1937

Analgesics from dibenzofurans

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NOTE TO USERS

ANALGESICS FROM DIBENZOFURANS

BY

Paul Thomas Parker

A Thesis Submitted to the Graduate Faculty
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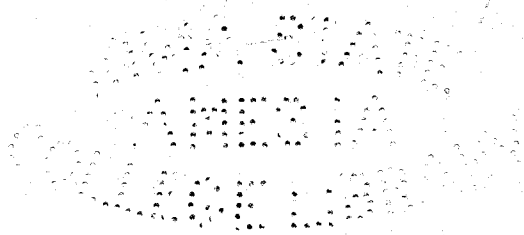
DOCTOR OF PHILOSOPHY

Major Subject Organic Chemistry



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1937

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The author wishes to express his sincere appreciation to Dr. Henry Gilman, whose helpful criticisms and suggestions have been an invaluable aid in the course of this research.

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INTRODUCTION

In accord with the work being carried out in this laboratory on dibenzofuran with the two-fold purpose of determining its orientation and the physiological action of certain of its derivatives, this investigation has been specifically directed towards the synthesis of compounds containing the dibenzofuran nucleus which hold promise of possessing analgesic activity. The stimulus for this phase of the research lies primarily in the occurrence of a partially reduced dibenzofuran nucleus in the chemical structure of morphine (1), and also in our as yet rather meager knowledge of the structural factors necessary for analgesic activity in an organic compound.

The term "analgesic" is one of several which are applied to that class of drugs employed in the alleviation of pain. The differentiation between the terms is not sharply defined, but lies in the type of effect produced as well as the manner in which it is brought about. Thus, a drug which produces sleep may be classified as a hypnotic, narcotic or anesthetic. However, a true hypnotic may be considered as one which induces sleep without essential distortion of the relationship of the faculties to the outside world and without suspension

(1) This has been more fully elaborated by W. H. Kirkpatrick, Doctoral Dissertation, Iowa State College, 1935.

of pain from consciousness (2). Narcotics do both. The sleep of an anesthetized patient is one of relative relaxation in contradistinction to the more or less tense muscular state obtained in the administration of hypnotic drugs.

Reference to an encyclopedia of medicine (2) provides a definition of analgesics as "remedies that relieve pain either by direct depression of the centers of perception and sensation in the cerebrum, or by impairing the conductivity of the sensory nerve fibers." Anodynes, on the other hand, "are nearly all hypnotic or narcotic." Accordingly, it is apparent that loss of consciousness is not a necessary characteristic of analgesia.

Because of the necessity of using animals as test subjects, an exact and quantitative determination of the analgesic action of chemical compounds is a practical impossibility (3) since pain is a subjective symptom and its objective expression bears no parallelism to the intensity of the stimulus. Such reactions as do become manifest are often reflexive and cannot give rise to a quantitative comparison. In addition, variations of technique in the hands of different investigators do not always give equivalent results, and the problem is further complicated by the difference in analgesic

(2) Scott, "Encyclopedia of Medicine and Surgery," P. Blackiston's Sons & Co., Philadelphia, 4th edition, 1919.
(3) Starkenstein, Arch. exptl. Path. Pharmakol., 165, 325 (1932).
Hesse and Reichelt, ibid., 169, 453 (1933).

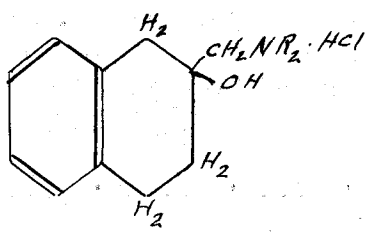
power which may be exhibited by any certain compound when its action is compared in different types of test animals or between animals and man. As an example, pyramidon (1-phenyl-2,3-dimethyl-4-dimethyleminopyrazolone) induces a significant analgesia in man in non-toxic doses (4), whereas in the mouse and guinea pig little or no analgesic effect is apparent (5). However, in the event that the therapeutic ratio of a group of compounds is such that it is permissible to use man as the test subject, a relatively precise comparison can be made with a technique recently reported (6) in which graded pain stimuli are obtained by a series of voltages applied to a sound tooth. The decrease in sensitivity resulting from the administration of the analgesic compounds can then be determined from the voltage increase necessary to reach the pain threshold.

The physiological property of analgesic activity in organic compounds is apparently confined almost exclusively to derivatives containing aromatic nuclei. Certain anesthetic gases, namely, cyclopropane, nitrous oxide and ethylene produce analgesia in sub-anesthetic concentrations (7); however, the primary action of these compounds is that of anesthesia.

(4) Starkenstein, Arch. exptl. Path. Pharmakol., 165, 332 (1932).
(5) Hesse, et al., ibid., 158, 233, 247 (1930). Hildebrandt, ibid., 174, 405 (1934).
(6) Freund, ibid., 180, 209 (1936).
(7) Severs, Bennett, Pohle and Reinardy, J. Pharmacol., 59, 291 (1937).

A curious example of analgesic action in inorganic material (8) is found with a mixture of potassium chloride, potassium bicarbonate, sodium bicarbonate, calcium bicarbonate, and sodium acid phosphate in amounts corresponding to those found in blood serum. When the mixture is injected subcutaneously an analgesia is produced effective in cases of neuralgia and lasting for varying periods of time up to several days.

Although hypnotic, narcotic and anesthetic action is often encountered among aliphatic derivatives, and the hypnotic efficiency of the clinically important barbituric acid derivatives is well known, definite analgesic action largely centers in a few specific nuclei: namely, benzene, pyrazolone, quinoline and isoquinoline, dibenzofuran and phenanthrene. In the light of its exceptionally powerful physiological effect, morphine, of course, assumes a unique position as an analgesic nucleus. The absence of naphthalene in this group is conspicuous. Certain tetrahydronaphthalene derivatives of the type



, which were

(8) Walinski, Deut. med. Wochschr., 53, 647 (1927).

examined specifically for analgesic action with cats, induced an emetic effect but no analgesia (9).

The derivatives of benzene, particularly that group derived from p-aminophenol and salicylic acid, come under the class of antipyretic and antineuralgic agents. The antipyretic effect is perhaps attributable to the benzene nucleus since even its simpler derivatives such as phenol, aniline and phenylhydrazine exhibit this effect (10). Certain other cycles related to benzene such as pyridine, naphthalene and phenanthrene do not have this property, but it appears in quinoline derivatives (10). p-Aminophenol in the form of its N-acyl-O-alkyl derivatives is found in numerous proprietary medicines under a variety of trade-names (11). Acetphenetidine is less toxic than acetanilide and is more effective towards neuralgic pains than other antipyretics (10).

Although decidedly efficacious in neuralgia, headache, migraine and like ailments, a comparison of this class of compounds with morphine and its derivatives in their action on man shows a lower order of efficiency (12), and in animal experiments almost no effect is elicited except in near-toxic

(9) Woods and Eddy, J. Pharmacol., 48, 174 (1933).
(10) McGuigan, "Textbook of Pharmacology and Therapeutics," W. B. Saunders Company, Philadelphia, 1928 pp. 136 and 137.
(11) Crohn, Med. Klin., 26, 1755 (1930).
(12) Haffner, Deut. med. Wochschr., 55, 731 (1929).

doses (5)(12)(13). With an increase in the size of the O-alkyl group in p-acetaminophenol the antipyretic and antineuralgic effect decreases (14a). The maximum antipyretic and antineuralgic action occurs with the methyl group and the minimum toxicity with the ethyl group.

Of the three hydroxybenzoic acids only salicylic acid and its derivatives have any antipyretic or antineuralgic action, the other two isomers being practically inert (14b). Introduction of a methyl group in the nucleus of salicylic acid increases the toxicity. This is the reverse of the effect of introducing a methyl group in phenol, since the cresols are less toxic than phenol (14c). Within the group of methyl-substituted salicylic acids the o-cresotic acid is the most active (14d). In this instance, as well as with salicylic acid, the vicinal position of the substituent groups proves to be the most advantageous. A voluminous literature exists on the chemistry and pharmacology of salicylic acid and p-aminophenol derivatives (15).

Observing that guanylthiourea possessed an antipyretic

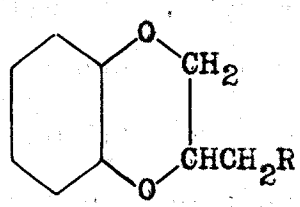
(13) Sivadjian, Arch. intern. pharmacodynamie, 52, 142 (1936). / C.A. 30, 6449 (1936). /

(14) (a) Fränkel, "Arzneimittel-Synthese," Julius Springer, Berlin, 6th edition, 1927, p. 286. (b) ibid., p. 556. (c) ibid., p. 558. (d) ibid., p. 557.

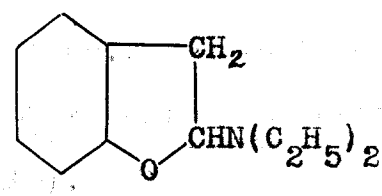
(15) See Houben, "Fortschritte der Heilstoffchemie," Walter De Gruyter & Co., Berlin, 1932, Vol. II, Part 2, pp. 416 ff. and 852 ff.

action, Hesse and Taubmann (16) examined a series of aliphatic and aromatic guanylthioureas conforming to the structure RNH-C(=S)-NH-C(=NH)-NH_2 which were synthesized by Slotta, Tscherche and Dressler (17). The aliphatic derivatives had good antipyretic properties, but were too toxic for use. A clinical trial of the aromatic derivatives proved them to be without antipyretic action, but to have an analgesic effect instead, and especially so with the 4-hydroxyphenyl-, 4-ethoxyphenyl- and 4-carboethoxyphenylguanylthioureas which were effective in cases of neuralgia, rheumatism and headache.

Certain benzodioxan derivatives and related compounds comprise another group of benzene derivatives in which analgesic action has been found (18). Piperidinomethylbenzodioxan (I) and diethylaminomethylbenzodioxan (II) have ap-

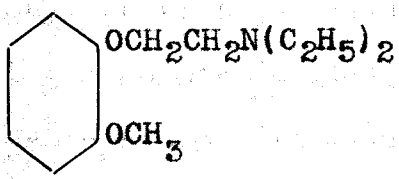


(I, R = Piperidino-)
(II, R = Diethylamino-)



III

(16) Hesse and Taubmann, Arch. exptl. Path. Pharmakol., 146, 113 (1929).
(17) Slotta, Tscherche and Dressler, Ber., 63, 208 (1930).
(18) Bovet, Simon and Depierre, Compt. rend. soc. biol., 117, 961 (1934).
Bovet, Anesthesie et analgesie, 1, 21 (1935). [C.A., 30, 7221 (1936).]



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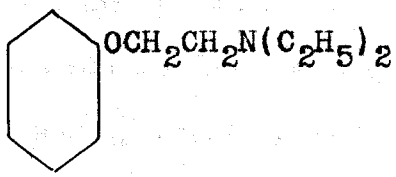


V

proximately the same order of activity. Diethylaminocoumaran (III) is somewhat less active, o-methoxy-β-diethylaminoethoxybenzene (IV) is feebly active and β-diethylaminoethoxybenzene (V) is inactive. In the rabbit piperidinomethylbenzodioxan (I) produces its maximum analgesic effect in dosages of fifty milligrams per kilogram or about one-third of the maximum tolerated dose; the minimum effective dose is ten milligrams per kilogram. A compound somewhat related to this group, namely, benzyloxyethanol, $C_6H_5CH_2OCH_2CH_2OH$, has also been mentioned as having anesthetic and analgesic properties (19).

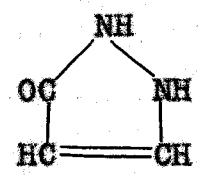
A group of compounds reported in the patent literature as having bactericidal and analgesic properties (20) have the general formula R'-N=N-R-N=N-R", in which R is a phenyl, biphenyl or diphenylmethane residue; R' is a diamine or alkoxyamine in the benzene series; and R" is an amino- or hydroxycarboxylic acid or carboxylate of the benzene series. A

(19) U.S. Pat. 1,651,458. [C.A., 22, 845 (1928).]
(20) U.S. Pat. 1,979,534. [C.A., 29, 1585 (1935).]

similar group (21) in which R' is o-hydroxyquinoline, and R" is either o-hydroxyquinoline or a diamine, alkoxy-amine, amino- or hydroxy-carboxylic acid or carboxylate of the benzene series is stated to have like therapeutic properties.

An antineuralgic, antirheumatic and antiarthritic compound is found in the diacetyl derivative of the product formed by the coupling of methylenebis-p-phentidine with methylenedisalicylamide (22).

The derivatives of pyrazolone are similar to those of



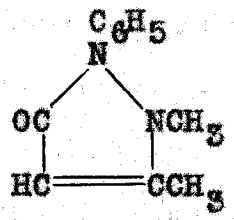
Pyrazolone

p-aminophenol in their physiological action (23), and constitute an important class of the antipyretic-analgesic drugs. Although better known, perhaps, for their antipyretic action, certain of their derivatives also exhibit an effective analgesia in cases of neuralgia, heart disease, nephritis and headache (24) and are clinically used for this purpose.

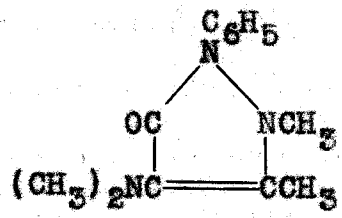
Two well known members of this group are antipyrine (I) and pyramidon (II), both of which show significant analgesic

(21) U.S. Pat. 1,979,678. [C.A., 29, 1585 (1935).]
(22) U.S. Pat. 1,813,365. [C.A., 25, 5249 (1931).]
(23) A review and bibliography covering the pharmacology of pyrazolone derivatives is found in Heffter, "Handbuch der Experimentellen Pharmakologie," Julius Springer, Berlin, 1923, Vol. I, pp. 1106 to 1146.
(24) McGuigan, Ref. 10, pp. 134 and 135.

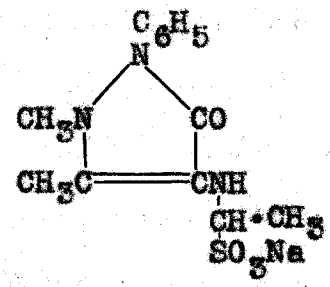
action in man (24). Novalgin (III) has been mentioned as a specific for polyarthritis and muscle rheumatism (25). How-



I



II



III

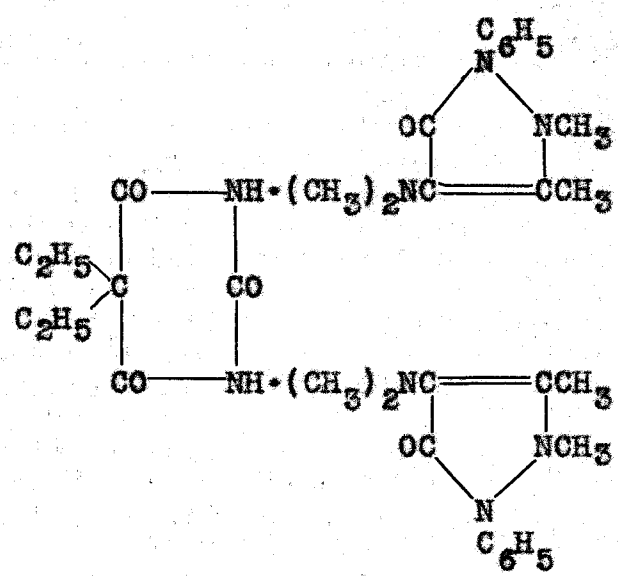
ever, as with the p-aminophenol derivatives, this class of drugs is less effective than the morphine group when tested with animals (5).

For analgesic purposes advantage is taken of the synergistic effect which often exists between antipyretic and hypnotic compounds. A rule, known as Bürgi's rule (26), which is often applied to such combinations states, in effect, that if two compounds have the same physiological action and the same point of attack in the body, then in combination their effect will be additive. However, if they possess the same action but a different point of attack, the resultant effect will be greater than the sum of the two effects.

The combinations most often employed are principally antipyrine or pyramidon, and either urethanes or certain barbituric acid derivatives. Other combinations are also en-

(25) Auer, Deut. med. Wochschr. 48, 91 (1922).
(26) Bürgi, Ibid., 37, 281 (1910).

countered, and a large number have been protected by patents. These combinations may be in the form of mechanical mixtures or more usually as molecular compounds. An example is the molecular compound formed between two molecules of pyramidon and one molecule of diethylbarbituric acid to which was assigned the structure (27):



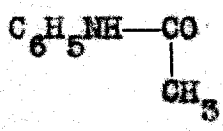
The compound was stated to have satisfactory analgesic action in cases of headache.

There is well founded experimental support for the belief that with certain combinations an antagonism exists between the toxicity of the one and the toxicity of the other, and also that a significant synergism may be elicited (28).

(27) Starkenstein, Therap. Halbmonatsh., 35, 629 (1921).
(28) Kaer and Loewe, Arch. exptl. Path. Pharmakol., 114, 327, 339 (1926).
Starkenstein, Klin. Wochschr., 4, 114 (1925).

A detailed investigation of a number of such mixtures (29) showed that not all antipyretic-hypnotic combinations are synergistic with respect to analgesic activity. Those in which a potentiation of effect does take place have an optimum ratio between constituents in which the maximum activity is obtained. Often a decrease in the toxicity results with a concomitant increase in the therapeutic index.

Hepner and Frenkenberg (30) prepared 1-methyl-3-phenylbarbituric acid (II), as a structural compromise between acetanilide (I) and antipyrine (III). Compound II proved to



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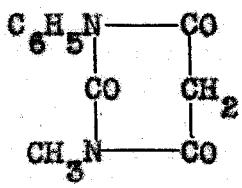
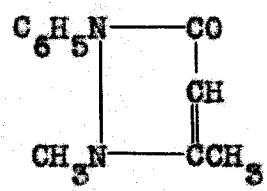


II



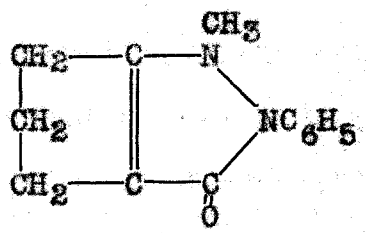
III

be an antipyretic. Mono- and disubstitution of the methylene group in compound II with aliphatic and aromatic radicals yielded N,N-substituted barbiturates having analgesic properties.

A variation of the antipyrine structure is found in

(29) Pohle and Spieckermann, Arch. exptl. Path. Pharmacol., 162, 685 (1931).
Pohle and Vogel, ibid., 162, 706 (1931).
Pohle and Dittrich, ibid., 162, 716 (1931).
(30) Hepner and Frenkenberg, Ber., 65, 123 (1932).

2-methyl-1-phenyl-3,4-cyclotrimethylenepyrazolone,



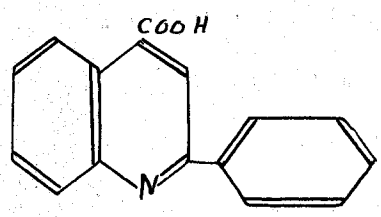
, which was synthesized by Mannich (31). Extensive tests indicated that the compound exceeded antipyrine in its antipyretic and analgesic action. Szancer (32) reports a "dioxypyramidon", prepared by treating pyramidon in the cold with concentrated hydrogen peroxide, as a stable compound having hypnotic and analgesic properties.

Both quinoline and isoquinoline have few derivatives exhibiting analgesic action. The most evident physiological effects furnished by these compounds are of an antipyretic and central depressant nature (33). The clinical use of the quinoline derivatives is limited, however, because of the tendency towards renal injury as well as other undesirable side-reactions which often accompany their administration in man.

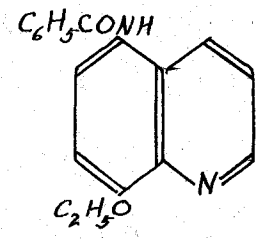
Cinchophen, aside from its antipyretic action, is analgesic to about the same extent as salicylic acid (34) and

(31) Mannich, Arch. Pharm., 267, 699 (1929).
(32) Szancer, Pharm. Zentr., 71, 675 (1930). [Chem. Zentr., 102, I, 480 (1931).]
(33) Frankel, Ref. 14, pp. 225 to 233.
(34) McGuigan, Ref. 10, pp. 259 to 260.

depends upon the decreased excitability of the central nervous system for its effect (35). Analgen has both anti-



Cinchophen



Analgen

pyretic and antineuralgic action, but because of its insolubility in water, erratic and undependable results frequently follow its administration. The importance of the substituent groups on the nucleus is shown in this case by the inactivity of 5-acetamino-8-methoxyquinoline (33), which differs from analgen only in the groups attached to the nitrogen and oxygen. Several other derivatives of quinoline closely related to cinchophen and analgen have also been used in clinical practice.

The comparative investigation of various analgesics using the mouse and guinea pig as test subjects carried out by Hesse and his co-workers (5), revealed an interesting variation in the analgesia induced by cinchophen (atophan) in different subjects. Although it is an effective analgesic in

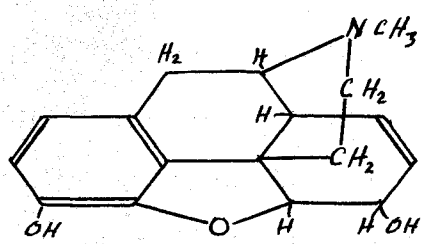
(35) Raszeja and Billewicz-Stankiewicz, Arch. intern. pharmacodynamie, 45, 361 (1933). [C.A., 27, 5817 (1933).]

human subjects, in healthy mice it failed completely to show any analgesic action towards a pain stimulus produced by applying a clamp at the base of the tail. In the tests with the guinea pig a variation of the technique was introduced. By injecting a small amount of croton oil beneath the skin on the back of the animal a very sensitive, inflamed area was produced, and a slight pressure was sufficient to elicit definite response from the animal. Cinchophen, salicylic acid derivatives and several proprietary mixtures, which had given negative results in the mouse tests, showed definite action when tested with this method. Conversely, a number of p-aminophenol and pyrazolone derivatives, which had shown some action in the tests with mice, were ineffective in the latter instance. The divergence shown by the several groups of compounds was attributed to a difference in their point of attack in the organism.

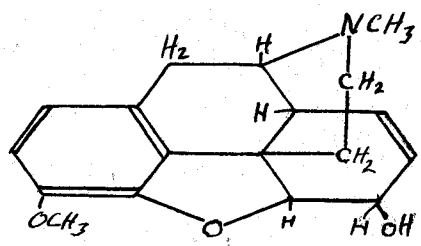
Among the opium alkaloids (36) are several containing a substituted isoquinoline nucleus. An interesting comparison of the relative analgesic potency of two of these, papaverine and narcotine, along with morphine, codeine, narceine and thebaine, was made by Macht, Herman and Levy (37). The

(36) For a complete review see Small, "Chemistry of the Opium Alkaloids," Supp. 103, Public Health Reports, U.S. Public Health Service, Washington, D. C., 1932.
(37) Macht, Herman and Levy, J. Pharmacol., 8, 1 (1916).

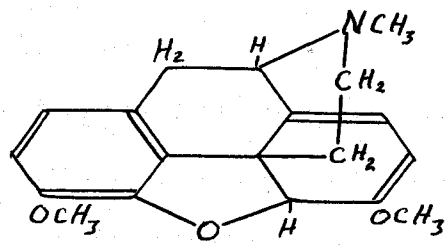
authors themselves served as test subjects, and pain stimuli were obtained by applying a controlled electrical voltage to sensitive areas on the body. The chemical relationship of the compounds employed in their experiments is shown by the following structures (36):



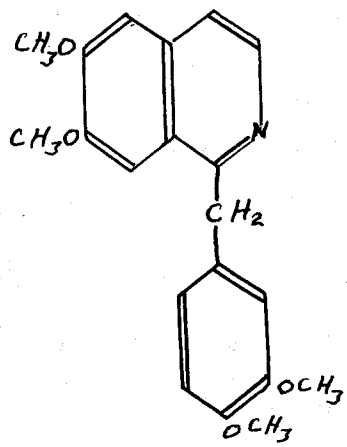
Morphine



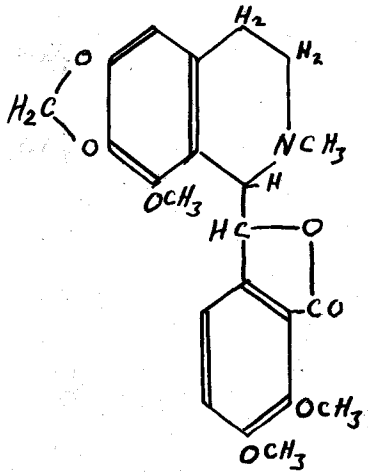
Codeine



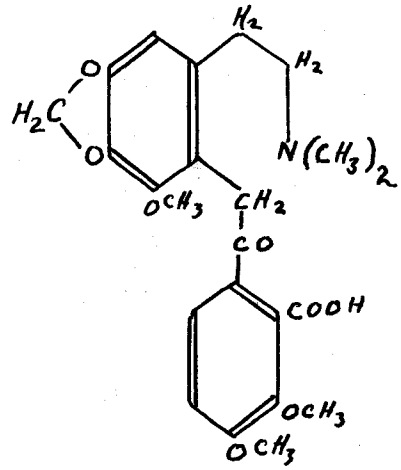
Thebaine



Papaverine



Narcotine

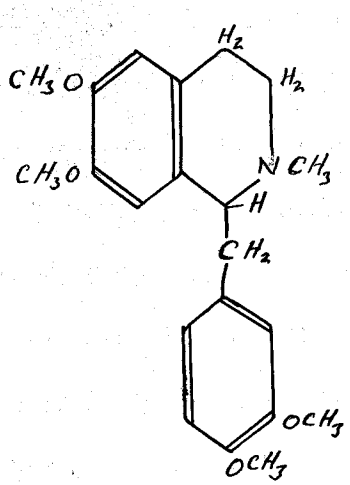


Narceine

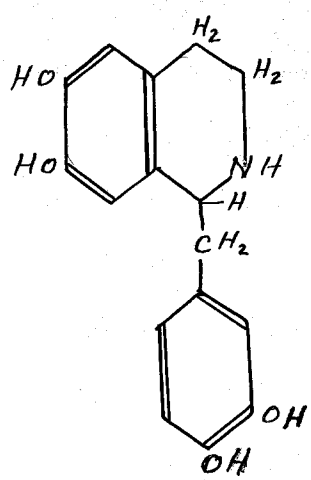
In the course of their experiments a number of interesting observations were made. With one of the subjects morphine induced a hypersensitivity to pain instead of the analgesia experienced by the other two. Other effects of morphine, nausea and incoördination, were present to a high degree. This idiosyncrasy did not extend to any of the other alkaloids tested. Papaverine was found to rank next to morphine in its analgesic action. The administration of narcotine caused an initial hypersensitiveness followed by a short period of slight dulling of the pain sensation. Neither narceine or thebaine showed any analgesic effect. Of those showing analgesic action morphine was the most powerful followed by papaverine, codeine and narcotine in descending order. A mixture of

morphine and narcotine produced the highest degree of analgesia encountered in their research. A combination of the total alkaloids of opium, known as pantopon, gave a higher degree of analgesia than would have been produced by its morphine content.

Methylation and reduction of papaverine to give the N-methyl-py-tetrahydropapaverine (laudanosine) destroys its analgesic properties and markedly increases its toxicity and convulsant action (38). On the other hand, demethylated and reduced papaverine (pavoline) has only slight physiological action (38).



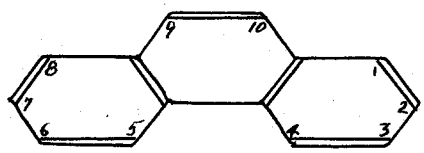
Laudanosine



Pavoline

(38) Frünkel, Ref. 14, pp. 435 and 436.

The phenanthrene nucleus more closely approximates the skeletal structure of the morphine molecule than any of the nuclei hitherto considered. Accordingly, it is reasonable to



Phenanthrene

assume, and experimental evidence has borne out such an assumption, that among its derivatives some would possess analgesic activity. Within recent years a systematic study of phenanthrene and its derivatives has been carried out by Dr. Nathan B. Eddy of the University of Michigan Medical School in collaboration with other groups. Inasmuch as these studies have been accomplished under a standardized procedure the results obtained possess an especial value.

When administered orally to cats, phenanthrene itself is definitely depressant (39) as shown by weakness, incoördination and relaxation. It has, however, no significant analgesic action. Hexahydrophenanthrene produces a narcosis in the dog (40a) and marked depression in the guinea pig (40b).

(39) Eddy, J. Pharmacol., 48, 183 (1933).
(40) (a) Brissemoret and Joanin, Compt. rend., 151, 1151 (1910).
(b) Brissemoret, Compt. rend. soc. biol., 68, 10 (1910).

Of the monosubstituted phenanthrene compounds, those in the 3-position are the most active physiologically (39). The 2-, 3-, and 9-acetylphenanthrenes are all hypnotic but show no analgesic action. With a dosage of two hundred milligrams per kilogram definite analgesic action was found with 3-phenanthrenecarboxylic acid, but no significant action was produced with the 2- or 9-acid. Similar results were obtained with the hydroxy-compounds in the same positions, although a tendency was shown by the 2-hydroxyphenanthrene towards activity. The aminophenanthrenes were all more toxic than the other derivatives, and both the 2- and 3-aminophenanthrenes were analgesic, although the 2-amine was so only in approximately fatal doses. The least toxic of the three was the 9-amine. From the standpoint of depressant action the order of decreasing action found with the substituent groups is as follows: amino, carboxylic acid, hydroxyl, and acetyl. All of the derivatives were more depressant than the unsubstituted phenanthrene.

The effect of blocking the hydroxyl group in the 2- and 3-hydroxyphenanthrenes by substituting a methyl, ethyl or acetyl group for the hydrogen is to decrease the analgesic activity of these compounds (41). The effect was the same regardless of which radical was present. The effect was more pronounced, however, with the more active 3-hydroxyphenanthrene

(41) Eddy, J. Pharmacol., 51, 75 (1934).

than with the hydroxyl group in the 2-position.

The effect of adding a second substituent to a monosubstituted phenanthrene was also investigated (42), comparison being made directly with the monosubstituted compounds. Observations were also made as to general depression, muscular disturbance, heart rate, respiratory rate, temperature and emetic effect. The analgesic effects are given in Table I. The letter N and the figure following refers to the number of animals (cats were used as in all previous experiments) in the group in which an increase in the pain threshold above normal was not apparent. The letters S, M and D with the accompanying figures indicate the number of animals in which the effect was slight, moderate and marked, respectively. Within each group shown the dosage was the same in every case.

(42) Eddy, J. Pharmacol., 52, 275 (1934).

TABLE I

PHENANTHRENE DERIVATIVES	ANALGESIA
3-Hydroxy-	N-1; S-4.
3,4-Dihydroxy-	N-0; M-3; D-2.
3-Hydroxy-4-amino-	N-1; S-2; M-2.
3-Acetoxy-	N-2; S-3.
3,4-Diacetoxy-	N-3; S-2.
3,6-Diacetoxy-	N-6; M-5.
3-Hydroxy-	N-0; M-3; D-2.
3-Hydroxy-6-acetyl-	N-2; S-3.
3-Acetyl-	N-2; S-3.
9-Hydroxy-	N-1; S-4.
9-Hydroxy-10-acetyl-	N-2; S-3.
9-Acetyl-	N-4; S-1.
9-Acetyl-	N-2; S-3.
9-Acetyl-3-methoxy-	N-2; S-3.
3-Methoxy-	N-3; S-2.
9-Amino-3-methoxy-	N-1; S-4.
9-Diacetylamino-3-methoxy-	N-4; S-1.

TABLE I (cont'd.)

PHENANTHRENE DERIVATIVES	ANALGESIA
9-Amino-	N-1; S-4.
9-Amino-3-hydroxy-	N-2; S-3.
3-Hydroxy-	N-1; S-4.
9-Amino	N-4; S-6.
9-Amino-10-hydroxy-	N-5; S-2; M-3.
9-(or 10-) Hydroxy-	N-3; S-4; M-3.
9-Amino-	N-3; S-2.
9-Amino-10-methoxy-	N-2; S-3.
9-Hydroxy-	N-2; S-3.
9-Acetamino-10-hydroxy-	N-1; S-4.
9-Acetamino-	N-2; S-3.
9-Acetamino-10-methoxy-	N-3; S-2.
9-Acetamino-10-ethoxy-	N-3; S-2.
9-Carboxylic acid	N-3; S-2.
3-Methoxy-9-carboxylic acid	N-3; S-3.
3-Methoxy-	N-3; S-2.
- - - - - - - - - - - - - - -	
3-Hydroxy-4,5-Phenanthrylene Oxide	N-1; M-4.
3-Methoxy- " " "	N-3; S-1; M-1.

TABLE I (cont'd.)

PHENANTHRENE DERIVATIVES	ANALGESIA
3-Acetoxy-4,5-Phenanthrylene Oxide	N-3; S-2.
3-Hydroxyphenanthrene	N-0; M-3; D-2.
3-Methoxyphenanthrene	N-3; S-2.
3-Acetoxyphenanthrene	N-2; S-3.

From the table it is evident that the hydroxyl group is the most effective of any of the groups studied in promoting the analgesic activity of the phenanthrene nucleus. The general effect seems to be that the hydroxyl group enhances the activity of a compound containing another group, and conversely, the introduction of a second group (not including the hydroxyl group) into a hydroxyphenanthrene usually lessens its activity. The 3,4-dihydroxy- and 3-hydroxy-4-aminophenanthrenes were the most analgesic and also the most toxic of the group. The decrease in activity resulting from muzzling a free hydroxyl group is well illustrated in this series, and a similar effect is also apparent in the acetylation of an amino group.

Another interesting change is that produced by the oxygen bridge in the phenanthrylene oxide derivatives. All were less active than the correspondingly substituted phenanthrene com-

pounds. An increased emetic effect was observed, however, with the 3-hydroxyphenanthrylene oxide over its phenanthrene analogue.

The results found with a second series of monosubstituted phenanthrene derivatives (43) containing carboxylic acids, their amides and methyl esters, carbinols, ketones and the aldehyde group are summarized in Table II. The letters and the numbers which follow have the same connotation as in Table I.

TABLE II

PHENANTHRENE DERIVATIVES	ANALGESIA
3-Phenanthrene-	
Carboxylic acid	N-0; S-3.
Carboxylic acid methyl ester	N-4; S-1.
Carboxylic acid amide	N-5.
Carboxylic acid dimethylamide	N-0; S-3; M-2.
β-3-Phenanthryl-	
Propionic acid	N-2; S-2; M-3; D-1.
Propionic acid methyl ester	N-2; S-1.
Propionic acid amide	N-2; S-3.

(43) Eddy, J. Pharmacol., 55, 354 (1935).

TABLE II (Cont'd.)

PHENANTHRENE DERIVATIVES	ANALGESIA
3-Phenanthrylaldehyde	N-5.
3-Acetylphenanthrene	N-2; S-3.
3-Propionylphenanthrene	N-4; S-1.
9-Phenanthrylaldehyde	N-3; S-2.
9-Acetylphenanthrene	N-3; S-2.
3-Phenanthrylmethyl alcohol	N-2; S-2; M-1.
Methyl-3-phenanthrylcarbinol	N-2; S-1; M-2.
2-Acetylphenanthrene	N-4; S-1.
Methyl-2-phenanthrylcarbinol	N-2; S-2; M-1.
9-Phenanthrylmethyl alcohol	N-2; S-2; M-1.
Methyl-9-phenanthrylcarbinol	N-3; S-1; M-1.
9-Phenanthrene-	
Carboxylic acid	N-3; M-2.
Carboxylic acid methyl ester	N-5.
Carboxylic acid amide	N-5.
2-Phenanthrene-	
Carboxylic acid	N-3; S-2.
Carboxylic acid methyl ester	N-4; S-1.
Carboxylic acid amide	N-4; S-1.

A comparison of 3-phenanthrenecarboxylic acid and its derivatives with β-3-phenanthrylpropionic acid and its corresponding derivatives shows that the latter group of compounds are the more effective of the two. It is an interesting point that the formation of either the ester or amide of the 3-phenanthrenecarboxylic acid serves to decrease its activity, yet the dimethylamide again becomes equally as effective as the original acid. The aldehyde and ketone groups were not significantly active, however, reduction to the corresponding alcohol increased the activity somewhat.

Of the simple monosubstituted phenanthrenes so far described the 3-aminophenanthrene is the most active analgesic and also the most toxic. With the hope that this activity might be maintained and the toxicity reduced, a group of twelve monosubstituted phenanthrenes were submitted to test (44) carrying the amino group in a side-chain. With one exception the substituents were all in the 3-position, and the group conformed to the general formulas

$R'COCH_2NR_2$

$R'CHOHCH_2NR_2$

$R'CHOHCH(CH_3)NR_2$, in which R' is the phenanthrene nucleus and $-NR_2$ is either piperidino-, diethylamino-, ethylamino-, dimethylamino- or the unsubstituted

(44) Eddy, J. Pharmacol., 55, 419 (1935).

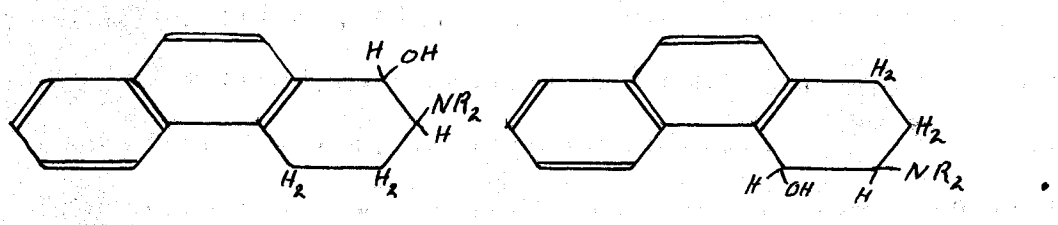
amino- group.

The most analgesic compound in the group was the diethylaminomethyl-3-phenanthrylcarbinol, $R'CHOHCH_2N(C_2H_5)_2$. This compound had twice the analgesic effect of 3-aminophenanthrene and was less toxic. The minimal effective dose intramuscularly administered was less than three times that of codeine. In cats the compound produced considerable analgesia and other morphine-like effects. In mice, rabbits and dogs its action was not as characteristic.

All of the amino-ketones were analgesic, but to a lesser extent than the corresponding carbinols. The order of effectiveness of the $-NR_2$ groups in the two series was not the same, that is, in the ketones the decreasing order of effectiveness was dimethylamino-, diethylamino- and piperidino-, whereas with the carbinols the order was diethylamino-, piperidino- and dimethylamino-. The carbinols having a primary amine were locally irritant, and their administration resulted in such prompt emesis that other physiological effects could not be noted.

In connection with this series of compounds it is interesting to note that neither phenanthrene nor diethylaminoethanol is analgesic, yet in chemical combination an analgesic compound is produced. Also, the tertiary amines of the carbinol series were all more analgesic than the carbinol without the amino group present.

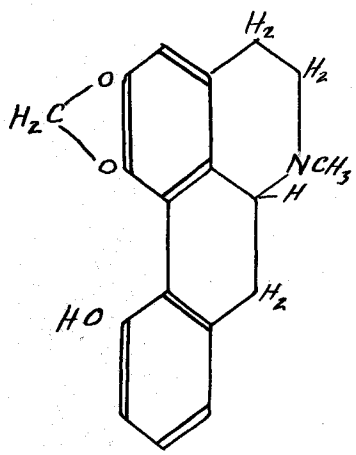
In the 1- or 4-keto-1,2,3,4-tetrahydrophenanthrene is found a more effective analgesic nucleus than the unreduced cycle (45). The 1-keto isomer shows a marked analgesic action in sufficient doses without much other effect. The 4-keto isomer is considerably less effective. Mosettig and Burger (45) have prepared a series of derivatives of 1,2,3,4-tetrahydrophenanthrene conforming to the formulas



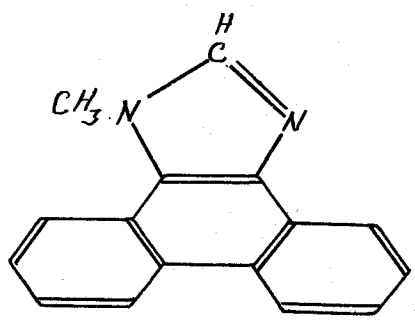
Two of these compounds approached the morphine derivative codeine in their analgesic power. 2-Piperidino-1-hydroxy-1,2,3,4-tetrahydrophenanthrene in doses of twenty milligrams per kilogram, and 3-isoquinolino-4-hydroxy-1,2,3,4-tetrahydrophenanthrene in doses of fifteen milligrams per kilogram were comparable in their analgesic effect to that of codeine in ten milligram doses.

Two other compounds of phenanthrene are of interest, namely pukateine and N-methyl-9,10-phenanthroimidazole (Epiosin), since each contains a heterocycle fused to the phenanthrene nucleus.

(45) Mosettig and Burger, J. Am. Chem. Soc., 57, 2189 (1935).



Pukateine



Episosin

Pukateine (46) is a naturally occurring alkaloid that is found in the bark of the Pukatea tree (Laurelia Novae-Zealandiae, Monimiaceae). Its structure was established by Schlittler (47) through the synthesis of its methyl ether. Pharmacologically the drug produces a central depression and excitation, muscular disturbance and depression of the respiratory center. In its power to alleviate pain in man, present work indicates that it is approximately as effective as morphine (48).

Episosin was synthesized by Vahlen (49). A dose of 0.1

(46) Aston, J. Chem. Soc., 97, 1381 (1910).
(47) Schlittler, Helv. Chim. Acta, 15, 581 (1932).
(48) Fogg, J. Pharmacol., 54, 167 (1935).
(49) Vahlen, Arch. exptl. Path. Pharmakol., 47, 368 (1902).

grem was claimed to produce approximately the same analgesia in man as 0.015 gram of morphine hydrochloride.

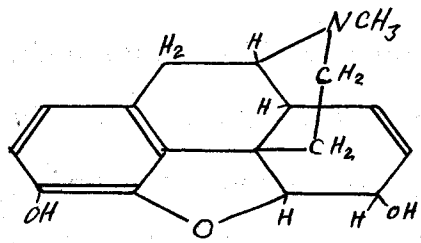
Concurrently with the studies on phenanthrene derivatives, Eddy has carried out a similar comparative investigation of morphine derivatives. The numerous variations of the morphine structure which have been introduced in the hope of attaining an increased analgesic power with a decrease in the less desirable effects attending the administration of this drug is the subject of an extensive literature, and its review could scarcely be undertaken at this time (50). However, a brief mention of some of the more recent work is of interest here since these studies have been made under definitely comparable conditions, thus, lending added value to such correlations between structural changes and analgesic activity which can be made.

As in the studies of phenanthrene derivatives, cats were the test animals used in determining the analgesic effect of the compounds (51). The method of producing a pain stimulus consisted in applying a measured pressure to the terminal two inches of the tail. Only when a substance in a certain dose necessitated an increase in pressure beyond the normal vari-

(50) For a review of the earlier work on the pharmacology of the opium alkaloids and their derivatives see Heffter, "Handbuch der Experimentellen Pharmakologie," Julius Springer, Berlin, 1924, Vol. II, Part 2, p. 821 ff., and also Fränkel, Ref. 14, p. 410 ff.

(51) Eddy, J. Pharmacol., 45, 339 (1932).

ability of the group in at least four out of five animals was definite analgesic action considered to be present.

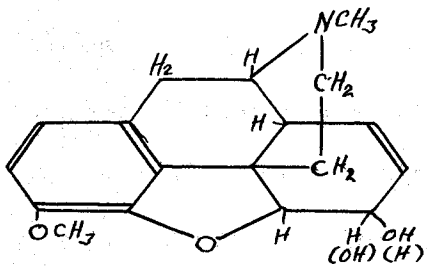


Morphine

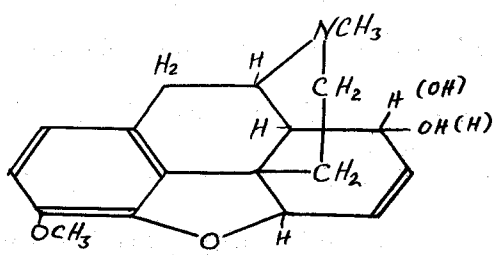
The individual influence which the two hydroxyl groups in the morphine molecule exerts upon its analgesic power is quite different. Eddy has shown (52) with a series of fifteen pairs of morphine derivatives, which differed from each other only in the methylation of the phenolic hydroxyl, that such a change increases the excitability and convulsant effect and decreases the analgesic activity of the compounds. In a similar series of thirty pairs of morphine derivatives in which the alcoholic hydroxyl of one of each pair was varied by substitution, removal, methylation, acetylation or hydrogenation of the adjacent double bond, the effect has been to greatly increase the analgesic action. From these results it can be concluded that the free phenolic hydroxyl serves to promote analgesic activity, which is an effect similarly found with the phenanthrene derivatives, and that the alcoholic hydroxyl

(52) Eddy, J. Pharmacol., 48, 271 (1933).

exerts an inhibitory influence.



Codeine and Isocodeine



Pseudo- and Allopseudocodeine

Among the isomeric codeines, the formulas of which are given above, the effect of positional isomerism is shown by the following order of decreasing analgesic activity (53): codeine, isocodeine, allopseudocodeine and pseudocodeine. However, if the toxicity and convulsant action of these compounds are taken into consideration, the order of decreasing analgesic usefulness is found to be: pseudocodeine, isocodeine, codeine and allopseudocodeine.

The gain in analgesic efficiency of the isomeric codeines following the elimination of the double bond in the partially reduced ring is shown in Table III (54), in which the minimal effective dose for each substance in milligrams per kilogram is tabulated.

The marked increase in analgesic effectiveness attending

(53) Eddy, J. Pharmacol., 45, 361 (1932).
(54) Eddy, ibid., 51, 35 (1934).

TABLE III

NAME OF COMPOUND	M. E. D. in mg. per kg.
Codeine	8.0
Dihydrocodeine	7.2
Isocodeine	13.0
Dihydroisocodeine	0.9
Pseudocodeine	17.8
Dihydropseudocodeine	4.2
Allopseudocodeine	13.3
Dihydroallopseudocodeine	7.0

the hydrogenation of the double bond is apparently a characteristic of all methyl ethers of morphine and codeine as well as of morphine itself. This is indicated by the results found with a similar group of morphine and codeine ethers, which are listed in Table IV (55).

Apart from the increase in analgesic action shown by the dihydro-compounds, the activating influence produced by muzzling the alcoholic hydroxyl group is also well demonstrated. Dihydroheterocodeine represents a culmination of the two

(55) Eddy, J. Pharmacol., 55, 127 (1935).

TABLE IV

NAME OF COMPOUND	M. E. D. in mg. per kg.
Morphine	0.75
Dihydromorphine	0.26
Heterocodeine*	0.48
Dihydroheterocodeine	0.17
Codeine	8.04
Dihydrocodeine	7.20
Codeine methyl ether	6.00
Dihydrocodeine methyl ether	1.16
Pseudocodeine	17.82
Pseudocodeine methyl ether	8.34

* Heterocodeine results from the methylation of the alcoholic hydroxyl of morphine.

effects and is the most active of the series from the standpoint of analgesic power, however, it has about the same toxicity as codeine. Methylation of the alcoholic hydroxyl group, as also the methylation of the phenolic hydroxyl, is usually accompanied by an increase in toxicity. The dihydro-compounds show a variable increase in toxicity as well. The least toxic of this group was pseudocodeine, and even in fatal doses no convulsant action was apparent.

Acetylation of the alcoholic hydroxyl group in morphine, like methylation, produces an increase in analgesic action and also an increase in toxicity and convulsant action. Table V summarizes the results found with a group of acetyl derivatives (56).

TABLE V

NAME OF COMPOUND	M. E. D. in mg. per kg.
Morphine	0.75
Dihydromorphine	0.26
α-Monoacetylmorphine*	0.18
Monoacetyldihydromorphine*	1.35
Diacetylmorphine (Heroin)	0.43
Diacetyldihydromorphine	1.82

* The alcoholic hydroxyl is the one acetylated in these compounds.

A significant point in this series is the decrease in analgesic action which accompanies hydrogenation, an opposite effect from that observed with the series of morphine ethers. The toxicity is increased by hydrogenation as with the other

(56) Eddy and Howes, J. Pharmacol., 53, 430 (1935).

compounds, however.

Substitution of the alcoholic hydroxyl by a ketonic oxygen effects an increase in the analgesic action of morphine and codeine similar to that observed with other variations of this group (57). The minimal effective dose for several related compounds is included in Table VI for comparison.

TABLE VI

NAME OF COMPOUND	M. E. D. in mg. per kg.
Morphine	0.75
Dihydromorphine	0.26
Dihydromorphinone (Dilaudid)	0.17
Codeine	8.04
Dihydrocodeine	7.20
Dihydrocodeinone (Dicodide)	1.28

The codeine-like effect of reducing the analgesic action following methylation of the phenolic hydroxyl is equally apparent in this series. However, the ratio of the analgesic dose of dihydrocodeinone to that of codeine or dihydrocodeine is twice as large as the ratio of the toxic doses, whereas the

(57) Eddy and Reid, J. Pharmacol., 52, 468 (1934).

ratio of the analgesic dose of dihydromorphinone to that of morphine is the same as the ratio of their toxic doses.

Further substantiation of the hypothesis that the alcoholic hydroxyl exerts an inhibiting effect on the analgesic power of morphine and its derivatives is shown by the results obtained with a series of compounds in which this group has been eliminated entirely (58). These results are summarized with respect to analgesic effect in Table VII.

TABLE VII

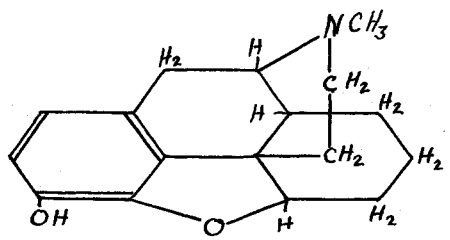
NAME OF COMPOUND	M. E. D. in mg. per kg.
Morphine	0.75
γ-Isomorphine	7.09
Desoxymorphine-C	0.45
Dihydrodesoxymorphine-D	0.08
Dihydromorphine	0.26
Tetrahydro-γ-isomorphine	8.90
Tetrahydrodesoxymorphine	0.62
Codeine	8.04
Pseudocodeine	17.82
Desoxycodeine-C	1.00

(58) Eddy and Howes, J. Pharmacol., 55, 257 (1935).

TABLE VII (Cont'd.)

NAME OF COMPOUND	M. E. D. in mg. per kg.
Dihydrodesoxycodeine-D	1.96
Dihydrocodeine	7.20
Tetrahydropseudocodeine	26.79
Tetrahydrodesoxycodeine	4.43

The group of compounds listed in table VII contains six pairs of derivatives, in which one member of each pair differs from the other only in the replacement of the alcoholic hydroxyl by hydrogen. In each case, removal of the hydroxyl results not only in an increase in analgesic action, but the compound is more toxic, convulsant and depressant in its effect, although not necessarily to the same extent in every case. Dihydrodesoxymorphine-D, the most powerfully analgesic member of



Dihydrodesoxymorphine-D

the group, is approximately ten times as analgesic as morphine

yet has only three times its toxicity. It possesses very little convulsant action and no emetic effect. Its analgesia is rapid, but is of shorter duration than that of morphine.

The opening of the oxygen bridge, represented in this series by the tetrahydro-derivatives, apparently decreased the analgesic activity somewhat; however, this result is probably affected by the appearance of a new phenolic hydroxyl.

In briefly summing up the major effects involved in the structural changes of the morphine nucleus just considered, the following points stand out:

1. In regard to the positional isomerism of the alcoholic hydroxyl, greater analgesic effect is found with those derivatives in which the hydroxyl is found in the 6-position (morphine, codeine, isocodeine) than when it occurs in the 8-position (γ-isomorphine, pseudo- and allopseudocodeine). However, a considerably decreased toxicity and convulsant action is shown by those compounds having the hydroxyl in the 8-position.

2. Methylation of the phenolic hydroxyl serves to decrease the analgesic efficiency of the compound.

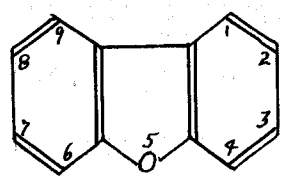
3. Muzzling of the alcoholic hydroxyl by either methylation or acetylation, or replacement of the hydroxyl by a ketone group effects an increase in the analgesic power.

4. With the exception of the acetyl derivatives, hydrogenation of the double bond produces an increase in analgesic

activity.

5. The complete elimination of the alcoholic hydroxyl results in a considerable augmentation of the analgesic power of the compound, and coupled with the hydrogenation of the double bond culminates in a very effective analgesic substance.

As a nucleus, dibenzofuran possesses as great an interest, perhaps, as that of phenanthrene since both are present as a component in the complete structure of morphine. The ultimate effect of either the diphenyl-linkage or the oxygen bridge on the analgesic action of its derived compounds can only be conjectured since the analgesic properties, if any, of analogous compounds in which either of the two linkages is lacking seems not to have been investigated. One exception is



Dibenzofuran

found in the acyl derivatives of 4,4'-diaminodiphenyl which have been mentioned in a patent (59) as having antipyretic, antineuralgic and analgesic properties.

Some early reports on the physiological effect of dibenzofuran derivatives were not encouraging. Thus, amino-

(59) U.S. Pat. 1,900,442. [C.A., 27, 3036 (1933).]

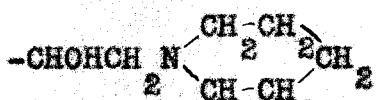
hexahydrodibenzofuran and α-aminoethylhexahydrodibenzofuran were both reported to be inactive (60). Also no morphine-like action was found with 2-(γ-aminopropyl)-dibenzofuran or 2-(γ-aminopropyl)-tetrahydrodibenzofuran (61).

A direct comparison of the analgesic efficiency of compounds having like substituents in both the dibenzofuran and phenanthrene nuclei is of considerable interest. Such a comparison has been carried out by Eddy (62), and the results are shown in Tables VIII and IX. In every case the 3-phenanthrene derivatives were the ones employed. With the exception of 3-aminodibenzofuran the substituents were all in the 2-position of dibenzofuran where comparison with the phenanthrene analogue was made. The values given under "analgesia" are the minimum effective dose in milligrams per kilogram of the derivatives shown. Table IX lists those dibenzofuran derivatives which had no phenanthrene analogue.

The analgesic effect in nearly every case is exhibited more strongly by the dibenzofuran derivatives than with their phenanthrene analogues. This advantage is more apparent than real, however, since the toxicity and convulsant action of the dibenzofuran compounds were greater in most instances. The increase in activity that accompanies an increase in the

(60) Von Braun, Ber., 55, 3767 (1922).
(61) Mayer and Krieger, Ber., 55, 1659 (1922).
(62) Eddy, J. Pharmacol., 58, 159 (1936).

TABLE VIII

SUBSTITUENT	ANALGESIA* Phenanthrene derivative	Dibenzofuran derivative
None	None	None
-COOH	200	None
$-COOCH_3$	None	None
$-COCH_3$	None	None
$-COCH_2CH_3$	400	400
$-CHOHCH_3$	None	300
$-COCH_2N(CH_3)_2$	100	75
$-COCH_2N(C_2H_5)_2$	150	50
$-CHOHCH_2NH_2$	100	75
$-CHOHCH_2N(CH_3)_2$	60	50
$-CHOHCH_2N(C_2H_5)_2$	40	50
	50	60
$-NH_2$	75	40

* Values refer to M.E.D. in milligrams per kilogram.

length of the side-chain is evident in both series, and the advantage of an attached amino group is quite obvious. In regard to other effects there was no consistent or significant difference observed between either series of derivatives.

TABLE IX

DIBENZOFURAN DERIVATIVES	ANALGESIA*
β-Ethylaminoethyl-2-dibenzofurylcarbinol	60
3-Dimethylaminodibenzofuran	40
Benzofuro-[2,3-f]-quinoline	None
1,2,3,4-Tetrahydrobenzofuro-[2,3-f]-quinoline	None
N-Methyl-1,2,3,4-tetrahydrobenzofuro-[2,3-f]-quinoline	200
Benzofuro-[3,2-g]-quinoline	300
1,2,3,4-Tetrahydrobenzofuro-[3,2-g]-quinoline	None
N-Methyl-1,2,3,4-tetrahydrobenzofuro-[3,2-g]-quinoline	200

* Values refer to M.E.D. in milligrams per kilogram.

Of those derivatives listed in Table IX the N-methyl-tetrahydro-compounds show a slight advantage over the unreduced cycles, but are not as effective as some of the simpler derivatives.

Up to the time of this writing a total of seventy-eight compounds have been submitted from this laboratory and examined for analgesic activity. With the exception of nine compounds comprising some of the simpler derivatives of benzofuran, phenoxthin and dibenzothiophene, these have all been compounds of dibenzofuran representing a variety of substit-

uents in the several positions available in the nucleus. The complete list of these compounds, with their toxicity values, is given in Table X, and the pharmacological results as to analgesic action (M.A.D. = minimal analgesic dose) are given in the footnotes appended to the table (63). White mice were the test animals used, and administration was usually made by intraperitioneal injection of a suitable solution of each derivative. These tests were occasionally supplemented by oral administration to either rabbits or guinea pigs when sufficient material was available.

TABLE X

HD No.	NAME OF COMPOUND	M. L. D.* in mg. per g.
1	Dibenzofuran	4**
2	Tetrahydrodibenzofuran	4**
3	2-Aminodibenzofuran	10**
4	2-Hydroxydibenzofuran	2**
5	3-Hydroxydibenzofuran	2**
6	2-Dibenzofurancarboxylic acid	6**

(63) The pharmacological tests on compounds prepared in this laboratory and listed in Table X were carried out in the laboratories of Parke, Davis and Company, and the results have been made available through the courtesy of Dr. Dox and Dr. Bywater of that firm.

TABLE X (Cont'd.)

HD No.	NAME OF COMPOUND	M. L. D.* in mg. per g.
7	3-Aminodibenzofuran	2**
8	4-Dibenzofurancarboxylic acid	10**
9	4-Hydroxydibenzofuran	3**
10	3-Dibenzofurancarboxylic acid	---
11	Pyrido-[3,2-b]-dibenzofuran (a)	---
12	1,2,3,4-Tetrahydropyrido-[3,2-b]-dibenzofuran	---
13	Pyrido-[2,3-b]-dibenzofuran (a)	---
14	7-Amino-1,2,3,4-tetrahydrodibenzofuran	---
15	2-β-Diethylaminoethyldibenzofuran (b)	6**
16	3-Diethylaminodibenzofuran	---
17	3-n-Propylaminodibenzofuran	---
18	3-Methylaminodibenzofuran	---
19	3-Ethylaminodibenzofuran	---
20	3-Dimethylaminodibenzofuran	---
21	2-ω-Diethylaminoacetyldibenzofuran (b)	8**
22	3-Piperidinodibenzofuran	---
23	Piperidinomethyl-2-dibenzofurylcarbinol (c)	4**
24	2-ω-Piperidinoacetyldibenzofuran	6**
25	4-Aminodibenzofuran (d)	0.5
26	4-Acetaminodibenzofuran (e)	0.12
27	4,6-Dihydroxydibenzofuran	0.4

TABLE X (Cont'd.)

HD No.	NAME OF COMPOUND	M. L. D.* in mg. per g.
28	1,2,3,4-Tetrahydrodibenzofuran-6-carboxylic acid	0.3
29	6-Methoxy-1,2,3,4-tetrahydrodibenzofuran	0.5
30	4-β-Diethylaminoethyldibenzofuran	0.175
31	Diethylaminomethyl-2-dibenzofurylmethyl-carbinol	0.20
32	4-β-Diethylaminoethoxydibenzofuran	0.20
33	4-β-Piperidinoethoxydibenzofuran	0.25
34	1-β-Diethylaminoethyl-4-methoxydibenzofuran	0.20
35	2-β-Piperidino-α-ethoxyethyldibenzofuran	0.25
36	Tetrahydropyrido-[5,4-c]-dibenzofuran	0.15
37	1,2,3,4-Tetrahydrodibenzofuran-6-carboxylic acid	0.15
38	2-α-Diethylaminoethyldibenzofuran	0.15
39	4-β-Aminoethyldibenzofuran	0.125
40	2-β-Aminoethyldibenzofuran	0.20
41	3-Dibenzofurandiazonium chloride	0.25
42	2-α-Aminoethyldibenzofuran	0.30
43	1,2,3,4-Tetrahydrodibenzofuran-4-carboxylic acid	0.5
44	3-γ-Dimethylaminopropyldibenzofuran	0.30
45	3-Amino-4-methoxydibenzofuran	0.30
46	1-Amino-4-methoxydibenzofuran	0.35

TABLE X (Cont'd.)

HD No.	NAME OF COMPOUND	M. L. D.* in mg. per g.
47	4-Aminoacetaminodibenzofuran (f)	0.25
48	3-Amino-1,2,3,4-tetrahydrodibenzofuran (g)	---
49	6-Amino-1,2,3,4-tetrahydrodibenzofuran	0.45
50	1-Acetamino-4-ethoxydibenzofuran (h)	0.15
51	1-Aminodibenzofuran (i)	0.35
52	2-Aminodibenzofurothiazole (j)	0.2
53	1-(4-Dibenzofuryl)-isoquinoline	0.15
54	2-Methyldibenzofuro-[2,3-d]-imidazole (k)	0.7
55	1,2,3,4-Tetrahydro-1-aminobrazan (l)	0.1
56	2-Benzofurancarboxylic acid	0.7
57	Benzofuran	(m)
58	2,3-Dihydrobenzofuran	(m)
59	Perhydrobenzofuran	(n)
60	2,3-Dihydrobenzofuran-2-carboxylic acid	1.1
61	5-Amino-2-benzofurancarboxylic acid	1.25
62	7-Methoxy-2-benzofurancarboxylic acid	0.6
63	1(or 4)-phenoxthincarboxylic acid	0.2
64	2-Methoxy-3-dibenzofurancarboxylic acid	0.04
65	2-Methoxy-1-dibenzofurancarboxylic acid	0.15
66	1-Allyl-2-hydroxydibenzofuran	0.10
67	3,4-Dimethoxydibenzofuran	0.12

TABLE X (Cont'd.)

HD No.	NAME OF COMPOUND	M. L. D.* in mg. per g.
68	3-Hydroxy-4-methoxydibenzofuran	0.24
69	4-Hydroxy-6-methoxydibenzofuran	0.10
70	4,6-Dimethoxydibenzofuran	0.15
71	1,4-Dihydro-7-acetyldibenzofuran	0.15
72	1,4-Dihydro-7-α-aminoethyldibenzofuran	0.12
73	1,2-Dihydro-2-dibenzofurancarboxylic acid	0.3
74	1,4-Dihydro-6-methoxydibenzofuran	0.15
75	1,4-Dihydro-2,3-dibromodibenzofuran	0.04
76	1,4-Dihydro-6-hydroxydibenzofuran	0.10
77	4-Dibenzothiophenecarboxylic acid	0.15
78	2-Methyl-5-methoxydibenzofuro-[1,2-d]-imidazole	0.40

* Except for those values marked (**), the M.L.D. is in mg./g. Where values have not been given, the compound was either not submitted to test or the M.L.D. was not reported.

** These values are the total dose administered to each mouse.

(a) These compounds were ineffective in 50 and 100 mg./kg. doses.

(b) The compounds produced morphine-like excitement, but no analgesia or hypnosis.

(c) M.A.D. = 6 mg. Analgesic only in lethal doses.

(d) M.A.D. = 0.1 mg./g. Analgesia produced by this compound equivalent to 10% of that of morphine.

(e) M.A.D. = 0.04 mg./g. Weakly analgesic.

(f) Weak analgesic action.

(g) Inactive and very toxic.

(h) M.A.D. = 0.075 mg./g.

(i) M.A.D. = 0.2 mg./g.

(j) M.A.D. = 0.08 mg./g.

(k) M.A.D. = 0.15 mg./g.

(l) M.A.D. = 0.04 mg./g.

(m) M.L.D. = 0.00015 cc./g.

(n) M.L.D. = 0.0002 cc./g.

DISCUSSION

In considering the relationship which may exist between the analgesic action of organic compounds and their chemical structure, one must bear in mind that any comparison is subject to the limitations involved in the methods by which the data are obtained. The ideal subject to use for experimentation in this direction would be, of course, man, inasmuch as the ultimate purpose is to develop materials suitable for application in human therapy. However, the hazards inherent in such a procedure, necessitating, as it does, the initial use of animals until thorough investigation presents results of sufficient promise to warrant clinical trial, naturally precludes this more direct approach. The determination of analgesia rests upon a measurement of the outward manifestation of a subjective condition, and as a consequence, modifications in procedure or a difference in the test animal used may easily introduce a lack of concordance in the final results obtained by separate investigators. When a group of compounds has been examined with a consistent experimental procedure, it may be assumed that fairly valid comparisons can be made within the group. In any event the data, by whatever means obtained, may well serve to indicate the direction most promising for future research.

The divergence in the physiological effect following the

administration of certain analgesic materials to different species of animals has been previously mentioned (64). Among the compounds of dibenzofuran examined by Eddy and listed in Tables VIII and IX are several also appearing among those listed in Table X that have been submitted from this laboratory and tested on white mice. Dibenzofuran (HD 1), 2-dibenzofurancarboxylic acid (HD 6) and 1,2,3,4-tetrahydropyrido-[3,2-b]-dibenzofuran (HD 12) (65) were all found to be inactive in both instances. Pyrido-[3,2-b]-dibenzofuran (HD 11) was found to be active in 300 mg./kg. doses in cats (see Table IX) (66), but was inactive in 50 and 100 mg./kg. doses in white mice. Piperidinomethyl-2-dibenzofurylcarbinol (HD 23) was found to be analgesic only in lethal doses corresponding to approximately 200 mg./kg. in mice. Table VIII shows this compound to be analgesic in 60 mg./kg. doses in the cat.

The three remaining compounds contained in Table X which also appear in the group investigated by Eddy are 3-aminodibenzofuran (HD 7), 3-dimethylaminodibenzofuran (HD 20) and 2-ω-diethylaminoacetyldibenzofuran (HD 21). Eddy's results show these to be among the most active of the group of di-

(64) This thesis, p. 19.
(65) This compound corresponds to the 1,2,3,4-tetrahydrobenzofuro-[3,2-g]-quinoline in Table IX.
(66) The compound is called benzofuro-[3,2-g]-quinoline in Table IX.

benzofuran derivatives which were examined. As shown in Table X these derivatives were inactive in white mice. This discrepancy is probably attributable to the difference in the test animal used, and it may be possible that the white mouse offers a more severe test to an analgesic than does the cat.

An important point in regard to the comparison of phenanthrene and dibenzofuran derivatives as shown in Table VIII, is that the substituents were attached at the most favorable position of the phenanthrene nucleus, i.e. the 3-position. The results shown in Tables I and II indicate that for simple monosubstituted phenanthrene derivatives the 3-position yields the most active compounds. With the exception of the 3-aminodibenzofuran and 3-dimethylaminodibenzofuran the comparison was made in each case with 2-substituted dibenzofuran derivatives. The most advantageous position in dibenzofuran in regard to analgesic action is the 4-position, which is the one corresponding to the 3-position in phenanthrene. This is shown by comparing the four isomeric monoaminodibenzofurans (HD 3, HD 7, HD 25 and HD 51) listed in Table X. The 4-aminodibenzofuran is the least toxic and the most analgesic of the group followed by the 1-aminodibenzofuran. The 2- and 3-aminodibenzofurans are inactive and more toxic than the other two. A more valid comparison between the phenanthrene and dibenzofuran derivatives would have resulted had the sub-

stituents occurred in the corresponding positions in each case.

The most active monosubstituted phenanthrene derivative shown in Eddy's results (44) is the diethylaminomethyl-3-phenanthrylcarbinol (see Table VIII). Despite the unfavorable position of its substituent group, the dibenzofuran analogue, diethylaminomethyl-2-dibenzofurylcarbinol, exhibited a slightly greater activity. It is probable that the corresponding 4-substituted dibenzofuran would have shown a greater contrast. It may be predicted also, that 2-piperidino-1-hydroxy-1,2,3,4-tetrahydrodibenzofuran and 3-isoquinolino-4-hydroxy-1,2,3,4-tetrahydrodibenzofuran would show significant analgesic activity similar to that reported by Mosettig and Burger (45) for their phenanthrene analogues.

None of the hydroxydibenzofurans listed in Table X was found to be analgesic. Those in which the hydroxyl group appears in the 4-position, namely 4-hydroxydibenzofuran (HD 9) and 4,6-dihydroxydibenzofuran (HD 27), are less toxic than their isomers. The equivalent phenanthrene derivatives, 3-hydroxyphenanthrene, 3-hydroxy-4,5-phenanthrylene oxide, and 3,6-diacetoxyphenanthrene (Table I) were all found to have significant analgesic action. A direct comparison of the hydroxy-compounds of the three nuclei represented would be of interest, since some insight might be gained as to the influence of both the oxygen bridge and the ethylenic bridge on the analgesic activity of their derived compounds. Insuf-

ficient data are available, however, to allow valid conclusions to be drawn.

The ratio between the minimal lethal dose and the minimal analgesic dose of those derivatives of dibenzofuran listed in Table X having analgesic properties is of interest since it demonstrates the relative analgesic effectiveness of the compounds concerned. These ratios are given in Table XI.

TABLE XI

NAME OF COMPOUND	M.L.D.	M.A.D.	RATIO
Piperidinomethyl-2-dibenzofuryl-carbinol	4	6	0.67
4-Aminodibenzofuran	0.5	0.1	5
4-Acetaminodibenzofuran	0.12	0.04	3
4-Aminoacetaminodibenzofuran	0.25	?	?
1-Acetamino-4-ethoxydibenzofuran	0.15	0.075	2
1-Aminodibenzofuran	0.35	0.2	1.75
2-Aminodibenzofurothiazole	0.2	0.08	2.5
2-Methyldibenzofuro-[2,3-d]-imidazole	0.7	0.15	4.67
1,2,3,4-Tetrahydro-1-aminobrazan	0.1	0.04	2.5

Obviously, the greater the ratio between the M.L.D. and the M.A.D., the more effective is the compound as an analgesic

material. The most effective compounds of this group are 4-aminodibenzofuran (HD 25) and 2-methyldibenzofuro-[2,3-d]-imidazole (HD 54) with ratios of 5 and 4.67, respectively. The effectiveness of these compounds when compared to morphine is slight. Morphine has an average fatal dose in white mice of 379.5 mg./kg. and a minimal effective dose in cats of 0.75 mg./kg., which yields a value of 560 for the therapeutic index. These values, of course, do not take into consideration any difference in toleration which may exist between the mouse and the cat. They do, however, furnish a basis for an approximate comparison. A more dependable value for comparison is obtained from the effective and fatal doses of morphine in man. Because of individual idiosyncrasy the fatal dose for man varies greatly, however, a dose of 0.06 g. of morphine is considered dangerous, and 0.2 to 0.4 g. is fatal in most cases (67). An effective analgesic dose is 0.008 to 0.016 g. for an adult. Accordingly, the therapeutic index here is within the range of 25 to 40.

If the toxicity values of the dibenzofuran compounds are compared to those for morphine and codeine it is seen that both series have approximately the same degree of toxicity. Expressed in equivalent units, morphine and codeine have an average fatal dose of 0.38 and 0.24 mg./g., respectively,

(67) McGuigan, Ref. 10, p. 483.

both values falling within the toxicity range of 0.1 to 0.7 mg./g. exhibited by the analgesic dibenzofuran compounds. The conclusion to be drawn from these data is that the lack of effectiveness of the dibenzofuran derivatives so far examined for analgesic activity is not the result of an abnormally high toxicity.

That analgesic action in a compound is a function of the nucleus as well as of the substituent groups is, perhaps, axiomatic. Given a nucleus capable of conferring analgesic activity upon certain of its derivatives, then the probability that a suitable modification can be found possessing an effective analgesic power is greatly increased. It seems evident that the dibenzofuran nucleus is potentially the equal of either phenanthrene or phenanthrylene oxide in this respect. Analogous derivatives of both phenanthrene and dibenzofuran are apparently closely equivalent in their analgesic action, and the resemblance of phenanthrylene oxide to phenanthrene makes it probable that none of the three nuclei will exhibit a large divergence in the analgesic action of their simpler derivatives.

It is doubtful whether any isolated portion of the morphine molecule can be considered to be the principal causative agent in its powerful analgesic action. The total effect is very probably a resultant of the cumulative influence from several factors. Those points of major importance to the

analgesic activity of the molecule are apparently the following.

1. The hydroaromatic ring.

The lack of analgesic activity in thebaine furnishes evidence towards the necessity of at least a tetrahydrogenated ring in morphine. The occurrence of a methylated phenolic hydroxyl in place of the alcoholic hydroxyl originally present is probably not an important factor in this loss of activity, since other evidence indicates that the alcoholic hydroxyl group exerts an inhibiting influence upon the analgesic action of morphine, and the presence of a second methylated hydroxyl in the phenanthrene derivatives does not lessen their activity. In addition it is to be noted that hydrogenation of the double bond to give a completely hydrogenated ring generally serves to increase analgesic action except in the case of diacetylmorphine.

2. The phenolic hydroxyl group.

The decrease in activity accompanying methylation of this hydroxyl would indicate a definitely positive influence on the part of this substituent. Although its complete elimination would, perhaps, not entirely destroy the activity of the compound, it is probable that a serious impairment would result.

3. The N-methylated nitrogen-containing ring.

The reduced heterocyclic ring is apparently of major importance to the analgesic action of morphine. Opening of

this ring to give the methylmorphimethines results in nearly a complete loss of activity (68). Eliminating the ring entirely with the accompanying dehydrogenation yields morphenol (3-hydroxy-4,5-phenanthrylene oxide), the analgesic action of which is given in Table I of the preceding section. Normorphine, which differs from morphine only in the loss of the N-methyl group, is less toxic and also less active than morphine. The gain in activity produced by the N-methylation of a reduced nitrogen cycle is illustrated by the series of benzofuroquinolines reported in Table IX.

4. The point of attachment of the substituents to the nucleus.

The most advantageous position for the alcoholic hydroxyl in morphine is at the 6-position where it is found. Shifting it to the 8-position results in a lowering of the analgesic action. Its inhibiting influence is shown by the increase in analgesic effectiveness following its replacement by hydrogen. By analogy with phenanthrene, the location of the phenolic hydroxyl at the 3-position in morphine is probably the most effective in relation to the other substituents in the molecule.

That the unusual position of the nitrogen-containing chain of atoms between the 9- and 13-positions has considerable bearing upon the analgesic action of morphine might be

(68) Fränkel, Ref. 14. pp. 421 and 426.

inferred from the lack of analgesic action found in apomorphine, in which the point of attachment has been changed. In this case, however, the effect is obscured by the opening of the oxygen bridge to form a second phenolic hydroxyl and by the dehydrogenation of the hydroaromatic ring.

A compound very closely related to apomorphine in its chemical structure is pukateine (69), differing from it only in the absence of one hydroxyl and the presence of a methylenedioxy group in the other ring. Its analgesic activity, reported to be comparable to that of morphine, would lend support to the conclusion that the location of the side-chain at the 13-position is not a vital necessity except in the influence which any change might have upon the other parts of the molecule. It is surprising that this relatively simple modification of the apomorphine structure should result in such a contrast in the analgesic activity.

5. Spatial arrangements in the molecule.

The spatial arrangement of the alcoholic hydroxyl has a limited effect on the analgesic action of morphine and its derivatives. This is well illustrated by the variations in the minimal effective doses of the isomeric codeines and their dihydro-derivatives shown in Table III of the introductory section. A systematic variation is not apparent, however.

(69) This thesis, p. 35.

The effect of optical isomerism has been investigated recently by Goto and Takebe (70), who compared six levorotatory morphine derivatives with their optical antipodes, which were obtained from the dextrorotatory sinomenine. The dextro isomers were found to be convulsant poisons without analgesic action.

Whether factors such as those just enumerated will have a similar influence when applied to the dibenzofuran nucleus is an interesting speculation, but is one to which a decisive answer can scarcely be given from the data so far at hand. So few of the derivatives have shown analgesic action when tested with white mice that an adequate evaluation of the effect of structural changes can not be made. The effect of similar structural modifications when applied to analgesic derivatives of different nuclei is not always comparable. The variations encountered would lead one to believe that the result of any change, either beneficial or deleterious, is a characteristic property of each compound, and the outcome of an equivalent change in any other compound cannot be predicted with confidence. Hydrogenation of the methyl ethers of morphine increases their analgesic action. With the acetylmorphines the effect is quite the opposite. Methylation of the phenolic hydroxyl in morphine reduces its activity, yet

(70) Goto and Takebe, Proc. Imp. Acad. (Tokyo), 9, 390 (1933).

demethylation of papaverine causes a loss of its analgesic action. The pronounced change in effect accompanying the change from apomorphine to pukateine, essentially involving three hydroxyl groups, could scarcely have been forseen in the data accumulated for the hydroxyphenanthrenes.

The effect produced by a nucleus in conjunction with its substituents is illustrated by two of the dibenzofuran derivatives. 2-Methyldibenzofuro-[2,3-d]-imidazole (HD 54) was found to be analgesic, whereas its benzene analogue, 2-methylbenzimidazole, produces a light narcosis (71). 2-Aminobenzothiazole at first stimulates and then paralyzes the respiratory center and produces reflex excitability (72). The 2-aminodibenzofurothiazole (HD 52) is analgesic to some extent. Piperidinoethoxybenzene is a strong local anesthetic (73), however, its dibenzofuran equivalent, 4-piperidinoethoxydibenzofuran (HD 33), shows no analgesic action.

Aside from positional isomerism within the nucleus, the factors most likely to enhance the analgesic activity of dibenzofuran compounds are not clearly discernible. The effect of hydrogenation in some instances is apparently detrimental. Heterohydrogenation of 4-aminodibenzofuran (HD 25) to give the 6-amino-1,2,3,4-tetrahydrodibenzofuran (HD 49) destroys the

(71) Frankel, Ref. 14, p. 104.
(72) Bogert and Husted, J. Pharmacol., 45, 189 (1932).
(73) Brill, J. Am. Chem. Soc., 47, 1134 (1925).

analgesic action originally present. In Table IX it is seen that hydrogenation of the benzofuroquinolines tends towards a decrease in activity when present at first, although N-methylation accomplishes a recovery in activity. Analgesic action is shown by 1,2,3,4-tetrahydro-1-aminobrazan in which the amino group occurs in the alicylic ring. The pharmacology of the 4-amino-1,2,3,4-tetrahydrodibenzofuran when it becomes available will be of interest in relation to the action of these other similar derivatives.

The instances in the series of dibenzofuran compounds in which another substituent has been added to an analgesic derivative are not in sufficient number to readily indicate the most likely modification to be introduced. The analgesic 1-aminodibenzofuran (HD 51) loses its activity when a methoxyl group is substituted in the same ring <u>para</u> to the amine (HD 46). Conversely, 1-acetamino-4-ethoxydibenzofuran (HD 50) is more analgesic than 1-aminodibenzofuran. Whether the appearance of activity in this compound in contrast to the inactivity of 1-amino-4-methoxydibenzofuran (HD 46) is a result of the acetylation of the amine or the replacement of the methoxyl group by an ethoxyl can not be ascertained definitely from the available data. Acetylation of the 4-aminodibenzofuran (HD 25) gives the less analgesic 4-acetaminodibenzofuran (HD 26), an effect also observed with the phenanthrylamines (42). No difference between an ethoxyl and a methoxyl

group was found in the phenanthrene series (41), and ethylation of the phenolic hydroxyl in morphine produces the same effect on its analgesic action as methylation (50). Either an ethoxyl group is more effective than a methoxyl group in promoting analgesic action in dibenzofuran compounds, or the 1-acetamino-4-ethoxydibenzofuran represents a unique case in the series. The synthesis and comparison of 1-amino-4-ethoxydibenzofuran and 1-acetamino-4-methoxydibenzofuran would assist in deciding this point.

A general effect following the introduction of a methoxyl group into a compound is to decrease the toxicity. It is to be noticed, however, that in those cases where a comparison can be made, methylation of the free hydroxyl groups already present often serves to increase the toxicity. Examples of this effect are furnished by 4,6-dihydroxydibenzofuran (HD 27), 4-hydroxy-6-methoxydibenzofuran (HD 69) and 4,6-dimethoxydibenzofuran (HD 70); and also by 3-hydroxy-4-methoxydibenzofuran (HD 68) and 3,4-dimethoxydibenzofuran (HD 67). An exception is found in the 1,4-dihydro-6-hydroxydibenzofuran (HD 76) and 1,4-dihydro-6-methoxydibenzofuran (HD 74) in which methylation has decreased the toxicity somewhat.

Although toxicity values furnish a poor basis for predicting the possible occurrence of analgesic action in organic compounds, there is a point to be noticed in regard to the morphine derivatives. Quite often the result has been to in-

crease the toxicity to a certain degree when a modification has been introduced to yield a more powerfully analgesic material. Accordingly, if the analogy can be considered to extend to the dibenzofuran derivatives, it might be assumed that within reasonable limits modifications likely to increase the toxicity of the compound have a greater likelihood of inducing analgesic action or enhancing such action if already present. It would seem to be well worth while to investigate the introduction of free hydroxyl groups into the analgesic derivatives of dibenzofuran, since the phenolic hydroxyl of morphine is of definite benefit in its action.

It does not seem likely that any nitrogen-free compound of dibenzofuran will be found having significant analgesic action. With two exceptions all of the analgesic derivatives of dibenzofuran so far encountered have contained nitrogen either as a member of a cycle or as a basic substituent. The exceptions to this statement are the 2-propionyldibenzofuran and methyl-2-dibenzofurylcarbinol reported by Eddy (62) to be analgesic in relatively high dosages. Practically all of the effective analgesic compounds possess a nitrogen-containing group or cycle in conjunction with one or more hydroxyl groups, either free or substituted. Accordingly, the evidence would indicate the most fruitful course to be in the direction of more complex dibenzofuran derivatives containing one or more hydroxyl groups and fused to a nitrogen heterocycle. For

example, hydroxylated benzofuroquinolines might be expected to show greater analgesic activity than the unsubstituted compounds, especially after hydrogenation of the heterocycle and methylation of the imino group. Especial interest would, perhaps, accrue to derivatives in which preference is given to the 1-,4-,6- and 9-positions, since apparently these have a greater advantage over the other positions in the nucleus in promoting analgesic action. The accumulation of more data as to the relative effects of substituents and positional isomerism should yield results of definite interest and value.

EXPERIMENTAL

Preparation of 2-α-Aminoethyldibenzofuran Hydrochloride

The preparation of this compound from 2-acetyldibenzofuran by the Leuckart reaction (74) under the conditions employed by Wallach (75) in preparing primary amines from various ketones gave a poor yield of the desired amine. An improved general procedure has subsequently appeared (76) which might be used to better advantage.

A mixture of 10.5 g. (0.05 mole) of 2-acetyldibenzofuran, 20 g. of ammonium formate and 5 cc. of acetic acid contained in a 200 cc. balloon flask was heated by means of an oil bath to a bath temperature of 180-190° for seven hours. The viscous product was washed with water, taken up in alcohol and the alcoholic solution saturated with dry hydrogen chloride. After boiling a few minutes the solution was cooled and diluted with ether. The precipitated crude amine hydrochloride melted at 217-219°. Recrystallization from an acetone-alcohol mixture gave 1.0 g. of pure product (an 8% yield) melting at 222-223°. A recovery of 1.8 g. of 2-acetyldibenzofuran was made from the resinous by-product.

Anal. Calcd. for $C_{14}H_{13}ONCl$: N, 5.66. Found: N, 5.57 and 5.92.

(74) Leuckart, Ber., 18, 2341 (1885).
(75) Wallach, Ann. 343, 54 (1905).
(76) Ingersoll, et al, J. Am. Chem. Soc., 58, 1808 (1936).

Preparation of 2-α-Diethylaminoethyldibenzofuran

Crude methyl-2-dibenzofurylcarbinol (77) was obtained by adding a solution of 12.0 g. (0.27 mole) of acetaldehyde in 25 cc. of ether to the ice-cold Grignard solution prepared from 50 g. (0.2 mole) of 2-bromodibenzofuran and 5.5 g. (0.2 atom) of magnesium in a mixture of 300 cc. of ether and 25 cc. of benzene. After warming to room temperature the solution was refluxed for fifteen minutes and then hydrolyzed with ice and dilute hydrochloric acid. The ether solution was decanted from an insoluble gummy residue, dried and evaporated under reduced pressure. Thirty-six grams of an oil remained which could not be induced to crystallize.

Dry hydrogen bromide was bubbled through the crude product at 100° for an hour. The washed and dried product could not be crystallized and an attempted distillation under reduced pressure produced decomposition and was immediately discontinued. Twenty grams of the crude bromo-compound was heated three and one-half hours at 100° with 20 g. of diethylamine in a pressure bottle. The cooled mixture was made alkaline with 5% sodium hydroxide solution, extracted with ether and the ether extract dried and distilled under reduced pressure. A second distillation yielded a clear, colorless oil which was

(77) This compound has been prepared by Mosettig and Robinson, J. Am. Chem. Soc., 57, 2186 (1935), by the catalytic hydrogenation of 2-acetyldibenzofuran. Melting point (corr.) 63-64°.

characterized as the picrate. The picrate, precipitated from an aqueous solution of the hydrochloride by adding a saturated solution of picric acid, was purified by crystallizing from aqueous acetone and melted at 173-174°.

Anal. Calcd. for $C_{24}H_{24}O_8N_4$: N, 11.29. Found: N, 11.45.

The hydrochloride and hydrobromide salts of the compound were so extremely hygroscopic they could not be handled in the open air.

Preparation of 1-Bromo-4-methoxydibenzofuran

A solution of 27.5 g. (0.17 mole) of bromine in 170 cc. of acetic acid was added in several portions to a solution of 34 g. (0.17 mole) of 4-methoxydibenzofuran in 340 cc. of acetic acid at room temperature with shaking. Decolorization was immediate. After standing over night the product was thrown out of solution by diluting with water and filtered off. Crystallization from 95% ethyl alcohol gave 42 g. or an 88% yield of material melting at 96-97°. A second recrystallization gave the pure product melting at 97-97.5° which showed no depression in melting point when mixed with the material obtained by P. R. VanEss (78) from the methylation of 1-bromo-4-hydroxydibenzofuran. Mr. VanEss has amply demonstrated that the bromination of 4-hydroxydibenzofuran takes place

(78) P. R. VanEss, Doctoral Dissertation, Iowa State College, 1936, pp. 15 and 16.

in either the 1- or 9-position (78). Although it has not been experimentally proven, the positive nature of the hydroxyl group leaves little doubt but that homonuclear substitution occurs in this instance.

Preparation of 4-Methoxy-1-dibenzofurancarboxylic Acid

The Grignard reagent prepared from 5 g. (0.018 mole) of 1-bromo-4-methoxydibenzofuran and 0.5 g. (0.02 atom) of magnesium in a mixture of 25 cc. of ether and 10 cc. of benzene was carbonated in the customary manner. The crude product was purified by crystallizing from alcohol. A yield of 2.7 g. (62% of theoretical) of the pure compound was obtained melting at 279-280° with decomposition.

Anal. Calcd. for $C_{14}H_{10}O_4$: C, 69.40; H, 41.6. Found: C, 69.67 and 69.00; H, 4.61 and 4.90.

Preparation of 1-β-Hydroxyethyl-4-methoxydibenzofuran

The Grignard reagent from 22.2 g. (0.08 mole) of 1-bromo-4-methoxydibenzofuran and 2.2 g. of magnesium filings (40-100 mesh) was prepared in a mixture of 100 cc. of ether and 25 cc. of benzene in the customary manner. To the ice-cold solution of the Grignard reagent was added 8.0 g. (0.18 mole) of ethylene oxide through a dropping funnel. The solution was allowed to warm up to room temperature and then refluxed for one hour. After standing over night, most of the ether was distilled off and replaced by dry benzene, and refluxing continued for one

hour. The resulting mixture was hydrolyzed by ice and 30% sulfuric acid, and the benzene layer was washed with sodium carbonate solution, dried and distilled under reduced pressure. The material distilled as a viscous oil between 195-206°/2 mm., eventually solidifying in the receiver. The product weighed 11.5 g. equivalent to a 59% yield. Recrystallization from petroleum ether (b.p. 60-68°) gave a pure crystalline product melting at 96-96.5°.

Anal. Calcd. for $C_{15}H_{14}O_3$: C, 74.35; H, 5.85. Found: C, 74.42; H, 6.03.

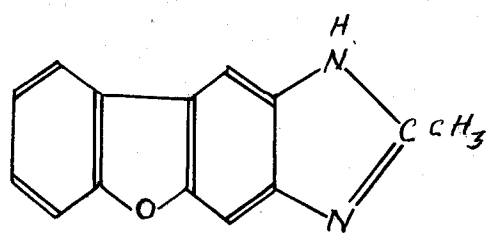
Preparation of 1-β-Diethylaminoethyl-4-methoxydibenzofuran Hydrochloride

Dry hydrogen bromide was slowly bubbled through 8.8 g. (0.028 mole) of molten 1-β-hydroxyethyl-4-methoxydibenzofuran for two and one-half hours at 100°. After washing with water, the dark, oily product was dissolved in hot alcohol and the solution cooled. A crystalline product separated which, after recrystallizing from ethyl alcohol, weighed 2.0 g. and melted at ~~191-191.5°~~ 91-91.5°. Dilution of the mother liquor with water precipitated an oil which soon resinified to a hard amorphous product insoluble in the usual organic solvents. This material was not further investigated. The product melting at ~~191-191.5°~~ 91-91.5° was used directly in the preparation of the amine without further characterization.

The 2.0 g. (0.0066 mole) of the 1-β-bromoethyl-4-methoxydibenzofuran was mixed with 2.0 g. (0.016 mole) of diethylamine and 2 cc. of alcohol in a pressure bottle and heated for six hours at 100°. When cool the reaction product was treated with 5% sodium hydroxide solution and extracted with ether. The ether solution was evaporated and the residue warmed to drive off the excess diethylamine. Saturating an ether solution of the residual oil with dry hydrogen chloride precipitated the salt which was purified by recrystallizing from an acetone-ether mixture. The yield was 1.5 g. of the hydrochloride melting at 187° with decomposition. This is a 68% yield based on the amount of bromo-compound used.

Anal. Calcd. for $C_{19}H_{24}O_2NCl$: N, 4.20. Found: N, 4.26 and 4.43.

Preparation of 2-Methyldibenzofuro-[2,3-d]-imidazole



This compound was prepared from 2-nitro-3-acetaminodibenzofuran. Some modifications in the procedure for obtaining this intermediate were found to be more convenient than that

given elsewhere (79). 3-Aminodibenzofuran was monoacetylated by adding 12 g. (0.12 mole) of acetic anhydride to a solution of 20 g. (0.11 mole) of 3-aminodibenzofuran in a mixture of 150 cc. of acetic acid and 200 cc. of water at a temperature between 40 and 50° with vigorous stirring. A thick, heavy precipitate resulted in a few seconds which was poured into water and filtered off to give a 97% yield of material suitable for nitration.

Nitration was effected by adding 3.5 cc. of fuming nitric acid (sp.g. 1.50) to a solution of 10 g. (0.04 mole) of 3-acetaminodibenzofuran in 60 cc. of glacial acetic acid at 85-90°. The 2-nitro-3-acetaminodibenzofuran separated almost at once. The mixture was poured into an excess of water and filtered. Crystallizing the crude product from acetic acid yielded 9.2 g. or 76% of light yellow crystals melting at 196° (80).

To a hot solution of 2.0 g. (0.0074 mole) of 2-nitro-3-acetaminodibenzofuran in 25 cc. of acetic acid was cautiously added in several portions with shaking a solution of 8.0 g. (0.035 mole) of hydrated stannous chloride in 8.0 cc. of concentrated hydrochloric acid and the solution heated on a hot plate for a few minutes. The solution became colorless and a

(79) W. H. Kirkpatrick, Doctoral Dissertation, Iowa State College, 1935, pp. 68 and 69.
(80) Gilman, Brown, Bywater and Kirkpatrick, J. Am. Chem. Soc., 56, 2473 (1934).

voluminous precipitate quickly formed. The mixture was poured into twice its volume of water and made strongly alkaline with 30% sodium hydroxide solution. The undissolved residue was filtered off and to ensure completion of the reaction it was refluxed five hours with 45 cc. of acetic acid. The solution was diluted with water and made alkaline with dilute sodium hydroxide solution. The precipitated crude imidazole was purified through its hydrochloride by recrystallizing from dilute hydrochloric acid. The hydrochloride melting above 335° was converted to the free base which melts at 270°. The yield of pure product was 0.9 g. or 55%.

Anal. Calcd. for $C_{14}H_{10}ON_2$: N, 12.61. Found: N, 12.79 and 12.87.

Acetylation of 4-Methoxydibenzofuran

A solution of 10.0 g. (0.05 mole) of 4-methoxydibenzofuran in 50 cc. of carbon disulfide was placed in a 200 cc. three-necked flask fitted with a mercury-sealed stirrer, dropping funnel and reflux condenser. The flask was immersed in a water bath at room temperature and 6.8 g. (0.05 mole) of aluminum chloride was added followed by 4.0 g. (0.05 mole) of acetyl chloride. The mixture was stirred for one and one-half hours at room temperature and then refluxed gently for forty-five minutes. The solution was then poured on ice and the carbon disulfide layer separated and evaporated. One recrystallization of the crude material from ethanol gave 8.0 g.

(66%) of product melting at 132-133°. A second recrystallization gave the pure compound melting at 134-134.5°.

Anal. Calcd. for $C_{15}H_{12}O_3$: C, 74.97; H, 5.04. Found: C, 74.66 and 75.30; H, 5.42 and 5.39.

Oxidation of 1 g. (0.004 mole) of this compound in 130 cc. of water containing 2 g. of sodium hydroxide with 3 g. (0.019 mole) of potassium permanganate gave a 90% yield of material which did not depress the melting point when mixed with the 4-methoxydibenzofurancarboxylic acid obtained from the 1-bromo-4-methoxydibenzofuran.

Preparation of 1-Acetyl-4-methoxydibenzofuran Oxime

To a solution of 5 g. (0.02 mole) of 1-acetyl-4-methoxydibenzofuran in 75 cc. of alcohol was added a solution of 5 g. (0.11 mole) of potassium hydroxide in 10 cc. of water and a solution of 1.9 g. (0.027 mole) of hydroxylamine hydrochloride in 5 cc. of water, and the mixture refluxed for five hours. The solution was poured into several times its volume of water and the precipitate collected by filtration. The crude material melted at 173-175°, and weighed 4.7 g. equivalent to an 88% yield. Recrystallization from alcohol gave the pure oxime, melting at 176-177.5°.

Anal. Calcd. for $C_{15}H_{13}O_3N$: N, 5.49. Found: N, 5.44 and 5.58.

Beckmann Rearrangement of 1-Acetyl-4-methoxydibenzofuran Oxime

To a slightly warm suspension of 2 g. (0.0074 mole) of 1-acetyl-4-methoxydibenzofuran oxime in 25 cc. of dry benzene was added cautiously in several portions 2 g. (0.0096 mole) of phosphorous pentachloride. Heat was evolved and a dark, greenish-colored solution resulted. After standing several minutes the solution was poured on ice, made alkaline with 10% sodium carbonate solution, and then just acid with acetic acid. The benzene was steam distilled off and the solid residue collected by filtration. The crude material weighed 1.9 g. equivalent to a 95% yield and recrystallization from alcohol gave the pure 1-acetamino-4-methoxydibenzofuran melting at 222-223°.

Anal. Calcd. for $C_{15}H_{13}O_3N$: N, 5.49. Found: N, 5.43 and 5.47.

Refluxing a solution of 2 g. (0.008 mole) of the 1-acetamino-4-methoxydibenzofuran in 200 cc. of 95% alcohol with 50 cc. of concentrated hydrochloric acid gave a 91% yield of 1-amino-4-methoxydibenzofuran hydrochloride. The free base melting at 103-104° showed no depression in melting point when mixed with the 1-amino-4-methoxydibenzofuran obtained by Mr. A. L. Jacoby from the reduction of 1-nitro-4-methoxydibenzofuran (81).

(81) Unpublished work by Mr. A. L. Jacoby.

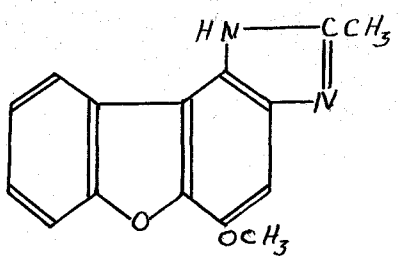
Nitration of 1-Acetamino-4-methoxydibenzofuran

Eight-tenths of a gram (0.003 mole) of 1-acetamino-4-methoxydibenzofuran was dissolved in 35 cc. of glacial acetic acid at 30-35°. One cubic centimeter of fuming nitric acid (sp.g. 1.50) was added and the solution shaken. In a few seconds crystals began to appear and the nitro-compound rapidly separated out with a slight evolution of heat. The mixture was allowed to stand for five minutes, then poured into an excess of water and filtered. Nine-tenths of a gram of crude material melting at 240-242° was obtained. Two recrystallizations from acetic acid gave a 74% yield of the pure mononitro-compound melting at 244°.

Anal. Calcd. for $C_{15}H_{12}O_5N_2$: N, 9.33. Found: N, 9.30 and 9.69.

That nitration took place at the 2-position, ortho to the acetamino group, is shown in the following preparations by which the compound in one case was converted to an imidazole, and in the other instance the acetamino group was eliminated (two steps) to give a nitro-4-methoxydibenzofuran differing from the known 3-nitro-4-methoxydibenzofuran (81).

Preparation of 2-Methyl-5-methoxydibenzofuro-[1,2-d]-imidazole



To a hot solution of 3.0 g. (0.01 mole) of 1-acetamino-2-nitro-4-methoxydibenzofuran in 75 cc. of glacial acetic acid was added in several portions a solution of 12.5 g. (0.055 mole) of hydrated stannous chloride in 13.5 cc. of concentrated hydrochloric acid. The mixture was then refluxed five and one-half hours on the hot plate. After diluting with 200 cc. of water the solution was made alkaline with 33% sodium hydroxide solution and the precipitate filtered off. The crude material was purified by boiling its methanol solution with Norite and saturating the cooled solution with dry hydrogen chloride. The hydrochloride precipitated in fine needles melting at 306-307° with decomposition. From the hydrochloride was obtained the pure free base in a yield of 1.8 g. or 72.5% melting at 222-222.5°.

Anal. Calcd. for $C_{15}H_{12}O_2N_2$: N, 11.10. Found: N, 10.95 and 11.16.

Preparation of 1-Amino-2-nitro-4-methoxydibenzofuran

A suspension of 1.4 g. (0.0047 mole) of 1-acetamino-2-nitro-4-methoxydibenzofuran in a mixture of 35 cc. of alcohol and 15 cc. of concentrated hydrochloric acid was refluxed for two and one-half hours. An additional 8 cc. of hydrochloric acid was then added and the treatment repeated. The 1-amino-2-nitro-4-methoxydibenzofuran separated out of the reaction mixture as a red, crystalline material in a quantitative yield melting at 205-207°. Recrystallization from toluene gave a

pure product melting at 206-207°.

Anal. Calcd. for $C_{13}H_{10}O_4N_2$: N, 10.85. Found: N, 10.36 and 10.70.

Preparation of 2-Nitro-4-methoxydibenzofuran

Because of the insolubility of the 1-amino-2-nitro-4-methoxydibenzofuran, diazotization could not be accomplished by the ordinary means. DeMilt and Van Zandt (82) have developed a method for diazotizing insoluble and weakly basic amines, and use was made of their procedure.

A mixture of 15 cc. of concentrated sulfuric acid and 7.5 cc. of water was cooled to 5° in an ice bath. Six-tenths of a gram (0.009 mole) of sodium nitrite was added and the mixture was warmed gently on the steam bath until a clear solution had resulted. This solution was cooled to 5-10° and a solution of 0.6 g. (0.0023 mole) of the 1-amino-2-nitro-4-methoxydibenzofuran in 12 cc. of pyridine was added dropwise over a period of forty-five minutes with continuous shaking. The temperature was maintained below 10° at all times. Following the addition of the pyridine solution the reaction was allowed to stand at this temperature for one-half hour and then stirred into 50 g. of ice. To remove the excess of nitrous acid, 0.6 g. of urea was added and the mixture stirred until foaming had ceased. Fifteen cubic centimeters of ethyl

(82) DeMilt and Van Zandt, J. Am. Chem. Soc., 58, 2044 (1936).

alcohol was added and the clear solution was refluxed for five minutes on the hot plate. When cool, the red-brown precipitate was repeatedly recrystallized from methanol until a constant melting point was reached. A 35% yield of the 2-nitro-4-methoxydibenzofuran as light yellow, feathery needles was obtained melting at 185-186°.

Anal. Calcd. for $C_{13}H_9O_4N$: N, 5.76. Found: N, 5.72 and 5.66.

Preparation of 2-Amino-4-methoxydibenzofuran

A suspension of 0.1 g. of the 2-nitro-4-methoxydibenzofuran in 25 cc. of alcohol was reduced at room temperature under forty-five pounds gage pressure of hydrogen using Raney nickel as a catalyst. The solution of the amine was filtered to remove the catalyst, and evaporated under reduced pressure. The residual oil was dissolved in ether and the hydrochloride precipitated with dry hydrogen chloride. The free base precipitated from an aqueous solution of the hydrochloride was recrystallized from alcohol. The amine was obtained in fine slightly colored crystals melting at 127-127.5°.

Anal. Calcd. for $C_{13}H_{11}O_2N$: N, 6.57. Found: N, 6.74.

Preparation of 3-Dibenzofurylurea

Various substituted ureas have been reported to have hyp-

notic and anesthetic properties (83). It was thought to be of interest to prepare a dibenzofuran derivative of urea to determine whether such effects or possibly an analgesic action might be present. The compound proved to be insufficiently soluble in any solvent suitable for administration and was not submitted to test.

A solution of 9.15 g. (0.05 mole) of 3-aminodibenzofuran and 6.0 g. (0.057 mole) of nitrourea in 150 cc. of alcohol (84) was allowed to stand at room temperature. A pearly, crystalline precipitate of pure 3-dibenzofurylurea had settled at the end of two days weighing 7.5 g., equivalent to a yield of 66.5%. In a capillary tube the material shows signs of softening at 215-220°, but does not melt up to 325°. On a nickel block the substance melts and resolidifies immediately (formation of biuret derivative) at 222-223°.

Anal. Calcd. for $C_{13}H_{10}O_2N_2$: N, 12.38. Found: N, 12.65 and 12.52.

Preparation of 2-β-Dimethylaminopropionyldibenzofuran

This compound was prepared by condensing 2-acetyldibenzofuran with trioxymethylene and dimethylamine hydrochloride by a procedure employed by Mannich and Lammering (85) in similar

(83) Buck, Hjort and deBeer, J. Pharmacol., 54, 188 (1935). Hjort, deBeer, Buck and Ide, ibid, 55, 152 (1935).
(84) Buck and Ferry, J. Am. Chem. Soc., 58, 854 (1936), have found the reaction between amines and nitrourea to yield better results in alcohol than in aqueous solution.
(85) Mannich and Lammering, Ber., 55, 3510 (1922).

syntheses.

A mixture of 20.0 g. (0.095 mole) of 2-acetyldibenzofuran, 7.8 g. (0.096 mole) of dimethylamine hydrochloride and 3.0 g. (0.096 mole) of trioxymethylene suspended in 40 cc. of absolute ethanol was heated on the steam bath for twelve hours. When cool the precipitate was filtered off and the filtrate evaporated. The combined residues were shaken with ether to remove unchanged 2-acetyldibenzofuran. The ether-insoluble crude 2-β-dimethylaminopropionyldibenzofuran hydrochloride weighing 21.4 g. (a 74% yield) was purified by recrystallizing from alcohol several times. The pure hydrochloride melts at 195-196°. The free base was obtained by adding dilute ammonium hydroxide to an aqueous solution of the salt. Recrystallized from petroleum ether (b.p. 60-68°) the free base melted at 88-89°.

Anal. Calcd. for $C_{17}H_{17}O_2N$: N, 5.24. Found: 5.30

Preparation of 1-(4-Dibenzofuryl)-isoquinoline

The procedure given here is patterned after that used by Ziegler and Zeiser (86) for preparing 1-n-butylisoquinoline.

A solution of n-butyl-lithium prepared from 27.4 g. (0.2 mole) of n-butyl bromide and 2.8 g. (0.4 atom) of lithium in 300 cc. of ether was refluxed with 30 g. (0.18 mole) of dibenzofuran under a nitrogen atmosphere for four and one-half

(86) Ziegler and Zeiser, Ann., 485, 174 (1931).

hours. The resulting solution of 4-dibenzofuryl-lithium was cooled to 0-5° in an ice bath and 19.3 g. (0.15 mole) if isoquinoline in 50 cc. of dry ether was added through a dropping funnel over a period of twenty minutes with stirring. A light yellow precipitate was formed immediately. The cold mixture was hydrolyzed with 5 cc. of water and the ether distilled off under nitrogen. The residue was refluxed for ten minutes with 150 g. of nitrobenzene to oxidize the dihydro-compound to the isoquinoline derivative and then steam distilled to remove the nitrobenzene. The crude product was taken up in ether, washed with water and the ether solution extracted several times with dilute hydrochloric acid. The addition of ammonium hydroxide to the acid solution deposited an oily precipitate which was subjected to steam distillation to remove the isoquinoline present. Several recrystallizations from ethyl alcohol gave 5.0 g. of the pure base melting at 137-138°. Based on the isoquinoline used this is an 11.3% yield.

Anal. Calcd. for $C_{21}H_{13}ON$: N, 4.74. Found: N, 4.83 and 4.82.

The hydrochloride of this compound is immediately hydrolyzed in water.

Preparation of 3-Amino-2-dibenzofurylthiocyanate

A simple method for the thiocyanogenation of aromatic

amines has been reported by Kaufmann and Oehring (87) using thiocyanogen prepared *in situ* in acid solution. The thiocyanate group enters the ring *para* to the amine unless that position is blocked, in which case it substitutes *ortho* to the amine. Depending upon the conditions employed, the thiazoles can either be prepared directly or the first formed o-aminothiocyanate compound can be subsequently rearranged to the corresponding thiazole. A number of substituted benzo- and naphthothiazoles have been prepared by Kaufmann (88) using this procedure, and Brewster and Dains (89) have shown that N-alkylamines also undergo this reaction to yield alkylated thiazoles.

A run carried out at a temperature of 5-10° gave a mixture of products which proved difficult to separate and purify. The second run, which is described in the following procedure was made at a lower temperature with better results.

Five grams (0.027 mole) of 3-aminodibenzofuran and 8.5 g. (0.11 mole) of ammonium thiocyanate were dissolved in 400 cc. of 95% acetic acid and cooled to 1-3°. A solution of 4.3 g. of bromine in 25 cc. of acetic acid was then added dropwise over a period of fifteen minutes to the vigorously stirred mixture. Despite the addition of 100 cc. more of 95% acetic

(87) Kaufmann and Oehring, *Ber.*, *59*, 187 (1926).
(88) Kaufmann, *Arch. Pharm.*, *266*, 197 (1928).
(89) Brewster and Dains, *J. Am. Chem. Soc.*, *58*, 1364 (1936).

acid a complete solution could not be maintained at this temperature and towards the end of the bromine addition the mixture became a thick sludge. The mixture was immediately poured into 1200 cc. of water and the precipitate filtered off and washed with water. The crude material was dissolved in hot alcohol, in which it is slowly soluble. When cool, 2.8 g. or a 43% yield of slightly crude 3-aminodibenzofurylthiocyanate gradually separated out. Further recrystallization gave the pure product melting at 175° with immediate resolidification.

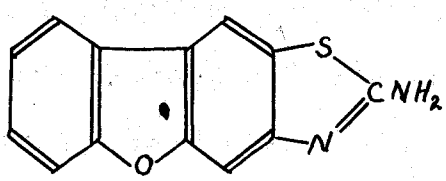
Anal. Calcd. for $C_{13}H_8OSN_2$: N, 11.66. Found: N, 11.88 and 11.62.

That this compound is the thiocyanate and not the thiazole derivative was indicated by its resolidification upon melting (rearrangement to thiazole), and also by the yellow precipitate which forms upon adding an alkaline lead tartrate solution to an alcoholic solution of the compound (90), a reaction characteristic of the thiocyanates. The thiazole compound under the same conditions gives a white precipitate.

Whether the thiocyanate group entered the 2- or the 4-position was not proven experimentally. However, it is to be expected that thiocyanogenation would occur at the 2-position similar to bromination, which has been shown to take place at the 2-position ortho to the amine group (80). The compound is most probably 3-amino-2-dibenzofurylthiocyanate.

(90) Söderbäck, Ann., 443, 156 (1925).

Preparation of 2-Aminodibenzofuro-[3,2-d]-thiazole



Rearrangement of the 3-amino-2-dibenzofurylthiocyanate to the thiazole compound was effected by refluxing its alcoholic solution with hydrochloric acid for one-half hour. A quantitative yield of the crude compound was obtained which was recrystallized several times from benzene to give the pure product melting at 268-269°.

Anal. Calcd. for $C_{13}H_8OSN_2$: N, 11.66. Found: N, 11.64 and 11.68.

The hydrochloride, precipitated from an ether solution of the base by dry hydrogen chloride, decomposes above 300°.

Preparation of β-2-Dibenzofuroylpropionic Acid

This compound was reported by Mayer and Krieger (91), but the method by which it was obtained was not given. The following procedure is based on the one used by Fieser and Hershberg (92) for the Friedel-Crafts reaction of succinic anhydride with phenol ethers.

Dibenzofuran, 84.0 g. (0.5 mole), and succinic anhydride,

(91) Mayer and Krieger, Ber., 55, 1659 (1922).
(92) Fieser and Hershberg, J. Am. Chem. Soc., 58, 2314 (1936).

55.0 g. (0.55 mole), were suspended in a mixture of 400 cc. of tetrachloroethane and 200 cc. of nitrobenzene contained in a three-necked flask fitted with a stirrer and immersed in an ice bath. With the temperature of the mixture held at 0-5°, 147.0 g. (1.1 moles) of powdered aluminum chloride was added in small portions over a period of an hour with vigorous stirring. Stirring was continued for four hours at this temperature and the reaction packed in ice over night. The reaction was again stirred for eight hours at 0-5° and then hydrolyzed by adding 250 g. of ice and 150 cc. of concentrated hydrochloric acid. The temperature was held below 25° during hydrolysis. The resulting mixture was subjected to steam distillation until a soft cake had formed in the flask and about 450 cc. of the mixed solvents had been removed. The aqueous layer was decanted from the residue in the flask and the cake washed by decantation. Forty-five grams of sodium carbonate in approximately 300 cc. of water was then added and the steam distillation continued until the remainder of the nitrobenzene and tetrachlorethane had been carried over. The residue was filtered and extracted several times with hot sodium carbonate solution until all soluble material had been removed. The combined filtrates were acidified with dilute hydrochloric acid and the dried precipitate recrystallized from ethyl acetate to give 111 g. or an 83% yield of the purified compound which melts at 185-186° in agreement with the

value reported by Mayer and Krieger (91).

Preparation of γ-2-Dibenzofurylbutyric Acid

For the reduction of the dibenzofuroylpropionic acid, the modified Clemmensen method reported by Martin (93) was employed.

Fifty-five grams of β-2-dibenzofuroylpropionic acid was suspended in a mixture of 100 cc. of toluene, 75 cc. of water and 175 cc. of concentrated hydrochloric acid, and refluxed for twenty-five hours with 100 g. of amalgamated zinc. Three additional 50 cc. portions of concentrated hydrochloric acid were added at approximately six hour intervals. The toluene was steam distilled off and when cool the residual cake was broken up and filtered off. Crystallization from petroleum ether (b.p. 80-100°) gave 43.6 g. or an 83% yield of the purified compound. The pure material melts at 112-113° in agreement with the melting point reported in the literature (91).

Cyclization of γ-2-Dibenzofurylbutyric Acid

Attempted cyclization of this compound with stannic chloride gave erratic results. Because of the ease with which dibenzofuran undergoes sulfonation, the use of sulfuric acid as the agent in this procedure required considerable experimentation to determine the most favorable conditions of temperature and concentration. The procedure giving the best

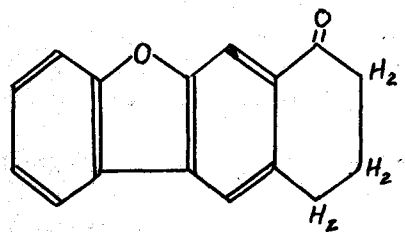
(93) Martin, J. Am. Chem. Soc., 58, 1438 (1936).

yields is the one following.

Five grams (0.02 mole) of γ-2-dibenzofurylbutyric acid was stirred into 100 g. of 88% sulfuric acid and the mixture allowed to stand at room temperature for fifteen minutes. The resulting deep-red solution was poured on ice and the dilute acid decanted from the precipitate. The crude material was washed by decantation and warmed with 50 cc. of 10% sodium carbonate solution. The insoluble product was filtered off and recrystallized from alcohol to give 2.0 g. or a 45% yield of pure ketotetrahydrobrazan melting at 137°.

Anal. Calcd. for $C_{16}H_{12}O_2$: C, 81.32; H, 5.12. Found: C, 81.53; H, 5.56.

Only one product was isolated from this reaction. Depending upon the position involved in the ring-closure, there are two isomeric brazan derivatives possible. If ring-closure has taken place at the 3-position, the product will be the 1-keto-1,2,3,4-tetrahydro-β-brazan (I), otherwise it must be the 1-keto-1,2,3,4-tetrahydro-γ-brazan (II) in which closure has been effected through the 1-position. Present data as to the orientation of dibenzofuran derivatives with ortho and para directing substituents in the 2-position indicate that either compound may be expected, and no experimental determination of the position assumed by the newly-formed ring was made.



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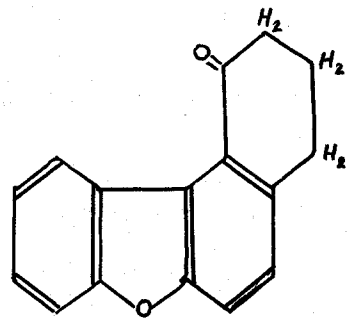

II

Preparation of the Oxime of 1-Keto-1,2,3,4-tetrahydro-β(orγ)-brazan

A solution of 1.0 g. (0.0043 mole) of the brazan derivative in 25 cc. of alcohol was refluxed five hours with 0.33 g. (0.0048 mole) of hydroxylamine hydrochloride and 1.0 cc. of 50% potassium hydroxide solution. The solution was poured into water and acidified with acetic acid. Crystallizing the precipitate from alcohol gave an 85% yield of the pure oxime melting at 212-213°.

Anal. Calcd. for $C_{16}H_{13}O_2N$: N, 5.58. Found: N, 5.48.

Preparation of 1-Amino-1,2,3,4-tetrahydro-β(orγ)-brazan Hydrochloride

Fifty grams of freshly prepared 2% sodium amalgam was added in small portions over a period of one and one-half hours to a well stirred solution of 1.7 g. (0.007 mole) of the 1-keto-1,2,3,4-tetrahydrobrazan oxime in 65 cc. of abso-

lute alcohol at a temperature of 55-60°. The solution was constantly maintained slightly acid by the dropwise addition of acetic acid. When reduction was complete the solution was decanted away from the mercury into several times its volume of water. The solution was made acid to litmus with acetic acid and extracted once with ether. The ether extract was discarded and the aqueous layer was made alkaline with dilute sodium hydroxide solution and extracted twice with ether. The ether extracts were dried, and dry hydrogen chloride passed into the solution. The crude amine hydrochloride resulting was purified by crystallizing from an alcohol-ether mixture. The pure hydrochloride was obtained in a 54% yield and melted at 266-267°.

Anal. Calcd. for $C_{16}H_{16}ONCl$: N, 5.12. Found: N, 4.95 and 5.23.

Preparation of 1-Keto-2-dimethylaminomethyl-1,2,3,4-tetrahydro-β(orγ)-brazan Hydrochloride

The method of Mannich and Braun (94) for preparing amino ketones as modified by Burger and Mosettig (95) was employed for this synthesis.

A suspension of 2.4 g. (0.01 mole) of the 1-keto-1,2,3,4-tetrahydrobrazan, 1.0 g. (0.012 mole) of dimethylamine hydro-

(94) Mannich and Braun, Ber., 53, 1874 (1920).
(95) Burger and Mosettig, J. Am. Chem. Soc., 58, 1570 (1936).

chloride and 0.9 g. (0.03 mole) of trioxymethylene in 25 cc. of amyl alcohol was refluxed for five minutes. A clear solution was formed at the end of this time and a few drops of alcoholic hydrogen chloride solution were added to depolymerize the excess trioxymethylene. When cool the solution solidified to a crystalline mass. This was diluted with double its volume of ether and extracted twice with dilute hydrochloric acid. The addition of dilute ammonium hydroxide to the acid extract precipitated the free base. Dry hydrogen chloride was passed into an ether solution of the base, and the precipitated hydrochloride purified by carefully reprecipitating it several times from an absolute alcoholic hydrogen chloride solution with ether. The salt formed lustrous prisms melting at 185-186°. The yield of pure compound was 0.45 g. or 14.3% of theoretical.

Anal. Calcd. for $C_{18}H_{18}O_2NCl$: N, 4.43. Found: N, 4.39

A repetition of this procedure with a longer time of refluxing gave no improvement in the yield.

Acetylation of 3-Nitrodibenzofuran

Mr. J. C. Bailie in this laboratory found that 3-nitrodibenzofuran could be successfully acetylated by a Friedel-Crafts reaction. Oxidation of the acetyl derivative gave the same acid as that obtained from the nitration and hydrolysis of 2-carbomethoxydibenzofuran. Since meta-directing groups in the 2- and 3-positions of dibenzofuran enforce heteronu-

clear substitution there is little doubt but that the acetyl derivative is the 2-acetyl-7-nitrodibenzofuran.

In repeating this preparation it was found that by using an excess of acetyl chloride in the reaction an excellent yield of product could be obtained.

A suspension of 56 g. (0.26 mole) of 3-nitrodibenzofuran in 400 cc. of nitrobenzene contained in a three-necked flask was cooled to 0-5° in an ice bath and 53 g. (0.4 mole) of powdered aluminum chloride was added. The flask was fitted with a stirrer and 33 g. (0.42 mole) of acetyl chloride was added dropwise through a dropping funnel. Stirring was continued for one hour at the temperature of the ice bath and then continued for ten hours while the reaction was allowed to warm up to room temperature. After standing overnight the reaction mixture was poured into a mixture of 300 g. of ice and 100 cc. of concentrated hydrochloric acid. The aqueous layer was decanted from the resulting gelatinous precipitate and nearly all of the nitrobenzene was removed by steam distillation. Complete removal of the solvent was effected by shaking the residue with methanol, filtering and washing the material with an additional small quantity of methanol. The crude product weighed 62 g., equivalent to a 93.5% yield, and melted at 208-210°. Crystallization from acetic acid gave the pure compound melting at 212-213°. The material was washed with dilute ammonium hydroxide and thoroughly dried before using in

the following procedure.

Preparation of 2-Acetyl-7-aminodibenzofuran

Providing the nitro-compound used in this preparation has been washed with dilute ammonium hydroxide and thoroughly dried it is easily hydrogenated with Raney nickel catalyst.

Twenty grams (0.079 mole) of 2-acetyl-7-nitrodibenzofuran suspended in 150 cc. of absolute ethanol was reduced with hydrogen at steam temperature under forty-five pounds gage pressure using approximately 10 cc. of an alcoholic suspension of Raney nickel catalyst. Reduction required about an hour and gave practically a quantitative yield of the crude amine melting at 156°. After recrystallization from alcohol the pure product melted at 158-159°.

Anal. Calcd. for $C_{14}H_{11}O_2N$: N, 6.22. Found: N, 6.26 and 6.54.

Preparation of 2-Acetyl-7-acetaminodibenzofuran

A nearly quantitative yield of the crude monoacetamino-compound was obtained by adding 8.7 g. (0.08 mole) of acetic anhydride to a well stirred solution of 15.3 g. (0.068 mole) of the 2-acetyl-7-aminodibenzofuran in 150 cc. of acetic acid diluted with 35 cc. of water at 25-30°. The acetamino-compound, which precipitates immediately, was filtered off and recrystallized from alcohol and finally from benzene to yield cotton-like needles melting at 203°.

Anal. Calcd. for $C_{16}H_{13}O_3N$: N, 5.24. Found: N, 5.32.

A portion of this compound was converted to the oxime to make certain that reduction of the ketone group had not occurred in the preceding hydrogenation. A solution of 0.5 g. of potassium hydroxide in 5 cc. of water was added to a solution of 1.35 g. (0.005 mole) of the 2-acetyl-7-acetaminodibenzofuran and 0.5 g. (0.007 mole) of hydroxylamine hydrochloride in 75 cc. of alcohol. After four and one-half hours of refluxing the solution was poured into water and the precipitate filtered off. Crystallization from alcohol gave colorless crystals melting at 203° in a 64% yield. A mixed melting point with the starting material melted at 176-178°.

Anal. Calcd. for $C_{16}H_{14}O_3N_2$: N, 9.92. Found: N, 9.92.

Nitration of 2-Acetyl-7-acetaminodibenzofuran

A solution of 5.4 g. (0.02 mole) of 2-acetyl-7-acetaminodibenzofuran in 120 cc. of glacial acetic acid was heated on the steam bath with stirring, and 6 cc. of fuming nitric acid (sp.g. 1.50) was added in one portion. Stirring and heating were continued for fifteen minutes and the mixture was cooled. A yellow crystalline precipitate consisting of practically pure mononitro-compound was filtered off. The material thus obtained weighed 4.0 g. (a 64% yield) and melted 269-270°. Crystallization from acetic acid gave a purified product melting at 270-271°.

Anal. Calcd. for $C_{16}H_{12}O_5N_2$: N, 8.97. Found: N, 9.19 and 9.00.

This material was used in the following procedure for the preparation of an imidazole, thus proving that the nitro group had entered the ring ortho to the acetamino group. Orientation studies in this laboratory and elsewhere have revealed no case in which a substitution reaction such as nitration, halogenation, sulfonation and acylation of dibenzofuran has ever resulted in the direct introduction of a substituent in the 4- or 6-positions. The only means so far available for gaining entrance into these positions is by metalation (96). Consequently, with the 8-position open it is hardly probable that the compound obtained in this nitration is other than the 2-acetyl-7-acetamino-8-nitrodibenzofuran.

Preparation of 2-Methyl-8-acetyldibenzofuro-/2,3-d/-imidazole

Four grams (0.013 mole) of 2-acetyl-7-acetamino-8-nitrodibenzofuran was suspended in 80 cc. of alcohol and reduced with hydrogen at 100° under a gage pressure of forty-five pounds using Raney nickel catalyst. Reduction required one-half hour. The product, which had largely separated from the alcohol, was filtered off and the catalyst was dissolved out of the residue with dilute hydrochloric acid. Evaporation of the alcohol filtrate from the reduction yielded a small quan-

(96) Gilman and Young, J. Am. Chem. Soc., 56, 1415 (1934).

tity of material which was combined with that remaining from the hydrochloric acid treatment. The crude 2-acetyl-7-acetamino-8-aminodibenzofuran was refluxed one hour with 50 cc. of glacial acetic acid. The crude imidazole was obtained by diluting the acetic acid solution with water and making alkaline with ammonium hydroxide. The substance was dissolved in hot methanol, boiled with Norite, and the solution saturated with dry hydrogen chloride. The pure hydrochloride precipitated in fine needles melting with decomposition at approximately 325°. From the hydrochloride was obtained the pure base melting at 298° in a yield of 2.3 g. or 55%.

Anal. Calcd. for $C_{16}H_{12}O_2N_2$: N, 10.59. Found: N, 10.73 and 10.96.

Preparation of 4-Dibenzofurylacetamide

Arndt and Eistert (97) found that diazomethyl ketones, prepared from diazomethane and carboxylic acid chlorides, can be rearranged under suitable conditions to yield the next higher homologous acid, amide or ester. The method of preparation here reported is based on representative procedures found in their publication.

4-Dibenzofurancarboxylic acid chloride was prepared by treating the acid with thionyl chloride in the usual manner (98). A more convenient purification was effected, however,

(97) Arndt and Eistert, Ber., 68, 200 (1935).
(98) Kirkpatrick and Parker, J. Am. Chem. Soc., 57, 1126 (1935).

by recrystallizing the acid chloride from petroleum ether (b.p. 60-68°).

A diazomethane solution in ether, prepared from 50 g. (0.485 mole) of nitrosomethylurea according to the directions of Arndt (99), and having a volume of approximately 300-350 cc., was placed in a one liter, three-necked flask surrounded by an ice bath and fitted with a motor driven stirrer. With good stirring, 25 g. (0.11 mole) of 4-dibenzofurancarboxylic acid chloride was added in several portions over a period of five minutes. Solution took place at once and little, if any, heat of reaction was apparent. After thirty minutes of stirring in the cold, the ice bath was removed and the solution stirred for two hours at room temperature. The ether was evaporated under reduced pressure, and the residual oil soon solidified to a light yellow solid. The crude diazomethyl 4-dibenzofuryl ketone was obtained in a quantitative yield, and a portion once recrystallized from petroleum ether (b.p. 60-68°) melted at 72-75°. This material was used directly in the following procedure.

Conversion of the diazo-compound to the 4-dibenzofuryl-acetamide is accomplished in a better yield if too large a run is not made. A solution of 5.0 g. (0.02) mole of the diazomethyl 4-dibenzofuryl ketone in 100 cc. of dioxane was placed in a 500 cc. three-necked flask fitted with a stirrer

(99) Arndt, "Organic Syntheses," Vol. XV, p. 3.

and reflux condenser. The solution was heated on the steam bath, and, with good stirring, 25 cc. of concentrated ammonium hydroxide was added followed by 5 cc. of a 10% solution of silver nitrate. The heating and stirring were continued for from forty-five minutes to an hour, and the hot solution filtered from the silver oxide and shaken with an excess of cold water. The precipitated crude 4-dibenzofurylacetamide was obtained in a 67% yield. Recrystallization from ethyl alcohol gave the pure compound melting at 211-212°.

Anal. Calcd. for $C_{14}H_{11}O_2N$: N, 6.22. Found: N, 6.10 and 5.98.

Preparation of 4-Dibenzofurylacetic Acid

Five grams (0.022 mole) of the 4-dibenzofurylacetamide suspended in 150 cc. of 15% sodium hydroxide solution was refluxed for five hours. Acidification of the solution with dilute hydrochloric acid precipitated the crude 4-dibenzofurylacetic acid in an 82% yield, which was purified by recrystallization from ethyl alcohol. The pure compound melts at 213.5-214.5°.

Anal. Calcd. for $C_{14}H_{10}O_3$: C, 74.31; H, 4.46. Found: C, 74.57; H, 4.66.

Preparation of 3,4-Dimethoxy-α-(4-dibenzofurylacetamino)-acetophenone

Two grams (0.009 mole) of 4-dibenzofurylacetic acid and

10 cc. of thionyl chloride were gently refluxed together for three hours. The excess thionyl chloride was removed under reduced pressure and the residual oil dissolved in petroleum ether (b.p. 60-68°) and filtered to remove a slight amount of insoluble residue. Evaporation of the petroleum ether left the 4-dibenzofurylacetyl chloride as a viscous oil. This material was dissolved in 95 cc. of ether and added to 20 cc. of an aqueous solution of 1.5 g. (0.0065 mole) of 3,4-dimethoxy-α-aminoacetophenone hydrochloride (100). A solution of 2.5 g. of potassium hydroxide in 15 cc. of water was added, and the mixture shaken for ten minutes and allowed to stand over-night. The emulsion which had formed was filtered, leaving a residue of 2.6 g. of the crude amide. Acidification of the filtrate yielded 0.3 g. of crude 4-dibenzofurylacetic acid. The crude amide was recrystallized from benzene to yield 1.5 g. (a 57% yield based on the quantity of amine used) of the pure amide melting at 186-187°.

Anal. Calcd. for $C_{24}H_{21}O_5N$: N, 3.47. Found: N, 3.71 and 3.72.

Preparation of 3,4-Dimethoxy-α-(4-dibenzofuroylamino)-acetophenone

The reaction between 0.1 g. of 4-dibenzofurancarboxylic

(100) Prepared according to the procedure of Pictet and Gams, Ber., 42, 2943 (1909).

acid chloride and 0.1 g. of 3,4-dimethoxy-α-aminoacetophenone hydrochloride was carried out by the same procedure as that just given. The product was recrystallized from alcohol and melted at 178-179°. A mixed melting point with the 3,4-dimethoxy-α-(4-dibenzofurylacetamino)-acetophenone was depressed.

Anal. Calcd. for $C_{23}H_{19}O_5N$: N, 3.71. Found: N, 3.68.

Nitration of 1-Bromo-4-methoxydibenzofuran

A solution of 10 g. (0.036 mole) of 1-bromo-4-methoxydibenzofuran in 75 cc. of glacial acetic acid was heated on the steam bath to 90-95°, and 10 cc. of fuming nitric acid (sp.g. 1.50) was added in one portion with good stirring. The solution was stirred at this temperature for one and one-half hours and allowed to cool. The precipitated nitro-compound was filtered off and recrystallized to yield 5.5 g. (a 47.5% yield) of pure mononitro-1-bromo-4-methoxydibenzofuran melting at 160-161°.

Anal. Calcd. for $C_{13}H_8O_9NBr$: N, 4.35. Found: N. 4.31.

The acetic acid filtrate from the nitration contains the unreacted starting compound, which can be recovered easily and used in a second nitration.

The position of the nitro group was established by a simultaneous reduction and dehalogenation to yield the known 3-amino-4-methoxydibenzofuran (81), thus proving the compound

to be 1-bromo-3-nitro-4-methoxydibenzofuran.

Reduction and Dehalogenation of 1-Bromo-3-nitro-4-methoxydibenzofuran

Four-tenths of a gram (0.0008 mole) of the 1-bromo-3-nitro-4-methoxydibenzofuran was suspended in 40 cc. of absolute alcohol with 2.0 g. of palladium-calcium carbonate catalyst (101) and shaken with hydrogen under a gage pressure of twenty-five pounds for thirty minutes at room temperature. The catalyst was filtered off and the filtrate saturated with dry hydrogen chloride. Dilution with ether precipitated the amine hydrochloride in a quantitative yield. The salt was converted to the free base which, after recrystallization from alcohol, melted at 75-76°. When mixed with an authentic specimen of 3-amino-4-methoxydibenzofuran no depression in melting point was observed.

Preparation of 1-Bromo-3-amino-4-methoxydibenzofuran

A solution of 8.5 g. (0.038 mole) of hydrated stannous chloride in 10 cc. of concentrated hydrochloric acid was added to a solution of 4.0 g. (0.012 mole) of 1-bromo-3-nitro-4-methoxydibenzofuran in 50 cc. of glacial acetic acid and the mixture warmed on the steam bath for fifteen minutes. A brown precipitate separated out which was filtered off. The pre-

(101) Busch and Stöve, Ber., 49, 1063 (1916).

cipitate was triturated with an excess of 10% sodium hydroxide solution, washed and filtered. The light yellow, crude amine was obtained in nearly a quantitative yield. The material was purified by dissolving in hot alcohol and cooling the solution in the ice box several hours. The free amine separated as a bulky precipitate and melted at 135-136°.

Anal. Calcd. for $C_{13}H_{10}O_2NBr$: N, 4.79. Found: N, 4.95.

The acetamino compound was prepared by adding 0.5 cc. (0.005 mole) of acetic anhydride to a solution of 1.0 g. (0.0034 mole) of the amine in 25 cc. of acetic acid diluted with 8 cc. of water. After five minutes the solution was poured into water and the precipitate recrystallized from alcohol. The yield was 0.7 g. or 60% of the 1-bromo-3-acetamino-4-methoxydibenzofuran melting at 178-179°.

Anal. Calcd. for $C_{15}H_{12}O_3NBr$: N, 4.19. Found: N, 4.50.

NOTE ON NOMENCLATURE

The names which were applied to those compounds of dibenzofuran containing thiazole and imidazole rings, and which appear in this thesis, were tentatively assigned by the author. An inquiry directed to Dr. E. J. Crane, Editor of Chemical Abstracts, regarding the preferred nomenclature to be employed with this class of derivatives was referred to Dr. Leonard T. Capell (102), who very kindly returned the following comments in reply.

"I believe it would be better to name the compounds shown in your letter as benzimidazole and benzothiazole derivatives thus making the parent system larger and the substituents smaller and simpler. Thus compound I (103) would be 2-methyl-1-benzofuro[2,3-f]benzimidazole, compound II (104) would be 2-methyl-5-methoxy-1-benzofuro[3,2-e]benzimidazole and compound III (105), 2-aminobenzofuro[2,3-f]benzothiazole. The -1- before the benzofuro indicates the position of the extra H atom.

"By use of the 1- before the benzofuro part of the name it is possible to express isomerism due to the extra H atom without changing the numbers or letters in the bracket. Thus

(102) Associate Editor of Chemical Abstracts.
(103) 2-Methyldibenzofuro-[2,3-d]-imidazole. This thesis, p. 77.
(104) 2-Methyl-5-methoxydibenzofuro-[1,2-d]-imidazole. This thesis, p. 82.
(105) 2-Aminodibenzofuro-[3,2-d]-thiazole. This thesis, p.91.

compound II is 2-methyl-1-benzofuro[3,2-e]benzimidazole and its isomer is 2-methyl-3-benzofuro[3,2-e]benzimidazole.

"The dibenzofuroimidazole and dibenzofurothiazole names are correctly formed according to our rules of naming such systems, except as indicated above. I realize that you probably are interested primarily in the dibenzofuran ring and are influenced in your choice of a name by such an interest. However, I believe the names which I have suggested are more easily understood since dibenzofuro is somewhat misleading as a name of the substituent."

Dr. A. M. Patterson appended the following note.

"At Doctor Capell's request I have checked the names he proposes and I agree with all he says. I would have named the compounds exactly . . . as he has done . . . ."

According to this system 2-methyl-8-acetyldibenzofuro-[2,3-d]-imidazole (106) is more properly called 2-methyl-8-acetyl-1-benzofuro-[2,3-f]-benzimidazole. It should be noted, however, that the hydrogen attached to the nitrogen of imidazole and benzimidazole compounds is actually tautomerically held between the two nitrogen atoms of the ring (107), and only when it is replaced by some other group will isomeric compounds be obtained.

(106) This thesis, p. 101.
(107) Fischer and Rigaud, Ber., 34, 4202 (1901).
Gabriel, Ber., 41, 1926 (1908).

SUMMARY

A review of those organic compounds of known structure having analgesic activity has been made. These compounds have been classified according to their parent nuclei and consist of derivatives of benzene, pyrazolone, quinoline, isoquinoline, phenanthrene, dibenzofuran and morphine. A comparison of the relative analgesic efficiency of the various compounds has been made, and certain correlations between chemical structure and analgesic action have been pointed out where these have become apparent.

A complete list of the derivatives of dibenzofuran which, up to this time, have been submitted from this laboratory and tested for analgesic activity, has been included. The pharmacological results have been discussed in relation to the data given in the literature for similar derivatives in the phenanthrene and morphine series. The available evidence indicates that dibenzofuran derivatives may reasonably be expected to show analgesic activity in a degree comparable to that of similar derivatives of related nuclei.

A number of dibenzofuran derivatives, containing nitrogen either in a substituent group or as a member of a fused heterocycle, have been synthesized. Three of these have shown some analgesic activity when tested with white mice.

A note regarding the approved nomenclature for imidazole and thiazole derivatives of dibenzofuran has been appended.