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Decahydroquinoxaline : stereoisomers and derivatives

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DECAHYDROQUINOXALINE: STEREOISOMERS AND DERIVATIVES

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The writer expresses sincere gratitude to those who have made this work possible. Heartfelt thanks is extended to his parents for their encouragement and assistance during the course of his studies. Particularly, is appreciation expressed to Dr. H. Smith Broadbent under whose guidance this work proceeded.

This work is dedicated to my wife, Mary, for her love, patience, and understanding.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF ILLUSTRATIONS

I: INTRODUCTION

The decahydroquinoxalines comprise a class of compounds, the chemistry of which is very recent and new. Since 1947 four different reports of the preparation of decahydroquinoxaline have appeared. Two of the methods utilize the ring closure of saturated, substituted cyclohexanes (1,2), while the other two methods of preparation were by catalytic hydrogenation of the well known parent compound, quinoxaline (3,4). Physical property data and diacetyl and dinitroso derivatives of these purported decahydroquinoxalines indicated at least one of these four methods of preparation of decahydroquinoxaline did not give the presumed product, and further indication was that two of the methods of preparation gave the same decahydroquinoxaline.

Previous to the most recently developed method of preparation of decahydroquinoxaline by Dr. H. S. Broadbent and C. Whittle (4), no more than a mere mention of the possibility of stereoisomerism in the decahydroquinoxalines was made (3). The work of Broadbent and Whittle indicated strongly that decahydroquinoxaline existed in the theoretically possible cis and trans forms. These workers tentatively made the configurational assignment of cis to the low melting isomer which they were first to prepare. Before absolute assignment of configuration could be made more positive evidence, such as the resolution of the theoretically possible optical isomers of the trans-decahydroquinoxaline, needed to be made.

The melting point of the low melting decahydroquinoxaline increased greatly with time and material presumed to be the high melting isomer was found to decrease in melting point on standing (4). Further evidence obtained by Broadbent and Whittle indicated the two geometrical isomers of decahydroquinoxaline isomerized on standing, yet other evidence did not completely substantiate the supposed isomerization. Difficulty was encountered in obtaining ultraviolet spectra of both the isomers of decahydroquinoxaline which were free of indications of unsaturation. The possibility was present that a different hydroquinoxaline, such as octahydroquinoxaline, had been obtained

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(1) Beck, Hamlin and Weston, J. Am. Chem. Soc., 74, 607 (1952).

(2) Mousseron and Combes, Bull. soc. chim. France, 1947, 82.

(3) Christie, Rhode, and Shultz, J. Org. Chem., 21, 243 (1956).

(4) Whittle, Master's Thesis, Department of Chemistry, Brigham Young University, Provo, Utah, 1956.

rather than the deca form. This possibility became more evident when hydrogen analyses of some samples of the decahydroquinoxalines were slightly inaccurate for the deca form.

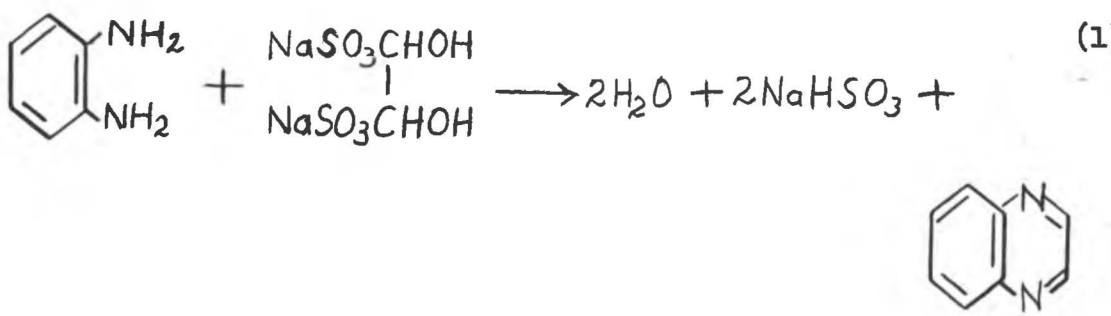
The research outlined in this thesis was concerned with the solutions to the preceding problems. Both cis- and trans-decahydroquinoxaline were prepared by the available known methods, the trans was also prepared by a new stereospecific synthetic route, and assignment of configuration was made. It was established that the two isomers of decahydroquinoxaline did not isomerize. Pure trans-decahydroquinoxaline was found not to change melting point with time and the cause of the change of the melting point of the cis-decahydroquinoxaline with standing was found to be due to absorption of carbon dioxide from the air to give the carbonate salt. By fractional sublimation and crystallization techniques both isomers of decahydroquinoxaline were purified from the various preparations of decahydroquinoxaline, the ultraviolet spectra of which were free from evidence of unsaturation confirming the assignment of structure. In addition various new derivatives of decahydroquinoxaline were prepared and submitted for testing of physiological activity. These last results will be reported elsewhere.

II: LITERATURE REVIEW

A review covering the chemistry of the quinoxalines up through 1949 is available (5). Recently two theses (4,6) covering briefly some aspects of the stereochemistry and pharmacological possibilities of decahydroquinoxaline were written. This present review covers the chemistry of the quinoxalines, and more specifically the preparation and physical properties of the derivatives of quinoxaline, for the period 1950-1955, 1955 being the last year for which the index to Chemical Abstracts was currently available. The chemistry of the hydroquinoxalines was further covered from 1955 to the present by scanning the organic sections of Chemical Abstracts for this period.

A. Quinoxaline.

Quinoxaline, the parent compound, is a weak base, pK_a ca. 0.8 in water at 20° C. (7). It is conveniently prepared according to equation 1 by the condensation of sodium glyoxal bisulfite and o-phenylenediamine



(1)

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(5) Simpson, "Condensed Pyridazine and Pyrazine Rings", Interscience Publishers, Inc., New York, 1953, pp. 203-366.

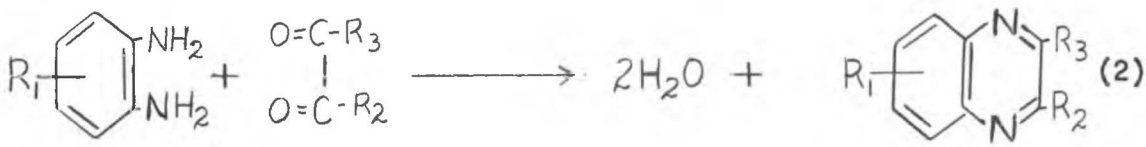
(6) Allred, Master's Thesis, Department of Chemistry, Brigham Young University, Provo, Utah, 1955.

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

(8-11), and under proper conditions (8) may be obtained in 93% yields.

B. Quinoxaline Derivatives.

The condensation of primary o-phenylenediamines with 1,2-dicarbonyl compounds according to equation 2 has long been recognized as a convenient

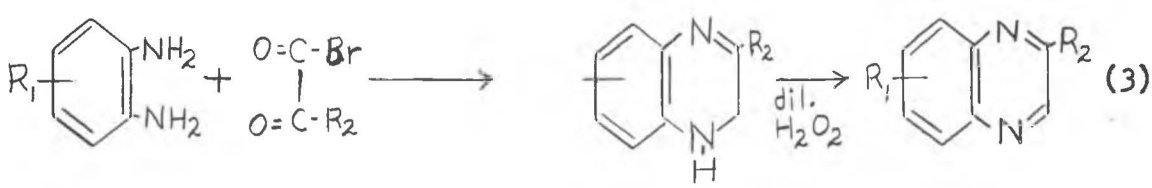


(2)

method of identification of these two types of compounds. The chemistry involved in the preparation of these derivatives has seldom been investigated as previous interest in these compounds has only been for purposes of identification. Consequently, the only information available on most of the derivatives is physical property data. Most of the information in this review is presented in the form of tables with information, as available, on methods of preparation and properties. No attempt has been made to present the pharmacological properties or spectral data of these derivatives.

1. Alkyl, Aryl, Aralkyl, Alkenyl or Acyl Substituted Quinoxalines.

The preparation of this group of compounds is almost exclusively by the condensation of primary o-phenylenediamines with 1,2-dicarbonyl (equation 2) or α-bromo carbonyl compounds according to equation 3. The reaction



(3)

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(8) Billman and Rendall, J. Am. Chem. Soc., 66, 540 (1944)

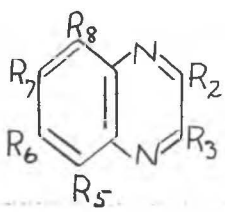
(9) Cavagnol and Wiselogle, J. Am. Chem. Soc., 69, 795 (1947).

(10) Hinsberg, Ber., 17, 320 (1884).

(11) Jones and McLaughlin, Org. Syn., 30, 86-90 (1950).

is usually run in alcohol, acetic acid, or water, the products generally being readily crystallizable solids. Table I lists the quinoxaline derivatives in this group, and, from the substituents present in the quinoxaline nucleus, the substituted dicarbonyl or α-bromo carbonyl and substituted primary o-phenylenediamine compounds used in preparing the derivative may be deduced.

Table I. Alkyl, Aryl, Aralkyl, or Acyl Substituted Quinoxalines.



$R_2, R_3, R_5, R_6, R_7, R_8$ are Hydrogen except as indicated differently by the table.

No.	R	Group	% Yld	Xtalzn Solvent	M. P. °C.	Remarks	Ref.
1	2	$-CH_2CHOHCCl_3$	93		105.5-106		12
2	2	$-CHCHCO_2H$	70		219-220 dec.	from 1	12
3	2	$-CH_2CH_2CO_2H$	92		115-115.5	From 2	12
4	2	$-CH_2CH_2CO_2CH_3$			39-40	by esterification of 3	12
5	2	$-CH_2CH_2CONH_2$			152-152.5	ammonolysis of 4	12
6	2	$-CH_2CH_2NH_2$	from 5 and NaOCl, compound not isolated				12
7	2	$-CH_2CH_2NH_2 \cdot 2HCl$	76		184-186 dec.	salt of 6	12
8	2	$-CH_2CHNH_2CO_2H$	20		194	by hydrogenation of Et 3-(2-quinoxalinyl) pyruvate oxime hydrochloride salt	13

(12) Jones, Kornfeld and McLaughlin, J. Am. Chem. Soc., 72, 3539-42 (1950).

(13) Ried and Schiller, Chem. Ber., 86, 730-4 (1953).

No.	R	Group	% Yld	Xtalzn Solvent	M. P. °C.	Remarks	Ref.
9	2	$-CH_2C(NH)CO_2Et$	40		122	ammonolysis of 8, picrate derivative, m. 146°	13
10	2	$-CHCHOHCO_2H$	90		224	9 and NaOH	13
11	2	2-thienyl		EtOH	118		14
12	2	p-aminophenyl				no constants	15
13	2	p-N-(p-aminophenylsulfonyl)aminophenyl				No constants	15
14	2	m-nitrophenyl	100		196		15,16
15	2	m-aminophenyl			165	redn of 14	15
16	2	m-(2,5-diMe-1-pyrryl)phenyl			141	15 and $(CH_2Ac)_2$	15
17	5	-CN		EtOH	176-8		17
18	2	p-nitrophenyl			191-2		16
19	2	o-nitrophenyl			114.8-15.2		16
20	2	p-hydroxyphenyl			204		18
21	2	m-methoxyphenyl			85	methylation of 2-(m-hydroxyphenyl)quinoxaline	19

(14) Musante and Parrini, Sperimentale Sez. chim. biol., 3, 140-53 (1952).

(15) Buu-Hoi and Khoi, Bull, soc. chim. France, 1950, 753-7.

(16) Steinbach and Becker, J. Am. Chem. Soc., 76, 5808-10 (1954).

(17) Landquist, J. Chem. Soc., 1953, 2816-21.

(18) Fodor, Beke and Kovacs, Magyar Kem. Folyoirat, 56, 24-30 (1950).

(19) Kovacs and Tombacz, Acta Univ. Szeged., Chem. et Phys., 3, 35-7 (1950).

No.	R	Group	% Yld	Xtalzn Solvent	M. P. °C.	Remarks	Ref.
22	2	m-acetoxyphenyl			207	acetylation of 2-(m-hydroxyphenyl)quinoxaline	19
23	2	m-benzoyloxyphenyl			118	benzoylation of 2-(m-hydroxyphenyl)quinoxaline	19
24	2	p-methoxyphenyl			102	compounds 24-30 prepared by methods similar to those used for the preparation of compounds 21-23	19
25	2	p-acetoxyphenyl			125		19
26	2	p-benzyloxyphenyl			130		19
27	2	p-benzoyloxyphenyl			152		19
28	2	3,4-dimethylphenyl			120		19
29	2	3,3-dibenzoyloxyphenyl			172		19
30	2	3,4-dibenzyloxyphenyl			118		19
31	2	p-acetamidophenyl			218-20		20
32	2	p-aminophenyl			167-9	Hydrolysis of 31	20
33	2	p-benzylideneaminophenyl			140	benzaldehyde and 32	20
34	2	p-fluorophenyl			121.8-2.3		21
35	2	3-fluoro-4-hydroxyphenyl			221.8-2.9		21
36	2	5-fluoro-2-methoxyphenyl			117		22

(20) Musante and Parrini, Gazz. chim. ital., 81, 451-63 (1951).

(21) Minor and Vanderwerf, J. Org. Chem., 17, 1425-30 (1952).

(22) Buu-Hoi, Lavit and Xuong, J. Org. Chem., 19, 1617-21 (1954).

No.	R	Group	% Yld	Xtalzn Solvent	M. P. °C.	Remarks	Ref.
37	2	3-hydroxy-4-methoxyphenyl		EtOH-water	142-3		23,24
38	2	p-(N-tolyl)iminomethyl			120-1		25
39	2	p-(N-carboxyphenyl)iminomethyl			288		25
40	2	p-(N-carboxyphenyl)aminomethyl			160-190		25
41	2	phthalimidomethyl	60	EtOH	227-8		26
42	2	1-phthalimidoethyl	66	EtOH	124-5	from nitrone of $o\text{-}C_6H_4(CO)_2NCH_2COCHN(O)\text{-}p\text{-}C_6H_4NMe_2$ and o-phenylenediamine	26
43	2	(+) 1-phthalimidoethyl		EtOH	119	from (-) 1-phthalimidoethyl glyoxal and o-phenylenediamine; $[\alpha]_D^{25}$ 9.38 ± (0.1°)	27
44	2	2-phthalimidoethyl	70	EtOH-Et_2O	194-6	prepared by same method as compound 42	26
45	2	2-phthalimidopropyl	no constants				26
46	2	4-biphenylyl			128-30		27
47	2	4'-chloro-4-biphenylyl	no constants				27
48	2	1,5-di-p-bromophenyl-1,2,4,5-tetraaza-1,3-penta-1,3-dienyl-2			208-12		28

(23) Fodor, Kovacs and Mecher, Acta Chim. Acad. Sci. Hung., 1, 395-402 (1951).

(24) Kovacs and Fodor, Chem. Ber., 84, 795-801 (1951).

(25) Leese and Rydon, J. Chem. Soc., 1955, 303-9.

(26) Borkovec, Michalsky, Rabusic and Hadacek, Chem. Listy, 48, 717-21 (1954).

(27) Balenovic, Cerar and Filipovic, J. Org. Chem., 18, 868-71 (1953).

(28) Ried and Hoffschmidt, Ann., 581, 23-9 (1953).

No.	R	Group	% Yld	Xtalzn Sol-vent	M.P. °C.	Remarks	Ref.
49	2	6-methylthio-2-naphthyl			179		29
50	2	3-phenanthryl		EtOH	189-90		30
51	2	Δ^4-17α-hydroxy-11-oxoandrostene-17β			242-3 dec.		31
52	5	methyl			20-21		17
53	5	ethyl			b.p. 97-100/3 mm.		32
54	5	nitro	70		93-4		33
55	2	3-sulfanilamidophenyl			233		34
56	2	m-(N^4-acetylsulfanilamidophenyl)			255		34
57	2 3	Et n-Pr			45		32
58	2 3	isoPr isoPr			74		32
59	2 3	Et Et			35-7 (b.p. 149/16 mm)		35

(29) Buu-Hoi, Hoan and Lavit, J. Chem. Soc., 1953, 485-9.

(30) Meadow and Whaley, J. Chem. Soc., 1954, 1162-3.

(31) Leansa, Conbere, Rogers and Pfister, J. Am. Chem. Soc., 76, 1691-4 (1954).

(32) Landquist and Stacey, J. Chem. Soc., 1953, 2822-30.

(33) Schultz, J. Am. Chem. Soc., 72, 3824 (1950).

(34) Bower, Stephens and Wibberly, J. Chem. Soc., 1950, 3341-3344.

(35) Landquist and Stacey, Brit. 668,412, Mar. 19, 1952.

No.	R	Group	% Yld	Xtalzn Solvent	M. P. °C.	Remarks	Ref.
60	2 3	Pr Pr			43-5 (b.p. 172-4/22mm)		35
61	2 3	Me Pr			60-1		35
62	2 3	Me isoPr			40-2.5 (b.p. 130-2/12mm)		35
63	2 3	Me Me		Skelly-solve C	100-1		17
64	2 3	Me 1-thia-3,4-diaza-2-aminopenta-1,4-dienyl-5	30		251-2 dec.		28
65	2 3	p-chlorophenyl p-chlorophenyl			225		36
66	2	p-bromophenyl p-bromophenyl			244		36
67	2	p-methoxyphenyl p-methoxyphenyl			192		36
68	2 3	1-naphthyl 1-naphthyl			251		36
69	2 3	2-naphthyl 2-naphthyl			227		36
70	2 3	isobutyl isobutyl			147		36
71	2 3	dimethyl methyl phosphonate dimethyl methyl phosphonate	70.8		115-16		37

(36) Keglevic, Malnar and Tomljenovic, Arkiv. Kem., 26, 67-9 (1954).

(37) Arbuzov and Zoroastrova, Izvest. Akad. Nauk, S. S. S. R., Otdel. Khim. Nauk, 1954, 806-11.

No.	R	Group	% Yld	Xtalzn Solvent	M. P. °C.	Remarks	Ref.
72	2	methyl phosphonic acid			234 dec.		37
	3	methyl phosphonic acid					
73	2	diethyl methyl phosphonate			92-3		37
	3	diethyl methyl phosphonate					
74	2	diisopropyl methyl phosphonate			102-3		37
	3	diisopropyl methyl phosphonate					
75	2	di-n-propyl methyl phosphonate			non-crystalline		37
	3	di-n-propyl methyl phosphonate					
76	2	methyl			136		38
	3	p-nitrophenyl					
77	2	bromomethyl			200-1	from o-phenylene-	
	3	p-nitrophenyl				diamine with either p-nitrobenzoyl acetyl or 1-(p-nitrobenzoyl)1-acetamido-2-bromoethyl-ene	
78	2	phenylmethyl			167		39
	3	p-nitrophenyl					
79	2	p-nitrophenyl			148-9		39
	3	p-methoxyphenylmethyl					
80	2	methyl			131	from o-phenylene-	40
	3	p-nitrophenyl				diamine and p-nitrophenylmethyl glyoxal or from o-phenylenediame and p-nitrobenzoyl acetyl	39

(38) Sicker, Svoboda, Farkas and Sorm, Collection Czechoslov. Chem. Communs, 19, 317-29 (1954)

(39) Petrov, Stephenson and Sturgeon, J. Chem. Soc., 1953, 4066-75.

(40) Alberti, Bernardi, Camerino, Redaelli and Vercellone, Gazz. chim. ital., 83, 922-9 (1953).

No.	R	Group	% Yld	Xtalzn Solvent	M. P. °C.	Remarks	Ref.
81	2 3	methyl 2-benzsuberonyl ethylenyl-1			243-4		41
82	2 3	methyl 2-(4-ethoxy-3-methoxy-benzoyl)-4-ethoxy-5-methoxyphenyl			217-19		42
83	2 3	cyano phthalimidomethyl	74		225		43
84	2 3	cyano phthalimidoethyl	70		204		43
85	2 3	cyano phthalimidopropyl	65		180		43
86	2 3	cyano 1-phthalimidoethyl	78		183		43
87	2 3	cyano 2-phthalimidopropyl	74		196		43
88	2 3	phenyl $-CH_2NHC(O)NHC(O)CH_3$			268-70		44
89	2 3	phenyl 3-thienyl		EtOH	131-2		45

(41) Ott and Tarbell, J. Am. Chem. Soc., 74, 6266-72 (1952).

(42) Muller, Toldy, Halni and Meszaros, J. Org. Chem., 16, 481-91 (1951).

(43) Michalsky, Borkovec and Hadacek, Chem. Listy, 49, 1379-84 (1955).

(44) Szekeres and Fodor, Izvest. Akad. Nauk S. S. S. R., Otdel. Kim. Nauk, 1953, 996-1002.

(45) Campaigne and Burgeois, J. Am. Chem. Soc., 75, 2702-4 (1953).

No.	R	Group	% Yld	Xtalzn Solvent	M. P. °C.	Remarks	Ref.
90	2	3-thienyl		EtOH	134-5		45
	3	3-thienyl					
91	2	o-methylphenyl			135		46
	3	o-methylphenyl					
92	2	phenyl			124-5		47
	3	o-chlorophenyl					
93	2	phenyl			96-7		48
	3	Phenylmethyl					
94	2	benzoyloxymethyl			137		49
	3	benzoyloxymethyl					
95	2	5-bromo-2-hydroxyphenyl			225	from 5,5'-dibromo-salisil and o-phenylenediamine; boiling the quinoxaline with Ac_2O gave the diacetate, m. p. 193-4° C. An isomeric diacetate, m. p. 147-8° C., was obtained by the reaction of o-phenylenediamine with $(5,2\text{-Br(AcO)}C_6H_3CO)_2$. The latter diacetate was converted to the former diacetate by refluxing acetic acid.	50
	3	5-bromo-2-hydroxyphenyl					
96	2	2'-ethoxyethyl			67		32
	3	methyl					
97	2	methyl			156-6.5		32
	3	2'-phenoxyethyl					
98	2	3-methoxy-4-hydroxyphenyl			228.2-9.5		51
	3	3-methoxy-4-hydroxyphenyl					

(46) Bell, J. Chem. Soc., 1952, 5047-8.

(47) Shapiro and Becker, J. Am. Chem. Soc., 75, 4769-75 (1953).

(48) House, J. Am. Chem. Soc., 76, 1235-7 (1954).

(49) Lederer, Ann., 583, 29-36 (1953).

(50) Kuhn and Birkofer, Chem., Ber., 84, 659-66 (1951).

(51) Johnson and Marshall, J. Am. Chem. Soc., 77, 2335-6 (1955).

No.	R	Group	% Yld	Xtalzn Solvent	M. P. °C.	Remarks	Ref.
99	2 3	phenyl benzhydryl			198-9		48
100	2 5	2-thienyl nitro			170-1		14
101	2 7	2-thienyl nitro			245-7		14
102	2 3	2-(6-methylquinolyl) 2-(6-methylquinolyl)			202-3		52
103	2 3	5-chloro-2-methoxyphenyl 5-chloro-2-methoxyphenyl			215-16		53
104	2 3 7	methyl methyl methyl			72-3; b.p. 134-7/10mm		32
105	3 6 7	methyl methyl methyl			116		32
106	2 3 6	phenyl phenyl isopropyl	100	EtOH	136-7		54
107	2 3 5	phenyl phenyl trifluoromethyl			139		55

(52) Buehler and Edwards, J. Am. Chem. Soc., 74, 977-9 (1952).

(53) Deliwala and Rajagopalan, Proc. Indian Acad. Sci., 31A, 107-16 (1950).

(54) Biekart, Verkade and Webster, Rec. trav. chim., 71, 340-2 (1952).

(55) Sykes and Tatlow, J. Chem. Soc., 1952, 4078-9.

No.	R	Group	% Yld	Xtalzn Solvent	M. P. °C.	Remarks	Ref.
108	2	methyl			93		32
	3	methyl					
	8	trifluoromethyl					
109	2	phenyl			127		56
	3	phenyl					
	6	trifluoromethyl					
110	2	phenyl			196-8	acetate, m. 215-7	57
	3	phenyl					
	5	p-N-methylaminophenyl					
111	2	methyl			199-200		35
	3	methyl					
	6	cyano					
112	2	5-chloro-2-methoxyphenyl			165-6		53
	3	5-chloro-2-methoxyphenyl					
	6	methyl					
113	2	p-acetamidophenyl			198-9		34
	3	p-acetamidophenyl					
	6	cyano					
114	2	p-aminophenyl			280-2		34
	3	p-aminophenyl					
	6	cyano					
115	2	p-acetamidophenyl			254		34
	3	p-acetamidophenyl					
	6	amidino					
116	2	p-aminophenyl			190		34
	3	p-aminophenyl					
	6	amidino					
117	2	2-thienyl		AcOH	245-7		14
	5	nitro					
	7	nitro					

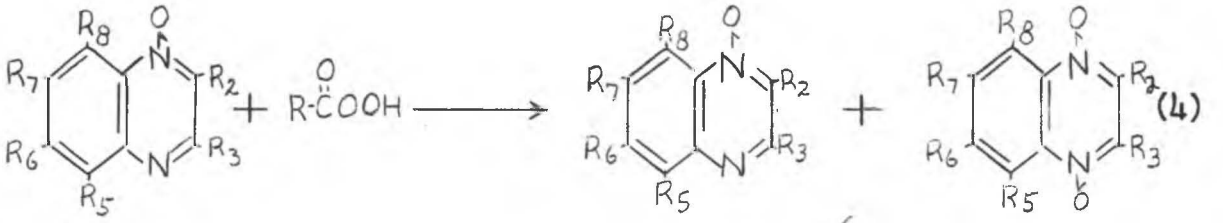
(56) Whalley, J. Chem. Soc., 1950, 2792-4.

(57) Clemo and Lee, J. Chem. Soc., 1954, 2417-19.

No.	R	Group	% Yld	Xtalzn Solvent	M. P. °C.	Remarks	Ref.
118	2	phenyl			142.5-3.5		58
	3	phenyl					
	5	methyl					
	8	methyl					
119	2	2-thienyl			185		14
	6	methyl					
	(?)	nitro					
	(?)	nitro				two nitro groups in thienyl ring, one in quinoxaline ring	
	(?)	nitro					

2. Quinoxaline N-Oxides.

The quinoxaline N-oxides are readily prepared by the oxidation of the quinoxalines with peroxy acids according to equation 4. Negative substituents



promote the simultaneous formation of 2,3-dihydroxyquinoxalines, and resistance to N-oxidation, due to steric and/or polar influences, is encountered in 5- and 8-substituted quinoxalines (17). The reaction of phosphorous oxychloride on the mono- and di-N-oxides of unsubstituted quinoxaline gives 2-chloro and 2,3-dichloroquinoxalines, respectively. The N-oxides of 5-methyl and 5,6-benzoquinoxalines similarly give chloroquinoxalines (17).

Landquist (59) reported the photochemical decomposition of quinoxaline 1-oxide to give 2-hydroxyquinoxaline. Other oxides also decomposed under

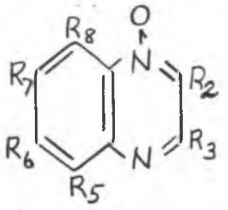
(58) Helden, Verkade and Wepster, Rec. trav. chim., 73, 39-59 (1954).

(59) Landquist and Stacey, J. Chem. Soc., 1953, 2830-3.

the same treatment, but a complex mixture of unidentified products resulted.

Tables II and III list the quinoxaline oxides prepared.

Table II. Quinoxaline N-Oxides.



R_2, R_3, R_5, R_6, R_7, R_8 are hydrogen except as indicated differently by the table. Recrystallization solvent, when given, is in parentheses following the melting point.

No.	R	Substituent	M. P. °C.	Remarks	Ref.
1	8	hydroxy	132		60
2	3	ethyl carboxylate	156-7 (MeOH)	Yield 80.1%	61
3	3	carboxylic acid	180-2 (EtOH) 230-30.5 (EtOH), amide of 3 216-7 (EtOH-water), hydrazide of 3 185-6 (water), potassium hydroxamate of 3		61
4	3	phenyl	137-8		32
5	2 3	methyl methyl	92-3		32
6	2 3	methyl isopropyl	72-3		32
7	2 3	acetyl methyl	238		32
8	2 3	phenyl phenyl	197		32

(60) Evans and Linsker, U. S. 2,518,130, Aug. 8, 1950.

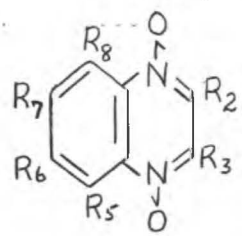
(61) Elina and Magidson, Zhur. Obschchei Khim., 25, 161-8 (1955).

No.	R	Substituent	M. P. °C.	Remarks	Ref.
9	2	methyl	98-9		32
	3	methyl			
	5	methyl			
10	2	methyl	133-5		32
	6	methyl			
	7	methyl			
11	2	methyl	169-71		32
	3	methyl			
	6	cyano			
12	2	methyl	157-8		32
	3	methyl			
	5	nitro			
13	2	p-methoxyphenyl	156		32
	3	p-methoxyphenyl			
14	2	methyl	114-6		32
	3	methyl			
	5	chloro			
15	2	methyl	238		32
	3	methyl			
	6	chloro			
	7	chloro			
16	2	methyl	100-120		32
	3	methyl			
	5,6	benzo			
17	5	methyl	131-2		62
18	5,6	benzo			
19	5	ethoxy	114-6		62
20	3	chloro	150-2		62
21	5	chloro	177-9		62
22	6	chloro	151-2		62

(62) Kyryacos and Schultz, J. Am. Chem. Soc., 75, 3597-8 (1953).

No.	R	Substituent	M. P. °C.	Remarks	Ref.
23	5	acetamido	175-8		62
24	5 6	methoxy methoxy	138-40		62
25	6 7	chloro methyl	166-8		62
26	6 7	bromo methyl	167-8		62
27	5,6 7,8	benzo benzo	243-4		62

Table III. Quinoxaline N,N'-Dioxides.



R_2, R_3, R_5, R_6, R_7, R_8 are hydrogen except as indicated differently by the table.

No.	R.	Substituent	M. P. °C.	Remarks	Ref.
1	2	ethyl	150-2		32
2	2	phenyl	202-3		32
3	2	carboxaldehyde	189-90		32
4	2	carboxylic acid	208-9		32
5	6	amino	245 dec.		32
6	5	methyl	192-4		62
7	6	methyl	218-9		62
8	5	methoxy	222		62
9	6	methoxy	227-8		62

No.	R	Substituent	M. P. °C.	Remarks	Ref.
10	6	ethoxy	192-4		62
11	6	chloro	211-2		62
12	6	bromo	223-5		62
13	5	acetamido	230-2		62
14	6	acetamido	245-6		62
15	6	$-NHCOCH_2CH_2CO_2H$	242-4		62
16	3,4	benzo	215-6		62
17	2 3	methyl methyl	189-90		32
18	2 3	methyl ethyl	139-40		32
19	2 3	methyl n-propyl	108-110		32
20	2 3	methyl isopropyl	193-4		32
21	2 3	methyl phenyl	193-4		32
22	2 3	benzyl methyl	155		32
23	2 3	methyl 2-p-chlorophenylethyl	168-9		32
24	2 3	methyl 2'-phenoxyethyl	146		32
25	2 3	methyl 2'-ethoxyethyl	117		32
26	2 3	ethyl ethyl	108		32
27	2 3	ethyl n-propyl	85-7		32

No.	R	Substituent	M. P. °C.	Remarks	Ref.
28	2	n-propyl	74-6		32
	3	n-propyl			
29	2	phenyl	216		60,32
	3	phenyl			
30	2	p-methoxyphenyl	183-4		32
	3	p-methoxyphenyl			
31	2	2-p-chlorophenylethyl	150-1		32
	3	2-p-chlorophenylethyl			
32	6	methyl	220		32
	7	methyl			
33	5	methoxy	220-2		32
	6	methoxy			
34	6	methoxy	264-5		32
	7	methoxy			
35	6	chloro	206-8		32
	7	chloro			
36	6	chloro	227		32
	7	methyl			
37	6	bromo	222-4		32
	7	methyl			
38	2	methyl	165-6		32
	3	methyl			
	6	methyl			
39	2	methyl	185-7		32
	6	methyl			
	7	methyl			
40	2	methyl	206-8		32
	3	methyl			
	5	methoxy			
41	2	methyl	197-8		32
	3	methyl			
	6	methoxy			
42	2	methyl	160-2		32
	3	methyl			
	6	ethoxy			

No.	R	Substituent	M. P. °C.	Remarks	Ref.
43	2	methyl	175-6		32
	3	methyl			
	6	chloro			
44	2	methyl	155-6		32
	3	methyl			
	6	trifluoromethyl			
45	2	methyl	186-8		32
	3	methyl			
	6	bromo			
46	2	methyl	216-18		32
	3	methyl			
	6	cyano			
47	2	methyl	192-4		32
	3	methyl			
	6	nitro			
48	2	methyl	268 dec.		32
	3	methyl			
	6	amino			
49	2	methyl	259-60		32
	3	methyl			
	6	acetamido			
50	2	methyl	198-201		32
	3	methyl			
	6	diethylmalonimido			
51	2	methyl	276 dec.		32
	3	methyl			
	6	p-toluenesulphonamido			
52	2	propyl	------		32
	3	propyl			
	6	chloro			
53	2	methyl	247-9		32
	3	methyl			
	6	methyl			
	7	methyl			
54	2	methyl	275-7		32
	3	methyl			
	6	methoxy			
	7	methoxy			

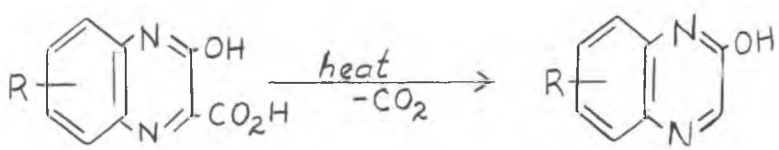
No.	R	Substituent	M. P. °C.	Remarks	Ref.
55	2	methyl	250-2		32
	3	methyl			
	7	methyl			
	6	chloro			
56	2	methyl	242-4		32
	3	methyl			
	6	bromo			
	7	methyl			
57	6	bromo	222-4		62
	7	methyl			
58	6	chloro	227		62
	7	methyl			
59	6	chloro	206-8		62
	7	chloro			
60	6	methoxy	264-5		62
	7	methoxy			
61	5	methoxy	220-2		62
	6	methoxy			
62	6	methyl	220		62
	7	methyl			

The preparation of one salt of the quinoxaline oxides has been reported by Landquist (32). This salt is 2-amino-1,6-dimethyl-4-(2',3'-dimethyl-6'-quinoxalinyl)aminopyridinium iodide, m. p. 240° C. dec.

3. Hydroxyquinoxalines.

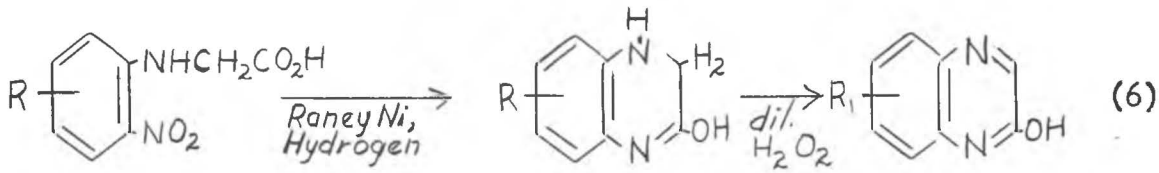
This group of compounds may be prepared by the following general methods:

(a) Decarboxylation of the corresponding acids as in equation 5.



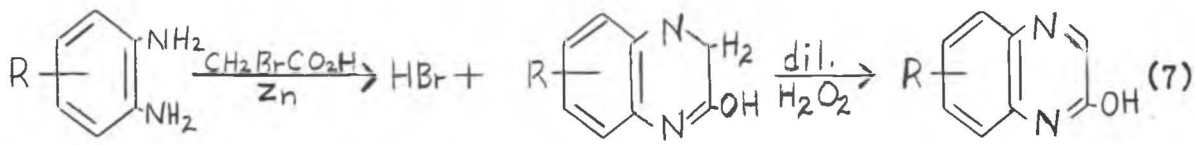
(5)

(b) Reduction of the appropriately substituted 2-nitrophenylglycine with subsequent oxidation of the initially formed 3,4-dihydroquinoxaline according to equation 6.



(6)

(c) Interaction of an o-phenylenediamine with bromoacetic acid, equation 7. If the amine is substituted at position 3 or 4 an isomeric mixture will result.



(7)

(d) Condensation of an o-phenylenediamine with an ester of glyoxylic acid, equation 8. As in the 3rd method of preparation of hydroxyquinoxalines,

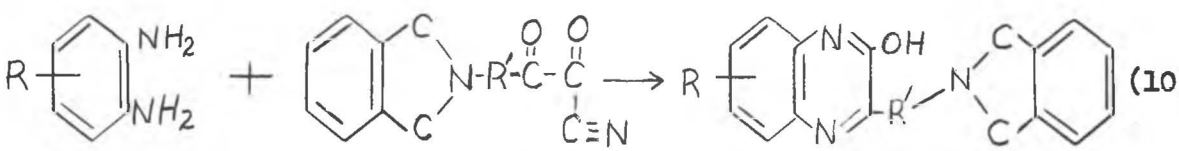
(8)

an isomeric mixture may result if the o-phenylenediamine is substituted at position 3 or 4.

(e) Reaction of alpha-keto acids with an o-phenylenediamine gives 2-hydroxy-3-alkylquinoxalines according to equation 9.

(9)

(f) Reaction of an o-phenylenediamine with phthalimido-N-alkyl-2,3-diketopropionitrile to give 2-hydroxy-3-o-phthalimidoquinoxalines according to equation 10.



(10)

In the preceding methods, if the diamine contains a hydroxy or other substituent in the benzene ring, then the corresponding hydroxy substituted (or alkyl substituted) quinoxaline will result.

Hinsberg (63, 64, 65) early reported the preparation of 2-hydroxy-3,7-dimethylquinoxaline and the isolation of another hydroxyquinoxaline. His synthesis route, however, was not unambiguous. Marks and Shultz (66) have now prepared both 2-hydroxy-3,6-dimethylquinoxaline and 2-hydroxy-3,7-dimethylquinoxaline by unequivocal methods. The ethyl ester of N-(2-acetamido-5-methyl-phenyl)-dl-α-alanine was treated with water and concentrated sulfuric acid for 4 hours on the steam bath, cooled, neutralized, precipitate filtered, heated 2 hours on the steam bath in 8% sodium hydroxide solution and 3% hydrogen peroxide, cooled, brought to a pH of 4, and the

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(63) Hinsberg, Ann., 237, 351 (1887).

(64) Hinsberg, Ann., 248, 77 (1888).

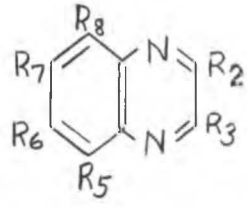
(65) Hinsberg, Ann., 25, 2419 (1892).

(66) Schultz and Marks, J. Am. Chem. Soc., 73, 1368-70 (1951).

yellow crystals of 2-hydroxy-3,6-dimethylquinoxaline, m. p. 254-5° C., obtained in 9% yield. The 2-hydroxy-3,7-dimethylquinoxaline compound, m. p. 243-4° C., was obtained in 43% yield from N-(2-nitro-4-methylphenyl-dl-α-alanine.

Table IV lists the hydroxyquinoxaline compounds prepared since 1950.

Table IV. Hydroxyquinoxalines.



R_2, R_3, R_5, R_6, R_7, R_8 are hydrogen except as indicated differently by the table.

No.	R	Substituent	% Yld	M. P. °C.	Remarks	Ref.
1	6	hydroxy	Compounds 2-9, yields averaged			67
2	5	hydroxy	80%	99.5	Compounds 2-9 prepared from alpha-keto acids	68
3	2 3	hydroxy ethyl		198	and o-phenylenediamine. The yields and m. p.s given in parentheses are	69
4	2 3	hydroxy methyl		250	for the preparation of the same compounds, but from the 2-halo acids and	69
5	2 3	hydroxy n-propyl	(15)	182-3 (184-5)	o-phenylenediamine, reference 70.	70,69
6	2 3	hydroxy isopropyl	(14)	228.5 (233-4)		70,69
7	2 3	hydroxy butyl	(34)	153.5-4 (154-5)		70,69

(67) Sorkin and Roth, Helv. Chim. Acta, 34, 427-30 (1951).

(68) Albert and Hampton, J. Chem. Soc., 1952, 4985-93.

(69) Morrison, J. Am. Chem. Soc., 76, 4483 (1954).

(70) Goldweber and Schultz, J. Am. Chem. Soc., 76, 287-8 (1954).

No.	R	Substituent	% Yld	M. P. °C.	Remarks	Ref.
8	2 3	hydroxy isobutyl		186-7		69
9	2 3	hydroxy tert-butyl		above 300, dec.		69
10	2 3	hydroxy sec-butyl		180-1		69
11	2 3	hydroxy phthalimidomethyl	83	315		43
12	2 3	hydroxy phthalimidoethyl	76	307-8		43
13	2 3	hydroxy phthalimidopropyl	82	286-8		43
14	2 3	hydroxy phthalimidoethyl-1	87	225-6		43
15	2 3	hydroxy 2-phthalimido-2methylethyl	88.5	235-6		43
16	2 3 6	hydroxy methyl methyl	9	254-5		43
17	2 3 7	hydroxy methyl methyl	43	243-4		43
18	2 3	hydroxy amyl		151-2		70
19	2 3	hydroxy hexyl	31	140-1		70
20	2 3	hydroxy bromomethyl		225 dec.		25
21	2 3	hydroxy p-carboxyaminomethylphenyl		200 dec.		25
22		phloroglucinol		131-2	Salt of quinoxaline.	71

(71) Verkade and van Leeuwen, Rec. trav. chim., 70, 142-5 (1951).

No.	R	Substituent	% Yld	M. P. °C.	Remarks	Ref.
					2:1 mole ratio of hydroxy compound to base	
23	2 3	hydroxy -CHOHCHOHCHOHCH$_2$OH		160	$[\alpha]_D^{20}$ -7°	72
24	2 3	hydroxy 2,4,5-trihydroxyphenyl		above 350		73
25	2 3	hydroxy n-3-oxa-2-oxopentyl	75-80	210		74
26	2 3	hydroxy -CH(CH$_3$)CO$_2$Et	100	160-2		74
27	2 3	hydroxy ethyl	75	198	monohydrate; by hydrolysis of ethyl alpha-(2-hydroxy-3-quinoxalyl)propionate	74
28	2 3	hydroxy 2'-(3-hydroxyquinoxalyl)ethyl	80	327		75
29	2 3	hydroxy carboxyureide	90	250	by condensing o-phenylenediamine and alloxan	76
30	2 3	hydroxy carboxylic acid			by hydrolysis of compound 29	76
31	2 3 6 7	hydroxy carboxyureide methyl methyl		274-5 dec.	from 4,5-dimethyl-o-phenylenediamine and alloxan	77

(72) Ettel, Liebster and Tadra, Chem. Listy, 46, 45-8 (1952).

(73) Ralph and Robertson, J. Chem. Soc., 1950, 3380-3.

(74) L'Italien and Banks, J. Am. Chem. Soc., 73, 3246-7 (1951).

(75) Kuhn and Dury, Ann., 571, 44-68 (1951).

(76) King and Clark-Lewis, J. Chem. Soc., 1951, 3379-82.

(77) Haley and Lambooy, J. Am. Chem. Soc., 76, 2926-9 (1954).

No.	R	Substituent	% Yld	M. P. °C.	Remarks	Ref.
32	2 3	hydroxy 1-(2-azacarbazole)		343-5	from 5-hydroxycanthinone and o-phenylenediamine	78
33	2 3	hydroxy 2-hydroxy-4-methoxyphenyl	82	312		79
34	2 3	hydroxy 4-ethoxy-2-hydroxyphenyl	78	277-8		79
35	2 3	hydroxy 4-hydroxy-2-methoxyphenyl	73	294-9		79
36	2 3	hydroxy 2-hydroxy-4,5-dimethoxyphenyl	73	287-8		79
37	2 3	hydroxy 4-hydroxynaphthalene-1	70	above 340		79
38	2 3	hydroxy 1-hydroxynaphthalene-2	68	332-3		79
39	2 3	hydroxy $-C(Et)_2CH_2CO_2H$		201-2		80
40	2 6	hydroxy nitro		294 dec.		81
41	2 3	hydroxy $-C(Pr)_2CH_2CO_2H$		248	from N-(2-nitro-3-methylphenyl)-dl-alanine	80
42	2 3	2-thienyl hydroxy				14

(78) Haynes, Nelson and Price, Australian J. Sci. Research, A5, 563-9 (1952).

(79) Chatterjea, J. Indian Chem. Soc., 31, 194-202 (1954).

(80) Bhattacharyya, Current Sci., 21, 312-13 (1952).

(81) Horner, Schwenk and Junghanns, Ann., 579, 212-34 (1953).

No.	R	Substituent	% Yld	M. P. °C.	Remarks	Ref.
43	2	hydroxy		256.5-7.5		62
	3	methyl				
	5	methyl				
44	2	hydroxy	34	256.5-7.5		62
	3	methyl				
	8	methyl				
45	2	hydroxy		252 dec.		81
	3	methyl				
	7	nitro				
46	2	hydroxy	1			17
	3	hydroxy				
	8	methyl				
47	2	hydroxy	30			17
	3	hydroxy				
	7	chloro				
48	2	hydroxy	15-30	Compounds 47-55 obtained by the oxidation of the quinoxaline with peroxy acids. No melting points given for these compounds.		17
	3	hydroxy				
	8	chloro				
49	2	hydroxy	28			17
	3	hydroxy				
	8	bromo				
50	2	hydroxy	65			17
	3	hydroxy				
51	2	hydroxy	43			17
	3	hydroxy				
	6	chloro				
	7	chloro				
52	2	hydroxy	10			17
	3	hydroxy				
	6	chloro				
	7	methyl				
53	2	hydroxy	12-16			17
	3	hydroxy				
	6	bromo				
	7	methyl				

No.	R	Substituent	% Yld	M. P. °C.	Remarks	Ref.
54	2	hydroxy	50			17
	3	hydroxy				
	8	cyano				
55	2	hydroxy	60	355		64,17
	3	hydroxy				
	8	nitro				
56	2	hydroxy		270		64
	3	hydroxy				
	6	nitro				
	8	nitro				

4. Quinoxalinealdehydes.

The syntheses of two quinoxaline aldehydes by the selenium dioxide oxidation of 2,3-dimethylquinoxaline were reported during the period 1950-1954 (82). The products obtained were: 3-methyl-2-quinoxalinecarboxaldehyde, m. p. 138° C., p-nitrophenylhydrazone derivative, m. p. 250° C.; and 2,3-quinoxalinedicarboxaldehyde, no melting point given, 2,4-dinitrophenylhydrazone derivative, m. p. 279° C. No yields or other properties were given for these compounds.

5. Quinoxalinecarboxylic Acids and Quinoxalinecarboxylic Acid Derivatives.

The preparation and properties of several new compounds of this group are given below.

(a) The condensation of 1,3-dimethylalloxazine with o-phenylenediamine gave the methyl amide of 3-hydroxy-2-quinoxalinecarboxylic acid, m. p. 305-12° C. dec. (83). Recrystallization solvent was water.

(b) The condensation of ethyl 3,4-diaminobenzoate with glyoxal sodium bisulfite in water solution gave 54% yield of ethyl 6-quinoxalinecar-

(82) Seyhan, Chem. Ber., 84, 477 (1951).

(83) Bredereck and Fhleiderer, Chem. Ber., 87, 1119-23 (1954).

boxalate, m. p. 66° C. (84). The free acid melted 266° C. In a similar manner ethyl 2,3-diphenyl-6-quinoxalinecarboxylate was prepared in 40% yield. The hydrazide of this ester was prepared and melted, 235° C.

(c) The condensation of 4,5-diaminosalicylic acid and benzil in acetic acid solution gave 7-carboxy-6-hydroxy-2,3-diphenylquinoxaline, m. p. 252-4° C. (85).

(d) The condensation of 2-thienylglyoxal with 4-methyl-o-phenylenediamine and oxidation of the product gave 2-(2-thienyl)-7-quinoxalinecarboxylic acid, m. p. 288-90° C. (14).

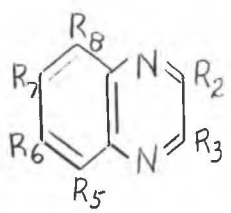
(e) The condensation of 2-thienylglyoxal with 3-hydroxy-4-carboxy-o-phenylenediamine gave 3-(2-thienyl)-6-hydroxy-7-quinoxalinecarboxylic acid, m. p. 213-15° C. dec. (14).

6. Haloquinoxalines.

These compounds were prepared by either the action of phosphorous oxychloride and phosphorous pentachloride on hydroxyquinoxalines or by the condensation of halo substituted o-phenylenediamines with a dicarbonyl compound.

Table V lists the halo compounds prepared.

Table V. Haloquinoxalines.



R_2, R_3, R_5, R_6, R_7, R_8 are hydrogen except as indicated differently by the table.

No.	R	Substituent	% Yld	M. P. °C.	Ref.
1	2	chloro	60	256-7	43
	3	phthalimidomethyl			

(84) Birkofer and Widmann, Chem. Ber., 86, 1295-1302 (1953).

(85) Voorspuij and Nauta, Arzneimittel-Forsch., 4, 544-8 (1954).

No.	R	Substituent	% Yld	M. P. °C.	Remarks	Ref.
2	2 3	chloro phthalimidoethyl	76	155-6		43
3	2 3	chloro phthalimidopropyl	68	195		43
4	2 3	chloro 1-phthalimidoethyl	63.5	152-5		43
5	2 3	chloro 2-phthalimidopropyl	70	158		43
6	2 7	chloro nitro		188		81
7	2 6	chloro nitro		202		81
8	5	chloro		60-2		17
9	6	iodo		114-5		17
10	6	bromo		48-9	b. p. 146-9/18mm	17
11	6 7	chloro methyl		120-2		17
12	6 7	bromo methyl		127-8		17
13	2 6	2-thienyl chloro		119-21		14
14	2 3 5 8	phenyl phenyl fluoro fluoro		191-5		86
15	2 3 5 7	phenyl phenyl fluoro fluoro		137-8		86

(86) Finger, Reed, Burness, Fort and Blough, J. Am. Chem. Soc., 73, 145-9 (1951).

No.	R	Substituent	% Yld	M. P. °C.	Ref.
16	2	phenyl	75	169.5-170	86
	3	phenyl			
	5	fluoro			
	6	fluoro			
	8	fluoro			
17	5	chloro		78-80 b. p. 158/10mm	32
	2	methyl			
	3	methyl			
18	6	chloro		91-2	32
	2	methyl			
	3	methyl			
19	6	bromo		186-8	35
	2	methyl			
	3	methyl			
20	6	chloro		73	35
	2	propyl			
	3	propyl			
21	6	iodo		75-75.5	32
	2	methyl			
	3	methyl			
22	6	chloro		154	32
	2	methyl			
	3	methyl			
	7	methyl			
23	6	bromo		145	32
	2	methyl			
	3	methyl			
	7	methyl			
24	6	methyl		188-90	53
	2	5-chloro-2-methoxyphenyl			
	3	5-chloro-2-methoxyphenyl			
25	6	chloro		198-9	53
	2	4-chloro-2-hydroxyphenyl			
	3	5-chloro-2-hydroxyphenyl			
26	6	chloro		123-4	53
	2	phenyl			
	3	phenyl			

No.	R	Substituent	% Yld	M. P. °C.	Ref.
27	6	chloro		91-2	53
	2	methyl			
	3	methyl			
28	6	chloro		123-4	53
	2	2-chlorophenyl			
	3	2-chlorophenyl			
29	6	chloro		210	17
	7	chloro			
30	5	chloro		205-7	17
	8	chloro			
31	6	chloro		153	87
	7	chloro			
	2	phenyl			
	3	phenyl			
32	5	chloro		146-8	32
	8	chloro			
	2	methyl			
	3	methyl			
33	6	chloro		191-2	32
	7	chloro			
	2	methyl			
	3	methyl			

7. Aminoquinoxalines.

(a) Primary Amino Compounds.

The compounds in this group are prepared by various procedures. The individual methods of preparation, the compounds prepared and their properties are given below.

(87) Davis and Ross, J. Chem. Soc., 1951, 3258.

1. Ring closure of N-(o-aminophenyl)glycinenitriles with strong bases and then oxidation of the resulting 2-amino-3,4-dihydroquinoxalines gives the following aminoquinoxalines with yields and melting points when given (88): 2-amino, m. p. 154-4° C.; 2-amino-6-chloro; 2-(aminomethoxy), m. p. 217.5° C.; 2-aminomethyl, m. p. 136° C.; and 2-amino-7-chloro. Similarly (88), 2-amino-8-methoxyphenyl, m. p. 129-131° C., was obtained in 51% yield.

2. The reaction of 2,4-diamino-1-nitrosobenzene and cyanoacetic acid gives 3,6-diamino-2-quinoxalinecarboxylic acid (89,90). Decarboxylation of 3,6-diamino-2-quinoxalinecarboxylic acid (90) gives the diamino analog, m. p. 204° C. Similarly (89), 3,6-diamino-7-methyl-2-quinoxalinecarboxylic acid, m. p. 248° C., is obtained. This acid is decarboxylated by boiling it in nitrobenzene to give 3,6-diamino-7-methylquinoxaline, m. p. 221° C., picrate derivative, m. p. 288° C. dec. The diacetamidoquinoxaline is prepared by heating 3,6-diamino-7-methylquinoxaline with acetic anhydride. By using cyanoacetamide in place of cyanoacetic acid (89), 3,6-diamino-2-quinoxalinecarboxamide, m. p. 295° C. is obtained. Treatment of 3,6-diaminoquinoxaline with hot acetic anhydride gives the diacetamidoquinoxaline, m. p. 302° C.; picrate derivative, m. p. 200° C. dec. Similarly, 3,6-diamino-2-quinoxalinecarboxamide, m. p. 295° C.; 3,6-diacetamido-2-quinoxalinecarboxamide, softening above 260° C.; and, 6-acetamido-3-amino-7 methylquinoxaline-2-carboxamide, m. p. 315° C. is prepared, (90). The reaction of 6-aminoquinoxaline with acetic anhydride gives the acetamido derivative, m. p. 217° C. dec. (17).

3. The condensation of 3,4,5-triaminonitrobenzene hydrochloride with oxalic acid gives a product presumed to be 6-amino-1,2-dihydroxy-8-oxalamidoquinoxaline, which decomposes on recrystallization from water (81). Careful hydrolysis of the product gives the free diaminodihydroxyquinoxaline, m. p. ca. 300° C. (blackening).

4. Treatment of 6-amino-2,3-dihydroxy-8-methoxyquinoxaline with hydriodic acid gives 2,3,5-trihydroxy-7-aminoquinoxaline, darkening ca. 300° C. (81).

(b) Secondary Aminoquinoxalines.

1. Brederech and Pfleiderer (83), by treatment of 1,3-dimethylalloxazine with hot sodium hydroxide, obtained 3-methylamino-2-quinoxalinecarboxylic acid methyl amide (I), m. p. 171° C. (I) and ethyl chlorocarbonate gives 3-(carbethoxymethylamino)-2-quinoxaline carboxylic acid methyl amide

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(88) Pfister and Weijlard, U. S. 2,650,221, Aug. 25, 1953.

(89) Osdene and Timmis, Chemistry and Industry, 1954, 405-6.

(90) Osdene and Timmis, J. Chem. Soc., 1955, 2027-31.

(II), m. p. 148° C. By heating (II) with sodium hydroxide, then treating with sulfuric acid, 3-methylaminoquinoxaline-2-carboxylic acid (III), m. p. 156-8° C., is obtained. Treatment of (III) with diazomethane gives methyl 3-methylaminoquinoxaline-2-carboxylate.

2. The reaction of 2-chloroquinoxaline with p-aminobenzoate gives ethyl 4-[(2-quinoxaly)amino]benzoate, m. p. 220-1° C. The free acid melts 340° C. dec. (91).

3. Succinic anhydride and 6-aminoquinoxaline gives the N-6-succinamic acid derivative of the aminoquinoxaline (17).

(c) Sulfaquinoxalines.

1. Sulfaquinoxaline salts in yields of about 93% are prepared by refluxing sulfaquinoxaline with alkanolamines in aqueous alcohol solution (92). The alkanolamines used and the m. p. of the salts are given in Table VI.

Table VI. Salts of Sulfaquinoxaline.

Alkanolamine	M. P. °C.
$NH_2CH_2CH_2CH_2OH$	150 dec.
$CH_2OHCH_2NHCH_2CH_2OH$	above 270
$N(CH_2CH_2OH)_3$	140 dec., melts 182
$(CH_3)_2C(NH_2)CH_2OH$	255 dec., melts 257

2. The reaction of p-(p-tolyloxy)phenylsulfonyl chloride with 6-aminoquinoxaline gives the corresponding sulfonamide, m. p. 178.5-9.5° C.,

(91) Drumheller and Schults, J. Am. Chem. Soc., 77, 6637-8 (1955).

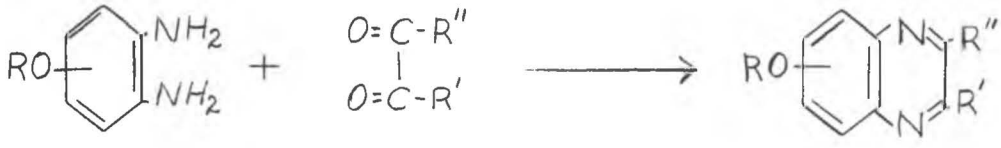
(92) Sweet and Benson, U. S. 2,578,761, Dec. 18, 1951.

hydrolysis of which gives p-hydroxysulfaquinoxaline in 31% yield, m. p. 232.5-34.5° C. (93,94). In a similar manner the 6-methyl analog was also prepared (94).

8. Alkoxy and Aryloxyquinoxalines.

(a) Methods of Preparation.

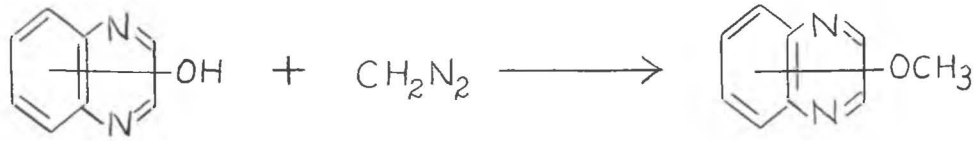
1. Condensation of alkoxy or aryloxy substituted o-phenylenediamines with diketo compounds according to equation 11. Other substituents may also



(11)

be present in either the benzene or the hetero rings.

2. Treatment of the corresponding hydroxy compound with diazomethane, equation 12.



(12)

3. Treatment of a chloroquinoxaline with a sodium alkoxy- or

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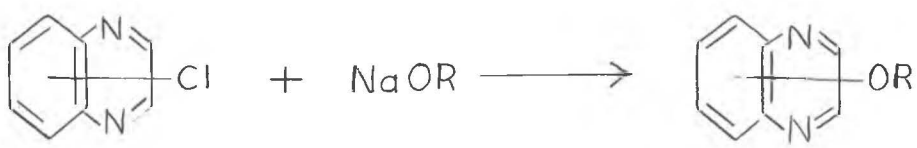
(93) Hultquist, Germann, Webb, Wright, Roth, Smith and SubbaRow, J. Am. Chem. Soc., 73, 2558-66 (1951).

(94) Hultquist and SubbaRow, U. S. 2, 572,728, Oct. 23, 1951.

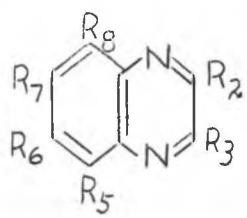
aryloxy- compound in alcohol solution, equation 13.



(13)

Table VII lists the compounds in this group.

Table VII. Alkoxy and Aryloxyquinoxalines.



R_2, R_3, R_5, R_6, R_7, R_8 are hydrogen except as indicated differently by the table.

No.	R	Substituent	% Yld	M. P. °C.	Method of Preparation	Ref.
1	5	methoxy		226-7	1	95
	8	methoxy				
	2	phenyl				
	3	phenyl				
2	5	methoxy		229-30	1	96
	7	methyl				
	2	phenyl				
	3	phenyl				
	8	acetamido				
3	2	methoxy	82	92-3	3	96
	3	methoxy				
4	2	ethoxy	70	77-8	3	96
	3	ethoxy				

(95) Kawai, Kosaka and Hatano, Proc. Japan. Acad., 30, 774-80 (1954).

(96) MacMillan, J. Chem. Soc., 1952, 4019-24.

No.	R	Substituent	% Yld	M. P. °C.	Method of Preparation	Ref.
5	2 3	propoxy propoxy	71	53-4	3	96
6	2 3	isopropoxy isopropoxy	55	93-4	3	96
7	2 3	butoxy butoxy	45	50-1	3	96
8	2 3	isobutoxy isobutoxy	76	d_4^{25} 1.040; n_D^{25} 1.5370	3	96
9	2 3	amyloxy amyloxy	68	1.022; 1.5304	3	96
10	2 3	isoamyloxy isoamyloxy	79	1.014; 1.5290	3	96
11	2 3	hexoxy hexoxy	60	60-5	3	96
12	2 3 5 8	methyl methyl methoxy methoxy		170	1	97
13	5	ethoxy		63-4	1	98
14	6 2	methoxy p-methoxystyryl		162-3	1	99
15	6 2	methoxy 3,4-dimethoxystyryl		137-8	1	99
16	6 2	methoxy 2,3-dimethoxystyryl-4-hydroxy		278-80	1	99

(97) Shinichi, Tanaka and Ichikawa, J. Chem. Soc. Japan, 75, 40-3 (1954).

(98) Easley and Sullivan, J. Am. Chem. Soc., 74, 4450 (1952).

(99) Towle, Iowa State Coll. J. Sci., 26, 308-9 (1952).

No.	R	Substituent	% Yld	M. P. °C.	Method of Preparation	Ref.
17	6	methoxy		140-1	1	99
	2	2,3-methoxystyrylpyridine				
	3	2,3-methoxystyrylpyridine				
18	3	methoxy		225	1	76
	2	carboxyureide				
19	2	methoxy	84	130	by hydrolysis of 18	76
	3	carboxylic acid				
20	5	methoxy		118	1	32
	2	methyl				
	3	methyl				
21	5	ethoxy		90-2	1	32
	2	methyl				
	3	methyl				
22	6	ethoxy		107-9	1	32
	2	methyl				
	3	methyl				
23	5	methoxy		105-7	1	32
	6	methoxy				
	2	methyl				
	3	methyl				
24	6	methoxy		173-4	1	32
	7	methoxy				
	2	methyl				
	3	methyl				
25	5	methoxy		212	2	81
	2	phenyl				
	3	phenyl				
	7	nitro				
26	8	methoxy		285 dec.	1	81
	2	phenyl				
	3	phenyl				
	6	amino				
27	2	methoxy		215	3	81
	3	methyl				
	7	nitro				

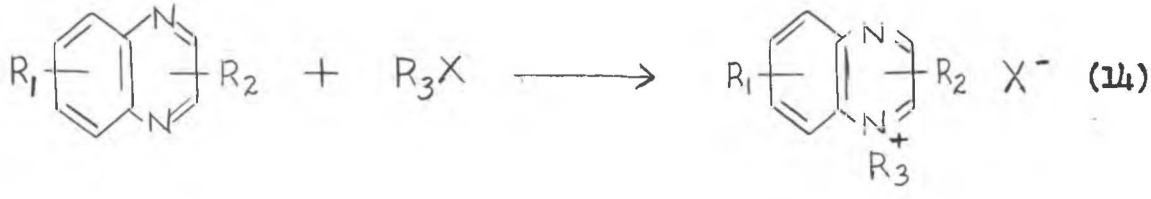
No.	R	Substituent	Yld	M. P. °C.	Method of Preparation	Ref.
28	8 2 6	methoxy hydroxy nitro		276 dec.	1	81
29	8 2 6	methoxy chloro nitro		224	treatment of 28 with $POCl_3$ and PCl_5	81
30	8 3 6	methoxy chloro nitro		168	by chlorination of a mixture of compounds of indefinite composition	81
31	8 6 3	methoxy nitro hydroxy		276-8	by hydrolysis of compound 30	81
32	5 7 2	methoxy amino hydroxy		318-20	by reduction of compound 31	81

9. Quinoxaline Quaternary Salts.

The compounds of this group are of two types: (1) quaternary salts of the nitrogen in the quinoxaline nucleus, Table VIII, and (68) quaternary salts of the nitrogen contained in substituents attached to the quinoxaline nucleus, Table IX.

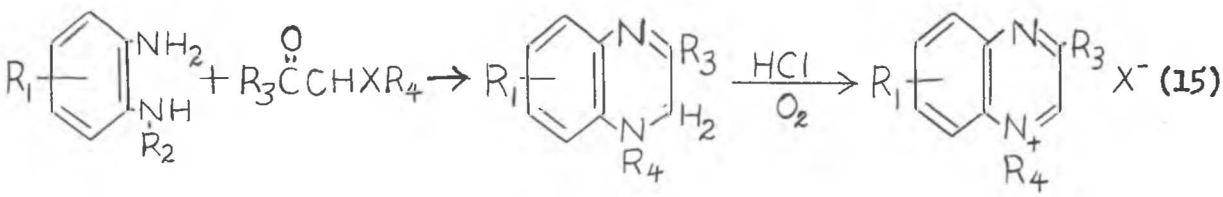
Compounds of the first type are prepared by the following methods:

(a) Direct quaternization of N-unsubstituted quinoxalines, equation 14.



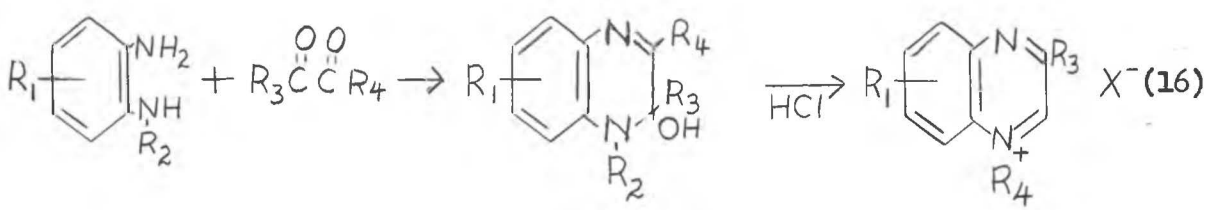
(14)

(b) Condensation of variously substituted N-alkyl o-phenylenediamines with substituted -halo keto compounds in ethanol followed by addition of alcoholic hydrogen chloride and acetate, equation 15.



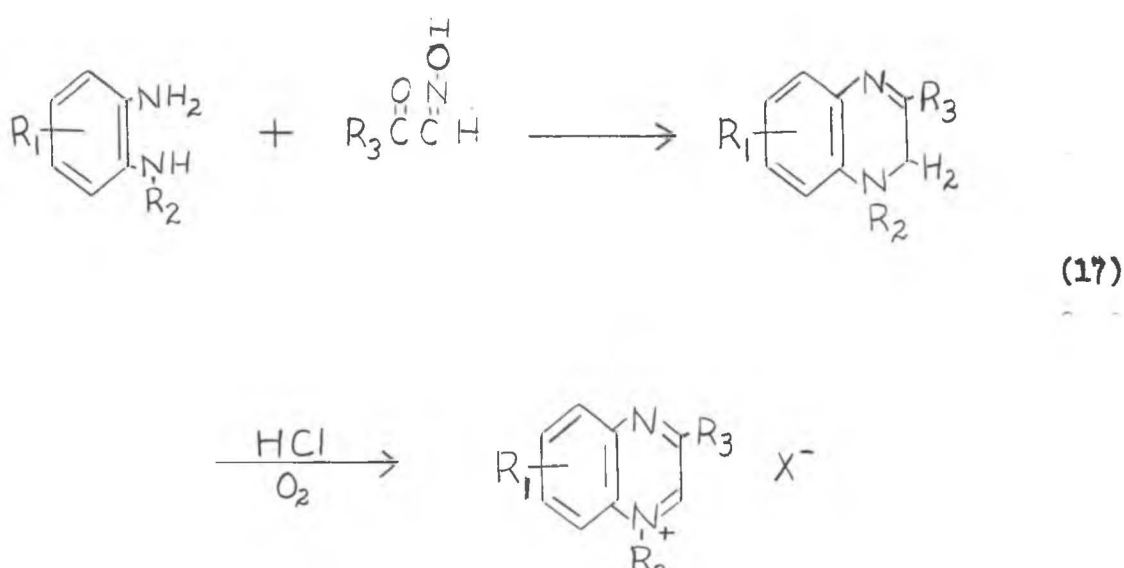
(15)

(c) Condensation of variously substituted N-alkyl o-phenylenediamines, in ethanol containing a slight excess of alcoholic hydrogen chloride, with substituted 1,2-diketo compounds, equation 16, or with the monoxime



(16)

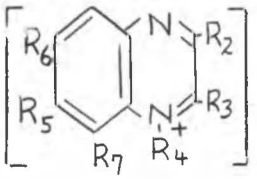
of 1,2-diketo compounds, equation 17.



(17)

Compounds of the second type are prepared by the condensation of a 1,2-diketo bromoalkyl substituted compound with o-phenylenediamine in the presence of pyridine or by the condensation of an α-halo keto compound containing a quaternary group with o-phenylenediamine.

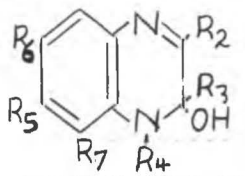
Table VIII. Quinoxaline Quaternary Salts.



X^-

R_2, R_3, R_5, R_6 Are hydrogen except as indicated differently by the table. The melting points given in parenthesis are for the pseudo base. The solvent used (when stated in the literature) is indicated by numbers following the method-of-procedure letter: 1, chloroform; 2, nitrobenzene; 3, no solvent.

Pseudo base



No.	R	Substituent	X^-	% Yld	M. P. °C.	Method of Preparation	Ref.
1	4	2-phenylethyl	iodide	7	146-8	a3	100
2	4	phenacyl	bromide	28	177	a1	100
3	4	p-chlorophenacyl	bromide	27	202.5	a2	100
4	4	p-bromophenacyl	bromide	27	206	a2	100
5	4	m-nitrophenacyl	bromide	72	181	a2	100
6	4	p-methoxyphenacyl	bromide	25	182.5	a2	100
7	4	2-naphthacyl	bromide	73	182	a1	100
8	N,N'	dimethyl	sulfate	17	144-5	a1	100
9	N,N'	diethyl	sulfate	11	171	a1	100
10	4 5	methyl methyl	iodide	88	174-5	a3	100

(100) Easley and Bahner, J. Am. Chem. Soc., 72, 3803-5 (1950).

No.	R	Substituent	X^-	% Yld	M. P. °C.	Method Preparation	Ref.
11	4 5	p-methylphenacyl methyl	bromide	69	192-3	a3	100
12	4 5	p-fluorophenacyl methyl	bromide	54	211	a2	100
13	4 5	p-chlorophenacyl methyl	bromide	29	226-7	a1	100
14	4 5	p-bromophenacyl methyl	bromide	32	226	a1	100
15	4 5	p-methoxyphenacyl methyl	bromide	89	198	a2	100
16	4 5	methyl chloro	iodide	94	190	a3	100
17	4 5	ethyl chloro	iodide	17	171	a3	100
18	4 7	methyl ethoxy	iodide		214-15	a	98
19	4 7	ethyl ethoxy	iodide		146-8 dec.	a	98
20	4 2	N,N-diethyl-2-amino- ethyl phenyl	chloride		184-6 (93-5)	a,b	101
21	4 2 3	methyl methyl methyl	methyl sulfate		150-3	a	101
22	4 2 3	ethyl methyl methyl	p-tolylsulfonate		180-2	a	101
23	4 2 3	2-hydroxyethyl methyl methyl	chloride		194-7	a	101

(101) Druey and Huni, Helv. Chim. Acta 35, 2301-14 (1952).

No.	R	Substituent	X^-	% Yld	M. P. °C.	Method of Preparation	Ref.
24	4	methyl	methyl sulfate		156-8	a	101
	2	phenyl					
25	4	methyl	p-tolylsulfonate		209-11	a	101
	2	phenyl					
26	4	methyl	methyl sulfate		232-4	a	101
	2	phenyl					
	5	chloro					
27	4	ethyl	iodide		188-90	a	101
	2	phenyl					
28	4	ethyl	p-tolylsulfonate		187-8	a	101
	2	phenyl					
29	4	2-hydroxyethyl	Chloride		189-90	a,c	101
	2	phenyl					
30	4	2-hydroxyethyl	chloride		199-201	a	101
	2	phenyl					
	5	methyl					
31	4	2-hydroxyether	chloride		169-71	a	101
	2	phenyl					
	5	chloro					
32	4	2,3-dihydroxypropyl	chloride		191-3	a	101
	2	phenyl					
33	4	N,N-dimethyl-2-amino-ethyl	chloride		191-3	c	101
	2	phenyl					
34	4	N,N-dibutyl-2-amino-ethyl	chloride		140-2	c	101
	2	phenyl					
35	4	2-piperidinoethyl	chloride		179-80	c	101
	2	phenyl					
36	4	N,N-diethyl-3-amino-propyl	chloride		192-4	c	101
	2	phenyl					

No.	R	Substituent	X^-	% Yld.	M. P. °C.	Method of Preparation	Ref.
37	4	N,N-diethyl-5-amino-3-thiapentyl	iodide		128-30	c	101
	2	phenyl					
38	4	phenyl	chloride		210-13	b	101
	2	phenyl					
39	4	N,N-diethyl-2-aminoethyl	iodide		182-3	c	101
	2	phenyl					
	6	methyl					
40	4	2-hydroxyethyl	chloride		188-9 (202-3)	b,c	101
	2	p-chlorophenyl					
41	4	N,N-dimethyl-2-aminoethyl	chloride		186-8	c	101
	2	p-chlorophenyl					
42	4	N,N-diethyl-2-aminoethyl	chloride		192-4	b	101
	2	p-chlorophenyl					
43	4	N,N-diethyl-5-amino-3-thiapentyl	iodide		165-8	c	101
	2	p-chlorophenyl					
44	4	N,N-diethyl-2-aminoethyl	chloride		191-3 (122-3)	c	101
	2	p-chlorophenyl					
	5	methyl					
45	4	N,N-diethyl-2-aminoethyl	chloride		176-8	b	101
	2	3,4-dichlorophenyl					
46	4	N,N-diethyl-2-aminoethyl	chloride		177-8	c	101
	2	p-methylphenyl					
47	4	2-hydroxyethyl	chloride		194-5	a	101
	5	2-thienyl					
48	4	2-hydroxyethyl	chloride		194-5	c	101
	2	phenyl					
	3	phenyl					

No.	R	Substituent	X^-	% Yld	M. P. °C.	Method of Preparation	Ref.
49	4	N,N-dimethyl-2-aminoethyl	chloride		185-6	c	101
	2	phenyl					
	3	phenyl					
50	4	N,N-diethyl-2-aminoethyl	chloride		181-2 (119-2)	b,c	101
	2	phenyl					
	3	phenyl					

Table IX. Quinoxaline Quaternary Salts of the Nitrogen in a Substituent attached to the Quinoxaline Nucleus

No.	Compound	M. P. °C.	Ref.
1	(3-hydroxy-2-quinoxalyl)methyl pyridinium bromide	255	49,102
2	N-(2-quinoxalyl)methyl pyridinium bromide	201	102
3	N-(3-hydroxy-6,7-dimethyl-2-quinoxalyl) methyl pyridinium bromide	273	102
4	N-(6,7-dimethyl-2-quinoxalyl) methyl pyridinium bromide	234	102
5	N-(6,7-dichloro-3-hydroxy-2-quinoxalyl) methyl pyridinium bromide	235	102
6	N-(6,7-dichloro-2-quinoxalyl)methyl pyridinium bromide	218	102
7	N-(3-hydroxy-2-quinoxalyl)methyl-4-methyl-5-(2-hydroxyethyl)thiazolium bromide	227	102

(102) Green and Delaby, Bull. soc. chim. France, 1955, 704-7.

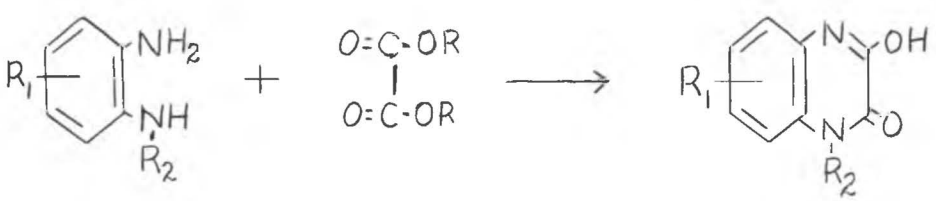
No.	Compound	M. P. °C.	Ref.
8	N-(3-hydroxy-6,7-dimethyl-2-quinoxalyl)methyl-4-methyl-5-(2-hydroxyethyl)thiazolium bromide	244	102
9	N-(6,7-dichloro-3-hydroxy-2-quinoxalyl)methyl-4-methyl-5-(2-hydroxyethyl)thiazolium bromide	224	102
10	quaternary picolinium compound of 2-(5-fluoro-2-methoxyphenyl)quinoxaline	117	22

10. Reduced Quinoxalines.

(a) 1,2- and 3,4-Dihydroquinoxalines.

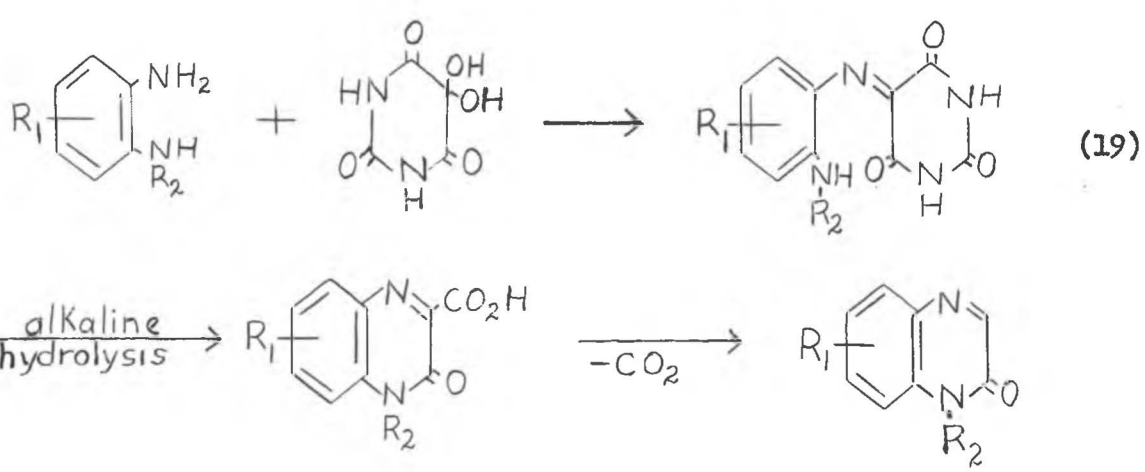
The methods of preparation of this group of compounds vary and are summarized as follows:

1. Condensation of an N-substituted o-phenylenediamine with ethyl oxalate, equation 18.



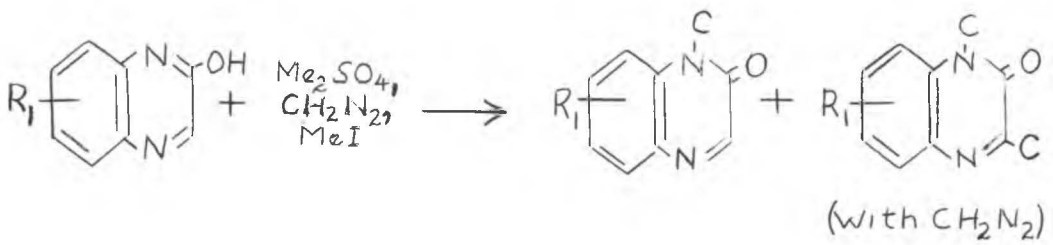
(18)

2. Condensation of alloxan with an N-substituted o-phenylenediamine, equation 19.



(19)

3. Methylation of 2-hydroxyquinoxalines with diazomethane, methyl sulfate or methyl iodide and alkali, equation 20.



(20)

Table X lists the 1,2- and 3,4-dihydroquinoxalines prepared, the method of preparation, and their properties.

Table X. 1,2- and 3,4-Dihydroquinoxalines.

No.	Compound	% Yld	M. P. °C.	Method of Preparation	Ref.
1	3,4-dihydro-3-keto-4-methylquinoxaline-2-carboxyureide			2	76
2	methyl 3,4-dihydro-3-keto-4-methylquinoxaline-2-carboxylate		126	treatment of 1 or 3 with diazomethane	76
3	3,4-dihydro-3-keto-4-methylquinoxaline-2-carboxylic acid		173-4	1	76
4	3,4-dihydro-3-keto-4-methylquinoxaline-2-carboxydimethylureide		194	treatment of 1 with MeI and potassium carbonate	76
5	3,4-dihydro-3-keto-4-phenylquinoxaline-2-carboxyureide	50	244	2	76
6	3,4-dihydro-3-keto-4-phenylquinoxaline-2-carboxylic acid	43	158-60	by hydrolysis of 5	76
7	3,4-dihydro-3-keto-4-(D-kribityl)-6,7-dimethyl-2-quinoxaline carboxyureide			2	77

No.	Compound	% Yld	M. P. °C.	Method of Preparation	Ref.
8	1,2-dihydro-1,3-dimethyl-2-oxo-quinoxaline		85-6	3	103
9	1,2-dihydro-1-methyl-2-oxo-quinoxaline		120-1	3	103
10	1,2-dihydro-3-hydroxy-1-methyl-2-oxoquinoxaline		286-7	1	103
11	3-chloro-1,2-dihydro-1-methyl-2-oxoquinoxaline		131-3	treatment of 10 with phosphorous trichloride	103
12	1,2-dihydro-3-methoxy-1-methyl-2-oxoquinoxaline		122-3	treatment of 11 with sodium methoxide in alcohol	103
13	1,2-dihydro-1-methyl-2-oxo-3-phenoxyquinoxaline		170-2	3	103
14	3-amino-1,2-dihydro-1-methyl-2-oxoquinoxaline		273.5	treatment of 11 with amonium acetate at 200-215°C.	103
15	4-methyl-3-quinoxalone-2-carboxlic acid methyl amide		167-8	3	83
16	4-methyl-3-quinoxalone-2-carboxylic acid		171-3	by hydrolysis of 15	83
17	2-hydroxy-3-methyl-7-nitro-3,4-dihydroquinoxaline		225	1	81
18	2-hydroxy-7-nitro-3,4-dihydroquinoxaline			1	81
19	2-hydroxy-5-methoxy-7-nitro-3,4-dihydroquinoxaline		262 dec.	1	81

(103) Cheeseman, J. Chem. Soc., 1955, 1804-9.

No.	Compound	% Yld	M. P. °C.	Method of Preparation	Ref.
20	tetraethyl 1,4-dihydro-2,3-quinoxalinebis(methyl phosphonate)		168-70	treatment of quinoxaline with ethyl phosphate and sodium ethoxide in alcohol	37
21	1,2-dihydro-6,7-dimethyl-2-oxo-1-D-ribityl-3-quinoxaline carboxylic acid			alkaline hydrolysis of riboflavin, or thermal hydrolysis of riboflavin	104 105

(b) 1,2,3,4-Tetrahydroquinoxalines.

The methods of preparations of this group of compounds are as follows:

1. Catalytic hydrogenation of the quinoxaline analog, or reduction with sodium and alcohol.

2. Condansation of N,N'-disubstituted o-phenylenediamines with ethylene dibromide or ethyl oxalate.

3. By addition of organo-lithium compounds to the two double bonds of the hetero ring of quinoxaline followed by the addition of water.

4. Alkylation of 2,3-dihydroxyquinoxalines.

During the period covered by this review no attempts were reported at resolution of the stereoisomers when positions 2 and/or 3 carried substituents.

Shinichi, Tanska and Ichikawa (97) reported the catalytic reduction of 2,3-diphenyl-5,8-dihydroxyquinoxaline and 2,3-diphenyl-5,8-dimethoxyquinoxaline to the tetrahydro state, but the compounds dehydrogenated on working

(104) Surrey and Nachod, J. Am. Chem. Soc., 73, 2336-40 (1951).

(105) Euler and Hasselquist, Arkiv. Kemi 2, 373-81 (1950).

up. By careful acetylation, immediately after hydrogenation and under an atmosphere of hydrogen, 1,4-diacetyl-2,3-diphenyl-5,8-dimetnoxy-1,2,3,4-tetrahydroquinoxaline was obtained.

Morley (106) reported some effects of solvent, pH and acetylating agent-solvent on the preparation of N-substituted and N,N'-disubstituted 1,2,3,4-tetrahydroquinoxalines. Table XI summarizes these findings.

Table XII lists the compounds of 1,2,3,4-tetrahydroquinoxaline reported the method of preparation being designated by numbers corresponding to the methods of preparation given above. The number 5 indicates preparation of 1,2,3,4-tetrahydroquinoxaline compounds by application of the findings of Morley.

Some salts of 1,2,3,4-tetrahydroquinoxaline compounds have been reported. These were prepared as follows:

(1) Hydrogenation of the unsaturated counterparts.

(2) From the 1,2,3,4-tetrahydroquinoxaline compound.

Table XIII lists these compounds.

Table XI. Solvent, pH and Reagent Effects on the Preparation of N-Substituted and N,N'-Disubstituted-1,2,3,4-tetrahydroquinoxalines. (106)

Effect of Solvent in Carbethoxylation of 1,2,3,4-Tetrahydroquinoxaline.

Solvent	% of Product Isolated N-Substituted	N,N'-Disubstituted
pyridine	54	46
acetone	50	50
ethanol	50	50
acetic acid	33	67

(106) Morley, J. Chem. Soc., 1952, 4002-8.

Effects of Solvent and Reagent in Acetylation of 1,2,3,4-Tetrahydroquinoxaline.

Reagent	Solvent	% of Product Isolated N-Substituted	% of Product Isolated N,N'-Disubstituted
acetic anhydride	ethanol	100	0
acetic anhydride	acetic acid	72	28
acetyl chloride	ethanol	38	62
acetyl chloride	acetic acid	32	68

Effect of pH in Carbethoxylation of 1,2,3,4-Tetrahydroquinoxaline Using Ethyl Chlorocarbonate.

pH	% Yield Based on 1,2,3,4-Tetrahydroquinoxaline Used N-Substituted	% Yield Based on 1,2,3,4-Tetrahydroquinoxaline Used N,N'-Disubstituted
7	75	0
6	75	0
5	75	trace
4	30	51
3	20	58

Table XII. 1,2,3,4-Tetrahydroquinoxaline Compounds.

No.	Compound	% Yld	M. P. °C.	Method of Preparation	Ref.
1	1-acetyl-1,2,3,4-tetrahydroquinoxaline		108-9	5	106
2	1-carbethoxy-1,2,3,4-tetrahydroquinoxaline		151-2	5	85
3	1-benzoyl-1,2,3,4-tetrahydroquinoxaline		147-8	5	85
4	1,4-diacetyl-1,2,3,4-tetrahydroquinoxaline		143-4	5	85
5	1,4-dicarbethoxy-1,2,3,4-tetrahydroquinoxaline			5	85
6	1,4-dibenzoyl-1,2,3,4-tetrahydroquinoxaline		204-5	5	106
7	1,4-dimethyl-2,3-dioxo-1,2,3,4-tetrahydroquinoxaline		252-3	2	103
8	2-methyl-1,2,3,4-tetra hydroquinoxaline	65	70-71	1	107
9	5-methyl-2-oxo-1,2,3,4-tetrahydroquinoxaline		177-8	1	17
10	2-(2-diethylaminoethyl)-1,2,3,4-tetrahydroquinoxaline	74	(b.p. 120-4/ 0.2mm)	1	108
11	2-(2-dimethylaminoethyl)-1,2,3,4-tetrahydroquinoxaline	85	(b.p. 140-2/ 0.2mm) n_D^{20} 1.5750	1	108

(107) Munk and Schultz, J. Am. Chem. Soc., 74, 3433-4 (1952).

(108) Wiley, J. Am. Chem. Soc., 76, 4924-5 (1954).

No.	Compound	% Yld	M. P. °C.	Method of Preparation	Ref.
12	2-(2-benzylethylamino-ethyl)-1,2,3,4-tetrahydroquinoxaline	28	(b.p. 178-85/ 0.2mm) n_D^{20} 1.5943	1	108
13	1,4-dicarbethoxy-2(2-dimethylaminoethyl)-1,2,3,4-tetrahydroquinoxaline	81		treatment of 11 with ethyl chlorocarbonate in pyridine	108
14	1,4-dicarbethoxy-2(2-diethylaminoethyl)-1,2,3,4-tetrahydroquinoxaline	40	(b.p. 160-4)	treatment of 10 with ethyl chlorocarbonate in pyridine	108
15	1,4-bis(ethylcarbamyl)-2-(2-dimethylaminoethyl -1,2,3,4-tetrahydroquinoxaline		127-9	treatment of 11 with EtNCO in benzene	108
16	1,4-bis(ethylcarbamyl)-2-(2-diethylaminoethyl)-1,2,3,4-tetrahydroquinoxaline	51.5	138-40	treatment of 10 with EtNCO in benzene	108
17	1,4-bis(phenylcarbamyl)-2-(2-diethylaminoethyl)-1,2,3,4-tetrahydroquinoxaline	47.7	191-2	treatment of 11 with PhNCO in benzene	108
18	1,4-bis(p-methylphenylsulfonyl)-1,2,3,4-tetrahydroquinoxaline	77	162	2	109
19	1,2,3,4-tetrahydroquinoxaline (new method of preparation)		98	treatment of o-2-hydroxyethylamino-aniline with HCl at 150-160° C.	110

(109) Stetter, Chem. Ber., 86, 197-205 (1953).

(110) Ramage and Trappe, J. Chem. Soc., 1952, 4406-9.

No.	Compound	% Yld	M. P. °C.	Method of Preparation	Ref.
20	2-methyl-1,2,3,4-tetrahydroquinoxaline		71	similar procedure used as for compound 19	110
21	6-nitro-1,2,3,4-tetrahydroquinoxaline		116	similar procedure used as for compound 19	110
22	2,3-dimethyl-1,2,3,4-tetrahydroquinoxaline		99-100	3	111
23	2,3-diphenyl-1,2,3,4-tetrahydroquinoxaline		105	3	111

Table XIII. Salts of 1,2,3,4-Tetrahydroquinoxaline.

No.	Compound	M. P. °C.	Method of Preparation	Ref.
1	1-(N,N-diethyl-2-aminoethyl)-3-phenyl-1,2,3,4-tetrahydroquinoxaline dihydrochloride	212-4	1	101
2	1-(N,N-diethyl-2-aminoethyl)-3-(p-chlorophenyl)-1,2,3,4-tetrahydroquinoxaline dihydrochloride	212-5	1	101
3	1-(N,N-diethyl-2-aminoethyl)-3-(3,4-dichlorophenyl)-1,2,3,4-tetrahydroquinoxaline dihydrochloride	158-60	1	101
4	1-(2-hydroxyethyl)-3-phenyl-1,2,3,4-tetrahydroquinoxaline hydrochloride	170-2	1	101

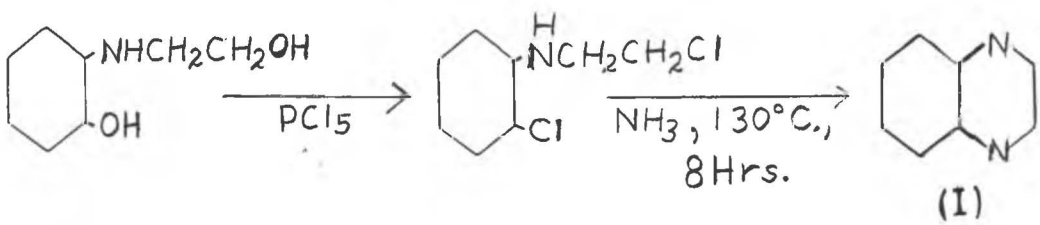
(111) Lane and Williams, J. Chem. Soc., 1954, 4106-8.

No.	Compound	M. P. °C.	Method of Preparation	Ref.
5	1-(N,N-diethyl-2-aminoethyl)-2,3-diphenyl-1,2,3,4-tetrahydroquinoxaline dihydrochloride	220-4	1	101
6	1-acetyl-4-methyl-1,2,3,4-tetrahydroquinoxaline hydrochloride	154-5	2	106
7	1-acetyl-4,4-dimethyl-1,2,3,4-tetrahydroquinoxalinium iodide	184-5	2	106
8	1-carbethoxy-4-methyl-1,2,3,4-tetrahydroquinoxaline hydrochloride	133-4	2	106

(c) Decahydroquinoxaline.

Three reports of the preparation of decahydroquinoxaline have been reported in the literature.

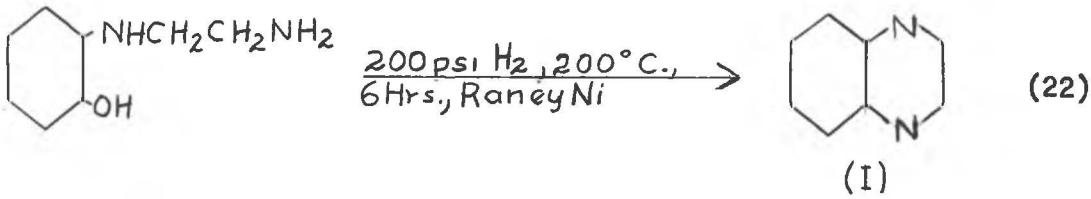
1. The first report of the preparation of decahydroquinoxaline (I) appeared in 1947 (2), equation 21, during the period covered by the review of Simpson. However, this preparation was not listed by Simpson. Neither



(21)

yield nor melting point was listed for this compound. A dinitroso derivative of melting point 160° C. dec. was, however, reported.

2. In 1952 (1) decahydroquinoxaline (I) was prepared as indicated by equation 22 by heating 2-(β-aminoethylamino)-cyclohexanol at 200° C. and 200 psi. hydrogen in the presence of Raney Ni catalyst. A yield of 24%, m. p. 150-1° C., was obtained. The dihydrochloride melted 365° C. No consideration of cis and trans stereoisomerism was given.

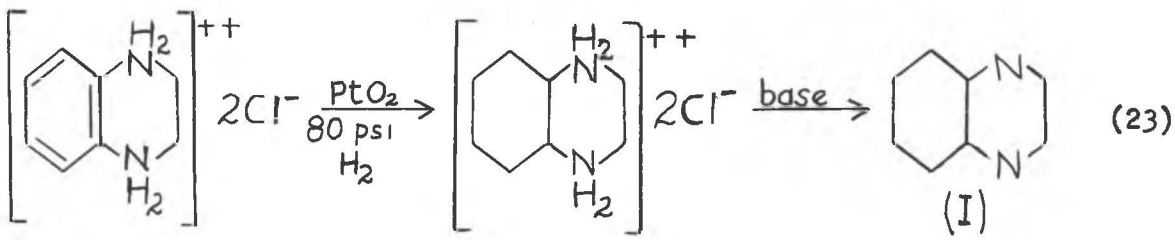


(22)

(I)

Carbethoxylation of I using ethyl chlorocarboante gave N-carbethoxydecahydroquinoxaline (II), b. p. 107-9° at 0.6 mm. Alkylation of II using formic acid and formalin gave 1-methyl-4-carbethoxydecahydroquinoxaline (III), b. p. 103-4° C. at 0.6 mm. Hydrolysis of III gave N-methyldecahydroquinoxaline (IV), b. p. 88-90° C. at 8 mm. Alkylatien of IV with p-chlorobenzhydryl chloride gave 4-p-chlorobenzhydryl-1-methyldecahydroquinoxaline, b. p. 196° C. at 0.6 mm. The dipicrate of the final product melted 263° C. dec.

3. The preparation of decahydroquinoxaline according to equation 23 by the catalytic low pressure hydrogenation of the tetrahydroquinoxalinium ion was reported in 1956 (3). The yield obtained was 12.5%,



(23)

(I)

m. p. 152.5-153° C. The dinitroso derivative was prepared and found to melt at 110-111° C. These workers conjectured the decahydroquinoxaline they had prepared was the cis isomer while the decahydroquinoxaline reported under (1) preceding was the trans isomer.

11. Condensed Quinoxalines.

The compounds in this group, reported during the period covered by this review, were prepared by the following general procedures:

(a) The condensation of 2,3-diaminonaphthalenes with glyoxal.

(b) Ring closure of 2-aminocarbonyl-3-alkylamidoquinoxalines to yield pteridines.

(c) The condensation of 3-bromoacenaphthoquinone and o-phenylenediamines.

(d) Ring closure of alkyl 2-hydroxy-3-quinoxalinecarboxylates.

(e) The condensation of substituted 5,6-quinones and cyanogen.

(f) Reaction of ethyl orthoformate with substituted quinoxalines to yield imidazoquinoxalines.

(g) Reaction of cyanoethylene with 1,2,3,4-tetrahydroquinoxaline to give 1,4-bis(2-cyanoethyl)-1,2,3,4-tetrahydroquinoxalines in 80% yield, m. p. 88.5-9° C., from which by various reactions, derivatives of 1,2,2a,3,4,5,8,9,10,10a-decahydro-5,8-diketo-2a,10a-diazapyrenes were obtained.

Table XIV lists the compounds prepared, the method of preparation, and the properties of the compounds.

Table XIV. Condensed Quinoxalines.

No.	Compound	% Yld	M. P. °C.	Method of Preparation	Ref.
1	2-chloro-7,8-benzoquinoxaline		128-9	a	75
2	2-oxo-7,7-benzo-1,2,3,4-tetrahydroquinoxaline		197-8	a	75
3	2-hydroxy-7,8-benzoquinoxaline		275-5.5	a	75
4	2-piperidino-7,8-benzoquinoxaline		177-8	a	75
5	2-piperidino-5,6-benzoquinoxaline		124-5	a	75
6	5,6-benzoquinoxaline 1-oxide		120.5	a	17
7	(?)-dichloro-5,6-benzoquinoxaline		187-8	treatment of 6 with chlorine	17
8	2,3-dimethyl-5,6-benzoquinoxaline		101	a	17
9	3-hydroxy-2-methyl-6,7-benzoquinoxaline		295 dec.	a	75
10	3'-acetamido-4-hydroxy-2-methyl-6,7-benzopteridine		above 280 dec.	b	83

No.	Compound	% Yld	M. P. °C.	Method of Preparation	Ref.
11	3'-acetamido-4-hydroxy-6,7-benzopteridine		above 300	b	83
12	3'-amino-4-hydroxy-6,7-benzopteridine		above 340	b	83
13	3'-acetamido-4-acetoxy-2,2'-dimethyl-6,7-benzopteridine		244-5	b	83
14	3'-acetamido-4-hydroxy-2,2'-dimethyl-6,7-benzopteridine		above 300	b	83
15	3-bromoacenaphtho(1,2-b)quinoxaline		276-7	c	112
16	3-hydroxyacenaphtho(1,2-b)quinoxaline			hydrolysis of 15	112
17	acenaphtho(1,2-b)quinoxaline			hydrolysis of 15	112
18	di [(cyclopenta) [b] (quinoxalino)] [1,2,3-cd-1',2',3'-lm] perylene			treatment of 17 with KOH and KOAc with heating	112
19	3-piperidinoacenaphtho(1,2-b)-quinoxaline		159	treatment of 15 with piperdine	112
20	5-bromoaceanthra(1,2-b)quinoxaline				112
21	5-hydroxyaceanthra(1,2-b)quinoxaline		320	c	112
23	3-methyl-2-furo(2,3-b)-quinoxaline	60	310	d	74
24	2-furo(2,3-b)quinoxalone			d	74
25	5,6-7,8-dipyride(5',6'-2",3")-quinoxaline		270	e	113

(112) Bradley and Pexton, J. Chem. Soc., 1954, 4436-9.

(113) Druey and Schmidt, U. S. Patent 2,590,075, Mar. 25, 1952.

No.	Compound	% Yld	M. P. °C.	Method of Preparation	Ref.
26	5,6-7,8-dipyrido(5',6'-2",3")-1,2,3,4-tetrahydroquinoxaline		187	e	113
27	5,6-7,8-dipyrido(5',6'-5",6")-quinoxaline		302-3	e	113
28	5,6-7,8-dipyrido(5',6'-5",6")-1,2,3,4-tetrahydroquinoxaline		171	e	113
				cmpds. 29-55, prepared by Meth. f. Ring closure reagent.	
29	imidazo(b)quinoxaline	41 86	286	formic acid trimethoxymethane	114
30	2-methylimidazo(b)quinoxaline	30 86 96	322	triethoxymethane acetyl chloride acetic anhydride	114
31	2-ethylimidazo(b)quinoxaline	77 61	313	propoyl chloride propionic anhydride	114
32	2-n-propylimidazo(b)quinoxaline	68	286	butyroyl chloride	114
33	2-n-butylimidazo(b)quinoxaline	60	250	pentanoyl chloride	114
34	2-n-pentylimidazo(b)quinoxaline	47	242	hexanoyl chloride	114
35	2-(3-pentyl)imidazo(b)quinoxaline	37	246	2-ethylbutanoyl chloride	114
36	2-isoamylimidazo(b)quinoxaline	45	223	4-methylpentanoyl chloride	114
37	2-(5-ethylheptyl)imidazo(b)-quinoxaline	42	221	6-ethyloctanal	114
38	2-(methoxymethyl)imidazo(b)-quinoxaline	56	233	3-oxa-butanoyl chloride	114

(114) Shipper and Day, J. Am. Chem. Soc., 73, 5672-5 (1951).

No.	Compound	% Yld	M. P. °C.	Method of Preparation	Ref.
39	2-n-heptylimidazo(b)-quinoxaline	60	324	octanal	114
40	2-benzylimidazo(b)quinoxaline	52	276	2-phenylacetaldehyde	114
41	2-styrylimidazo(b)quinoxaline	32 65	311	2-styrylacetaldehyde styrylmethanoyl chloride	114
42	2-phenylimidazo(b)quinoxaline	58	324	benzaldehyde	114
43	2-(2-carboxylethyl)imidazo(b)quinoxaline	87	284	succinic anhydride	114
44	2-hydroxyimidazo(b)quinoxaline	65 86	447	diketodichloroethane urea	114
45	6-methylimidazo(b)quinoxaline	74	246	trimethoxymethane	114
46	2,6-dimethylimidazo(b)-quinoxaline	84	305	acetic anhydride	114
47	2-ethyl-6-methylimidazo-(b)quinoxaline	67	273	propanoyl chloride	114
48	6-methyl-2-n-propylimidazo(b)quinoxaline	88	271	butanoyl chloride	114
49	2-isopropyl-6-methylimidazo(b)quinoxaline	54	250	isobutanoyl chloride	114
50	6-methyl-2-n-pentylimidazo(b)quinoxaline	55	224	hexanoyl chloride	114
51	6-methyl-2-(3-pentyl)imidazo(b)quinoxaline	52	247	2-ethylbutanoyl chloride	114
52	2-(2-carboxylethyl)-6-methylimidazo(b)quinoxaline	65	283	acetic anhydride	114
53	2-hydroxy-6-methylimidazo(b)-quinoxaline	96	400	urea	114

No.	Compound	% Yld	M. P. °C.	Method of Preparation	Ref.
54	6-chloro-2-methylimidazo(b)-quinoxaline	77	344	acetic anhydride	114
55	6-chloro-2-hydroxyimidazo(b)-quinoxaline	65	362	urea	114
56	1,2,2a,3,4,5,8,9,10,10a-decahydro-5,8-diketo-2a,10a-diazapyrene		245-6	g bisphenylhydrazone derivative, m. p. 242-4	115
57	1,4-bis-2'-carboxyethyl-1,2,3,4-tetrahydroquinoxaline	71	272-4	g	115
58	1,2,2a,3,10,10a-hexahydrodiindolo(3',2'-4,5)(2",3"-8,9)-2a-10a-diazapyrene	50	438-9	g	115
59	1,2,2a,3,10,10a-hexahydrodiquinolino(3',2'-4,5)(2",3"-8,9)-2a,10a-diazapyrene-4',4"-dicarboxylic acid	85	242-6	g	115
60	1,2,2a,3,10,10a-hexahydrodiquinolino(3',2'-4,5)(2",3"-8,9)-2a,10a-diazapyrene		156-8	g	115
61	1,2,2a,3,10,10a-hexahydro-3,10-diketo-quinolino(3',2'-4,5)(2",3"-8,9)-2a,10a-diazapyrene (yield 41%).		428-30	g	115

12. Miscellaneous Quinoxaline Compounds.

A few compounds not of any previous classification have been reported. These compounds and their preparation follow:

(a) Dihydroxy-6,6'-azoquinoxaline. Prepared by condensing 3,3',4,4'-tetraaminoazobenzene with butyl hydroxyacetate in alcohol solution (116).

(115) Mann and Almond, J. Chem. Soc., 1951, 1906-9.

(116) McIntyre, Atkinson, Brown and Simpson, J. Chem. Soc., 1954, 2023-7.

(b) Treatment of dihydroxy-6,6'-azoquinoxaline with phosphorous oxychloride and phosphorous pentachloride gives β-dichloro-6,6'-azoquinoxaline and β-dichloro-6,6'-azoquinoxaline, m. p. 232-45° (116).

(c) 2-Quinoxalinylisothiuronium chloride. Prepared by the reaction of 2-chloroquinoxaline with thiourea, yield 97%, m. p. 159-60 (117).

(d) 2-Quinoxalinethiol. Treatment of 3 with sodium hydroxide, yield 73%, m. p. 204-5° (117).

(e) 2-Quinoxalinyl-p-nitrophenyl sulfide. Prepared from 2-chloroquinoxaline and bis(p-nitrophenyl)disulfide by treating with sodium sulfide and sodium hydroxide, m. p. 151-2° (117).

(f) By methods similar to those used in preparing compounds 3-5 the following compounds were prepared (117): di-2-quinoxalinyl sulfide, m. p. 196°; 2-quinoxalinyl-p-nitrophenyl sulfone, m. p. 197-9°; and, di-2-quinoxalinyl sulfone (117).

(g) 2,3-Diphenyl-6-(trifluoromethylthio)quinoxaline. Prepared by the condensation of benzil and 3,4-diaminophenyltrifluoromethyl sulfide, yield 66%, m. p. 140-1 (85).

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(117) Wolf, U. S. Patent 2,537,870, Jan. 9, 1951.

III: EXPERIMENTAL

The reactions requiring high temperature and/or pressure were performed in either of two apparatuses: a Parr Instrument Co. No. 4011-H High Pressure Reaction Apparatus (Parr High Bomb) or an Autoclave Engineers, Inc. Magne Dash Autoclave (Magne Dash Bomb). The Parr High Bomb has a fixed agitation rate of 37 cycles per mimute. The agitation rate of the Magne Dash Bomb is variable. Reactions requiring low pressure and/or temperature under hermetical conditions were performed in a Parr Instrument Co. Series 3910 Low Pressure Shaker Type Apparatus (Parr Low Bomb).

All melting points were taken with a Fisher Scientific Co., Fisher-Johns Melting Point Apparatus. All melting and boiling points are reported uncorrected.

Analyses were performed by Straus and Weiler, Microanalytical Laboratory, 164 Banbury Road, Oxford, England.

A. Preparation of Catalysts.

1. Rhodium Catalyst.

This catalyst consists of 5% rhodium on alumina and was commercially available from Baker and Co., Inc., Newark, New Jersey.

2. Raney Nickel W-2 Catalyst.

This catalyst was prepared by the method of Mozingo (118). To a solution of 380 g. of sodium hydroxide in 1.5 liters of water was added, in portions and with stirring, 300 g. of nickel aluminum alloy. The temperature was maintained below 25° C. After the evolution of hydrogen became slow the solution was allowed to come to room temperature and, when the evolution of hydrogen again became slow, the solution was heated on a steam bath for 12 hours, water being added as necessary to maintain volume. The nickel catalyst, being very pyrophoric, was stored under absolute alcohol.

A second preparation of this catalyst was carried out using the same procedure. In this preparation, however, 328 g. of nickel aluminum alloy and the corresponding quantities of other reactants were used.

3. Platinum Oxide (Adam's Catalyst).

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(118) Mozingo, Organic Syntheses, Coll. Vol. III, 181 (1955).

This catalyst was commercially available from Baker and Co., Inc.

B. Preparation of Quinoxaline.

Four preparations of quinoxaline were carried out according to the method of Cavagnol and Wiselogle (9). The following procedure was typical.

To a solution of 108.1 g. (1.0 mole) of o-phenylenediamine in 500 ml. of 2 molar acetic acid was added 250 ml. of 4 molar sodium acetate solution. The mixture was heated to 60° C. and poured rapidly into a solution of 298.4 g. (1.05 mole) of sodium glyoxal bisulfite in 1500 ml. of water previously heated to 60°C. After stirring for one hour the solution was cooled to below 10° C., neutralized with 120 g. of sodium hydroxide pellets and 500 g. of potassium carbonate added. Mechanical extraction with 500 ml. of benzene removed most of the product. Extraction was completed by extracting the aqueous layer further in a liquid-liquid extractor for 24 hours with benzene. The combined extracts were dried over anhydrous magnesium sulfate, the benzene stripped off and the residue distilled at 44-45° C. and 1 mm. pressure to give quinoxaline in 84% yield, m. p. 30-31° C. Cavagnol and Wiselogle reported an 85% yield, m. p. 30.5-31.5° C.

In three other preparations of quinoxaline results were as follows: m. p. 27-30° (46%); 30-31° (73%); 30-31° (73%). The low 46% yield was due primarily to loss of product by foaming when the potassium carbonate was added to the reaction mixture. This foaming was not experienced in the other preparations.

One preparation of quinoxaline was carried out according to the method of Jones and McLaughlin (11). To a solution of 135 g. (1.25 mole) of o-phenlenediamine in 2 liters of water heated to 70° C. was added a solution of 344 g. (1.29 mole) of sodium glyoxal bisulfite in 1.5 liters of water heated to 80° C. After standing 15 minutes the solution was cooled to room temperature and 500 g. of sodium carbonate added. The dark oil which separated out was extracted three times with ether, the extracts dried over anhydrous potassium carbonate, the ether stripped off, and the product distilled at 105-110° C. and 11-12 mm. pressure to give 132.3 g. of quinoxaline, 82% yield, m. p. 29-30° C. Jones and McLaughlin reported a yield of 85-90%, m. p. 29-30° C., b. p. 108-111° C. at 12 mm. pressure.

C. Preparation of 1,2,3,4-Tetrahydroquinoxaline.

Two methods were employed in the preparation of tetrahydroquinoxaline.

1. Method of Christie, Rhode, and Shultz (3).

Three preparations of tetrahydroquinoxaline were carried out. The following procedure illustrates the preparations.

A mixture of 35 g. (0.27 mole) of quinoxaline, 125 ml. of 95% ethanol, 2 g. of potassium hydroxide pellets, and 3 g. of Raney nickel W-2 catalyst was placed in the Parr Low Bomb at 30° C. and 80 psi hydrogen. Over 36 hours a pressure drop equivalent to 100% reduction had occurred. The reaction mixture was heated on the water bath, thus effecting solution of the tetrahydroquinoxaline. The catalyst was removed by filtering and the ethanolic solution gave crystals of product on cooling. Yield 35 g., 97%, m. p. 94-6° C. Recrystallization from 95% ethanol gave a product, m. p. 96-98° C. Shultz reported, after purification by recrystallization, a yield of 86%, m. p. 99-99.5° C.

The results for the other two runs were as follows: m. p. 97-9° (50%); 96-7° (86%). The low 50% yield was due in part to loss of product caused by a plugged line in the hydrogenation apparatus. It was thought all pressure in the reaction flask had been released but on opening the flask considerable product was blown out of the flask by the remaining pressure.

2. Method of Morley (106).

Tetrahydroquinoxaline was prepared numerous times with the conditions varying somewhat. A typical preparation is outlined in detail but table XV gives the information on the other preparations.

A mixture of 48 g. (0.44 mole) of catechol and 40 ml. (0.49 mole) of ethylenediamine monohydrate was heated at 200-210° C. in a glass liner in the Parr High Bomb for 15 hours. The reaction mass was melted into water and the water suspension extracted with three 75 ml. portions of benzene. The benzene solution was washed twice with 250 ml. of normal sodium hydroxide solution and twice with water. After drying the benzene solution over anhydrous sodium sulfate and filtering to remove the drying agent, the benzene was reduced in volume by boiling and petroleum ether, b. p. 60-70° C., added to precipitate the tetrahydroquinoxaline. Recrystallization from benzene-Skellysolve B gave 29 g. of product, 50% yield, m. p. 93-4° C. Morley reported an average yield of 47%, m. p. 97-98° C.

A comparison of the results obtained under the varying conditions as indicated in Table XV indicates that a longer reaction time favors increased yields. Further, the low yields seem to be characteristic of the catechol received from the Fluka Chemical Company of Switzerland. This catechol was much darker in appearance than the catechol received from Eastman. Also the tetrahydroquinoxaline prepared from Fluka catechol required more purification. Two attempts were made to prepare tetrahydroquinoxaline using the Magne Dash Bomb with no glass liner. In both cases only tar was obtained, even at temperatures as low as 185° C. It was repeatedly observed that in the preparation of tetrahydroquinoxaline using the Parr High Bomb with a glass liner that usually a little of the reaction mixture slopped out through the small pressure equalization hole in the liner. Whenever this occurred and the material came in contact with the metal of the bomb, a black gummy tar resulted. It appears quite evident that the metal of the bombs initiates the formation of tar.

Under the conditions of the reaction the glass liners were greatly affected. Much etching and corrosion of the glass occurred. It was experienced that a liner would withstand about six runs after which it became very brittle and on one occasion was found broken while still in the bomb.

Table XV. Preparations of 1,2,3,4-Tetrahydroquinoxaline by the Method of Morley.

Catechol		Aqueous Ethylenediamine		Average	Reaction Time in	M. P.	%
Amt., g.	Supplier	Amt., ml.	Con.%	Temp. °C.	Hours	°C.	Yield
72	Eastman	60	76.8	207	15	95-6	35
48	Eastman	40	76.8	210	36	95-6	60
48	Eastman	40	76.8	220	15	93-4	50
48	Eastman	40	70-75	200	48	94-6	40
48	Eastman	40	70-75	200	48	95-6	40
48	Fluka	40	70-75	190	15	97-8	16
24	Fluka	20	70-75	210	15	96-8	19
48	Fluka	30	98-100	205	36	96-8	41
96	Fluka	96	76.8	205	68	92-6	40
72	Eastman	48	100	200	40	95-7	46
48	Eastman	33	98-100	205	36	96-7	36
48	Eastman	40	76.8	217	38	96-7	36
48	Eastman	40	76.8	210	24	94-6	42
48	Eastman	40	76.8	220	15	Magne Dash Bomb used for these last two runs. Only tar obtained.	
48	Eastman	40	76.8	185	15		

D. Preparation of 2-(β -Aminoethylamino)-cyclohexanol.

Six preparations of 2-(β -aminoethylamino)-cyclohexanol were carried out according to the procedure of Beck, Hamlin and Weston (1). The following procedure is representative.

A solution of 1200 g. (14 moles) of ethylenediamine (69% aqueous) in 1 liter of methanol (99%) was stirred and maintained at a temperature of 45-60° C. by external heating as necessary while 200 g. (2 moles) of cyclohexene oxide in 100 ml. of 99% methanol was added dropwise over a period of 4 hours. The mixture was fractionally distilled and the 2-(β -aminoethylamino)cyclohexanol collected as a colorless liquid, b. p. 135-40° C./1.5-2 mm. Yield 298 g., 90%. Beck reported an 84% yield, b. p. 122-3° C./1.2 mm. On standing, the liquid solidified.

The results of the other preparations of 2-(β-aminoethylamino)-cyclohexanol follow: b. p. 150-2°/3-4 mm. (88%); 135°/3 mm. (82%); 130-40°/1-2 mm. (80%); 130-40°/1-2 mm. (85%); 125-30°/1-1.5 mm. (84%).

E. Preparation of Decahydroquinoxaline.

1. Method of Broadbent and Whittle (4).

cis-Decahydroquinoxaline was prepared numerous times following the procedure of Broadbent and Whittle. The following procedure, below, illustrates the method of preparation. Some of the other preparations of cis-decahydroquinoxaline, b-k below, are outlined in some detail. These preparations are given when the results obtained or the procedure followed was other than that of Broadbent and Whittle. Table XVI gives data on other preparations of cis-decahydroquinoxaline.

(a) A mixture of 15.0 g. (0.11 mole) of tetrahydroquinoxaline, 1 g. of 5% rhodium on alumina and 40 ml. of absolute alcohol was placed in the Parr High Bomb at 2000 psi hydrogen. Reduction of the hetero ring occurred at room temperature in 1 hour. The benzene ring was reduced in 6 hours at 100° C. The reaction mixture was filtered to remove the catalyst, the ethanol stripped off and the residue vacuum distilled at 85-90° C. and 0.25 mm. pressure to give 14 g. of product, 89% yield, m. p. 55-60° C. Whittle reported yields of 70-90%, m. p. variable, 52-62° range.

(b) A mixture of 13 g. (0.1 mole) of quinoxaline, 1 g. of 5% rhodium on alumina and 50 ml. of absolute alcohol was placed in the Parr High Bomb at 100° C. and 4050 psi hydrogen. After 17 hours a drop in pressure equivalent to 60% reduction to cis-decahydroquinoxaline was observed. The catalyst was removed by filtration, the solvent removed under reduced pressure, and the residue vacuum distilled at 104° C. and 0.25 mm. pressure to give 8.5 g. of product, m. p. 57-59° C., yield 61%. This was the first preparation of cis-decahydroquinoxaline carried out during the course of this present research. With subsequent preparations and more experience better results were obtained.

(c) A mixture of 10 g. (0.077 mole) of quinoxaline, 0.68 g. of 5% rhodium on alumina, and 40 ml. of absolute alcohol was placed in the Parr High Bomb at 3150 psi hydrogen and room temperature. The hetero ring reduced at room temperature and the temperature was increased to 100° C. for 16 hours during which time a further pressure drop was observed. Filtration removed the catalyst and the solvent was removed under reduced pressure to give 8.5 g., 81% yield of crude product. After standing 24 hours the product was vacuum distilled to give a material of melting point, 60-105° C. The melting point indicated carbonate salt formation of the cis-decahydroquinoxaline during the time period before distillation.

(d) A mixture of 10 g. (0.077 mole) of quinoxaline, 0.68 g. of 5% rhodium on alumina, and 30 ml. of absolute alcohol was placed in the Parr High Bomb at 3000 psi hydrogen and 100° C. A pressure drop equivalent to

100% reduction to cis-decahydroquinoxaline was observed. The product was worked up in the usual manner to give 5 g. of cis-decahydroquinoxaline, m. p. 55-60° C., 47% yield. The low yield was accounted for in part by the presence of 2.1 g. of light brown material insoluble in alcohol, water, ether, benzene, hot dilute hydrochloric acid, hot sodium hydroxide, acetone, concentrated sulfuric acid, carbon tetrachloride, toluene, dioxane, Skellysolve C, pyridine and nitrobenzene. This light brown material was found to contain nitrogen, but no further identification was made. In three subsequent runs this same material was encountered.

(e) A mixture of 13.4 g. (0.1 mole) of tetrahydroquinoxaline, 1 g. of 5% rhodium on alumina, and 35 ml. of absolute alcohol was placed in the Parr High Bomb at 3000 psi hydrogen and 100° C. No pressure drop occurred and the tetrahydroquinoxaline was recovered. Previous to this run the bomb had been used to prepare tetrahydroquinoxaline by the method of Morley (106). As the tetrahydroquinoxaline prepared by this method leaves considerable decomposition products it is possible that the bomb was poisoned. A thorough cleansing of the bomb with boiling alcohol was carried out before the next attempt to prepare cis-decahydroquinoxaline. The following reduction was successful, indicating that the bomb had been poisoned. Subsequently, similar poisoning occurred and was similarly corrected by cleansing with boiling alcohol.

(f) A mixture of 20 g. (0.15 mole) of tetrahydroquinoxaline, 1.5 g. of 5% rhodium on alumina, and 40 ml. of absolute alcohol was placed in the Parr High Bomb at 3000 psi hydrogen and 100° C. No reduction occurred and the tetrahydroquinoxaline was recovered. The tetrahydroquinoxaline used in this preparation had been prepared a year previous to its use in this reaction and was quite dirty in appearance. Previously tetrahydroquinoxaline that was quite dark in appearance had been successfully used in the preparation of cis-decahydroquinoxaline. The tetrahydroquinocaline from this run was recovered, purified by recrystallization, and subsequently cis-decahydroquinoxaline was prepared from it.

(g) A mixture of 13 g. (0.1 mole) of tetrahydroquinoxaline, 1 g. of 5% rhodium on alumina, and 30 ml. of absolute alcohol was placed in the Magne Dash Bomb at 3000 psi hydrogen and 100° C. No reduction occurred and the tetrahydroquinoxaline was recovered. No reason was established for the failure of the reduction to proceed but undoubtedly poisoning of some nature was responsible.

(h) A mixture of 13 g. (0.1 mole) of tetrahydroquinoxaline, 1 g. of 5% rhodium on alumina, and 40 ml. of absolute alcohol was placed in the Parr High Bomb at 3000 psi hydrogen and 100° C. The theoretical pressure drop equivalent to 100% reduction to cis-decahydroquinoxaline was observed. The yield was 85%. The product was purified by fractional sublimation. The last material sublimed contained considerable tetrahydroquinoaline as evidenced by the melting point, 65-93° C. The melting point of the first fraction collected was 48-55° C. It was found that tetrahydroquinoxaline could be vacuum distilled easily at 100-110° C./0.080 mm. and sublimed under conditions similar to those used for the sublimation of cis-decahydro-

quinoxaline. Thus, it would be difficult by vacuum distillation to purify cis-decahydroquinoxaline free of tetrahydroquinoxaline, if in the reduction of tetrahydroquinoxaline to cis-decahydroquinoxaline, the reduction was not 100%. The obtaining of ultraviolet spectra of cis-decahydroquinoxaline free of indications of unsaturation would be difficult to achieve, especially in view of the much greater molar extinction coefficients of tetrahydroquinoxaline over cis-decahydroquinoxaline.

(i) A mixture of 4 g. of tetrahydroquinoxaline (0.03 mole), 0.3 g. of 5% rhodium on alumina, and 20 ml. of absolute alcohol was placed in the Parr High Bomb at 2500 psi hydrogen and 100° C. for 5 hours. The catalyst was removed by filtration, the solvent stripped off under reduced pressure, and the product purified by vacuum sublimation. Product melted 53-58° C., yield 90%. An ultraviolet spectrum of this cis-decahydroquinoxaline was made and found to be free of indications of unsaturation. This product was used in chromatography studies of cis-decahydroquinoxaline.

(j) A mixture of 10 g. (0.075 mole) of tetrahydroquinoxaline, 0.75 g. of 5% rhodium on alumina, and 50 ml. of absolute alcohol was placed in the Parr High Bomb at 100° C. and 2860 psi hydrogen for 6 hours. The product was purified by vacuum sublimation. A yield of 5.9 g., 56%, m. p. 55-59° C., was obtained. The sublimation was purposely stopped before all crude product had been sublimed. This was done to avoid as much as possible any contamination of the product by traces of tetrahydroquinoxaline. This product was used for chromatography studies of cis-decahydroquinoxaline.

(k) A mixture of 60 g. (0.46 mole) of quinoxaline, 3.5 g. of 5% rhodium on alumina, and 40 ml. of absolute alcohol was placed in the Parr High Bomb at 2750 psi hydrogen and room temperature. After reduction of the hetero ring the bomb was heated to 100° C. The theoretical pressure drop equivalent to 100% reduction was observed. The product was vacuum distilled to give 44 g. of product, m. p. 57-59° C., yield 68%. The low yield was attributed to slopping of product out of the glass liner during the hydrogenation.

2. Preparation of Decahydroquinoxaline by the Method of Christie, Rhode, and Shultz (3).

A mixture of 18 g. (0.13 mole) of tetrahydroquinoxaline, 1 g. of Adam's catalyst and 125 ml. of 3 normal ethanolic hydrochloric acid was placed in the Parr Low Bomb at room temperature and 50 psi hydrogen for 24 hours. A pressure drop equivalent to 100% reduction to decahydroquinoxaline was observed. Water was added to effect solution and the catalyst was removed by filtration. The solvent was removed by evaporation, the residue dissolved in 80 ml. of water and 18 g. of sodium hydroxide pellets added. The solution was extracted with benzene three times, the extracts dried over sodium hydroxide pellets for 24 hours and the benzene reduced in volume leaving a residue which was taken up in hot Skellysolve B. On

Table XVI. Preparations of cis-Decahydroquinoxaline.
QH = Quinoxaline
QH4 = Tetrahydroquinoxaline

Starting Material	Amount, Grams of Starting Material	M. P. of Product, °C.	% Yield	Remarks
QH	13	59-62	61	
QH	10	54-59	39	5.1 g. of insoluble brown material obtained as in preparation b above.
QH	13	53-60	57	2.5 g. of insoluble brown material obtained as in preparation b above.
QH	11	55-60	64	1 g. of insoluble brown material obtained as in preparation b above.
QH	13	55-60	66	Some product decomposed by heat in distillation process.
QH	10	55-60	78	
QH	10	55-60	77	
QH4	20	55-60	96	
QH4	17	56-59	87	
QH4	15	55-60	95	
QH4	15	57-62	91	
QH4	13	No product obtained.		Bomb poisoned by QH4 preparation.
QH4	13	No product obtained.		Bomb poisoned by QH4 preparation.
QH4	13	No product obtained.		Bomb poisoned by QH4 preparation.
QH4	12	55-65	80	
QH4	25	55-65	96	
QH4	15	55-60	92	
QH4	10	55-60	86	
QH4	10	52-60	81	
QH4	46	No product.		Bomb poisoned.
QH	18.5	No product.		Bomb poisoned.
QH	18	Mixture of QH4 and cis-decahydroquinoxaline obtained. Partial reduction.		

cooling, 4.5 g. of crystals deposited, m. p. 110° C. After repeated recrystallization 1 g. of material, m. p. 135-40° C., yield 9.4%, was obtained. Further recrystallization from Skellysolve B gave 0.2 g. of trans-decahydroquinoxaline, m. p. 146-8° C. Shultz reported a 12.5% yield of decahydroquinoxaline, m. p. 152.5-153° C.

Three other preparations of decahydroquinoxaline by the method of Shultz and co-workers were carried out. Data on these preparations are given in Table XVII.

Table XVII. Preparations of Decahydroquinoxaline by the Method of Shultz.

Size Run, g.	Product Isolated	Yield grams	Yield %	M. P. °C.
9.4	impure trans-decahydroquinoxaline	1	10	90-135
	impure cis-decahydroquinoxaline	2	20	57-69
9.2	impure trans-decahydroquinoxaline	2	19	110-115
	impure cis-decahydroquinoxaline	0.5	5	55-75
13.3	Starting material.	No pressure drop observed over 48 hours. Reaction flask inlet plugged three times. Following the last unplugging the reaction mixture was subjected to 75 psi hydrogen and 60° C. for 36 hours. No pressure drop observed. Bomb was apparently poisoned.		

3. Preparation of Decahydroquinoxaline by the method of Beck, Hamlin and Weston (1).

Numerous preparations of decahydroquinoxaline by the method of Weston, et. al., were carried out. One preparation is listed in detail while the data on the other preparations is given in Table XVIII.

A mixture of 52 g. (0.33 mole) of 2-(β-aminoethylamino)-cyclohexanol and 10 g. of Raney nickel W-2 catalyst was placed in the Magne Dash Bomb at 200° C. and 200 psi hydrogen for 12 hours. After cooling, the reaction mass was dissolved in a minimum of alcohol, filtered to remove the catalyst, and an excess of Skellysolve B added. The solution was reduced in volume by boiling. If, after the volume had been concentrated to about

250 ml., crystallization had not started, more Skellysolve B was added and the procedure repeated. Once crystallization had commenced, the solution was cooled in an ice bath. After filtration, the mother liquors on further concentration, gave a little more product. The product was recrystallized by dissolving the trans-decahydroquinoxaline in a minimum of hot alcohol and repeating the above procedure. Yield was 41%, m. p. 148-150° C. Weston reported a yield of 24%, m. p. 150-1° C. This preparation when run using the Parr High Bomb gave consistently yields of 25-30%. The increase in reaction time, being 12 hours instead of the 6 hours reported by Weston, and the different purification procedure are thought to be responsible for the yields obtained in excess of those obtained by Weston.

Table XVIII. Preparations of Decahydroquinoxaline by the Method of Beck, Hamlin and Weston.

2-(β-aminoethylamino)-cyclohexanol used, g.	Bomb Used	M. P. °C.	% Yield
35	Parr High	148-150	11
32	Parr High	149-150	22
30	Parr High	148-149	20
40	Parr High	149-150	20
38	Parr High	149-150	23
38	Parr High	147-148	26
40	Parr High	149-150	23
81	Parr High	148-150	25
80	Parr High	147-149	30
50	Parr High	151-152	24
60	Parr High	150-151.5	30
72	Parr High	150-151	28
41	Parr High	148-150	25
50	Parr High	148-150	33
80 (aged)	Parr High	No Product. After 2nd failure cat-	
40 (fresh)	Parr High	No Product. alyst found ineffective.	
40	Parr High	No Product. Defective equipment,	
40	Parr High	No Product. temperature too high.	
90	Magne Dash	148-150	41
75	Magne Dash	148-150	41
69	Magne Dash	148.5-151	44

F. Identification of the Two Geometrical Isomers of Decahydroquinoxaline.

In view of the discrepancies regarding the reports of the preparation of decahydroquinoxaline, see introduction, the preparation of derivatives of the reported decahydroquinoxalines and the preparation of the N,N'-dinitroso derivative of tetrahydroquinoxaline for purposes of identification was desired. A mixed melting point of Weston's decahydroquinoxaline (m. p. 147-8° C.) and Shultz's decahydroquinoxaline (m. p. 146-8° C.) was 147.5-148.5° C. Derivatives would further substantiate that the decahydroquinoxaline of Weston and Shultz was identical.

1. Preparation of the N,N'-Dinitroso Derivative of Shultz's Decahydroquinoxaline.

To a solution of 0.7 g. of Shultz's decahydroquinoxaline, m. p. 140-48° C., in dilute hydrochloric acid was added dropwise a cold solution of 3 g. of sodium nitrite in 10 ml. of water. After the evolution of gas ceased, the precipitate was filtered and recrystallized four times from ethanol-water to give a product, m. p. 107-8° C. Shultz reported a melting point of 110-111° C. for the dinitroso derivative of his decahydroquinoxaline.

2. Preparation of the N,N'-Dinitroso Derivative of Weston's Decahydroquinoxaline.

To a solution of 1 g. of Weston's decahydroquinoxaline in cold dilute hydrochloric acid was added a cold solution of 4 g. of sodium nitrite in water. After the evolution of gas ceased, the precipitate was filtered and recrystallized from ethanol-water to a melting point of 108-110° C. The mixed melting point of this dinitroso derivative and the dinitroso derivative of Shultz's decahydroquinoxaline prepared above was 106-9° C., thus indicating the two dinitroso derivatives were the same.

3. Preparation of the N,N'-Diacetyl Derivative of Weston's Decahydroquinoxaline.

A solution of 0.6 g. of Weston's decahydroquinoxaline in 0.9 g. of acetic anhydride was refluxed for one hour. The solution was poured into 5 ml. of water and neutralized with sodium hydroxide solution. The aqueous solution was extracted with benzene in a liquid-liquid extractor for 24 hours and the benzene removed by evaporation leaving a solid material, m. p. 85-90° C. Recrystallization from benzene-cyclohexane was carried out until a constant melting point of 93.5-94.5° C. was obtained.

Anal. Calc'd for $C_{12}H_{20}O_2N_2$: C, 64.22; H, 8.98. Found: C, 64.08; H, 8.78.

4. Preparation of the N,N'-Dinitroso Derivative of Broadbent's and Whittle's Decahydroquinoxaline, Freshly Prepared, M. P. 55-60° C.

A cold solution of 2.5 g. of sodium nitrite in 5 ml. of water was added dropwise to a cold solution of 0.85 g. of decahydroquinoxaline in

dilute hydrochloric acid. After evolution of gas ceased, the precipitate was filtered and recrystallized from ethanol-water to a constant m. p. of 86-88° C.

Anal. Calc'd for $C_8H_{14}O_2N_4$: C, 48.47; H, 7.16; N, 28.26. Found: C, 49.02; H, 6.84; N, 27.8.

5. Preparation of the N,N'-Dinitroso Derivative of Broadbent's and Whittle's Decahydroquinoxaline, Aged, M. P. 60-100° C.

To a cold solution of 0.4 g. of decahydroquinoxaline in dilute hydrochloric acid was added dropwise a cold solution of 2.3 g. of sodium nitrite in water. Purification of the precipitate by recrystallization from ethanol-water gave a product, m. p. 85-86.5° C.

Anal. Calc'd for $C_8H_{14}O_2N_4$: C, 48.47; H, 7.16. Found: C, 48.91; H, 7.55.

Mixed melting point of this derivative and the N,N'-dinitroso derivative of Broadbent's and Whittle's freshly prepared decahydroquinoxaline (see 4 preceding) was 85-86.5° C., thus indicating the two derivatives to be identical.

6. Preparation of the N,N'-Dinitroso Derivative of Decahydroquinoxaline, M. P. 90-110° C., Isolated in the Preparation of Shultz's Decahydroquinoxaline.

A cold water solution of 0.6 g. of sodium nitrite was added dropwise to a cold solution of 0.25 g. of decahydroquinoxaline in dilute hydrochloric acid. Purification of the precipitate by recrystallization from ethanol-water gave a derivative of m. p. 87-88° C. The mixed melting point of this derivative with the N,N'-dinitroso derivative of freshly prepared Broadbent's and Whittle's decahydroquinoxaline (see 4 preceding) was 86-87° C. The mixed melting point of this derivative with the N,N'-dinitroso derivative of aged decahydroquinoxaline prepared by the method of Broadbent and Whittle (see 5 preceding) was 85.5-87° C.

7. Preparation of the N,N'-Diacetyl Derivative of Broadbent's and Whittle's Decahydroquinoxaline, Freshly Prepared, M. P. 55-60° C.

A solution of 1 g. of decahydroquinoxaline in acetic anhydride was refluxed for 1½ hours. After neutralization of the reaction mixture with sodium hydroxide solution, extraction with benzene in a liquid-liquid extractor was carried out for 24 hours. Evaporation of the benzene gave crystals, m. p. 142-44° C., which were purified by recrystallization from benzenecyclohexane to give a product, m. p. 145-7° C.

8. Preparation of the N,N'-Diacetyl Derivative of Aged Decahydroquinoxaline, M. P. 60-100° C., Prepared by the Method of Broadbent and Whittle.

A solution of 1.5 g. of decahydroquinoxaline in acetic anhydride was refluxed for 12 hours, neutralized with ammonium hydroxide and extracted

with benzene in a liquid-liquid extractor for 5 hours. Evaporation of the benzene and recrystallization of the residue from cyclohexane, followed by recrystallization from Skellysolve D, gave crystals, m. p. 144-46° C.

Anal. Calc'd for $C_{12}H_{20}O_2N_2$: C, 64.22; H, 8.98. Found: C, 64.18; H, 9.32.

The mixed melting point of this derivative with the N,N'-diacetyl derivative of Broadbent's and Whittle's freshly prepared decahydroquinoxaline (see 7 preceding) was 145-7° C.

9. Preparation of N,N'-Dinitroso-1,2,3,4-tetrahydroquinoxaline.

To a cold solution of 2g. (0.014 mole) of tetrahydroquinoxaline in 13 ml. of dilute hydrochloric acid was added a cold solution of 2.33 g. (0.033 mole) of sodium nitrite in water. The precipitate was filtered and found to melt at 130° C. (dec.). One recrystallization from absolute ethanol gave a melting point of 155-65° C. (dec.). A second recrystallization gave a melting point of 156.5-64° C. With purification the decomposition on melting became much less evident. Yield was 2 g., 70%.

It is evident from the results obtained from the preparation of the dinitroso and the diacetyl derivatives of the various decahydroquinoxalines and the analyses of these derivatives that the two dinitroso and the two diacetyl derivatives, corresponding to the cis and trans isomers of decahydroquinoxaline, have been prepared. Further, the preparation of decahydroquinoxaline by the method of Shultz gave a mixture of both isomers, while from the aged decahydroquinoxaline prepared by the method of Broadbent and Whittle only one dinitroso and one diacetyl derivative were isolated, indicating, thus, that the change in melting point characterizing the aged decahydroquinoxaline of Broadbent and Whittle was not, as previously thought by these workers, due to isomerization of the cis isomer into the trans isomer. Apparently the dinitroso derivative reported by Mousseron and Combes (2), M. P. 160° C. (dec.), was not the derivative of decahydroquinoxaline. This derivative was the only evidence offered by Mousseron and Combes that they had prepared decahydroquinoxaline. It is quite possible that the dinitroso derivative reported by these last workers was the dinitroso derivative of tetrahydroquinoxaline. This possibility is supported not only by melting point data but also the observation that decahydroquinoxaline under some conditions (cf. page 86) readily dehydrogenates to give tetrahydroquinoxaline.

G. Studies on the Change of Melting Point, Isomerization, and Structure of cis- and trans-Decahydroquinoxaline.

These experiments are delineated below. Each experiment is followed by a brief conclusion or conclusions drawn from the observations.

1. Chromatography of Aged cis-Decahydroquinoxaline, M. P. 55-117° C.

This chromatographic separation of aged cis-decahydroquinoxaline was a repetition of work reported by Whittle (4). A saturated solution of the aged cis-decahydroquinoxaline in sodium dried ether was passed over a column of barium oxide to remove any carbonate present then poured on a nitrogen flushed 1 by 20 cm. column of neutral aluminum oxide (Woelm) activity grade 1. The column was eluted with alcohol-free chloroform (prepared by distillation of the chloroform over calcium turnings) and 95 one ml. fractions were collected under nitrogen. The fractions were examined by evaporating the chloroform under a stream of nitrogen and taking melting points of the residues. Table XIX summarizes the data on the fractions so examined.

Table XIX. Chromatography of Aged cis-Decahydroquinoxaline.

Fraction No.		M. P. °C.
5	trace of material, insufficient for melting point	
7	trace of material, insufficient for melting point	
8	little material, very slightly colored	139-143
9	material, slightly gummy, no melting point taken	
10	material	80-125
11	material	80-125
20	material	58-107
30	material	52-73
40	material	55.5-63
50	little material	52-60
80	very little material	48-60
90	trace of material, insufficient for melting point	

The results obtained above are in essential agreement with those of Whittle. Fractions corresponding to the two isomers of decahydroquinoxaline were separated from aged cis-decahydroquinoxaline. This does not necessarily indicate isomerization of the cis form into the trans form however, as conjectured by Broadbent and Whittle (4). The possibility of a small amount of the trans isomer being formed during the hydrogenation of quinoxaline or tetrahydroquinoxaline to cis-decahydroquinoxaline was still open.

2. Gas Chromatography of Aged cis-Decahydroquinoxaline.

Results substantiating those obtained in 1, preceding were obtained by gas partition chromatography. An Aereograph Gas Chromatographic Instrument, Master Model A-100, Wilkens Instrument and Research, Inc., Berkeley,

California was used. A sample of aged cis-decahydroquinoxaline in ethanol was chromatographically separated at 208° C. using a 10 ft. silicone column and helium gas as the carrier. Products of melting points 55-63° C. and 140-48° C., corresponding to cis- and trans-decahydroquinoxaline, were separated.

3. Chromatography of Freshly Prepared cis-Decahydroquinoxaline, M. P. 55-59° C.

A solution of 3 g. of cis-decahydroquinoxaline in anhydrous ether was poured on a nitrogen-flushed 4 by 18 cm. column of neutral aluminum oxide (Woelm), activity grade 1. The column was eluted with ninety 15 ml. fractions of chloroform. The fractions were examined by evaporation of the chloroform under a steam of nitrogen and taking melting points and ultraviolet spectra of the residues. Table XX lists this data.

Table XX. Chromatography of Freshly Prepared cis-Decahydroquinoxaline, M. P. 55-59° C. and Ultraviolet Spectral Data.

Fraction No.		M. P. °C.	Spectral Data λ(mμ) Max.	ε
10	no material			
20	little material	115-135		
30	material	55-115	310-12	0.0
40	material	55-100	310-12	0.0
50	material	52-57	310-12	0.0
60	material	53-57	310-12	206.7
70	material	52-54	310-12	215.5
80	material	52-55	310-12	174.5
90	very little material	53-58	310-12	158.3
91 (30ml)	no material			

Ultraviolet spectra, free of indications of unsaturation, were obtained for fractions 30, 40, and 50. Ultraviolet spectra of subsequent fractions indicated unsaturation indicative of tetrahydroquinoxaline contamination. The ultraviolet spectrum of tetrahydroquinoxaline has a maximum at the same wave length as the maximum obtained in the ultraviolet spectra of fractions 60-90. Tetrahydroquinoxaline would be expected to be more strongly adsorbed than decahydroquinoxaline, and any tetrahydroquinoxaline present in the cis-decahydroquinoxaline, prior to chromatographic separation, would be expected to be present in the latter fractions of the eluent. Its much greater molar extinction coefficent at 310-12 mu, as compared to the molar extinction co-

efficient of decahydroquinoxaline at this same wave length, would make minor contamination by tetrahydroquinoxaline evident.

This chromatographic separation showed that in the reduction of quinoxaline or tetrahydroquinoxaline to cis-decahydroquinoxaline by the method of Broadbent and Whittle a little trans-decahydroquinoxaline was obtained. This explains the results of these workers wherein they obtained by chromatographic separation both cis and trans isomers of decahydroquinoxaline from aged cis-decahydroquinoxaline. The possibility, however slight, still remained that the cis form isomerized to give an equilibrium mixture of both isomers.

4. Rechromatography of Chromatographed cis-Decahydroquinoxaline, M. P. 53-57° C., Evidence that cis-Decahydroquinoxaline Does Not Isomerize.

Fractions 50-90 from the preceding chromatographic separation were combined, the solvent removed under a stream of nitrogen, and the cis-decahydroquinoxaline obtained, stored under nitrogen for 15 days. During the storage the melting point did not change. This material was chromatographed in a manner similar to the previous separations. Sixty 10 ml. fractions of eluent were collected and examined. The data on these fractions is given in Table XXI.

Table XXI. Rechromatography of Chromatographed cis-Decahydroquinoxaline, M. P. 53-57° C.

Fraction No.		M. P. °C.
10	no material	
20	trace of material, insufficient for melting point	
21	little material	53-60
22	material	53-60
24	material	53-59
25	material	53-57
30	very little material	53-57
50	very little material	53-57
60	very little material	53-57

No high melting isomer was isolated. Fraction 26 after storage for two months under nitrogen had not changed melting point, indicating further that no isomerization had occurred.

5. Subjecting cis-Decahydroquinoxaline to the Conditions Used in Preparing Decahydroquinoxaline by the Method of Christie, Rhode, and Shultz.

If cis-decahydroquinoxaline were labile to any extent and did isomerize to the trans isomer then the subjecting of cis-decahydroquinoxaline to the conditions under which trans-decahydroquinoxaline had been prepared should hasten the isomerization. With this in mind the following experiment was conducted.

A mixture of 4.6 g. of decahydroquinoxaline, m. p. 55-60° C., 37.5 ml. of 3 N ethanolic hydrochloric acid and 0.2 g. of Adam's catalyst was placed in the Parr Low Bomb at 70 psi hydrogen and 60° C. for 4 hours. The dihydrochloride which formed was dissolved in water and the catalyst filtered off. The solvent was removed by evaporation, the residue dissolved in 20 ml. of water, 4.5 g. of sodium hydroxide pellets added, and the solution extracted with one 25 ml. and two 10 ml. portions of benzene. The benzene extracts were dried over sodium hydroxide pellets for 24 hours, the benzene removed under reduced pressure, and the residue taken up in 5 ml. of Skellysolve B. The solution was cooled, the precipitate filtered and rinsed. The product obtained was very colored (red-orange) and melted at 60-70° C. Several recrystallizations from Skellysolve B gave 0.1 g. of product, m. p. 135-140°, yield 1.1%. Further recrystallization would have given the pure trans-decahydroquinoxaline, but in less than 1%. The amount of trans-decahydroquinoxaline obtained was no more than the amount already present prior to this treatment, judging from the amount of trans-decahydroquinoxaline separated from freshly prepared cis-decahydroquinoxaline by chromatographic means. No evidence of isomerization of the cis isomer into the trans isomer was obtained by this experiment. It did illustrate that by crystallization the low melting isomer can be separated from the high melting isomer.

6. Subjecting trans-Decahydroquinoxaline to the Conditions Used in Preparing Decahydroquinoxaline by the Method of Broadbent and Whittle.

A mixture of 3.0 g. of trans-decahydroquinoxaline, m. p. 148-9° C., 10 ml. of absolute ethanol and 0.25 g. of 5% rhodium on alumina was placed in the Parr High Bomb at 2500 psi hydrogen and 100° C. for four hours. The catalyst was removed by filtration and the solvent evaporated to give a white solid, m. p. 148-9° C. No change occurred in the trans-decahydroquinoxaline. No isomerization was evident.

7. Preparation of the Carbonate Salt of cis-Decahydroquinoxaline.

All evidence thus far accumulated indicated that cis-decahydroquinoxaline did not isomerize. The change of melting point of the cis isomer on standing was caused by something else. Realizing many amines absorb carbon dioxide from the air forming salts, Whittle (4) stored samples of cis-decahydroquinoxaline under nitrogen, but still changes in melting point were noted with the passing of time. The results obtained under 4 preceding indicated that cis-decahydroquinoxaline when stored out of contact with the air did not change melting point. Faulty experimental technique was possibly responsible for the change in melting point observed by Whittle

of the cis-decahydroquinoxaline he had stored under nitrogen. To determine further the effect of carbon dioxide on cis-decahydroquinoxaline the following experiments were carried out.

A solution of 5.5 g. of cis-decahydroquinoxaline in 50 ml. of toluene was prepared. Carbon dioxide was bubbled through water and then through the toluene solution of the amine. Within several minutes a precipitate had begun to form, m. p. 65-80° C. After 24 hours and again after 60 hours of bubbling carbon dioxide through the solution, samples of the precipitate were removed, dried and melting points taken. Both samples melted 65-125° C. Yield of the salt was 6.8 g.

A second preparation of the carbonate salt was carried out, but in this preparation oxygen-free carbon dioxide (by passing the carbon dioxide through a copper tube heated to 475-500° C.) was used. After 22 hours of passing oxygen-free, water-saturated carbon dioxide through a solution of 3 g. of cis-decahydroquinoxaline in toluene, the precipitate which had formed was filtered, dried and weighed to give 4.1 g. of salt, m. p. 67-100° C.

The increase in the melting point of cis-decahydroquinoxaline on standing, though on occasion reached 125° C., was never noted to go beyond this. While this agreement of melting points of the prepared carbonate salt and the aged cis-decahydroquinoxaline does not have great significance in and of itself, yet considered in view of the other evidence given concerning the change of melting point of cis-decahydroquinoxaline, it further substantiates that cis-decahydroquinoxaline does not isomerize and that the change in melting point is due solely to carbonate salt formation.

Purification and analyses of this carbonate salt was desired, but no solvent was located that was suitable for recrystallization. The following solvents and solvent systems were tried but found unsuitable: isopropyl alcohol-ethanol, ethyl acetate, chloroform, acetone-ethanol, Skellysolve B-ethanol, and toluene. Dissolution in ethanol and precipitation by the addition of ethyl ether was tried and failed. Vacuum sublimation was carried out at 60-70° C. and 0.250 mm. pressure, but the lower limit of the melting point range became lower while the upper range did not change. This indicated some of the salt had been decomposed to give a greater portion of the low melting free amine. Treatment of a sample of the salt, m. p. 68-125° C., with boiling alcohol followed by several washings with cold absolute alcohol gave a product of melting point 86-125° C. A sample of this purified salt was thoroughly dried and submitted for analyses. No compound of definite constitution could be ascertained from the carbon and hydrogen analyses obtained.

That the aged cis-decahydroquinoxaline was a carbonate salt was supported further by infrared spectra (119), see figures 2 and 3 (cf.

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(119) Kindly run by Dr. Harold Boaz through the courtesy of Dr. Reugen Jones, Research Division, Eli Lilly and Company, Indianapolis, Indiana. Appreciation is expressed for their assistance.

pp.91-2). Indications of HCO_3^- and NH_2^+ bands were found to be present in the aged cis-decahydroquinoxaline. If the sample of cis-decahydroquinoxaline were passed over a calcium oxide column prior to making the spectrum, the HCO_3^- and NH_2^+ bands were absent from the spectrum.

8. Preparation of the Carbonate Salt of trans-Decahydroquinoxaline.

A solution of 1.8 g. of trans-decahydroquinoxaline, m. p. 148-150° C., in 150 ml. of toluene and sufficient alcohol to effect solution was treated with water saturated carbon dioxide. Within 6 hours the solution had become milky in appearance, and after 20 hours a precipitate had formed, m. p. 148-153° C. After bubbling carbon dioxide through the solution for 3 days, the precipitate was filtered and dried to give 2.3 g. of salt, m. p. 149-185° C. The slowness of formation of the carbonate salt under these conditions is consonant with the failure of the carbonate salt to form under atmospheric conditions. No purification or analyses of this salt was obtained and no more work was done with it.

9. Effect of Time on the Melting Point of trans-Decahydroquinoxaline.

Samples of trans-decahydroquinoxaline M. P. 149-50° C., were stored both under nitrogen and at room conditions. Melting points taken periodically over a seven month period showed no change in melting point in any of the samples. Whittle (4) reported that trans-decahydroquinoxaline changed melting point with standing. The material for which he observed the melting point change was very probably not pure trans-decahydroquinoxaline. The failure of trans-decahydroquinoxaline to change melting point indicates no isomerization.

10. Dehydrogenation of cis-Decahydroquinoxaline to 1,2,3,4-Tetrahydroquinoxaline.

A mixture of 2 g. of cis-decahydroquinoxaline, 0.5 g. of 5% rhodium on alumina, and 25 ml. of p-cymene was refluxed under a slow steam of nitrogen for 2½ hours. During the refluxing the mixture bumped and some product was lost out of the top of the condenser. The catalyst was removed by filtration and the solution on cooling deposited crystals of tetrahydroquinoxaline, m. p. 95-6° C. The mixed melting point of this product with a known sample of tetrahydroquinoxaline, m. p. 97-98° C., was 96-7° C. No other products were found.

The obtaining of tetrahydroquinoxaline by the dehydrogenation of cis-decahydroquinoxaline showed conclusively that cis-decahydroquinoxaline was cyclic in structure and not in any way an open chain isomer. The previous failure to obtain ultraviolet spectra of cis-decahydroquinoxaline free of indications of unsaturation had given rise to the possibility that the compound might be an isomeric substituted cyclohexane compound containing unsaturation in the substitutents. This work eliminated this latter possibility.

11. Attempted Dehydrogenation of trans-Decahydroquinoxaline.

A mixture of 2 g. of trans-decahydroquinoxaline, 0.3 g. of 5% rhodium on alumina, and 25 ml. of p-cymene was refluxed under a slow stream of nitrogen for 2 hours. The trans-decahydroquinoxaline was recovered unchanged from the reaction mixture by removal of the solvent by filtration and then evaporation of the solvent. The residue was recrystallized once from Skellysolve B-ethanol.

12. Ultraviolet Spectra of 1,2,3,4-Tetrahydroquinoxaline, cis-Decahydroquinoxaline and trans-Decahydroquinoxaline, Figure 1.

(a) A sample of tetrahydroquinoxaline was recrystallized several times from benzene to a constant melting point of 96-97° C. A final recrystallization from spectrograde issoctane was carried out. The spectrum was scanned from 340 mμ to 206 mμ on the Beckman DK-2 Spectrophotometer using spectrograde isooctane as the solvent. The concentration was 0.00008 molar. Table XXII gives the ultraviolet spectrum data. A plot of log ϵ vs. λ is given in Figure 1.

Maxima were found at 311 mμ, logϵ = 3.153; at 254 mμ, logϵ = 3.113; and at 220 mμ, logϵ = 4.001.

(b) The preparation of cis-decahydroquinoxaline for ultraviolet analyses has been given before (cf. pp. 72). The spectrum was scanned from 340 mμ to 225 mμ using spectrograde isooctane as the solvent. The concentration was 0.001 molar. No maxima were found. Table XXIII gives the ultraviolet spectrum data. A plot of log ϵ vs. λ is given in Figure 1.

(c) A sample of trans-decahydroquinoxaline was prepared for ultraviolet analyses by recrystallizing it several times from Skellysolve B-ethanol to a constant melting point of 152.5-153° C. A final recrystallization was carried out using spectrograde isooctane as the solvent. The spectrum was scanned from 340 m to 228 m using spectrograde isooctane as the solvent. No maxima were found. Table XXIV gives the ultraviolet spectrum data. A plot of log ϵ vs. λ is given in Figure 1.

13. Infrared Spectra and Physical Property Data of cis- and trans-Decahydroquinoxaline (119).

(a) Infrared Spectra.

Infrared sprectra of cis- and trans- decahydroquinoxaline were run by Boaz using both the mineral oil mulls (fig. 2) and chloroform solutions (fig. 3). The spectra indicated the two compounds differed molecularly -- not simply in crystalline form. The NH_2^+ and HCO_3^- bands previously mentioned (cf. p. 83) indicated carbonate salt formation. Consideration of the NH stretching frequencies and intensities at 2.7μ for both isomers (the cis isomer having a very narrow but much more intense band than the trans isomer) and the hydrogen bonded bands at 3.0 and 3.1μ gave evidence, based on present understanding of infrared spectra, that the high melting isomer

(Weston's product) had the trans configuration. The spectra at 7.5μ indicated that, perhaps, as much as 10% of the trans isomer was present in cis-decahydroquinoxaline prepared by Broadbent's and Whittle's procedure, thus substantiating the chromatographic separations of cis- and trans-decahydroquinoxaline that had been carried out (cf. p. 78). No indication of aromatic absorption between 6.2 and 6.9μ was present in the spectra. The bands indicative of the carbon-oxygen double bond, the carbon-nitrogen double bond, and the carbon-carbon double bond were absent.

(b) Physical Property Data.

Table XXV gives data on pKa's and molecular weights, as determined by Boaz, of both isomers of decahydroquinoxaline in water and dimethylformamide. The upper pKa of the cis isomer was found to be consistently about 0.2 unit higher than that of the trans isomer. The slightly high molecular weight results obtained for cis-decahydroquinoxaline was probably due to absorbed carbon dioxide and water.

Conclusions to be drawn from the infrared spectra and physical property data concerning the structure and nature of decahydroquinoxaline are consonant with the conclusions derived from the other phases of the research done on decahydroquinoxaline.

14. Aerial Oxidation of cis-Decahydroquinoxaline.

A solution of 5 g. of cis-decahydroquinoxaline, m. p. 55-60° C., in 50 ml. of phenyl ether was prepared. The phenyl ether was maintained at an average temperature of 60° C. while oxygen was bubbled through the solution with the aid of a gas dispersion tube. After 1 hour a 10 ml. sample of solution was withdrawn, diluted with ethyl ether to 25 ml., extracted with dilute hydrochloric acid, and the aqueous layer basified with 50% sodium hydroxide solution. On basifying, a precipitate formed, was filtered, washed and dried to give a product, m. p. 80-85° C. This sample was recrystallized from benzene to give a product identified by melting point and mixed melting point data as tetrahydroquinoxaline. A second sample taken after 3 hours time and processed as above, except for the recrystallization from benzene, gave a product of melting point 83-88° C. The balance of the phenyl ether solution of cis-decahydroquinoxaline was treated in a manner similar to that of the two samples which were withdrawn. The total yield of tetrahydroquinoxaline isolated was 2.2 g., 46%. A sample of this product was converted to the dihydrochloride by dissolving the tetrahydroquinoxaline in ether and bubbling through hydrogen chloride gas. The precipitate which formed was recrystallized from ethanol-Skellysolve B to give a product, m. p. 162-4° C. Literature value is 167-9° C. (106). The dihydrochloride turned a pale pink color on exposure to the air, which characteristic is also recorded in the literature (106). The aqueous layer from which the tetrahydroquinoxaline had precipitated on basifying was poured into concentrated sodium hydroxide solution. With standing more crystals formed on top of the aqueous layer. These crystals were also identified as tetrahydroquinoxaline. The only product isolated in this experiment was tetrahydroquinoxaline. It seemed, at this point, that cis-decahydroquinoxaline was easily air oxidized to tetrahydroquinoxaline.

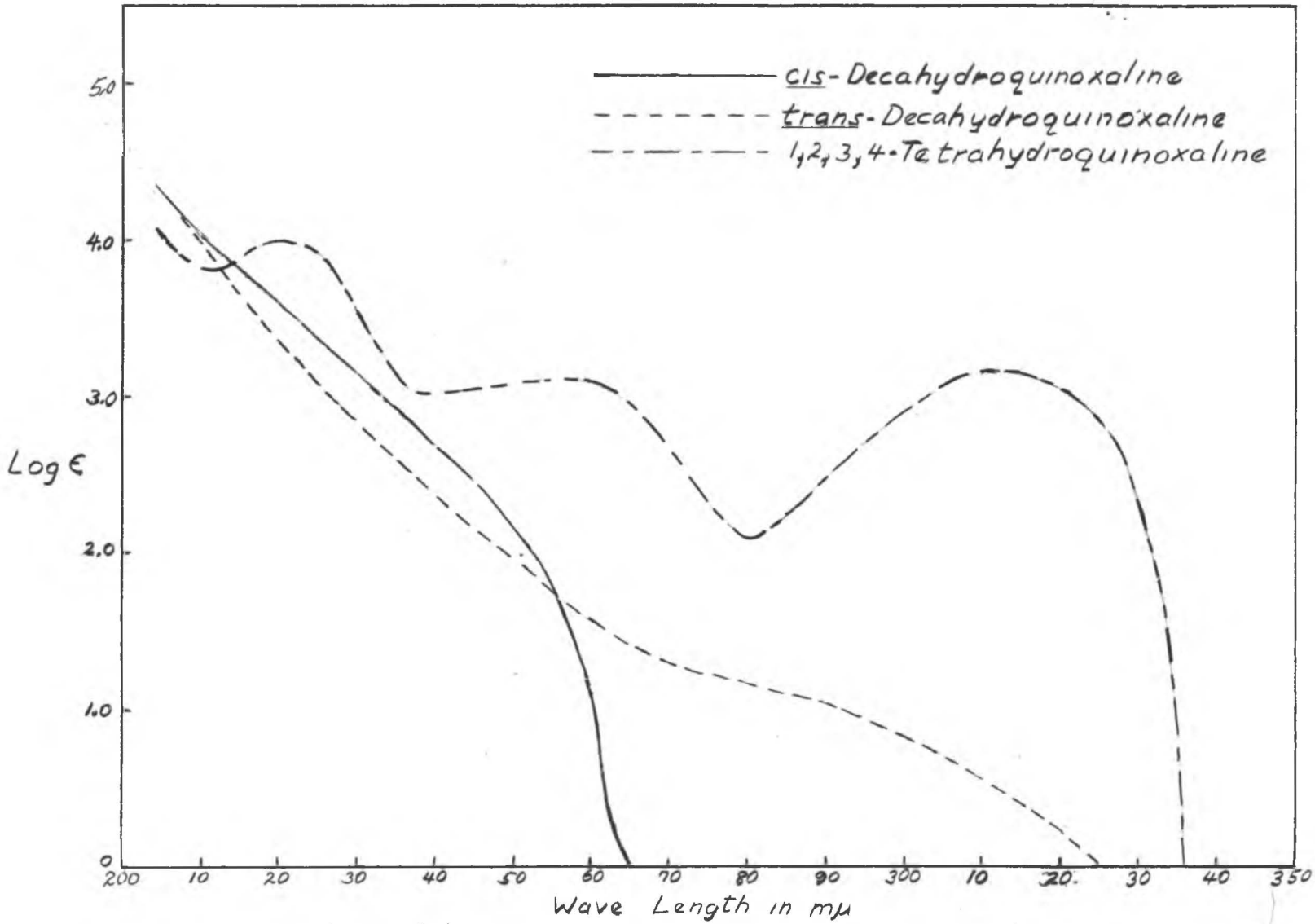

Figure 1. Ultraviolet Absorption Spectra of 1,2,3,4-Tetrahydroquinoxaline, cis-Decahydroquinoxaline, and trans-Decahydroquinoxaline.

Table XXII. Spectrophotometric Absorption of 1,2,3,4-Tetrahydroquinoxaline, 0.00008 Molar in 2,2,4-Trimethylpentane.

λ(mμ)	Absorbancy	ε	Log ε
336	0	0	undefined
332	.006	75	1.875
326	.050	625	2.796
320	.092	1150	3.060
314	.113	1412	3.150
312	.114	1424	3.153
310	.114	1424	3.153
308	.110	1374	3.138
304	.092	1150	3.060
300	.073	912	2.960
294	.041	512	2.709
290	.028	350	2.544
286	.016	200	2.300
283	.012	150	2.176
280	.010	125	2.097
277	.013	162.4	2.210
270	.040	499.9	2.699
264	.080	999.9	3.000
256	.104	1298	3.113
253	.104	1298	3.113
250	.101	1262	3.101
243	.091	1137	3.055
240	.091	1137	3.055
237	.0908	1134	3.054
235	.115	1437	3.157
233	.160	2000	3.301
230	.290	3624	3.558
226	.640	7992	3.902
223	.745	9310	3.969
221	.795	9938	3.997
220	.802	10020	4.001
219	.786	9821	3.992
215	.640	7998	3.903
212	.527	6582	3.818
209	.548	6847	3.835
205	.855	10685	4.029

Table XXIII. Spectrophotometric Absorption of cis-Decahydroquinoxaline, 0.001 Molar in 2,2,4-Trimethylpentane.

λ(mμ)	Absorbancy	ε	Log ε
340	0	0	undefined
330	0	0	undefined
320	0	0	undefined
310	0	0	undefined
300	0	0	undefined
290	0	0	undefined
280	0	0	undefined
270	0	0	undefined
265	0	0	undefined
260	.015	15	1.176
256	.050	50	1.699
252	.105	105	2.021
245	.290	290	2.462
240	.505	505	2.703
235	.840	840	2.924
233	.990	990	2.996

Table XXIV. Spectrophotometric Absorption of trans-Decahydroquinoxaline, 0.001 Molar in 2,2,4-Trimethylpentane.

λ(mμ)	Absorbancy	ε	Log ε
340	0	0	undefined
330	0	0	undefined
325	.001	1	0
310	.004	4	0.602
300	.007	7	0.845
290	.011	11	1.041
280	.015	15	1.176
270	.020	20	1.301
260	.045	45	1.653
250	.099	99	1.996

λ(mμ)	Absorbancy	ε	Log ε
245	.166	166	2.220
240	.274	274	2.438
235	.434	434	2.637
230	.660	660	2.819
227	.830	830	2.919

Table XXV. Physical Property Data of Decahydroquinoxaline.

Isomer	Solvent	Molarity	pKa's #1	#2	Apparent Mol. Wt.
trans	water	0.0050	9.66	5.33	140
trans	66% aq. DMF	0.0063	9.37	5.3	141
cis	water	0.0050	9.85	5.33	147
cis	66% aq. DMF	0.0060	9.62	5.3	164

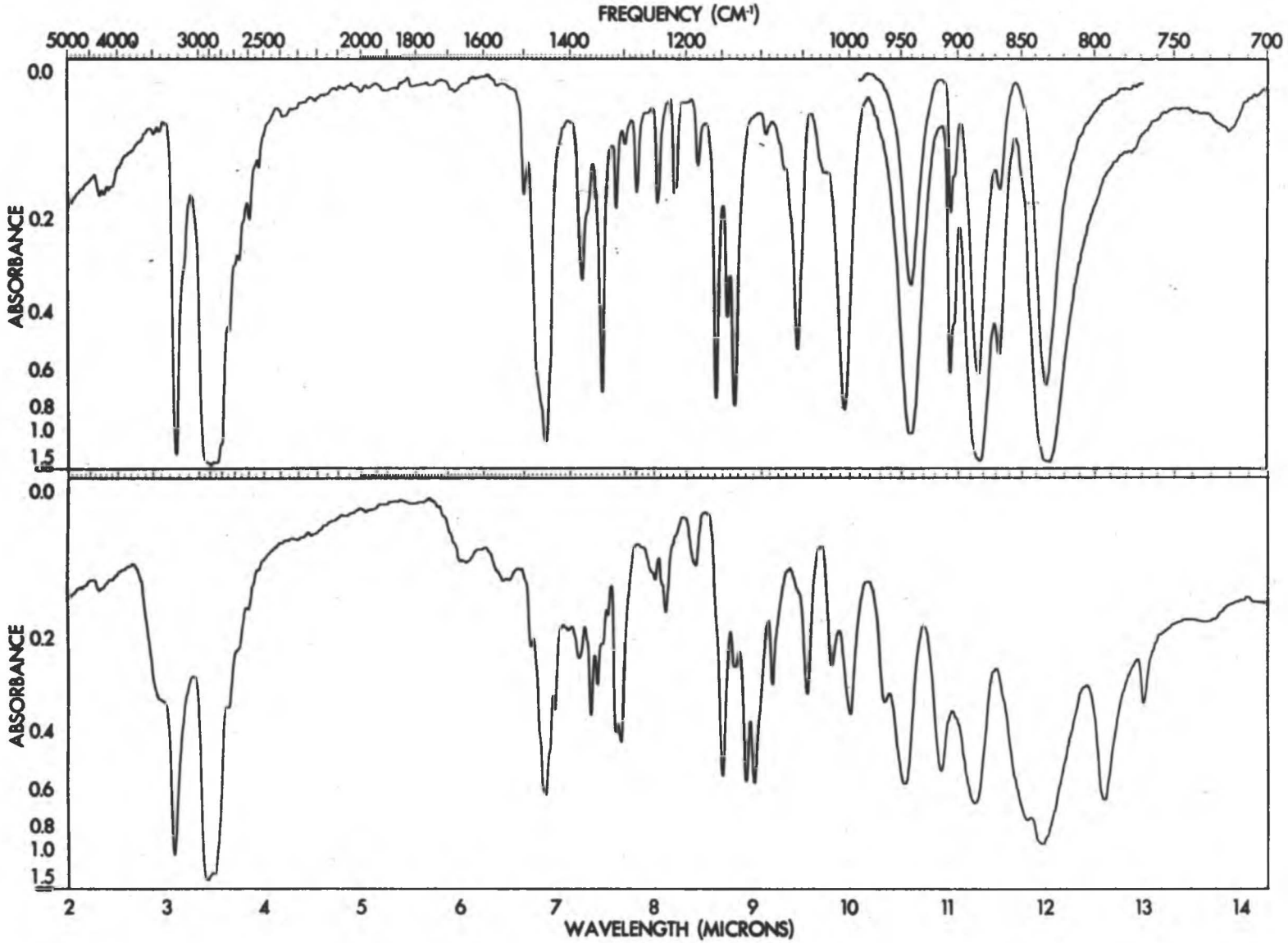

Figure 2. Infrared Mull Spectra of cis-Decahydroquinoxaline (bottom) and trans-Decahydroquinoxaline (top).

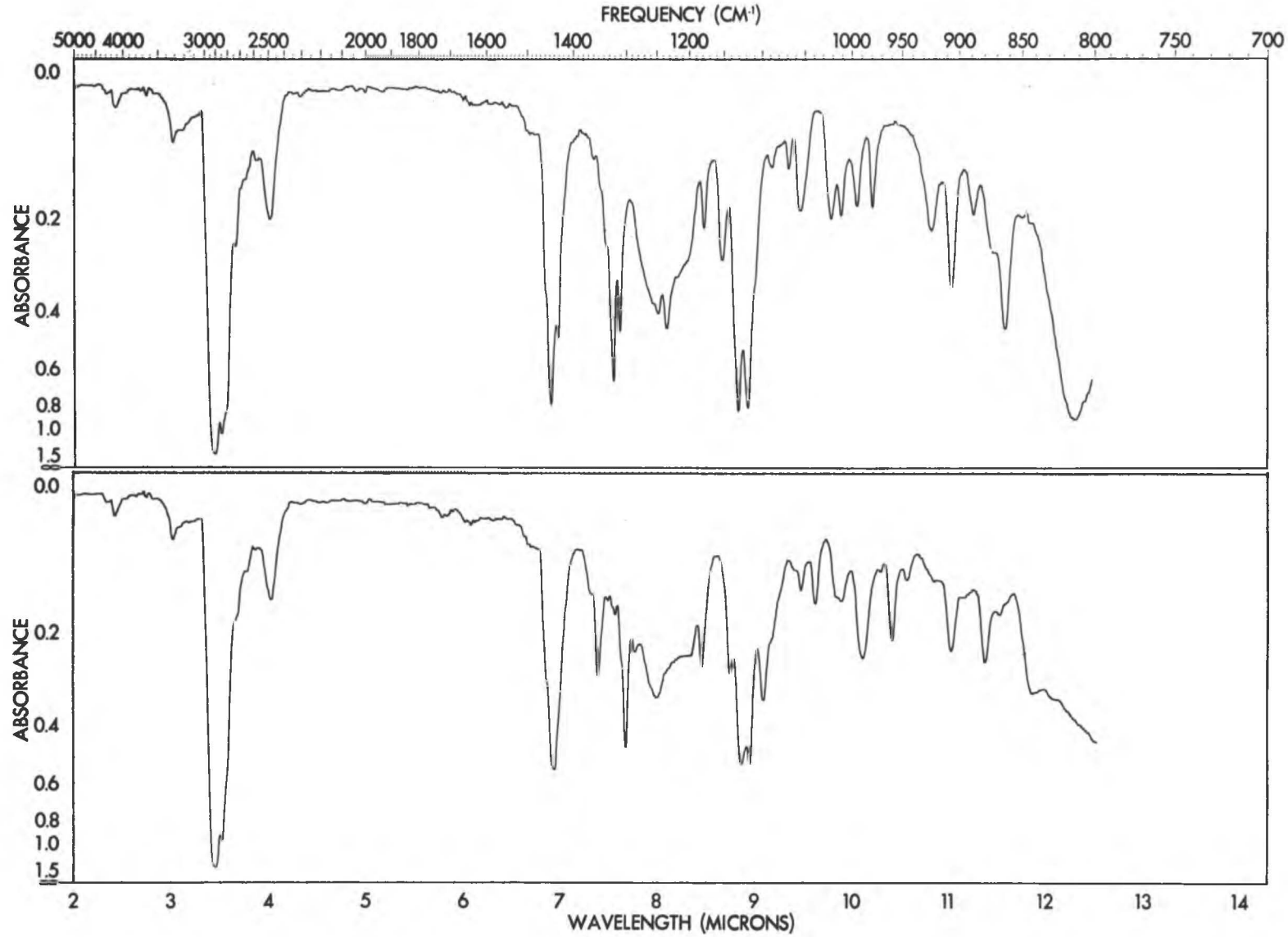

Figure 3. Infrared Spectra in 0.1288 mm. Chloroform of cis-Decahydroquinoxaline (bottom) and trans-Decahydroquinoxaline (top).

The aerial oxidation of cis-decahydroquinoxaline was repeated using benzene as the solvent. A solution of 9 g. of cis-decahydroquinoxaline in 60 ml. of benzene at room temperature was prepared. Oxygen was bubbled through the solution with the aid of a gas dispersion tube and samples were withdrawn periodically and evaporated to dryness to obtain the product. Melting points of the residues were taken. Table XXVI gives the data on this experiment.

Table XXVI. Aerial Oxidation of cis-Decahydroquinoxaline, Benzene Solvent, Using Carbon Dioxide-Free Oxygen.

Sample No.	Duration of Aerial Oxidation	Reaction Temp. °C.	M. P. °C.
1	5 min.	30	90-120
2	10 min.	30	85-120
3	15 min.	30	90-120
4	45 min.	30	90-120
5	1 hr. 40 min.	30	90-120
6	20 min.	50	75-102
7	40 min.	50	75-100
8	6 hrs.	50	75-100
9	18 hrs.	50	75-105

Sample 5 was withdrawn, extracted with dilute hydrochloric acid, basified, extracted with ether and the ether evaporated to dryness. In the preceding aerial oxidation employing phenyl ether as a solvent wherein tetrahydroquinoxaline was obtained, dilution with ether and extraction with dilute hydrochloric acid had been employed in the isolation of the product.

The product obtained from the aerial oxidation was not tetrahydroquinoxaline as tetrahydroquinoxaline melts below 100° C. (Even when dilute hydrochloric acid was employed as had been done in the aerial oxidation using phenyl ether as the solvent, no tetrahydroquinoxaline was obtained.) On the basis of melting point data it appeared as if the carbonate salt had formed during the evaporation of the solvent.

It would be logical to assume that if atmospheric oxygen were responsible for the formation of tetrahydroquinoxaline from cis-decahydroquinoxaline in the experiment employing phenyl ether as the solvent, then the use of benzene as the solvent in place of phenyl ether should not prohibit the formation of tetrahydroquinoxaline. This experiment was carried out again using benzene as a solvent and the same results were obtained -- no formation of tetrahydroquinoxaline.

Another aerial oxidation of cis-decahydroquinoxaline employing spectrograde isooctane as a solvent and following the course of the reaction with ultraviolet spectra was carried out as follows. A 0.0714 molar solution of cis-decahydroquinoxaline in spectrograde isooctane was prepared. The solution was passed over a calcium oxide column to remove any carbonate present and an ultraviolet spectrum made. A maximum at 311 mμ, ϵ = 34, indicated the presence of a little tetrahydroquinoxaline prior to oxidation. The solution was maintained at a temperature of 62-67° C. while carbon dioxide-free oxygen was bubbled through. Samples of the solution were withdrawn at intervals of 5 min., 25 min., 40 min., 3 hrs. 20 min., and 23 hrs. Ultraviolet spectra of these samples, at the time of withdrawal from the solution, were made and indicated that the oxygen had caused no change in the cis-decahydroquinoxaline. The ultraviolet spectra of the original solution and the sample withdrawn after 23 hours of bubbling through oxygen were identical. Further evidence that oxygen did not effect cis-decahydroquinoxaline was obtained by storing cis-decahydroquinoxaline under an oxygen atmosphere for 15 days. No change in melting point occurred.

In view of the results obtained in the aerial oxidation of cis-decahydroquinoxaline in phenyl ether solution, from which tetrahydroquinoxaline was obtained, the failure to obtain similar results using benzene or isooctane solvents was not expected. A rerun of the aerial oxidation of cis-decahydroquinoxaline in phenyl ether solution was carried out at 60° C. and again tetrahydroquinoxaline was obtained. Next, a sample of cis-decahydroquinoxaline was dissolved in phenyl ether and heated for 5 min. at 60° C., ether added, the solution extracted with dilute hydrochloric acid, and neutralized with concentrated sodium hydroxide solution. A precipitate of tetrahydroquinoxaline formed. The same procedure employing benzene as a solvent did not precipitate tetrahydroquinoxaline. Also, dissolving cis-decahydroquinoxaline directly in dilute hydrochloric acid and treating with concentrated sodium hydroxide failed to yield tetrahydroquinoxaline.

Treatment of cis-decahydroquinoxaline with phenyl ether caused, in some unknown manner, the dehydrogenation of cis-decahydroquinoxaline. It was established, however, that atmospheric oxygen did not effect cis-decahydroquinoxaline.

H. Determination of Geometrical Configuration of the Two Isomers of Decahydroquinoxaline.

Both of the two obvious approaches available, resolution of the trans isomer into its optical antipodes or stereospecifically synthesizing one of the isomers, were tried.

1. Resolution Studies on trans-Decahydroquinoxaline.

(a) Preparation of dl-trans-Decahydroquinoxalinium d-Tartrate and Attempted Resolution by Fractional Recrystallization.

A boiling solution of 2 g. (0.014 mole) of trans-decahydroquinoxaline

in 150 ml. of acetone was added to a boiling solution of 2.14 g. (0.014 mole) of d-tartaric acid in 45 ml. of acetone. A precipitate formed immediately, was filtered and dried to give 3.82 g. of the diastereoisomer, 92% yield, m. p. 295-300° C. dec. Analyses, by means of the silver tartrate salt, indicated the salt had formed in a 1:1 ratio of acid to amine.

Fractional recrystallization of the salt was carried out using the following solvent systems: water-ethanol, water-methanol, water-dioxane, water-methanol-n-propyl alcohol, water-methyl cellosolve, water-ethylene glycol dimethyl ether, and water-tetrahydrofuran. No change in rotation of the fractionally recrystallized salt was observable. No suitable solvent or solvent system for recrystallization was discovered, that excluded water.

(b) Preparation of dl-trans-Decahydroquinoxalinium Di-d-10-camphorsulfonate and Attempted Resolution by Fractional Recrystallization.

A hot solution of 2.0 g. (0.014 mole) of trans-decahydroquinoxaline in 100 ml. of acetone was added to 6.6 g. (0.028 mole) of d-10-camphor sulfonic acid in 40 ml. of acetone. A precipitate formed immediately, was filtered and dried to give 8.2 g. of salt, 95% yield, m. p. above 300° C. If the salt had formed in a 1:1 ratio of acid to amine a 100% yield would have been 5.3 g. The yield obtained, 8.2 g., indicates the salt had formed in a 2:1 ratio of acid to amine.

Fractional recrystallization was carried out using the following solvent systems: dioxane-water, acetone-methyl cellosolve, chloroform-acetone, chloroform-ethyl acetate, chloroform-benzene, chloroform-dioxane, chloroform-toluene, chloroform-isopropyl alcohol, chloroform-ethanol, methanol, ethanol, methanol-benzene, methanol-ethyl acetate, and methanol-aceton. No change in rotation of the fractionally recrystallized salt was observable.

(c) Preparation of dl-trans-Decahydroquinoxalinium d-Camphorate and Attempted Resolution by Fractional Recrystallization.

A solution of 1.46 g. of d-camphoric acid (0.007 mole) in 25 ml. of acetone was added to 1 g. (0.007 mole) of trans-decahydroquinoxaline in 200 ml. of acetone. The precipitate was filtered and dried to give 2.45 g. of salt, 100% yield, m. p. 225-8° C. The salt formed in a 1:1 ratio of acid to amine. When a 2:1 ratio of acid to amine was used in preparing the salt, the extra equivalent of free acid was recovered after the salt had been isolated.

Fractional recrystallization of the salt was carried out using the following solvent systems: toluene-ethanol-water-acetone, methanol-toluene-acetone, methanol-benzene, methanol-isopropyl alcohol-water, methanol-carbon tetrachloride-water, methanol-chloroform-ethyl acetate, methanol-Skellysolve B-acetone, methyl cellosolve-water-ethyl acetate, methanol-dioxane, methyl cellosolve-dioxane, methyl cellosolve-isopropyl alcohol, methyl cellosolve-benzene, methyl cellosolve, Skelly-

solve D-water-acetone and water. No change in rotation of the fractionally recrystallized salt was observable. Fractional recrystallization was carried out using dioxane. Fractions were isolated which had very marked changes in specific rotation. These fractions were identified as the original l-malic acid and the amine. Recrystallization from dioxane had separated the salt into its two components.

(d) Preparation of dl-trans-Decahydroquinoxalinium l-Malate and Attempted Resolution by Fractional Recrystallization.

A hot solution of 4.02 g. (0.03 mole) of l-malic acid in 30 ml. of acetone was added to 4.2 g. (0.03 mole) of trans-decahydroquinoxaline in 150 ml. of hot acetone. A precipitate formed immediately, was filtered and dried to give 7.6 g. of salt, 93% yield. Using a 2:1 mole ratio of acid to amine gave the same product.

Fractional recrystallization of the salt from the following solvent systems were carried out: ethanol-water, methanol-water, ethanol-water-acetone, chloroform-methanol-water, methyl cellosolve-water, ethylene glycol dimethyl ether-water, ethanol-water-acetone, and chloroform-methanol-water-acetone. No change in the fractionally recrystallized salt was observable.

(e) Preparation of dl-trans-Decahydroquinoxalinium Di-l-5-oxo-2-pyrrolidonecarboxylate and Attempted Resolution by Fractional Recrystallization.

The l-5-oxo-2-pyrrolidonecarboxylic acid (120) was prepared by heating a suspension of 100 g. of pure l-glutamic acid in an equal weight of water with stirring at 135-40° C. for 6 hours. Butanol was added to the hot syrupy liquid, the solution cooled and the precipitate filtered and dried to give 45 g. of product, 51% yield, m. p. 150-155° C. Dearborn reported a melting point of 159-60° C., but listed no yield. The mother liquors were being reduced in volume to obtain more product, but the solution boiled to dryness and the remaining product decomposed.

The diastereoisomer was prepared by adding an acetone solution of 0.5 g. (0.0035 mole) of trans-decahydroquinoxaline to 0.92 g. (0.007 mole) of l-5-oxo-2-pyrrolidone carboxylic acid in 200 ml. of acetone. A precipitate formed but was sticky in nature. Recrystallization of the salt from butanol was carried out and gave a crystalline precipitate while cold, but on warming to room temperature the precipitate again became very sticky. Only a small portion of the original salt came down in this recrystallization. The free amine was obtained from this recrystallized material by treatment with base and ether extraction. The free amine showed no optical rotary power.

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(120) Dearborn and Stekol, U. S. Patent, 2,528,267, October 31, 1950.

(f) Preparation of N,N'-bis(l-menthoxyacetyl)-dl-trans-decahydroquinoxaline and Attempted Resolution by Fractional Recrystallization.

l-Menthoxyacetic acid (121) was prepared in the following manner. A solution of 50 g. (0.32 mole) of l-menthol in 125 ml. of dry toluene and 8.75 g. of clean sodium metal (0.38 mole) was refluxed for 15 hours. A solution of 11.9 g. of chloroacetic acid (0.125 mole) in 100 ml. of dry toluene was added dropwise with stirring. The resulting mixture was refluxed and stirred for 48 hours. Dry toluene was added during the refluxing to keep the mixture sufficiently liquid to enable stirring. The reaction mixture was transferred to a separatory funnel and extracted with three 125 ml. portions of water. The water solution was acidified with 30% hydrochloric acid and extracted with ether. The ether was removed by evaporation and the residual liquid was vacuum distilled at 2 mm. at 134-7° C. to give 23.3 g. of product, yield 87% based on the chloroacetic acid used. Leffler and Calkins reported a yield of 78-84%.

The l-menthoxyacetic acid was converted into the crude l-menthoxyacetyl chloride by treatment with thionyl chloride (122). To this end a mixture of 10 g. (0.047 mole) of l-menthoxyacetic acid and 17 ml. of thionyl chloride was warmed at 50° C. for 3 hours. The excess thionyl chloride was removed under reduced pressure and the crude l-menthoxyacetyl chloride directly used for preparing N,N'-bis(l-menthoxyacetyl)-dl-trans-decahydroquinoxaline. For positive identification of the l-menthoxyacetyl chloride, conversion to the amide was accomplished by mixing a little l-menthoxyacetyl chloride with concentrated ammonium hydroxide. The amide melted at 93-95° C., which melting point is in agreement with the literature value (122).

The N,N'-bis(l-menthoxyacetyl)-trans-decahydroquinoxaline was prepared by adding the crude l-menthoxyacetyl chloride to trans-decahydroquinoxaline dissolved in 5% sodium hydroxide. The reaction mixture was shaken until clear then poured slowly into dilute hydrochloric acid containing crushed ice. The oil which formed solidified, but on warming to room temperature became gummy. Repeated recrystallization attempts failed to yield anything but a gummy viscous material. No resolution of trans-decahydroquinoxaline into its optical antipodes effected.

2. Preparation of trans-Decahydroquinoxaline by a Stereospecific Synthesis Route.

(a) Attempted Catalytic Reduction of o-Phenylenediamine to 1,2-Diaminocyclohexane.

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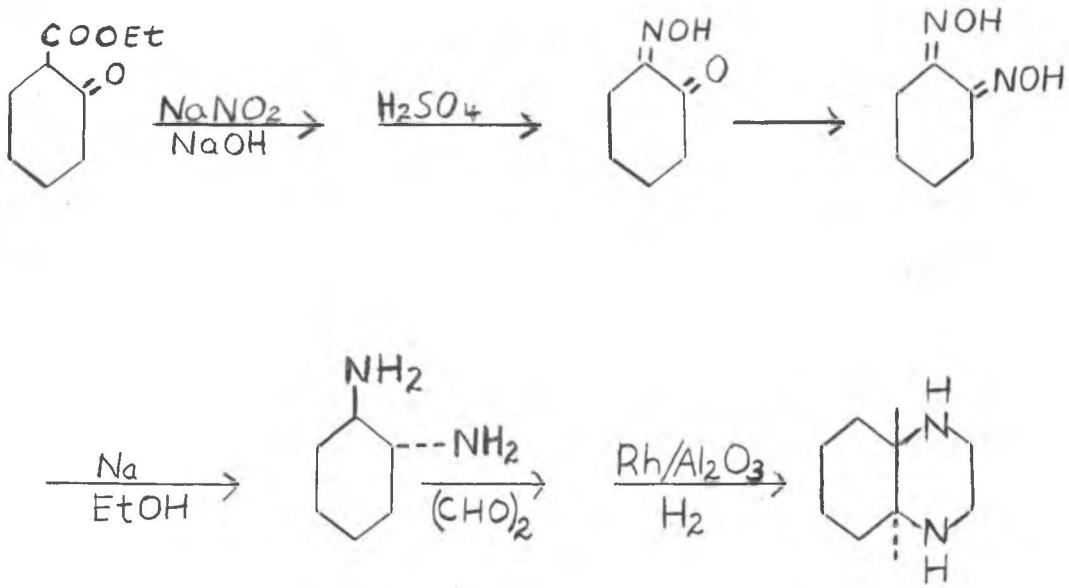
(121) Leffler and Calkins, Organic Syntheses, Collective Vol. III, 544 (1955).

(122) Holmes and Adams, J. Am. Chem. Soc., 56, 2093-4 (1934).

The catalytic reduction of p-phenylenediamine to the hexahydro analog is reported in the literature (123). The hydrogenation was conducted in the liquid phase using a Ni or Co catalyst at temperatures of 120-200° C. under a pressure of 300-500 atmospheres. The 1,2-diaminocyclohexane compound was desired as an intermediate in the preparation of decahydroquinoxaline, and the possibility of preparing the desired compound by the catalytic reduction of o-phenylenediamine was evident.

A solution of 10.8 g. (0.1 mole) of o-phenylenediamine in 30 ml. of absolute alcohol and 1 g. of 5% Rh on alumina were placed in the Parr High Bomb at 3000 psi hydrogen and 115° C. for 12 hours. No reduction occurred, and the o-phenylenediamine was recovered. Another reduction was attempted under more drastic conditions, 175° C. and 5700 psi hydrogen, but still no reduction occurred.

trans-1,2-Diaminocyclohexane was subsequently prepared by the following synthesis route:



(123) Sly, U. S. Patent, 2,175,003, October 3, 1940.

(b) Preparation of Ethyl 2-Ketohexahydrobenzoate.

The procedure of Snyder, Brooks, and Shapiro was followed (124). A solution of sodium ethoxide in a 2-liter 3-necked flask equipped with a dropping funnel, a stirrer and a reflux condenser carrying a calcium chloride tube was prepared by the addition of 46 g. (2 g. atoms) of clean sodium to 600 cc. of anhydrous ethanol. The solution was cooled to 10° C. and an ice-cold solution of 196 g. (2 moles) of cyclohexanone in 292 g. (2 moles) of ethyl oxalate was added from the dropping funnel over a period of about 15 minutes. The ice bath was maintained for an hour, then the solution stirred at room temperature for 8 hours during which time a precipitate formed. The reaction mixture was decomposed by the addition of ice-cold dilute sulfuric acid prepared by adding 56 ml. of concentrated sulfuric acid to 435 g. of ice. The solution was diluted with cold water to a volume of about 4 liters. The oil which separated was removed and the aqueous solution extracted with four 250 ml. portions of benzene. The oil and benzene extracts were combined and washed with two 200 ml. portions of water. The benzene was removed on a steam bath. The remaining solution was distilled under reduced pressure and the distillate collected that came over at 105-200° C. and 10-15 mm. pressure. The distillate was redistilled in the presence of a trace of iron powder and ca. 1 g. of ground soft glass. The pressure during the distillation was at about 80 mm. and the temperature at 150-160° C. The ethyl 2-ketohexahydrobenzoate was collected and redistilled at 0.25 mm. pressure and 59-63° C. to give 148 g. of product, 46% yield, refractive index 1.4763 at 20° C. Snyder reported a yield of 59-62%, refractive index 1.476-1.479 at 20° C.

Another run was made using double the amounts of reactants. A yield of 362 g., 52%, was obtained.

(c) Preparation of 2-Isonitrosocyclohexanone.

The procedure of Jaeger and van Dijk was followed (125). To 40 g. (0.24 mole) of ethyl 2-ketohexahydrobenzoate was added 16.2 g. (0.24 mole) of sodium nitrite and 456 g. of 6% potassium hydroxide solution (0.487 mole of potassium hydroxide). The solution was shaken for 48 hours then added slowly to 120 ml. of cold (5-15° C.) 30% sulfuric acid. The resulting solution was extracted mechanically with ether and then further for 3 days in a liquid-liquid extractor. The combined extracts were evaporated leaving 21.5 g. of viscous material, yield 72%, assuming the material to be isonitrosocyclohexanone.

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(124) Snyder, Brooks, and Shapiro, Org. Syn., 2, 531 (1943).

(125) Jaeger and van Dijk, Proc. Acad. Sci. Amsterdam, 39, 384-393 (1936).

In another preparation of 2-isonitroscyclohexanone about 25 ml. of viscous brown material was obtained from 50 g. of ethyl 2-ketohexahydrobenzoate. Vacuum distillation of the brown material was attempted, first with the vacuum attainable with an aspirator, and then under a vacuum of 1 mm. A small fore-run of a clear liquid, later identified by the oxime derivative as cyclohexanone, was obtained. The bulk of the material remained in the flask and decomposed to give a gummy tar. A second vacuum distillation of more of this brown material at 0.075 mm. pressure was attemped with the same results. A small fore-run was obtained as the temperature rose to 110° C. At this temperature a few drops of material distilled then a rapid decomposition occurred, but with no actual explosion.

The crude 2-isonitroscyclohexanone was thereafter used directly for the preparation of nioxime.

A number of other preparations of 2-isonitrosocyclohexanone were carried out. The yields obtained were 34%, 64%, 46%, 31%, 62%, 94%, and 74%. No reasons were established for the differences in yields obtained. Jaeger and van Dijk (125) did not give a yield for this preparation, but did state the product was a non-crystallizable oil. Other workers (126) were unable to repeat the work of Jaeger and van Dijk and failed in repeated attempts to prepare 2-isonitrosocyclohexanone.

(d) Preparation of Nioxime.

To a mixture of 14.3 g. (0.21 mole) of hydroxylamine hydrochloride and 11.1 g. (0.21 mole) of sodium methylate in methanol (absolute) was added a methanol solution of 21.5 g. (0.17 mole) of crude isonitrosocyclohexanone. The mixture stood overnight, the salt was removed by filtration, and the solvent removed under vacuum. The residue was washed with water to remove any remaining salt and was then recrystallized from methanol-water to give 5.65 g. of nioxime, m. p. 190-95° C., yield 35%. Jaeger and van Dijk listed no yield for this preparation. They listed a melting point of 187-89° C. for nioxime.

Several other preparations of nioxime were carried out and the yields were as follows: 58%, 37%, 22%, 35%, 32%, 29%, 45% and 48%. No reason other than the degree of purity of the crude 2-isonitrosocyclohexanone could be given to account for the difference in yields from run to run.

(e) Preparation of trans-1,2-Diaminocyclohexane.

To a solution of 1 g. (0.007 mole) of nioxime and 56 ml. of boiling absolute alcohol was added 7 g., (0.3 mole) of sodium metal. The flask was cooled and diluted with 70 ml. of water. The solution was distilled into a

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(126) Rauh, Smith, Banks and Diehl, J. Org. Chem., 10, 199 (1945).

flask containing 4.2 ml. of concentrated hydrochloric acid in 4.2 ml. of water. Toward the end of the distillation an additional 42 ml. of water was added and the distillation continued. The alcohol and water were removed from the acid distillate by heating under reduced pressure, 4.0 g. of sodium hydroxide pellets in 15 ml. of water was added, the mixture cooled, transferred to a separatory funnel and the aqueous alkaline layer removed. The remaining liquid was dried over solid sodium hydroxide for 48 hours then transferred to a micro distilling apparatus. On heating to 180° C. at 11-12 mm. pressure no product distilled. Jaeger and van Dijk reported that trans-1,2-diaminocyclohexane boiled at 79-81° C. at 15 mm. pressure. No desired product was obtained in this run.

Catalytic reduction of nioxime was next tried. A mixture of 3.4 g. (0.025 mole) of nioxime, 0.5 g. of 5% rhodium on alumina, and 15 ml. of absolute alcohol was placed in the Parr High Bomb at 100° C. and 2500 psi hydrogen for 12 hours. The apparatus leaked and it was not possible to determine the pressure drop due to reduction of the nioxime. The reaction mixture was filtered, the alcohol removed under reduced pressure and the residue distilled at 15 ml. pressure and 80-150° C. Most of the material distilled at 95-100° C. At this pressure the boiling point was 15-20° too high for trans-1,2-diaminocyclohexane. No more identification of the material was made, but it is possible the product was chiefly the cis-1,2-diaminocyclohexane.

Reduction of nioxime to the diamine compound was successfully accomplished following the procedure of Jaeger and van Dijk (125). To a solution of 10 g. (0.07 mole) of nioxime in 560 ml. of absolute alcohol heated to boiling was added 70.4 g. of sodium metal. The flask was cooled and diluted with 700 ml. of water and then steam distilled. The distillate was collected in a flask containing 42 ml. of concentrated hydrochloric acid in 42 ml. of water. The acid distillate was reduced to about 20 ml. by heating under reduced pressure. The concentrated acid solution was placed under vacuum over concentrated sulfuric acid and let stand until the salt crystallized. Yield of the salt was 54%. Jaeger and van Dijk listed no yield, nor did they give any physical constants of the dihydrochloride.

One gram of the hydrochloride salt was converted to the free amine by dissolving the salt in a minumum of water and adding an excess of sodium hydroxide pellets. The reaction mixture stood overnight, was extracted with benzene, the benzene removed under reduced pressure and the residue distilled at 15 mm. and 80° C. to give 0.5 g. of product, 82% yield. Jaeger and van Dijk reported a product, b. p. 79-81° C. at 15 mm. pressure. No yield was listed.

In a similar manner as above a 74% yield of free amine was obtained from 6 g. of the hydrochloride salt. The boiling point at 15 mm. pressure corresponded to the boiling point listed by Jaeger and van Dijk for this pressure.

In another reduction of 10 g. of nioxime, without isolation of the dihydrochloride salt intermediate, a 26% yield of trans-1,2-diaminocyclohexane, b. p. 80-82° C. at 15 mm. pressure, was obtained, the structure of which was established by resolution using d-tartaric acid (126a).

(126a) Jaeger and Bijkerk, Proc. Acad. Sci. Amsterdam, 40, 16 (1937).

(f) Preparation of trans-Decahydroquinoxaline from trans-1,2-Diaminocyclohexane.

Four attempts were made to prepare trans-decahydroquinoxaline from trans-1,2-diaminocyclohexane before success was achieved on the fifth attempt. The procedure used by Cavagnol and Wiselogle (9) in preparing quinoxaline by the condensation of o-phenylenediamine and sodium glyoxal bisulfite was followed in the first attempt. To a solution of 0.73 g. (0.006 mole) of trans-1,2-diaminocyclohexane in 3.2 ml. of 2 molar acetic acid was added 1.59 ml. of 4 molar sodium acetate. The resulting solution was added rapidly to a solution of 1.91 g. (0.0065 mole) of sodium glyoxal bisulfite in 9.8 ml. of water. Before mixing, both solutions were at 60° C. The solution was shaken for an hour, let stand overnight, neutralized with 0.77 g. of sodium hydroxide pellets and 3.2 g. potassium carbonate added. The mixture was extracted with benzene several times and the extracts dried over sodium hydroxide pellets. The solution was reduced to a small volume by evaporation of the benzene. The remainder of the solvent was removed under vacuum to leave a small amount of dark residue which decomposed when vacuum distillation and sublimation were tried. The remaining aqueous phase from the initial benzene extractions was saturated with sodium hydroxide pellets until a mushy consistency was obtained. This strongly alkaline mixture was warmed and then extracted with benzene. The benzene was evaporated to give a residue, m. p. 100-107° C. This residue was placed in the Parr Low Bomb at 60 psi hydrogen and 50° C. with 0.1 g. of 5% rhodium on alumina and let run overnight. The catalyst was filtered off and the solvent removed by evaporation to give a dark residue, m. p. above 100° C. (dec.). Recrystallization from alcohol-Skellysolve B, the solvent system used in the purification of decahydroquinoxaline prepared by the method of Weston, failed. No product was isolated from the hydrogenated material.

A second attempt to prepare trans-decahydroquinoxaline was tried by refluxing gently for 2 hours a solution of 1 g. (0.005 mole) of trans-1,2-diaminocyclohexane dihydrochloride and 1.59 g. (0.0056 mole) of sodium glyoxal bisulfite in water. The solution was saturated with potassium hydroxide pellets, let stand overnight and extracted with ether and benzene. No material was obtained from the extractions. The aqueous alkaline mixture was decanted, the solid residue digested with benzene, and the liquid layer extracted with benzene in a liquid-liquid extractor for 10 hours. The extracts from both phases were combined and the benzene evaporated. Traces of a white material were obtained. The aqueous alkaline layer remaining from the extractions was saturated with sodium hydroxide pellets, let stand overnight, brought to boiling, and extracted again with benzene. Evaporation of the benzene gave a little white solid which did not melt at 250° C. The material was presumably a salt. No desired product was isolated.

A third preparation employing the dihydrochloride salt of the diamine was attempted. The procedure of Cavagnol and Wiselogle was followed. A solution of 1.5 g. (0.0.3 mole) of trans-1,2-diaminocyclohexane in 6.6 ml. of 2 molar acetic acid and 3.3 ml. of 4 molar sodium acetate was added rapidly to a solution of 3.9 g. (0.013 mole) of sodium glyoxal bisulfite in 20.2 ml. of water. The solutions were heated to 50° C. before mixing. The

solution was stirred for 2 hours, sodium hydroxide pellets was added until a mushy consistency was attained, and extraction with benzene was carried out. Evaporation of the benzene gave a residue which did not melt at 220° C. The residue was digested with absolute alcohol and the alcohol solution plus 0.1 g. of 5% rhodium on alumina was placed in the Parr Low Bomb at 58 psi hydrogen and 60° C. for 14 hours. The reaction mixture was filtered, the solvent evaporated, and the dark residue subjected to vacuum sublimation to give 0.04 g. of white solid, m. p. 102-5° C. This material corresponded in melting point to the melting point of the material isolated in the first attempt to prepare trans-decahydroquinoxaline. It was evident no desired product had been obtained in this experiment. The 0.04 g. of white material isolated was then placed in the Parr High Bomb and 0.1 g. of 5% rhodium on alumina and 10 ml. of absolute alcohol were added. The bomb was heated to 110° C. at 3000 psi hydrogen for 16 hours, cooled, the catalyst removed, and the solvent evaporated to give a white material identical in melting point to that of the starting material. No positive results obtained.

In the fourth attempt to prepare trans-decahydroquinoxaline the same conditions were used as in the first attempt, except the solvent used was ethanol instead of water. The initial reaction mixture, after stirring and heating at 50-55° C. for several hours, was filtered and the alcoholic solution placed in the Parr High Bomb with 0.1 g. of 5% rhodium on alumina at 2500 psi hydrogen and 110° C. for 12 hours. The catalyst was removed by filtration, the solution decolorized with charcoal, reduced in volume on the hot plate, Skellysolve B added, the solution cooled, and the precipitate filtered to give a very water soluble precipitate that melted above 280° C. This precipitate was evidently inorganic in nature. No other product could be isolated.

The direct condensation of trans-1,2-diaminocyclohexane with 30% aqueous glyoxal was next tried. To 0.9 g. (0.008 mole) of trans-diaminocyclohexane was added 1.5 g. of 30% aqueous glyoxal. After standing 5 minutes, 10 ml. of absolute alcohol and 0.4 g. of 5% rhodium on alumina was added. The reaction mixture was placed in the Parr High Bomb at 1500 psi hydrogen and 200° C. for 4 hours. The reaction mixture was filtered, the solution decolorized with carbon, and the solution evaporated to dryness to give a colored residue, m. p. 70-135° C. with most of the material melting above 100° C. Some of the material sublimed during the melting point operation and the melting point of this sublimate was 147-8° C., corresponding to the melting point of decahydroquinoxaline prepared by the method of Weston, et al, (1). The remainder of the residue from the hydrogenation was vacuum sublimed to give a product melting 97-135° C. Further fractional sublimation gave an additional 0.05 g. of crude trans-decahydroquinoxaline, m. p. 115-35° C. A dinitroso derivative was made of this latter material by adding cold aqueous sodium nitrite to a cold dilute hydrochloric acid solution of the amine. After one recrystallization the dinitroso derivative melted 106-8° C. The dinitroso derivative of known trans-decahydroquinoxaline melted 110-112° C. The mixed melting point was 108-111° C. Thus, the product from this last experiment was shown to be the same as the decahydroquinoxaline prepared by the method of Weston, and the geometrical configuration of Weston's decahydroquinoxaline was established as being trans. The yield of trans-decahydroquinoxaline from this last preparation was 20%. No low melting isomer was isolated in any amount.

I. Preparation of New Derivatives of cis- and trans-Decahydroquinoxaline.

1. Preparation of N-Methyl-cis-decahydroquinoxaline.

To a cold solution of 14.9 g. (0.33 mole) of formic acid and 10.7 g. (0.135 mole) of formaldehyde was added 9 g. (0.063 mole) of cis-decahydroquinoxaline. The resulting soltuion stood for 12 hours, then was heated at 80-100° C. for 10 hours. The solution was vacuum distilled giving 16 g. of material at 83-87° C. and 0.400 mm. pressure. The 16 g. of material obtained was much in excess of a 100% yield of product even if the N,N'-dimethyl compound had formed. The material was acidic and very water soluble. Analyses and equivalent weight determinations did not definitely establish the identity of this product. This material was dissolved in benzene, treated with sodium hydroxide pellets for 36 hours, and the liquid poured off and fractionally distilled. The product distilled at 64-66° C. and 0.400 mm. pressure. Yield was 7.6 g., 72%.

Anal. Calc'd for $C_9H_{18}N_2$: C, 70.07; H, 11.76. Found: C, 70.54; H, 11.70.

2. Preparation of N-Methyl-trans-decahydroquinoxaline.

The procedure of Weston was followed (127). To a cold solution of 18.3 g. (0.40 mole) of formic acid and 13.1 g. (0.16 mole) of 40% formaldehyde was added slowly with stirring 11 g. (0.077 mole) of trans-decahydroquinoxaline. The solution darkened and was allowed to stand at room temperature for several hours after which it was heated at 80-90° C. for 12 hours. The reaction solution, now black, was fractionally distilled and the fraction coming over at 82-83° C. and 0.400 mm. pressure was dissolved in benzene and let stand over sodium hydroxide pellets for 48 hours. The benzene was removed by distillation and the residue vacuum distilled at 55-60° C. and 0.200 mm. pressure to give 7.8 g. of product, yield 87%. Five grams of the intermediate product was not treated with sodium hydroxide. As in the preceding preparation an intermediate water soluble, acidic material was isolated but not identified.

Anal. Calc'd for $C_9H_{18}N_2$: C, 70.07; H, 11.76. Found: C, 70.20; H, 12.00.

3. Preparation of N,N'-Dimethyl-cis-decahydroquinoxalinium Iodide.

To 4 g. (0.023 mole) of N-methyl-cis-decahydroquinoxaline was added, with cooling, 10.17 g. (0.07 mole) of methyl iodide. After standing overnight the solid product was recrystallized from absolute alcohol and a few drops of water to a constant melting point of 255-8° C. Yield was 6.7 g., 62%.

Anal. Calc'd for $C_{10}H_{21}N_2I$: C, 40.60; H, 7.15. Found: C, 40.54; H, 7.04.

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(127) Weston, Waukegan and Hamlin, U. S. Patent 2,636,032, April 21, 1953.

4. Preparation of N,N,N',N'-Tetramethyl-trans-decahydroquinoxalinium Diiodide.

A mixture of 4 g. (0.028 mole) of trans-decahydroquinoxaline, 28.4 g. (0.22 mole) of methyl iodide, 5.93 g. (0.056 mole) of sodium carbonate and 30 ml. of 95% alcohol was refluxed for 2 days. The reaction mixture was treated with hydriodic acid to decompose any base remaining and then evaporated to dryness. Extraction with cold alcohol was carried out to remove the sodium iodide, any unreacted decahydroquinoxaline and any dialkyl N,N'-decahydroquinoxaline. The residue was next treated with cold concentrated alcoholic sodium hydroxide to remove any hydroiodide which might have been formed. Recrystallization of the residue gave a product, m. p. 240-55° C. (dec). By preheating the melting point block to 265° C. before placing the sample for melting on it, a melting point of 270° C. (dec.) was obtained. Yield was 8.3 g., 64%.

Anal. Calc'd for $C_{12}H_{26}N_2I_2$: C, 31.87; H, 5.79. Found: C, 31.83; H, 5.95.

N,N,N'N'-Tetramethyl-trans-decahydroquinoxalinium diiodide was also prepared from N-methyl-trans-decahydroquinoxaline by treatment of the latter compound with an excess of methyl iodide. The product melted 268° C. (dec.).

Anal. Calc'd for $C_{12}H_{26}N_2I_2$: C, 31.87; H, 5.79. Found: C, 31.88; H, 5.84.

5. Preparation of N,N'-Bis(phenylsulfonyl)-cis-decahydroquinoxaline.

A mixture of 4 g. (0.028 mole) of cis-decahydroquinoxaline, 10 g. (0.056 mole) of benzenesulfonyl (chloride), and 35 ml. of 20% sodium hydroxide solution was warmed at 70-80° C. for 12 hours. The precipitate was removed by filtration, washed with water, and recrystallized from ethanol to a constant melting point of 194-5.5° C. Yield was 6.3 g., 55%.

Anal. Calc'd for $C_{20}H_{24}O_4N_2S_2$: C, 57.16; H, 5.71. Found: C, 57.18; H, 5.64.

6. Preparation of N,N'-Bis(phenylsulfonyl)-trans-decahydroquinoxaline.

A mixture of 3 g. (0.021 mole) of trans-decahydroquinoxaline, 6 g. (0.042 mole) of benzenesulfonyl chloride, and 27 ml. of 20% sodium hydroxide solution was refluxed for 10 minutes. The alkaline solution was decanted and the residue recrystallized four times from 95% alcohol to give 7 g., (80%), of N,N'-bis(phenylsulfonyl)-trans-decahydroquinoxaline, m. p. 127-129° C.

Anal. Calc'd for $C_{20}H_{24}O_4N_2S_2$: C, 57.16; H, 5.71. Found: C, 55.88; H, 5.68.

The analyses indicate the presence of impurities; however, the sharp melting point does not indicate the presence of impurities.

7. Preparation of N,N,N'N'-Tetrabenzyl-trans-decahydroquinoxalinium.

A mixture of 4 g. (0.028 mole) of trans-decahydroquinoxaline, 15 g. (0.118 mole) of benzyl chloride, 10 g. (0.094 mole) of sodium carbonate and 50 ml. of 95% alcohol was refluxed under nitrogen for 48 hours. The alcohol was poured off and evaporated to dryness yielding a solid, m. p. 165-75° C. This solid was extracted with ethyl acetate. The residue was repeatedly washed with ethyl acetate to give 6.2 g. of the dichloride salt, m. p. 175-6° C., yield 43%. From the ethyl acetate extraction was isolated a solid which after recrystallization from Skellysolve F gave 2.3 g. of material identified by analyses as N,N'-dibenzyl-trans-decahydroquinoxaline, m. p. 80-1° C., yield 21%.

Anal. Calc'd for $C_{36}H_{42}N_2Cl_2$: C, 75.41; H, 7.33. Found: C, 72.00; H, 7.71.

The analyses indicate the sample was not dry.

Anal. Calc'd for $C_{22}H_{28}N_2$: C, 82.58; H, 8.75. Found: C, 82.21; H, 8.69.

8. Preparation of N,N'-Dibenzyl-cis-decahydroquinoxaline.

A mixture of 3.6 g. (0.025 mole) of cis-decahydroquinoxaline, 15 ml. of benzyl chloride (an excess), 10.6 g. (0.1 mole) of sodium carbonate, and 30 ml. of 95% ethanol was refluxed for 3 days. The solvent was removed and the solid extracted with three 30 ml. portions of hot 95% alcohol. On cooling, crystals formed, m. p. 62-62.5° C. The product was recrystallized from 95% ethanol to yield 7.2 g., 88% yield, of N,N'-dibenzyl-cis-decahydroquinoxaline, m. p. 62-3° C.

Anal. Calc'd for $C_{22}H_{28}N_2$: C, 82.58; H, 8.75. Found: C, 82.60; H, 8.76.

In another preparation of N,N'-dibenzyl-cis-decahydroquinoxaline the reactants were refluxed for 18 hours. The yield in this preparation was only 16%, indicating the necessity of a longer reflux time. No quaternary salt was isolated in either of these preparations as was the case in the preparation of N,N'-dibenzyl-trans-decahydroquinoxaline.

9. Preparation of N-Benzhydryl-cis-decahydroquinoxaline.

A mixture of 4 g. (0.028 mole) of cis-decahydroquinoxaline, 11.45 g. (0.056 mole) of benzhydryl chloride, 5.94 g. (0.056 mole) of anhydrous xylene was refluxed for 36 hours. The reaction mixture was filtered, the residue digested with hot absolute alcohol, and on cooling of the alcohol solution, crystals formed, m. p. 196.5-197.5° C., yield 2 g., 23%.

Anal. Calc'd for $C_{21}H_{26}N_2$: C, 82.31; H, 8.55. Found: C, 82.28, H, 8.36.

10. Preparation of N,N'-Dibenzhydryl-trans-decahydroquinoxaline.

A mixture of 4 g. (0.028 mole) of trans-decahydroquinoxaline, 11.3 g. (0.056 mole) of benzhydryl chloride, 5.9 g. (0.056 mole) of anhydrous sodium carbonate and 50 ml. of dry benzene was refluxed for 6 days. After 2 days of refluxing, a little fluffy precipitate, m. p. 143-6° C., had formed. This precipitate was identified as unreacted trans-decahydroquinoxaline. The refluxing was continued for an additional 4 days, the reaction mixture was filtered, the residue digested with hot absolute alcohol, and the solvent and the alcohol from the extractions combined. On cooling, 2 g. of white crystals deposited, m. p. 218-225° C. On concentration of the mother liquors no more crystals were obtained, but rather a very dark viscous oil. Recrystallization of the oil from benzene-absolute alcohol (the solvent system out of which the initial crystals precipitated) failed. Recrystallization of the 2 g. of product gave pure N,N'-dibenzhydryl-trans-decahydroquinoxaline, m. p. 220-25° C., yield 15%.

Anal. Calc'd for $C_{34}H_{36}N_2$: C, 86.40; H, 7.68. Found: C, 86.70; H, 7.30.

11. Preparation of N,N'-Dibenzyl-N-methyl-trans-decahydroquinoxalinium Iodide.

To a solution of 4 g. (0.012 mole) of N,N'-dibenzyl-trans-decahydroquinoxaline in absolute alcohol was added an excess of methyl iodide. The flask was stoppered and let stand at 10° C. for several days. The precipitate, 4.6 g., was recrystallized from ethanol-water to a sharp melting point of 229-30° C., yield 69%.

Anal. Calc'd for $C_{23}H_{31}N_2$: C, 59.77; H, 6.76. Found: C, 59.23; H, 6.70.

12. Preparation of N,N'-Dipropyl-trans-decahydroquinoxaline.

The preparation of N,N'-dipropyl-trans-decahydroquinoxaline was accomplished by heating a mixture of 30 g. of n-propyl-p-toluenesulfonate (0.14 mole) and 9.8 g. (0.07 mole) of trans-decahydroquinoxaline at 100° C. The temperature rapidly increased to 150° C. and was maintained at 130° C. for 2 hours. Then the solution was basified with concentrated sodium hydroxide solution, extracted three times with ether, the ether extracts dried over anhydrous potassium carbonate, the ether removed under reduced pressure, and the residue distilled at 0.075 mm. pressure and 80-82° C. to give 9.5 g. of material, 61% yield assuming the dialkylated decahydroquinoxaline resulted. On standing the product separated into two layers, fraction A (1 g.) and fraction B (8.5 g.) A picrate derivative of fraction B was prepared by mixing 1 g. (0.0045 mole) in ethanol with 2.54 g. (0.011 mole) of picric acid in ethanol. A precipitate formed on mixing, was filtered and dried to give 3.2 g. of picrate derivative, m. p. 275-80° C. Recrystallization from dioxane, chloroform, ethyl acetate, ethanol, ethylene glycol dimethyl ether, methyl cellosolve, acetone, ethylene glycol diethyl ether, benzene, n-butyl alcohol, methyl alcohol, and toluene failed. Diethyl oxalate was found to be a satisfactory solvent for recrystallization and after two recrystallizations from this solvent a product of melting point 284-5° C. (dec.) was obtained. A picrate of fraction A was similarly prepared.

The derivative was recrystallized from diethyl oxalate to a melting point of 282-3° C. The two fractions, having the same boiling point and picrates of the same melting point, appear to be the same product. The separation of the initial product into two fractions on standing was probably due to the presence of some impurities.

Other N,N'-dialkyldecahydroquinoxalines were similarly prepared. The alkyl substituents in the other derivatives prepared were n-butyl, isoamyl, 3-phenyl-1-propyl, n-octyl, myristyl, cetyl, and l-menthyl. Results of analyses are pending and will be reported later.

J. Preparation of Intermediates.

These compounds were prepared by known methods of preparation and were (or will be) used for the preparation of new derivatives of decahydroquinoxaline. The information on these compounds is contained in Table XXVII.

Table XXVII. Preparation of Intermediate Compounds.

Compound	M. P. °C.	B. P. °C.	% Yld	Literature Values M. P. °C. or B. P. °C.	% Yld	Reference
ethyloxomalonate		110-15°/20-25mm	73	103-8°/15mm	74-6	128
		110-15°/20-25mm	42			
ethyl 3-hydroxy-	172-4		46	175.5-6.5	82	129
quinoxaline-2-	173-4		65			
carboxylate	172-4		50			
	172-4		52			
	173-4		60			
2-hydroxyquinoxa-	263-5		98	263-4 dec.	95	129
line-3-carboxylic	265-6		93			
acid	265-6		94			

(128) Dox, Org. Syn. Coll. Vol. I, 266 (1941).

(129) Gowenlock, Newbold and Spring, J. Chem. Soc., 1945, 622.

Compound	M. P. °C.	B. P. °C.	% Yld	Literature Values M. P. °C. B. P. °C.	% Yld	Reference
2-hydroxyquinoxaline	266-70 270-2 270-2		73 87 91	265-6	72	129
2-chloroquinoxaline	45-6		82	46-7	85	129
1-phenylsulfonyl-1,2,3,4-tetrahydroquinoxaline	133-7 134-7		66 82	138-9	87	9
1-phenylsulfonyl-4-butyl-1,2,3,4-tetrahydroquinoxaline	93-4		86	95-95.5	87-92	9
dimethyloxamide	216-17		79		80	130
diethyloxamide	174-6		70	176	80	130
diisopropyloxamide	215-17		60		80	130
di-n-butyloxamide	150-2		93	154	80	130
di-n-butyloxamide	152-4		71	154	80	130
dibenzyloxamide	219-20		73		80	130
N,N'-dimethylethylenediamine		150-60	9	150-60	50	131
N,N'-dibutylethylenediamine		90-5°/4mm	11	92°/4mm	50	132
		90-5°/4mm	42			
		80-110°/110mm	54			
		74-7°/3mm	33	74-7°/3mm	63	133
		74-8°/2-3mm	30			
n-butyl p-toluenesulfonate		165-70°/4mm	82	169°/4mm	86	134
		150-5°/1mm	79			

(130) Reid, J. Am. Chem. Soc., 75, 242 (1953).

(131) Kermack and Wight, J. Chem. Soc., 1935, 1421.

(132) Donia, J. Org. Chem., 14, 946 (1949).

(133) Rice, Armbrecht, Grogan and Reid, J. Am. Chem. Soc., 75, 1750 (1953).

(134) Marvel, J. Am. Chem. Soc., 55, 345 (1933).

Compound	M. P. °C.	B. P. °C.	% Yld	Literature Values M. P. °C. or B. P. °C.	% Yld	Reference
myristyl p-toluenesulfonate	34-5		35	35	66	134
cetyl p-toluenesulfonate	46-7		41	49	67	134
l-menthyl p-toluenesulfonate	91-1.5		72			
n-propyl p-toluenesulfonate		154-60°/0.7mm	71			
sec-butyl p-toluenesulfonate	decomposed on distillation					
isoamyl p-toluenesulfonate		174-6°/0.4mm	66			
n-octyl p-toluenesulfonate		crude yield	88			
3-phenyl-1-propyl p-toluenesulfonate		crude yield	80			

IV: DISCUSSION

Previous to the work on decahydroquinoxaline performed at the Brigham Young University, two reports on the preparation of decahydroquinoxaline appeared in the literature. The first of these was in 1947 by Mousseron and Combes by the treatment of 2(β-chloroethylamino)cyclohexyl chloride at 130° C. for 5 hours with ammonia. The failed to list any data on the compound except a dinitroso derivative of melting point 160° C. (dec.). The second report of the preparation of decahydroquinoxaline appeared in 1952. Beck, Hamlin, and Weston prepared decahydroquinoxaline by the cyclic dehydration of 2(β -aminoethylamino)cyclohexanol.

During the course of the work of Broadbent and Whittle, and after they had successfully prepared decahydroquinoxaline, m. p. 59-62° C., in near quantitative yields by the high pressure hydrogenation of quinoxaline or tetrahydroquinoxaline using 5% rhodium on alumina, Christie, Rhode, and Shultz in 1956 reported the preparation of decahydroquinoxaline by the low pressure hydrogenation of the tetrahydroquinoxalinium ion in ethanolic hydrochloric acid using Adam's catalyst. The product they obtained, m. p. 152.5-153° C., differed in melting point from the decahydroquinoxaline prepared by Broadbent and Whittle, but melted the same as the decahydroquinoxaline prepared by Beck, Hamlin, and Weston. Shultz, et. al., postulated that their decahydroquinoxaline was the same as the decahydroquinoxaline prepared by Beck, et. al. The dinitroso derivative of Shultz's decahydroquinoxaline melted at 110-111° C., thus differing from the melting point of the dinitroso derivative reported by Mousseron and Combes. Considering the possibility of geometrical isomerism in decahydroquinoxaline, and in view of the findings of Linstead, et. al., (135) concerning the geometrical isomers obtained upon catalytic hydrogenation, Shultz presented the possibility that his decahydroquinoxaline (and hence the decahydroquinoxaline of Beck, Hamlin and Weston) was the cis isomer and the decahydroquinoxaline of Mousseron and Combes was the trans isomer. Broadbent and Whittle, on the basis of epoxide ring opening, symmetry-physical property data, and hydrogenation considerations tentatively assigned the cis configuration to their decahydroquinoxaline and the trans configuration to the decahydroquinoxaline prepared by the method of Shultz and the method of Weston. (These tentative configurational assignments of Broadbent and Whittle proved to be correct.) The preparation of the dinitroso derivative of the decahydroquinoxaline of Broadbent and Whittle gave a product differing in melting point from either of the two previously reported dinitroso derivatives of decahydroquinoxaline. As decahydroquinoxaline can theoretically exist in either the trans (D,L)

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(135) Linstead, Doering, David, Levine and Whetstone, J. Am. Chem. Soc., 64, 1985 (1942).

and the cis (meso) forms, two different dinitroso derivatives are possible. The reporting of three different dinitroso derivatives of decahydroquinoxaline indicated that at least one of the reported preparations of decahydroquinoxaline did not give the presumed product. Analyses supported the contentions of all workers reporting the preparation of decahydroquinoxaline except Mousseron and Combes.

The previous work of Broadbent and Whittle suggested that both cis- and trans-decahydroquinoxalines isomerized on standing, each giving an equilibrium mixture of both isomers. cis-Decahydroquinoxaline, m. p. 58-62° C., on standing five days was found by Whittle to change melting point, giving a product melting over 58-102° C. By chromatography of this material both isomers of decahydroquinoxaline, melting points 147-50° and 58-61°, were isolated. The isomers so isolated were found on further standing to change melting point, the upper limit of the melting point of the cis isomer increasing about 50° while the lower limit of the trans isomer decreased about 25°. Especially were the melting point change and chromatographic separations indicative of isomerization when Whittle found that fresh samples of cis-decahydroquinoxaline stored under nitrogen changed melting point. Ultraviolet radiation and heat seemed to hasten the change in melting point.

However, in spite of the preceding evidence, other factors caused doubt concerning the validity of the suggested isomerizations. Some samples of fresh cis-decahydroquinoxaline stored under nitrogen changed melting point differently, or not all, from similar samples stored under supposedly identical conditions. Some of the analyses for active hydrogen obtained for cis-decahydroquinoxaline did not agree with the theoretically calculated value for the cis isomer and difficulty was encountered in obtaining ultraviolet spectra of cis-decahydroquinoxaline free of indications of unsaturation.

Clarification and solutions to the problems discussed above were obtained in the research covered by this thesis. The specific problems to be solved, then, were as follows: (1) determine which of the reported methods of preparation of decahydroquinoxaline gave decahydroquinoxalines, (2) determine if isomerization of the two isomers, one into the other, occurred, (3) if isomerization were not the cause of the observed changes in melting points of the isomers of decahydroquinoxaline, to definitely establish the cause, (4) determine with certainty the reasons for the indications of unsaturation in the ultraviolet spectra of cis-decahydroquinoxaline, and (5) establish the geometrical configuration of each isomer of decahydroquinoxaline. In addition it was desired to prepare new derivatives of both isomers for testing for physiological activity.

Preparation of decahydroquinoxaline by the methods of Broadbent and Whittle, Shultz and co-workers, and Beck, Hamlin and Weston, and the preparation and analyses of the diacetyl and dinitroso derivatives of each of the decahydroquinoxalines so prepared, proved three things. Each of the three methods gave decahydroquinoxaline. The decahydroquinoxaline prepared by Shultz and the decahydroquinoxaline prepared by Beck, Hamlin and Weston were identical. The method of preparation of decahydroquinoxaline employed

by Shultz gave a nearly quantitative yield of a mixture of substantial amounts of both isomers, the high melting trans isomer being obtained by recrystallization in a strikingly low yield (12.5%), while the low melting cis isomer remained in the mother liquors.

These preceding preparations established that Weston's method of preparation and Shultz's method of preparation gave the identical high melting isomer of decahydroquinoxaline. The product prepared by Broadbent and Whittle was the low melting isomer of decahydroquinoxaline, while the product reported by Mousseron and Combes was very probably not decahydroquinoxaline.

The problem of the possibility of isomerization of cis-decahydroquinoxaline was resolved by chromatographic means. Other work further supported the chromatographic evidence. Aged cis-decahydroquinoxaline, m. p. 60-120° C., was chromatographically separated into high and low melting isomers, thus substantiating the findings of Broadbent and Whittle. However, identical results were obtained by the chromatography of freshly prepared cis-decahydroquinoxaline, m. p. 53-58° C. The proof of isomerization of cis-decahydroquinoxaline based on the isolation of trans-decahydroquinoxaline from aged cis-decahydroquinoxaline was, therefore, invalid. The other proof offered in support of the isomerization of cis-decahydroquinoxaline to trans-decahydroquinoxaline was that samples of fresh cis-decahydroquinoxaline stored under nitrogen was observed to change melting point. This latter proof was shown to be equally invalid. Samples of pure cis-decahydroquinoxaline were stored under both nitrogen and carbon dioxide-free oxygen and these samples did not change melting point with standing. The possibility that the trans-decahydroquinoxaline present in aged cis-decahydroquinoxaline was due in part, however slight, to isomerization of the cis-decahydroquinoxaline was eliminated by the rechromatography of aged chromatographed cis-decahydroquinoxaline. No trans-decahydroquinoxaline was isolated. The evidence offered by Whittle in support of the isomerization of trans-decahydroquinoxaline was the observation of a change of melting point of the trans-decahydroquinoxaline with standing. Samples of pure trans-decahydroquinoxaline were stored at room conditions and also under nitrogen. No change of melting point was noted for any of the samples. The change of melting point with time observed not only by Whittle but also by Allred of freshly prepared cis-decahydroquinoxaline stored under "carbon dioxide-free" nitrogen indicated the sensitivity of this amine towards carbon dioxide. Minute amounts of carbon dioxide seemed to cause marked changes in the melting pont of cis-decahydroquinoxaline. Extreme care in storing the samples under carbon dioxide-free nitrogen was required and the difficulty encountered by Whittle and Allred indicated faulty experimental technique. That neither isomer tended to isomerize was further indicated by the subjecting of each isomer to the conditions under which the other isomer was initially prepared. No evidence of isomerization was detected.

On the basis of the evidence presented the conclusion was drawn that isomerization of either isomer of decahydroquinoxaline did not occur.

The cause of the melting point change of cis-decahydroquinoxaline previously attributed to isomerization was found to be due to absorption of carbon dioxide from the air to form a carbonate salt. cis-Decahydroquinoxaline kept free from carbon dioxide did not change melting point. An authentic speciman of the carbonate salt was identical in properties to aged cis-decahydroquinoxaline, which had experienced a changed melting point. Infrared spectra of aged cis-decahydroquinoxaline showed NH^+ and HCO_3^- bands which were nearly completely removed from the spectra of calcium oxide treated aged cis-decahydroquinoxaline.

That the melting point change on standing of cis-decahydroquinoxaline was not due to air oxidation of the amine to 1,2,3,4-tetrahydroquinoxaline was proved by two tests. First, the observed upper limit of the melting point range of aged cis-decahydroquinoxaline was approximately 25° higher than the melting point of 1,2,3,4-tetrahydroquinoxaline. Second, as mentioned before, cis-decahydroquinoxaline stored under carbon dioxide-free oxygen did not change melting point. The change in melting point was, thus, established to be due solely to carbonate salt formation.

Indications of unsaturation in cis-decahydroquinoxaline was found to be the result of contamination with 1,2,3,4-tetrahydroquinoxaline. Tetrahydroquinoxaline was found to sublime, though more slowly, under the same conditions necessary for the sublimation of cis-decahydroquinoxaline. cis-Decahydroquinoxaline purified by vacuum distillation invariably contained traces of tetrahydroquinoxaline. The maxima indicative of unsaturation in the ultraviolet spectra of cis-decahydroquinoxaline occurred at the identical wave length as the maxima in the spectra of tetrahydroquinoxaline. The tetrahydroquinoxaline impurity in cis-decahydroquinoxaline could be removed by very careful vacuum sublimation or chromatography and the spectram obtained of the purified cis-decahydroquinoxaline did not show indications of unsaturation. That the material presumed to be cis-decahydroquinoxaline was not an unsaturated isomer was shown by dehydrogenation of cis-decahydroquinoxaline to give tetrahydroquinoxaline. Also, infrared spectra did not indicate any carbon-carbon double bonds, carbon-nitrogen double bonds, or carbon-oxygen double bonds. Further, the other details of the infrared spectra and the pK_a data of both cis- and trans-decahydroquinoxaline were consonant for what would be expected for these compounds. Thus, the possibility of the indications of unsaturation in some of the ultraviolet spectra of cis-decahydroquinoxaline being due to some unsaturated compound isomeric with cis-decahydroquinoxaline was eliminated and the unsaturation indications were shown to be caused by traces of tetrahydroquinoxaline.

Two approaches were available for the determination of the geometrical configuration of the isomers of decahydroquinoxaline. The trans isomer could be resolved into its optical antipodes, or either of the isomers could be stereospecifially synthesized. Resolution of the trans isomers was tried by preparing the diastereoisomers of the amine to give the following optically active compounds: d-tartrate, d-tartranilate, d-10-camphorsulfonate, d-camphorate, l-malate, l-5-oxo-2-pyrrolidonecarboxylate, and the amide of l-menthoxyacetic acid. Fractional recrystallizations of

of the compounds were carried out using a variety and combination of solvents. No resolution was detected. Either the diastereoisomers could not be separated by fractional recrystallization using the solvents available or, if fractional recrystallization had effected separation, the change in optical rotation was too slight to be detected.

The high melting isomer of decahydroquinoxaline was finally identified as having the trans-configuration by stereospecifically synthesizing this isomer from authentic trans-1,2-diaminocyclohexane, the configuration of this latter compound having been established by other workers by the resolution technique using d-tartaric acid (126a).

The preparation of new derivatives of decahydroquinoxaline was carried out using standard procedures. The following new compounds were prepared: N,N'-diacetyl-cis-decahydroquinoxaline, N,N'-diacetyl-trans-decahydroquinoxaline, N-methyl-cis-decahydroquinoxaline, N-methyl-trans-decahydroquinoxaline, N,N'-dimethyl-cis-decahydroquinoxalinium iodide, N,N,N'N'-tetramethyl-trans-decahydroquinoxalinium diiodide, N,N'-bis(benzenesulfonyl)-cis-decahydroquinoxaline, N,N'-bis(benzenesulfonyl)-trans-decahydroquinoxaline, N,N'-dibenzyl-trans-decahydroquinoxaline, N,N'-dibenzyl-cis-decahydroquinoxaline, N-benzhydryl-cis-decahydroquinoxaline, N,N'-dibenzyhydryl-trans-decahydroquinoxaline, and N,N,N'N'-tetrabenzyl-trans-decahydroquinoxalinium dichloride.

In the preparation of these compounds the reactions were carried out employing an excess alkylating, or acetylating agent. In all preparations involving trans-decahydroquinoxaline, except for the monomethyl compound, the N,N'-dialkyl, N,N'-bis(benzenesulfonyl), or the diquaternary salt formed as was expected. Yields averaged 70% except for the N,N'-dibenzhydryl derivative where a 15% yield was obtained. This latter compound required a reaction period of six days during which time the reaction solution became very dark in appearance. A black gummy residue resulted from which only a 15% yield of the N,N'-dialkyl compound was isolated. It is possible more of the product had formed, or some of the mono N-alkylated derivative had formed, but if so neither could be isolated.

The alkylation of trans-decahydroquinoxaline in 95% ethanol using excess benzyl chloride gave a mixture of the quaternary salt and the N,N'-dialkylated derivative. The same reaction, but using p-dymene as the solvent, gave only the N,N'-dialkylated product and no quaternary salt. These results were not unexpected as ethanol, being the more polar solvent, would be more favorable to the formation of the quaternary salt than would the less polar solvent, p-cymene.

In the preparation of N-methyl-trans-decahydroquinoxaline using formic acid and formalin as the aslkylating agents, an intermediate acidic compound of unknown structure and of sharp boiling point was isolated. Treatment of this intermediate with base gave the free substituted amine. Distillation of the intermediate precluded the possibility of its being a salt. Analyses of this intermediate did not establish its structure although its sharp boiling point indicated a compound of definite composition. An identical situation was met in the preparation of N-methyl-cis-decahydro-

quinoxaline using formic acid and formalin to alkylate the amine.

In the preparation of the alkylated cis-decahydroquinoxaline considerable difference in reactivity of the cis isomer as contrasted to the trans isomer was noted. In the preparation of the N,N'-dibenzyl derivative of the cis isomer under the same conditions employed in preparing the trans analog, only the dialkyl product was formed using 95% ethanol as the solvent, whereas, the main product formed in the alkylation of the trans isomer was the quaternary salt. Under conditions that gave the dibenzhydryl derivative of the trans isomer, the monobenzhydryl derivative of the cis isomer formed. Quaternization of the monomethyl derivative of the cis isomer gave a monoquaternary salt compared to the diquaternary salt obtained from the monomethyl derivative of the trans isomer under the same conditions. These differences in reactivity are probably due predominantly to steric hindrance in the cis isomer. Before definite interpretations of these results can be made further investigation will be necessary.

V: SUMMARY

1. Decahydroquinoxaline was prepared by three of the four previously reported methods of preparation.

2. Comparison of the properties of the decahydroquinoxalines prepared and the preparation, comparison and analyses of the diacetyl and the dinitroso derivatives of these decahydroquinoxalines showed that two of the methods, Shultz's, et. al., and Weston's, et. al., gave the identical high melting decahydroquinoxaline, while the decahydroquinoxaline prepared by the method of Broadbent and Whittle gave the low melting isomer.

3. The preparation of decahydroquinoxaline by the method of Shultz gave a mixture of cis- and trans-decahydroquinoxaline, with the trans isomer being isolated by the recrystallization of the crude product, the cis isomer being discarded in the mother liquors.

4. Decahydroquinoxaline prepared by the method of Broadbent and Whittle gave a nearly quantitative yield of the cis isomer. However, a small amount of trans-decahydroquinoxaline and traces of 1,2,3,4-tetrahydroquinoxaline were also present.

5. Melting point data on N,N'-dinitroso-1,2,3,4-tetrahydroquinoxaline and the extreme case of dehydrogenation of cis-decahydroquinoxaline under some conditions, suggested strongly that the "decahydroquinoxaline" prepared by the fourth method (Mousseron's and Combes') was in actuality 1,2,3,4-tetrahydroquinoxaline.

6. In addition to analytical data, confirmation of the structure of decahydroquinoxaline was obtained by pK_a data, infrared spectral data, and the dehydrogenation of cis-decahydroquinoxaline to 1,2,3,4-tetrahydroquinoxaline.

7. Ultraviolet spectra of cis-decahydroquinoxaline free of indications of unsaturation were obtained by removal of the traces of 1,2,3,4-tetrahydroquinoxaline by either careful fractional vacuum sublimation or by chromatography.

8. Both cis- and trans-decahydroquinoxaline were isolated from fresh and aged cis-decahydroquinoxaline. Rechromatography of aged chromatographically pure cis-decahydroquinoxaline did not yield any trans-decahydroquinoxaline. Isomerization of cis- and trans-decahydroquinoxaline was shown not to occur.

9. Melting point studies showed isomerization of the two isomers (previously thought to occur) did not take place.

10. The cause of the melting point change of cis-decahydroquinoxaline on standing was found to be due solely to carbonate salt formation, while pure trans-decahydroquinoxaline was found not to change melting point with standing as previous evidence suggested.

11. Aerial oxidation was found to have no effect on either cis- or trans-decahydroquinoxaline.

12. The stereospecific synthesis of decahydroquinoxaline from authentic trans-1,2-diaminocyclohexane showed the high melting isomer, prepared by either the method of Shultz or the method of Weston, to be the trans isomer. The low melting isomer prepared by Broadbent and Whittle was, thus, the cis isomer.

13. The following new derivatives of decahydroquinoxaline were prepared: N,N'-diacetyl-cis-decahydroquinoxaline, N,N'-diacetyl-trans-decahydroquinoxaline, N-methyl-cis-decahydroquinoxaline, N-methyl-trans-decahydroquinoxaline, N,N'-dimethyl-cis-decahydroquinoxalinium iodide, N,N,N',N'-tetramethyl-trans-decahydroquinoxalinium diiodide, N,N'-bis(benzenesulfonyl)-trans-decahydroquinoxaline, N,N'-bis(benzenesulfonyl)-cis-decahydroquinoxaline, N,N'-dibenzyl-trans-decahydroquinoxaline, N,N,N',N'-tetrabenzyl-trans-decahydroquinoxalinium dichloride, N,N'-dibenzyl-cis-decahydroquinoxaline, N-benzhydryl-cis-decahydroquinoxaline, and N,N'-dibenzhydryl-trans-decahydroquinoxaline.

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DECAHYDROQUINOXALINE: STEREOISOMERS AND DERIVATIVES

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ABSTRACT

The preparation of decahydroquinoxaline by four different methods, with no determination of geometrical configuration made, was reported in the literature. The purpose of this thesis was to establish the geometrical configurations of the decahydroquinoxalines prepared by these four methods and to determine if, as the work of previous investigators suggested, the two pure isomers of decahydroquinoxaline isomerized, each giving an equilibrium mixture of both isomers.

Decahydroquinoxaline was prepared by three of the four previously reported methods of preparation. Comparison of the properties of the decahydroquinoxalines prepared and the preparation, comparison, and analyses of the diacetyl and the dinitroso derivatives of these decahydroquinoxalines showed that two of the methods, Shultz's, et. al., and Weston's, et. al., gave the same high melting decahydroquinoxaline, while the decahydroquinoxaline prepared by the method of Broadbent and Whittle gave the low melting isomer. The fourth method of preparation, that of Mousseron and Combes, gave a product which by comparison with the N,N'-dinitroso derivative of 1,2,3,4-tetrahydroquinoxaline and in view of the ease of dehydrogenation of cis-decahydroquinoxaline appeared to be 1,2,3,4-tetrahydroquinoxaline instead of decahydroquinoxaline.

It was found that the preparation of decahydroquinoxaline by the method of Shultz gave a mixture of cis- and trans-decahydroquinoxaline, with the trans isomer being isolated in suprisingly low yields (12.5%) by recrystallization from petroleum ether. In contrast, the decahydroquinoxaline prepared by the method of Broadbent and Whittle was obtained in nearly quantitative yields and had the cis configuration. A little trans-decahydroquinoxaline and traces of 1,2,3,4-tetrahydroquinoxaline were also obtained from the latter preparation.

Previously possibilities of the isomerization of each isomer of decahydroquinoxaline, one into the other, were considered. These were found not to occur, but that the change in melting point of cis-decahydroquinoxaline with standing was established as being due to absorption of carbon dioxide from the air forming the carbonate salt. The infrared spectra of aged cis-decahydroquinoxaline of changed melting point clearly indicated that carbonate salt formation had occurred. cis-Decahydroquinoxaline stored under carbon dioxide-free nitrogen did not change melting point on standing.

Chromatographic separations by previous workers of aged cis-decahydroquinoxaline suggested that isomerization occurred. However, fresh

cis-decahydroquinoxaline was similarly found, by chromatographic separations, to contain both isomers. Chromatographically pure cis-decahydroquinoxaline on standing did not give any trans-decahydroquinoxaline on being chromatographed. Neither isomer of decahydroquinoxaline was found to isomerize on standing and the melting point was established as being due to carbonate salt formation only.

In addition to analytical data, confirmation of the structure of decahydroquinoxaline was further obtained by pK_a data, infrared spectral data, and the dehydrogenation of cis-decahydroquinoxaline to 1,2,3,4-tetrahydroquinoxaline. Ultraviolet spectra of cis-decahydroquinoxaline was finally obtained which did not indicate the presence of unsaturation. It was found that the traces of 1,2,3,4-tetrahydroquinoxaline contaminating cis-decahydroquinoxaline and responsible for the indications of unsaturation in the spectra could be removed by careful vacuum fractional sublimation or by chromatography. The spectra of cis-decahydroquinoxaline so purified did not show indications of unsaturation.

Determination of the geometrical configuration of the isomers of decahydroquinoxaline was attempted by resolution of the racemic (D,L) trans isomer. Resolution was either not effected or not detectable. However, the stereospecific synthesis of decahydroquinoxaline from authenic trans-1,2-diaminocyclohexane showed the high melting isomer, prepared by either the method of Shultz or the method of Weston, to be the trans isomer. The low melting isomer prepared by Broadbent and Whittle was, thus, established as the cis isomer.

A number of new N-substituted and N,N'-disubstituted derivatives of decahydroquinoxaline was prepared. Table 1 lists these compounds. Very likely the predominant factor causing, in some instances, a lesser yield of the substituted cis compound compared with the trans compound was steric hindrance in the cis isomer.

TABLE I

NEW DERIVATIVES OF DECAHYDROQUINOXALINE

Compound	B. P. °C.	M. P. °C.	% Yield
N,N'-diacetyl-cis-decahydroquinoxaline		144-46	62
N,N'-diacetyl-trans-decahydroquinoxaline		93.5-4.5	73
N-methyl-cis-decahydroquinoxaline	48-50°/0.20mm.		72
N-methyl-trans-decahydroquinoxaline	44-46°/0.20mm.		87
N,N'-dimethyl-cis-decahydroquinoxalinium iodide		255-58	62
N,N,N',N'-tetramethyl-trans-decahydroquinoxalinium diiodide		229-30	64
N,N'-dibenzyl-cis-decahydroquinoxaline		62-2.5	88
N,N'-dibenzyl-trans-decahydroquinoxaline		79.5-80.5	21
N,N,N',N'-tetrabenzyl-trans-decahydroquinoxalinium dichloride		175-76	43
N,N'-dibenzyhydryl-trans-decahydroquinoxaline		220-25	15
N-benzhydryl-cis-decahydroquinoxaline		196.5-97.5	23
N,N'-bis(benzenesulfonyl)-cis-decahydroquinoxaline		194-195.5	55
N,N'-bis(benzenesulfonyl)-trans-decahydroquinoxaline		127-29	80