrum shows no N-H absorption, the structure, 4-methyl-3,4-dihydrocinnoline (IV), was assigned. Both the free base and the hydrochloride appeared to deteriorate upon standing, which would account for the poor analytical data obtained.

G. 2,3-Dihydroskatole.

This compound was obtained only once, with platinum oxide in acidic ethanolic solution. Information concerning the material is very limited. Vacuum-distillation resulted in five fractions having essentially the same infrared spectra. The picrate (m.p. 159-163, recrystallized once from ethanol) and picrolonate (m.p. 230-232) were prepared. From the analytical data, the formula $C_{9.01}H_{11.3}N_{1.00}$ was calculated.

Since the compound appeared to contain but one nitrogen atom per molecule, the logical assumption was that the compound was derived from skatole. Hence the structure 2,3-dihydroskatole (VI), $C_9H_{11}N$, was assigned. The boiling point is reported in the literature to be 112°/14 mm., while the picrate has a melting point of 149-150° (120).

H. 4-Methyl-1,2,3,4-tetrahydrocinnoline.

This compound was readily identified, since an authentic sample was on hand, prepared previously by Dr. H. Smith Broadbent.

It must be apparent that the amount of hydrogen absorbed in the high-pressure reactions was not a dependable indication of the product to be expected. Seemingly the apparatus leaked on various occasions. This leakage, however, would not be expected to prevent more complete hydrogenation than that actually obtained. Since each reaction was checked for leaks at the onset, escape of hydrogen probably occurred at elevated temperatures. In the initial phase of this program leaky equipment was a major problem.

I. pK_a Values.

In general, aliphatic amines are of the order 10^5 times more basic than aromatic amines (126). Thus, just approximate pK_a data could prove or disprove various structures. o-Amino-β-methylphenethylamine (II) theoretically should give 2 pK_a values.

---

(126) Braude and Nachod, "Determination of Organic Structures by Physical Methods," Academic Press, Inc., New York, 1955.

Actually, the data obtained were of little value. Titration of octahydroskatole (I) gave a pK_a of 10.14, indicating an aliphatic amine, which it is. The data for o-amino-β-methylphenethylamine (II) gave only one inflection, from which pK_a values of 8.92 and 3.68 were estimated by assuming that only the more basic center was titrated. Such an assumption requires a molecular weight of 244 g./mole.

J. Nonaqueous Titrations.

The titrations of octahydroskatole (I) and o-amino-β-methylphenethylamine (II) gave equivalent weights of 140.5 g./eq. and 127.0 g./eq. respectively. The latter value requires a molecular weight of 254 g./mole. The calculated molecular weights are 139.2 and 150.2, respectively. Thus the value for I is in good agreement, while the data for II have little meaning.

V. SUMMARY

1. High-pressure hydrogenations of 4-methylcinnoline in neutral and acidic ethanolic solutions were carried out at 2000-3000 psig. initial hydrogen pressure and 100-266°. The catalysts used were 5% rhodium on alumina, ruthenium oxide, 5% palladium on activated charcoal, 5% rhodium on activated charcoal, and platinum oxide.

2. Reaction products were isolated either by vacuum distillation of the reaction mixture or by neutralization, extraction, and vacuum-distillation. Both average and median material recoveries were 66 weight per cent.

3. Seven different products were variously obtained (in order of decreasing total yield): o-amino-β-methylphenethylamine, octahydroskatole, 1-ethyloctahydroskatole, 2,3-dihydroskatole, 4-methyl-3,4-dihydrocinnoline, 4-methyl-1,2,3,4-tetrahydrocinnoline, and an unknown compound.

4. 4-Methyl-3,4-dihydrocinnoline and 4-methyl-1,2,3,4-tetrahydrocinnoline were obtained by reduction of 4-methylcinnoline in acidic solution at 60 psig initial hydrogen pressure and room temperature. The catalysts were 5% rhodium on alumina and platinum oxide, respectively.

5. The structures of octahydroskatole, 1-ethyloctahydroskatole, and 4-methyl-1,2,3,4-tetrahydrocinnoline were proven by comparison with authentic samples, aided by infrared spectra and elemental analyses.

6. The structures of 2,3-dihydroskatole and 4-methyl-3,4-dihydrocinnoline were assigned on the basis of infrared specta, elemental analyses, and in the case of the latter, hydrogen absorption.

7. o-Amino-β-methylphenethylamine, a new composition of matter, was so designated on the basis of its infrared spectrum, elemental analyses, and chemical properties.

8. Diazotization of o-amino-β-methylphenethylamine in concentrated hydrochloric acid yielded 4-methylcinnoline, Diazotization in dilute aqueous sulfuric acid solution yielded 2-(o-aminophenyl)-1-propanol (a new composition of matter), based on infrared

absorption data and elemental analysis. The results of the diazotization reactions are in accord with the original structure assignment for the diamine.

9. With all compounds, the preparation of such derivatives as the hydrochloride, picrate, and picrolonate served mainly to provide more easily purified samples for elemental analyses. Determinations of pK_a values and nonaqueous titrations were of limited value in identification of hydrogenation products.

10. Hydrogenation of 4-methylcinnoline in neutral ethanolic solution with either 5% rhodium on activated charcoal or platinum oxide favored formation of o-amino-β-methylphenethylamine. In acidic ethanolic solution the main product was octahydroskatole.

11. Hydrogenation of 4-methylcinnoline in both neutral and acidic ethanolic solutions with 5% palladium on activated charcoal gave o-amino-β-methylphenethylamine as the main product.

12. Hydrogenations of 4-methylcinnoline with ruthenium oxide in neutral ethanolic solution gave 1-ethyloctahydroskatole. In acidic solution octahydroskatole was obtained; an unknown compound also was isolated as a minor product.

13. Low-temperature reductions ($< 132°$) of 4-methylcinnoline in acidic or neutral ethanolic solutions with 5% rhodium on alumina gave mainly o-amino-β-methylphenethylamine, while higher temperatures ($200°$) gave mainly octahydroskatole.

VI. BIBLIOGRAPHY

Adachi, J. Pharm. Soc. Japan, 75, 1426 (1955) [C.A., 50, 10105 (1956)].

Adkins and Coonradt, J. Am. Chem. Soc., 63, 1563 (1941).

Albert, Goldacre, and Phillips, J. Chem. Soc., 1948, 2240.

Albert and Hampton, J. Chem. Soc., 1952, 4985.

Albert and Hampton, J. Chem. Soc., 1954, 505.

Albert and Hampton, 2nd Cong. intern. biochim., Resumes Communs., (Paris, 1952), 444 [C.A., 49, 4648 (1955)].

Albert and Phillips, J. Chem. Soc., 1956, 1294.

Alder and Niklas, Ann., 585, 97 (1954).

Alexander and McElvain, J. Am. Chem. Soc., 60, 2285 (1938).

Alford, Irving, Marsh, and Schofield, J. Chem. Soc., 1952, 3009.

Alford and Schofield, J. Chem. Soc., 1952, 2102.

Alford and Schofield, J. Chem. Soc., 1953, 609.

Alford and Schofield, J. Chem. Soc., 1953, 1811.

Allan and van Allen, J. Am. Chem. Soc., 73, 5850 (1951).

Allen, Chem. Revs., 37, 233, 263 (1945).

Amstutz, J. Org. Chem., 17, 1508 (1952).

Atkinson and Sharpe, J. Chem. Soc., 1959, 2858.

Atkinson and Simpson, J. Chem. Soc., 1947, 1649.

Atkinson, Simpson, and Taylor, J. Chem. Soc., 1954, 165.

Atkinson, Simpson, and Taylor, J. Chem. Soc., 1954, 1381.

Atkinson and Taylor, J. Chem. Soc., 1955, 4236.

von Auwers, Ann., 453, 211 (1927).

Badger, Pearce, and Pettit, J. Chem. Soc., 1951, 3199.

Badger, Seidler, and Thompson, J. Chem. Soc., 1951, 3207.

Badger and Walker, J. Chem. Soc., 1956, 122.

Baumgarten, J. Am. Chem. Soc., 77, 5109 (1955).

Baumgarten and Anderson, J. Am. Chem. Soc., 80, 1981 (1958).

Baumgarten and DeBrunder, J. Am. Chem. Soc., 76, 3489 (1954).

Baumgarten, Creger, and Villars, J. Am. Chem. Soc., 80, 6609 (1958).

Baumgarten, Pederson, and Hunt, J. Am. Chem. Soc., 80, 1977 (1958)

Borsche and Herbert, Ann., 546, 293 (1941).

Bossel, Inaug.-Diss., Tübingen, May, 1925, pp. 31-33.

Braithwaite, Holt, and Hughes, J. Chem. Soc., 1958, 4073.

Braude and Nachod, "Determination of Organic Structures by Physical Methods," Academic Press, Inc., New York, 1955.

v. Braun and Bayer, Ber., 58B, 387 (1925) [C.A., 19, 1862 (1925)].

v. Braun, Bayer, and Blessing, Ber., 57B, 397 (1924) [C.A., 18, 2162 (1924)].

Broadbent, Unpublished results, Brigham Young University, Provo, Utah, 1960.

Broadbent, Allred, Pendleton, and Whittle, J. Am. Chem. Soc., 82, 189 (1960).

Brown and Bonner, J. Am. Chem. Soc., 76, 605 (1954).

Brown and Reagan, J. Am. Chem. Soc., 69, 1032 (1947).

Busch and Rast, Ber., 30, 521 (1897).

Calderbank and LeFevre, J. Chem. Soc., 1951, 649.

Castle and Cox, J. Org. Chem., 18, 1706 (1953).

Castle and Cox, J. Org. Chem., 19, 1117 (1954).

Castle, Cox, and Suttle, J. Am. Pharm. Assoc., 48, 135 (1959) [C.A., 53, 8810 (1959)].

Castle and Kruse, J. Org. Chem., 17, 1571 (1952).

Castle, Ward, White, and Adachi, J. Org. Chem., 25, 570 (1960).

Chandler, Brit. J. Pharmacol., 12, 44 (1957) [C.A., 51, 10753 (1957)].

Cornforth and Robinson, J. Chem. Soc., 1942, 680.

Curd, Hepworth, and Imperial Chemical Industries, Ltd., Brit. 663, 095, Dec. 19, 1951 [C.A., 46, 11250 (1952)].

Curd, Hepworth, and Imperial Chemical Industries, Ltd., Brit. 663, 096, Dec. 19, 1951 [C.A., 46, 11251 (1952)].

Dewar and Maitlis, J. Chem. Soc., 1957, 2521.

Diels and Alder, Ann., 450, 237 (1926).

Ebel, Huber, and Brunner, Helv. chim. Acta, 12, 16 (1929).

Fritz, "Acid-Base Titrations In Non-Aqueous Solvents", G. Fredrick Smith Chemical Company, Columbus, Ohio, 1952.

Hearn, Morton, and Simpson, J. Chem. Soc., 1951, 3318.

Hirt, King, and Cavagnol, J. Chem. Phys., 25, 574 (1956).

Horner and Naumann, Ann., 587, 81 (1954).

Horning and Amstutz, J. Org. Chem., 20, 707 (1955).

Horning and Amstutz, J. Org. Chem., 20, 1069 (1955).

Irving and Rossotti, J. Chem. Soc., 1954, 2910.

Irving and Rossotti, Analyst, 80, 245 (1955) [C.A., 49, 8728 (1955)].

Jacobs, Winstein, Henderson, and Spaeth, J. Am. Chem. Soc., 68, 1310 (1946).

Kendal, Wood, and Welford (to Ilford, Ltd.), U.S. 2,669,515, Feb. 16, 1954 [C.A., 48, 6892 (1954)].

Keneford, Lourie, Morley, Simpson, Williamson, and Wright, J. Chem. Soc., 1952, 2595.

Keneford, Morley, and Simpson, J. Chem. Soc., 1950, 1104.

Keneford, Morley, Simpson, and Wright, J. Chem. Soc., 1949, 1356.

Keneford, Schofield, and Simpson, J. Chem. Soc., 1948, 358.

King, Barltrop, and Walley, J. Chem. Soc., 1945, 277.

King and King, J. Chem. Soc., 1945, 824.

Kornfeld, J. Am. Chem. Soc., 70, 1373 (1948).

Krohnke and Vogt, Ann., 589, 26 (1954).

Longuet-Higgins and Coulson, J. Chem. Soc., 1949, 971.

Lourie, Morley, and Simpson, Brit. J. Pharmacol., 6, 643 (1951) [C.A., 46, 2695 (1952)].

Lourie, Morley, Simpson, and Walker (to National Research Development Corp.), Brit. 702, 664, Jan. 20, 1954 [C.A., 50, 5777 (1956)].

McIntyre and Simpson, J. Chem. Soc., 1952, 2606.

McIntyre and Simpson, J. Chem. Soc., 1952, 2615.

McKenzie and Hamilton, J. Org. Chem., 16, 1414 (1951).

Mizuno, Adachi, and Ikeda, Pharm. Bull. (Japan), 2, 225 (1954) [C.A., 50, 1034 (1956)].

Moore, Nature, 163, 918 (1949).

Morley, J. Chem. Soc., 1951, 1971.

Morley, J. Chem. Soc., 1959, 2280.

Morley and Simpson, J. Chem. Soc., 1949, 1014.

Morley and Simpson, J. Chem. Soc., 1949, 1354.

Morley and Simpson, J. Chem. Soc., 1952, 2617.

Mozingo, Org. Syn., Coll. Vol. III, 181 (1955).

Neber, Knoller, Herbst, and Trissler, Ann., 471, 113 (1929).

Nelson and Brown, J. Am. Chem. Soc., 73, 5605 (1951).

Nunn and Schofield, J. Chem. Soc., 1953, 3700.

Ockenden and Schofield, J. Chem. Soc., 1953, 3706.

Osborn and Schofield, J. Chem. Soc., 1955, 2100.

Pullman, Rev. Sci., 86, 219 (1948) [C.A., 43, 2095 (1949)].

von Richter, Ber., 16, 677 (1883).

Rogers and Campbell, J. Am. Chem. Soc., 75, 1209 (1953).

Rossotti, Rec. trav. chim., 75, 763 (1956).

Sako, Bull Chem. Soc. Japan, 9, 393 (1934) [C.A., 29, 1083 (1935)].

Schmidt and Druey, Helv. chim. Acta, 37, 134 (1954).

Schofield, J. Chem. Soc., 1949, 2408.

Schofield and Simpson, J. Chem. Soc., 1945, 512.

Schofield and Simpson, J. Chem. Soc., 1946, 472.

Schofield and Swain, J. Chem. Soc., 1949, 1367.

Schofield and Swain, J. Chem. Soc., 1949, 2393.

Schofield and Swain, J. Chem. Soc., 1950, 384.

Schofield and Swain, J. Chem. Soc., 1950, 392.

Schofield, Swain, and Theobald, J. Chem. Soc., 1949, 2399.

Schofield and Theobald, J. Chem. Soc., 1949, 2404.

Schofield and Theobald, J. Chem. Soc., 1950, 395.

Simpson, J. Chem. Soc., 1947, 1653.

Simpson, "Condensed Pyridazine and Pyrazine Rings", Interscience Publishers, Inc., New York, 1953, pp. 3-65, 358-361, 363-366.

Smith, Jr., and Ruby, J. Am. Chem. Soc., 76, 5807 (1954).

Stacy and Bresson, J. Org. Chem., 24, 1892 (1959).

Sterling and Bogert, J. Org. Chem., 4, 20 (1939).

Stoermer and Fincke, Ber., 42, 3115 (1909).

Tichwinski, J. Russ. Phys. Chem., 36, 1052 (1904) [C.Z., I, 79 (1905)].

Tichwinski, J. Russ. Phys. Chem., 36, 1056 (1904) [C. Z., I, 80 (1905)]

Wallenberger, O'Connor, and Moriconi, J. Chem. Ed., 36, 251 (1959).

Wenzig, Ann., 239, 242 (1887).

Weston, Ruddy, and Suter, J. Am. Chem. Soc., 65, 675 (1943).

Widman, Ber., 17, 722 (1884).

Wilson, Org. Syn., Coll. Vol. I, 277 (1941).

Woodward and Eastman, J. Am. Chem. Soc., 72, 399 (1950).

Zerner, Monatsh., 34, 1609 (1913).

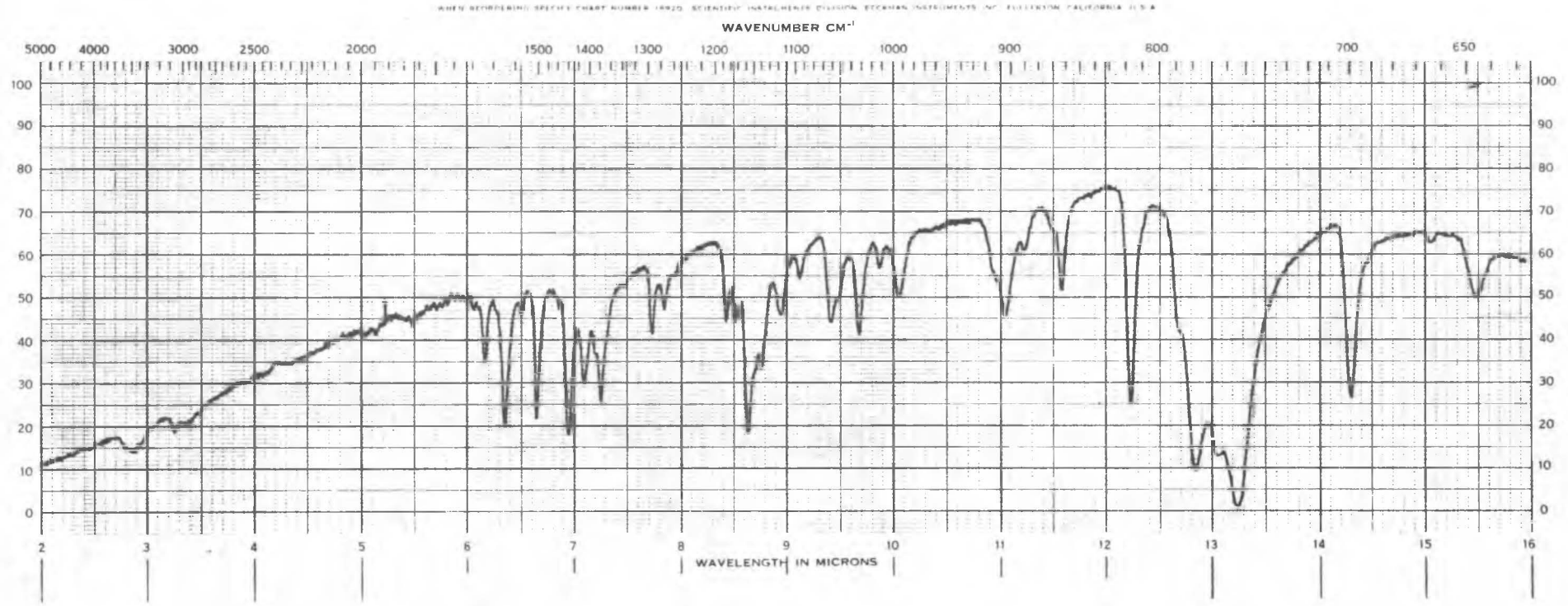


Figure 1. Infrared Spectrum of 4-Methylcinnoline. KBr Disc.

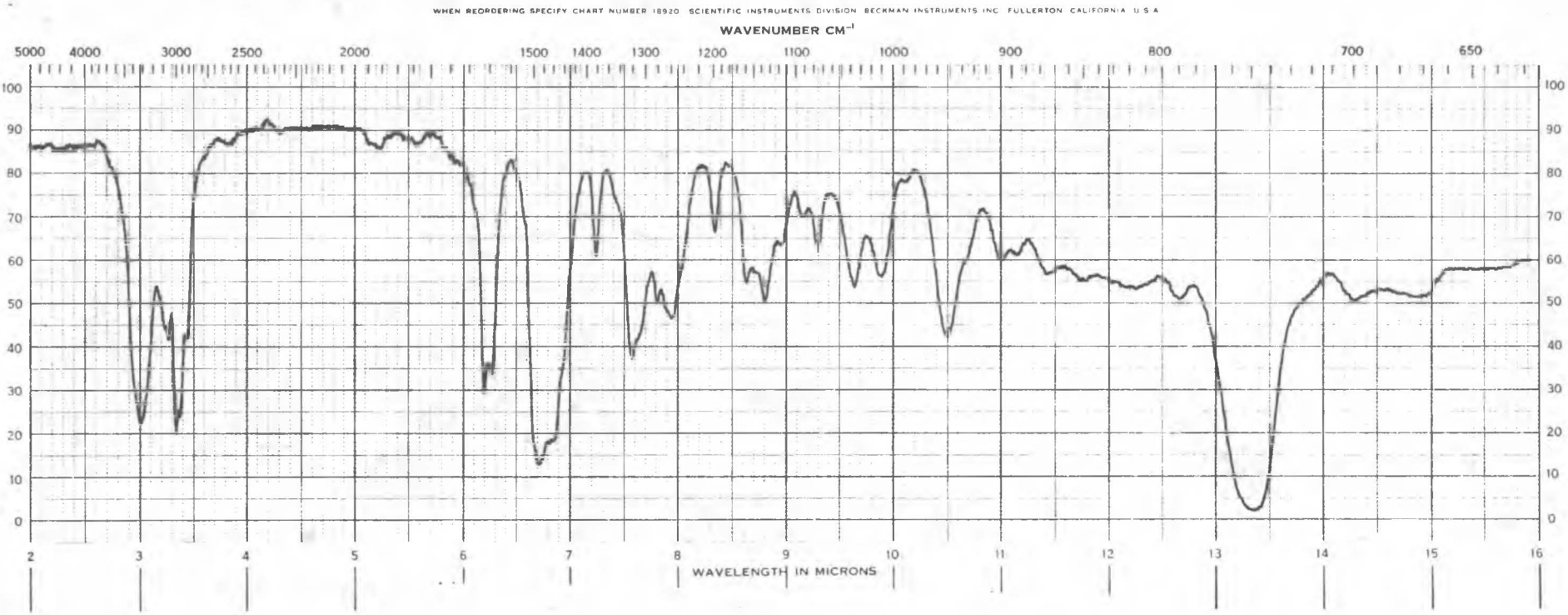


Figure 2. Infrared Spectrum of 4-Methyl-1, 2, 3, 4-tetrahydrocinnoline From The Hydrogenation of 4-Methylcinnoline. Neat (smear).

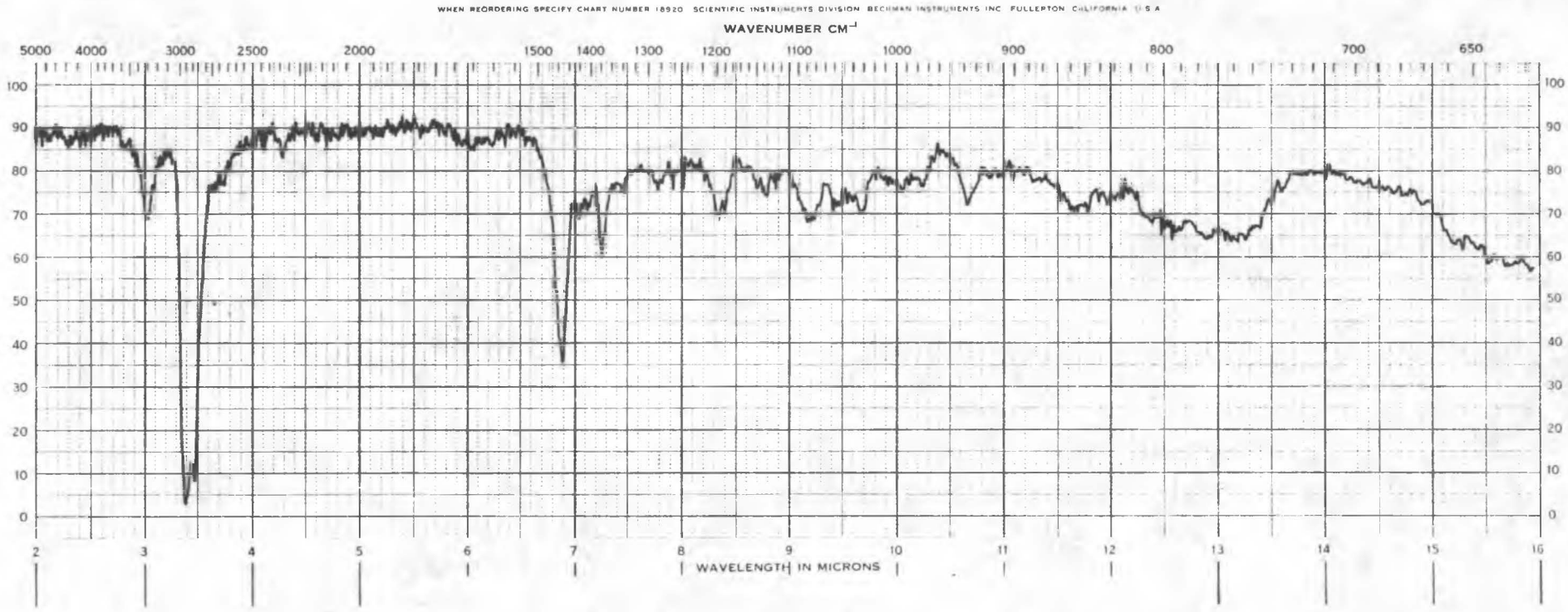


Figure 3. Infrared Spectrum of Octahydroskatole From the Hydrogenation of 4-Methylcinnoline. Neat (smear).

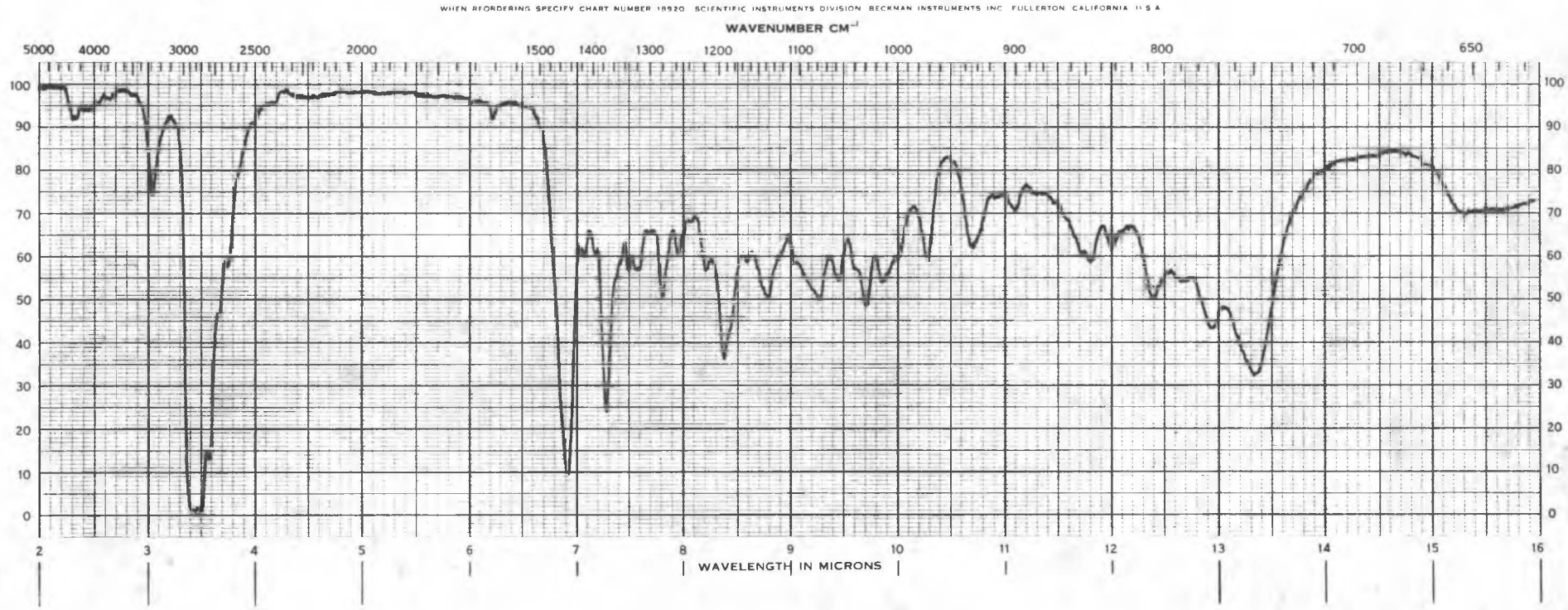


Figure 4. Infrared Spectrum of Octahydroskatole From the Hydrogenation of Skatole. Neat (0.0264 mm. cell).

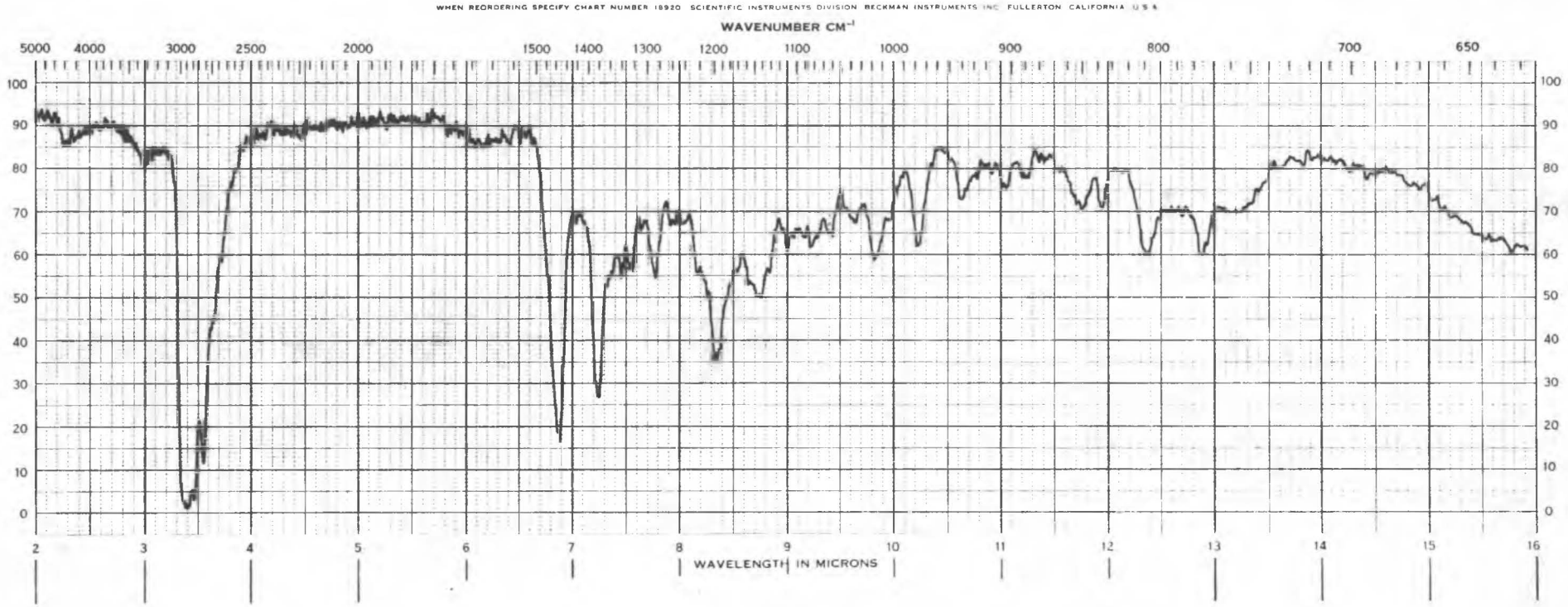


Figure 5. Infrared Spectrum of 1-Ethyloctahydroskatole From the Hydrogenation of 4-Methylcinnoline. Neat (smear).

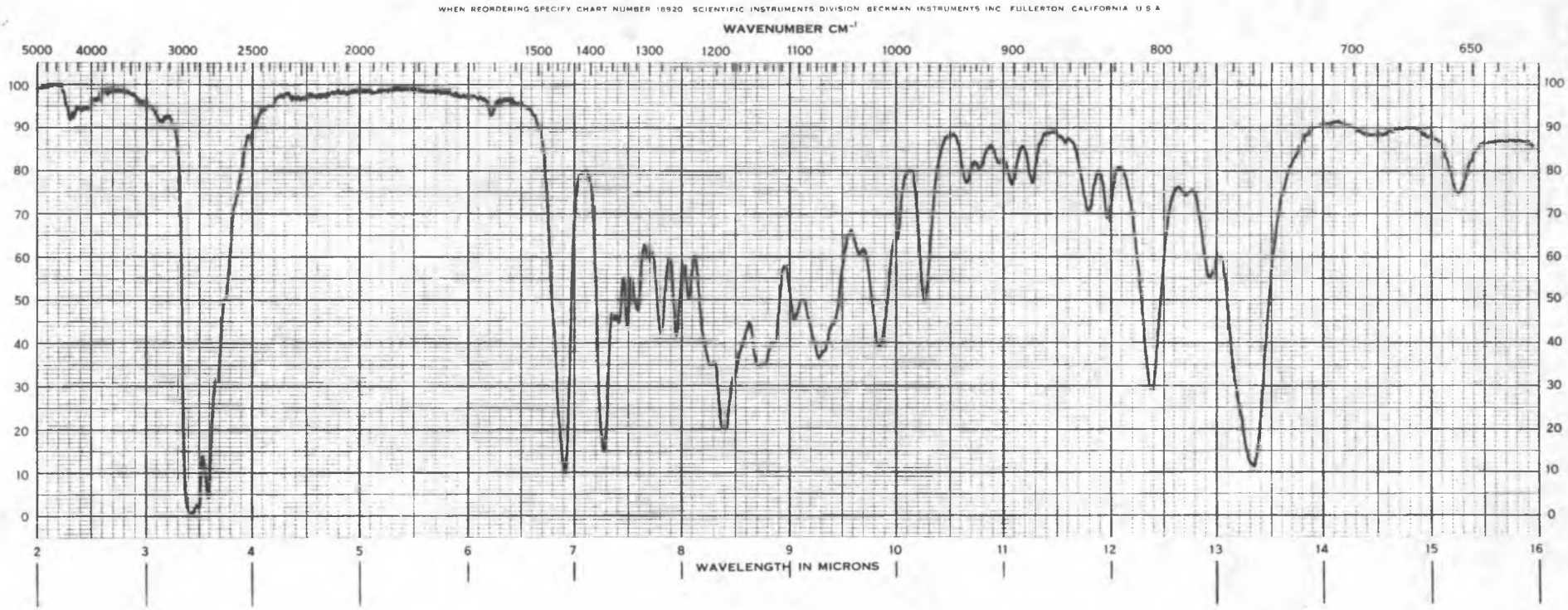


Figure 6. Infrared Spectrum of 1-Ethyloctahydroskatole From the Hydrogenation of Skatole. Neat (0.0264 mm. cell).

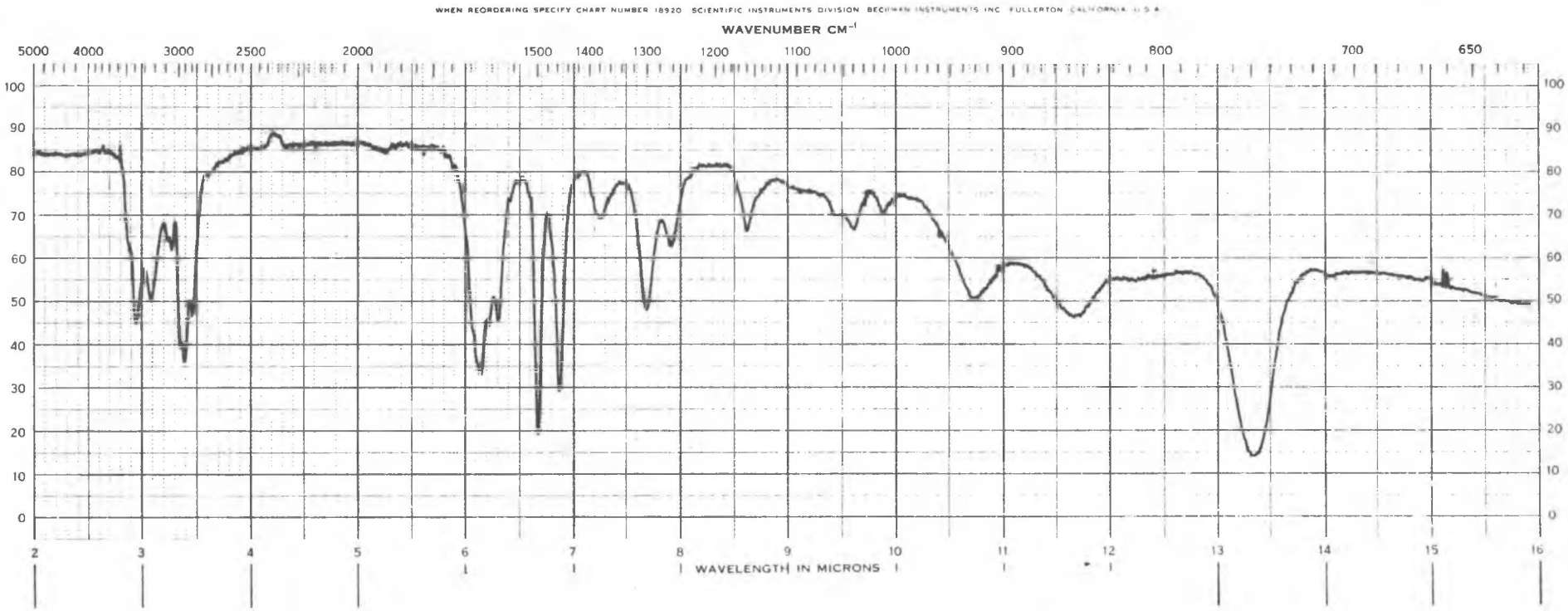


Figure 7. Infrared Spectrum of o-Amino-β-Methylphenethylamine From the Hydrogenation of 4-Methylcinnoline. Neat (smear).

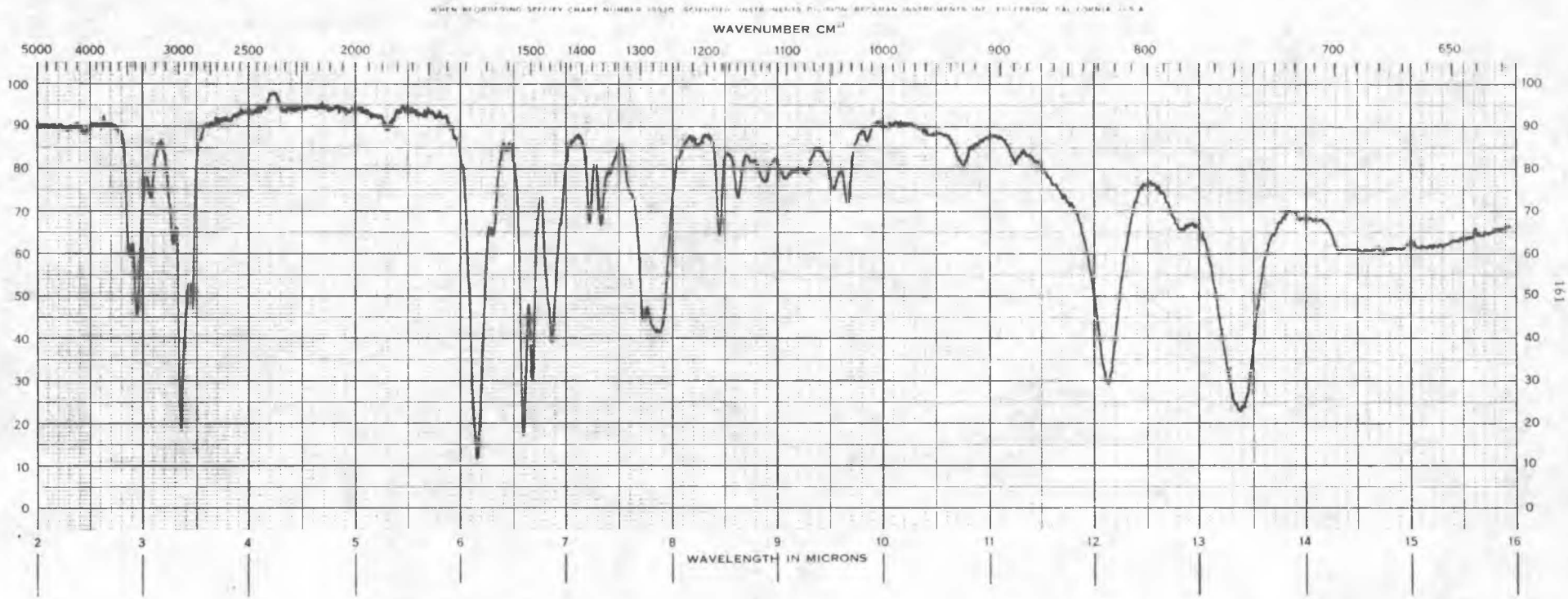


Figure 8. Infrared Spectrum of o-Cumidine From the Hydrogenation of o-Nitrocumene. Neat (smear).

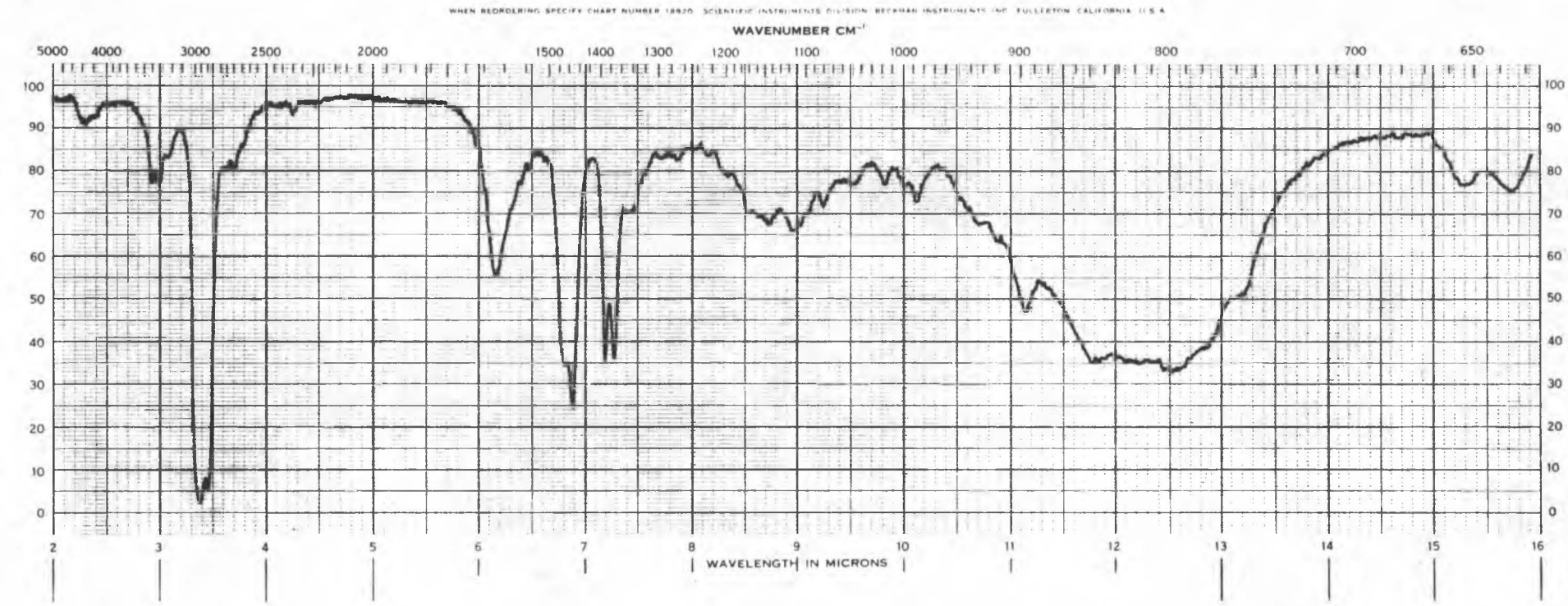


Figure 9. Infrared Spectrum of 2-Isopropylcyclohexylamine From the Hydrogenation of o-Cumidine. Neat (smear).

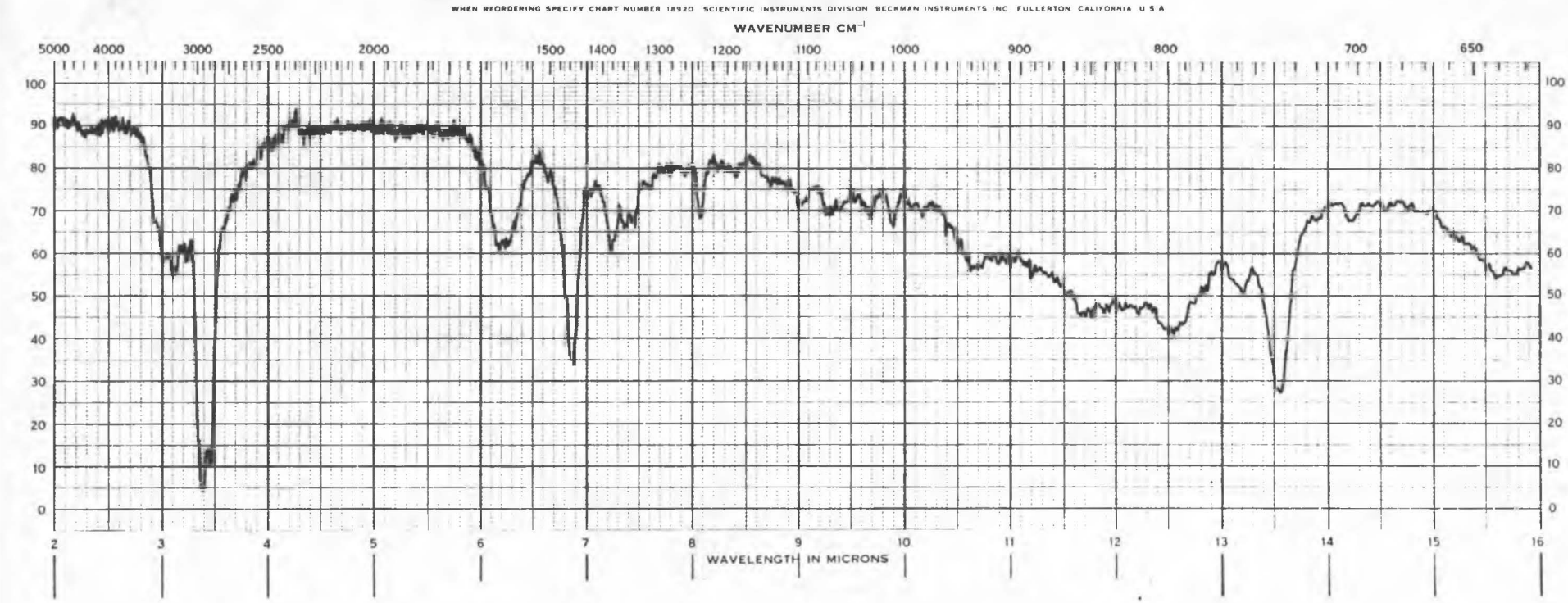


Figure 10. Infrared Spectrum of the Unknown Compound From the Hydrogenation of 4-Methylcinnoline. Neat (smear).

HYDROGENATION OF 4-METHYLCINNOLINE

Abstract of a Thesis

Submitted to the

Department of Chemistry

Brigham Young University

Provo, Utah

In Partial Fulfillment

of the Requirements for the Degree of

Master of Arts

by

William E. Maycock

September, 1964

ABSTRACT

The rapid expansion of knowledge of cinnoline chemistry since 1941 has not included the hydrocinnolines. Not one catalytic hydrogenation of a fully aromatic cinnoline had been reported. This thesis is an effort to enlarge knowledge of this particular area of cinnoline chemistry. The work is a natural outgrowth of that done at Brigham Young University on decahydroquinoxaline, both the cis- and trans- isomers having been prepared and characterized.

4-Methylcinnoline, prepared by the method of Jacobs, et.al., was hydrogenated in neutral and acidic ethanolic solutions at 2000-3000 psig. hydrogen pressure and 100-266°. The catalysts used were 5% palladium on alumina, ruthenium oxide, 5% palladium on activated charcoal, 5% rhodium on activated charcoal, and platinum oxide.

The filtered reaction mixtures were either vacuum-distilled or made basic, extracted, and then vacuum-distilled. Both the average and median material recoveries were 66 weight per cent.

Seven different products were variously obtained (in order of decreasing total yield): o-amino-β-methylphenethylamine, octahydroskatole, 1-ethyloctahydroskatole, 2,3-dihydroskatole, 4-methyl-3,4-dihydrocinnoline, 4-methyl-1,2,3,4-tetrahydrocinnoline, and an unknown compound. 4-Methyl-3,4-dihydrocinnoline and 4-methyl-1,2,3,4-tetrahydrocinnoline also were obtained by reduction of 4-methylcinnoline in acidic solution at 60 psig. hydrogen pressure and room temperature. The catalysts were 5% rhodium on alumina and platinum oxide, respectively.

The structures of octahydroskatole, 1-ethyloctahydroskatole, and 4-methyl-1,2,3,4-tetrahydrocinnoline were proven by comparison with authentic samples, aided by infrared spectra and elemental analyses. The structures of 2,3-dihydroskatole and 4-methyl-3,4-dihydrocinnoline were assigned on the basis of infrared spectra, elemental analyses, and, in the case of the latter, hydrogen absorption.

o-Amino-β-methylphenethylamine, a new composition of matter, was so designated on the basis of its infrared spectrum, elemental analyses, and chemical properties. Diazotization of the diamine in concentrated hydrochloric acid yielded 4-methylcinnoline. Diazotization in dilute aqueous sulfuric acid solution gave 2-(o-aminophenyl)-1-propanol (a new composition of matter), based on infrared absorption data and elemental analysis. The results of the diazotization reactions support the structure assignment for the diamine.

With all compounds, the preparation of such derivatives as the hydrochloride, picrate, and picrolonate served mainly to provide

more easily purified samples for elemental analyses. Determinations of pKa values and nonaqueous titrations were of limited value in structural assignment.

Hydrogenation of 4-methylcinnoline in neutral ethanolic solution with either 5% rhodium on activated charcoal or platinum oxide gave mainly o-amino-β-methylphenethylamine. In acidic solution the main product was octahydroskatole.

o-Amino-β-methylphenethylamine was the main product from the hydrogenation of 4-methylcinnoline with 5% palladium on activated charcoal in both neutral and acidic ethanolic solutions.

Hydrogenation of 4-methylcinnoline with ruthenium oxide in neutral ethanolic solution gave 1-ethyloctahydroskatole. In acidic solution octahydroskatole was the main product; an unknown compound was also isolated.

Low-temperature (< 132°) reductions of 4-methylcinnoline in acidic or neutral ethanolic solutions with 5% rhodium on alumina gave mainly o-amino-β-methylphenethylamine, while high temperatures (200°) favored formation of octahydroskatole.