[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA, No. 155]

Benzofuroquinolines[1]

BY ERICH MOSETTIG AND RICHARD A. ROBINSON

The study of a number of morphine derivatives in which the ether-like oxygen ring has been opened indicates that this ether linkage may be of considerable importance for the physiological action of morphine.[2] On the basis of this assumption it became desirable to include 4,5-phenanthrylene oxide (I) (the nitrogen-free ring skeleton of the morphine alkaloids) and its derivatives in the systematic chemical and pharmacological study of phenanthrene derivatives.[3] Since we are not yet able to synthesize this compound,[4] we directed our attention to a structurally somewhat similar compound, namely, dibenzofuran (II).[5] From this cheap and easily accessible product we are building up two principal groups of derivatives among which we hope to find compounds which will exert in some degree morphine-like effects (especially analgesia). The members of the one group contain the nitrogen atom in a hydrogenated ring condensed with dibenzofuran; those of the other group have nitrogen in a side chain, on the carbon atom in the β-position to the point of attachment.[6] The present communication deals with the first group, compounds of the quinoline type.

From application of Skraup's method to 3-aminodibenzofuran[7] two isomeric "quinolines" melting at 168–169 and 106−107° were obtained in nearly equal amounts, the ring closure

having taken place in both possible directions. The separation of the isomers can be effected through the different solubilities of the free bases and their hydrochlorides. The py-tetrahydro derivatives of the isomeric bases can be most conveniently prepared by catalytic high pressure reduction with copper–chromium–barium oxide catalyst, whereby under the conditions imposed neither the benzene nuclei nor the oxygen bridge are attacked. The resulting secondary bases were finally transformed in the usual way into their N-methyl derivatives (III and IV). In order to establish the constitutional formulas, the methochlorides of III and IV were degraded according to the method of Emde. Fortunately, of the three theoretically possible fissions,[8] the one between the nitrogen atom and the adjacent benzene nucleus predominates, and the resulting [γ-(dimethylamino)-n-propyl]-dibenzofurans can be relatively easily isolated and purified. The degradation base derived from the "quinoline 168–169°" proved to be in every respect identical with the 2-[γ-(dimethylamino)-n-propyl]-dibenzofuran prepared from 2-[γ-amino-n-propyl]-dibenzofuran; for the latter substance a strict constitutional proof has been offered by Mayer and Krieger.[6] Therefore the "quinoline 168–169°" must be a benzofuro-[3,2-g]-quinoline, and accordingly the "quinoline 106–107°" is a benzofuro-[2,3-f]-quinoline. Incidentally, it follows that the struc-

(1) The work reported in this paper is part of a unification of effort by a number of agencies having responsibility for the solution of the problem of drug addiction. The organizations taking part are: The Rockefeller Foundation, the National Research Council, the U. S. Public Health Service, the U. S. Bureau of Narcotics, the University of Virginia, and the University of Michigan.

(2) Unpublished results, N. B. Eddy.

(3) Nathan B. Eddy, J. Pharm. Exptl. Ther., 45, No. 3, 257 (1932); 48, No. 2, 183 (1933); 51, No. 1, 75 (1934); 52, No. 3, 275 (1934).

(4) We are at present engaged with attempts in this direction. Cf. Mosettig and Meitzner, THIS JOURNAL, 56, 2738 (1934).

(5) The numbering of dibenzofuran and the nomenclature of the nitrogen ring compounds included in this paper have been recommended to us by Dr. Capell through the kindness of Dr. Crane. Cf. Patterson, THIS JOURNAL, 50, 3074 (1928), and Gilman, Smith and Oatfield, ibid., 56, 1412, footnote 1 (1934). Benzofuran is numbered according to Patterson, ibid., 47, 556 (1925), oxygen having number 1.

(6) Mayer and Krieger, Ber., 55, 1659 (1922), submitted 2-[γ-amino-n-propyl]-dibenzofuran and its tetrahydro derivative to pharmacological investigation with the expectation of finding an action similar to that of morphine. The result was negative, due, we believe, to the γ-position of the amino group and its primary character.

(7) Constitutional proof (a) Cullinane, J hem. Soc., 2267 (1930); (b) Borsche and Bothe, Ber., 41, 1940 (1908); (c) Borsche and Schacke, ibid., 56, 2498 (1923) Cf. Ref. 6

I

II
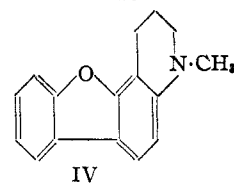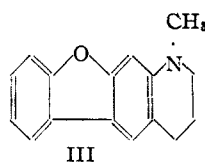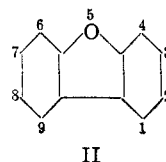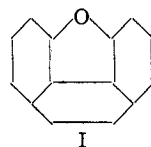
III
N-methyl-1,2,3,4-tetrahydro-benzofuro-[3,2-g]-quino-line
(derived from base m. p. 168–169°)

IV
N-methyl-1,2,3,4-tetrahy-drobenzofuro-[2,3-f]-quino-line
(derived from base m. p. 106–107°)

(8) Cf. Emde and Kull, "Degradation of Quaternary Ammonium Compounds with Sodium Amalgam, a Review," Arch. Pharm., 272, 469 (1934).

TABLE I

1, Benzofuro-[3,2-g]-quinoline; 2, benzofuro-[2,3-f]-quinoline; 3, 1,2,3,4-tetrahydrobenzofuro-[3,2-g]-quinoline; 4, N-benzoyl-1,2,3,4-tetrahydrobenzofuro-[3,2-g]-quinoline; 5, N-methyl-1,2,3,4-tetrahydrobenzofuro-[3,2-g]-quinoline; 6, 1,2,3,4-tetrahydrobenzofuro-[2,3-f]-quinoline; 7, N-benzoyl-1,2,3,4-tetrahydrobenzofuro-[2,3-f]-quinoline; 8, N-methyl-1,2,3,4-tetrahydrobenzofuro-[2,3-f]-quinoline; 9, 2-[γ-(dimethylamino)-n-propyl]-dibenzofuran; 10, 4-[γ-(dimethylamino)-n-propyl]-dibenzofuran; 11, 2-[γ-(dimethylamino)-n-propyl]-dibenzofuran

Compound	Solvent	M. p., °C (corr.)	Appearance	Formula	Carbon, % Found	Calcd.	Hydrogen, % Found	Calcd.	Nitrogen, % Found	Calcd.	Halogen, % Found	Calcd.
1[a]	EtOH	168–169	White lustrous leaflets	$C_{15}H_9ON$	82.36	82.16	4.17	4.14	6.55	6.39		
1-Hydrochloride[b]	EtOH	216–233	Small yellow-tinged crystals	$C_{15}H_{10}ONCl$							Cl, 13.76	13.88
2	Dil. EtOH	106–107	White crystals	$C_{15}H_9ON$	82.71	82.16	4.16	4.14	6.40	6.39		
2-Hydrochloride[c]	Dil. EtOH	266–285	Yellow-tinged needles	$C_{15}H_{10}ONCl$							Cl, 13.93	13.88
3[d]	EtOH	111–112	Colorless plates	$C_{15}H_{13}ON$	80.66	80.68	5.81	5.87	6.19	6.28		
3-Hydrochloride[e]	EtOH	196–226	Fine white needles	$C_{15}H_{14}ONCl$							Cl, 13.99	13.66
4	EtOH	198–200	Fine white needles	$C_{22}H_{17}O_2N$					4.17	4.27		
5[f]	Dil. EtOH	56–57	White crystals	$C_{16}H_{15}ON$	80.75	80.97	6.44	6.36	5.90	5.91		
5-Hydrochloride[g]	Dil. aq. HCl; EtOH–ether	195–200 dec.	White crystals	$C_{16}H_{16}ONCl$							Cl, 12.27	12.96
5-Methiodide[h]	EtOH or H₂O	207–209	Small white prisms	$C_{17}H_{18}ONI$							I, 33.29	33.48
6[d]	EtOH	80–81	Long heavy needle-shaped crystals	$C_{16}H_{13}ON$	80.57	80.68	5.93	5.87	6.50	6.28		
6-Hydrochloride[i]	EtOH	225–235	Fine white needles	$C_{16}H_{14}ONCl$							Cl, 14.02	13.66
7	EtOH	158–159	Small white prisms	$C_{22}H_{17}O_2N$					4.21	4.27		
8[f]	EtOH	72–73	Small colorless prisms	$C_{16}H_{15}ON$	80.61	80.97	6.35	6.36	6.08	5.91		
8-Hydrochloride	Dil. aq. HCl	204–209 dec.	White crystals	$C_{16}H_{16}ONCl$							Cl, 12.63	12.96
8-Methiodide[h]	H₂O or EtOH	193–194	Small lustrous white plates	$C_{17}H_{18}ONI$							I, 33.72	33.48
9-Hydrochloride[k]	EtOH–ether	195–197	Lustrous white leaflets	$C_{17}H_{20}ONCl$	70.28	70.44	7.06	6.96	4.89	4.84	Cl, 12.32	12.24
9-Picrate	EtOH	164–165	Bright yellow needles	$C_{23}H_{22}O_8N_4$					11.50	11.62		
9-Methiodide[l]	EtOH or H₂O	210–211.5	Small lustrous white prisms	$C_{18}H_{22}ONI$							I, 31.87	32.12
10-Hydrochloride[m]	MeOH–ether	168–169	White needles	$C_{17}H_{20}ONCl$	70.58	70.44	6.99	6.96	5.12	4.84	Cl, 12.28	12.24
10-Picrate	MeOH	148–149.5	Thick dull yellow crystals	$C_{23}H_{22}O_8N_4$					11.60	11.62		
10-Methiodide[n]	H₂O; MeOH–ether	237–238	Small white crystals	$C_{18}H_{22}ONI$							I, 31.97	32.12
11-Hydrochloride[o]	EtOH–ether	194–195	Lustrous white leaflets	$C_{17}H_{20}ONCl$	69.78	70.44	7.03	6.96	4.93	4.84	Cl, 12.33	12.24
11-Picrate[p]	EtOH	163–164	Bright yellow needles	$C_{23}H_{22}O_8N_4$					11.71	11.62		
11-Methiodide[q]	EtOH or H₂O	210–211.5	Lustrous white prisms	$C_{18}H_{22}ONI$							I, 32.11	32.12

[a] Moderately soluble in alcohol. [b] Soluble in water, moderately soluble in alcohol. [c] Soluble in water, sparingly soluble in alcohol. [d] Ten grams of the quinoline compound dissolved in 50 cc. of decalin (or absolute alcohol) and 1 g. of chromite catalyst were heated to about 150° during one and one-quarter hours and kept at this temperature for about two to three hours under a hydrogen pressure of 1500–1800 lb. Reduction started around 100°. The apparatus is described by Adkins and Cramer, THIS JOURNAL, 52, 4349 (1930); catalyst 37KAF (Connor, Folkers and Adkins, ibid., 54, 1138 (1932), was used. The reduction of 2 was also carried out with PtO₂ (free base in absolute alcohol), whereby 2 moles of hydrogen were taken up very slowly. In both ways the tetrahydro compounds were obtained practically quantitatively. [e] Difficultly soluble in alcohol and water (slight hydrolysis); the alcoholic solution turns purple on long standing. [f] Two and two-tenths grams of the tetrahydro base, 1.8 g. of methyl iodide, 2.0 g. of fused sodium acetate and 20 cc. of absolute alcohol were heated in a sealed tube at 100° for four hours. The reaction mixture was diluted with water, the base extracted with ether, and precipitated by alcoholic hydrogen chloride. About 2 g. of hydrochloride of the tertiary base and 0.5 g. of methiodide were obtained. The use of sodium acetate for partial N-methylation has been recommended to our knowledge for the first time by Dr. W. F. Hand at Mississippi State College, in another connection (Hand and Robinson, unpublished experiments). An alcoholic solution of the base turns pink, but on addition of water both solution and precipitated base are colorless. [g] Soluble with difficulty in alcohol and water, alcoholic solution turns red on standing. [h] Prepared by heating 3 in absolute alcohol with an excess of methyl iodide and fused sodium acetate in a sealed tube for several hours at 100°; yield, quantitative; also found as a by-product in the preparation of 5. [i] Dif-

ficultly soluble in alcohol and water; alcoholic solution turns yellow, and brown after long standing. [i] Difficultly soluble in water and alcohol; alcoholic solution turns red on standing. [k] Very soluble in methanol, ethanol or water. 9-Hydrochloride, picrate and methiodide were prepared from the base obtained by degradation of 5. [l] Prepared by heating 9-hydrochloride with excess of methyl iodide and sodium acetate in a sealed tube at 100° for twelve hours. Not affected by hot strong sodium hydroxide solution; soluble with difficulty in water or alcohol, more soluble in methanol. [m] Easily soluble in alcohol and water. 10-Hydrochloride, picrate and methiodide were prepared from the base obtained by degradation of 8. [n] Prepared by boiling the pure tertiary amine obtained by Emde's degradation with methanol and methyl iodide. Soluble with difficulty in water or ethanol, more soluble in methanol. [o] Mixed m. p. with 9-hydrochloride 194–196.5°. 11-Hydrochloride, picrate and methiodide were prepared from β-[2-dibenzofuroyl]-propionic acid. [p] Mixed m. p. with 9-picrate 163.5–164.5°. [q] Prepared from synthetic primary amine with excess of methyl iodide and fused sodium acetate in a sealed tube for 24 hours at 100°; mixed m. p. with 9-methiodide 210–211.5°.

ture of the degradation base derived from the "quinoline 106–107°" is that of a 4-[γ-(dimethylamino)-n-propyl]-dibenzofuran.

The physiological activity of this series increases progressively from the unhydrogenated benzofuroquinolines, through the py-tetrahydro compounds to the maximum in the N-methyl-py-tetrahydro compounds. No animals die with effective doses, and analgesia, general depression, muscular disturbance, emesis and temperature depression are observed. The members of the series of benzofuro-[2,3-f]-quinoline are slightly more active than the corresponding isomers.[2]

We intend to extend this series by building up iso-quinoline-like compounds in the dibenzofuran and partly hydrogenated dibenzofuran series.

Experimental

Benzofuro-[2,3-f]-quinoline and Benzofuro-[3,2-g]-quinoline and Derivatives.—Forty grams of 3-aminodibenzofuran (m. p. 94°, pure product, m. p. 98–99°),[9] 80 g. of nitrobenzene and 95 g. of glycerol were mixed, and 53 g. of concd. sulfuric acid was added in small portions. The mixture, a white pasty mass, was heated on a steam-bath. In the course of several hours, it changed through grayish-white to a brownish-yellow sticky paste. This was now gradually heated in an oil-bath. At about 145° a vigorous reaction set in. After the reaction had quieted, heating was continued at 140–150° for about four hours. The reaction mixture (several runs can conveniently be combined at this point) was worked up in the

ordinary way. After the nitrobenzene had been removed with steam, the crude bases were taken up in benzene from the alkalified medium. The benzene solution was washed well with water and extracted with aqueous hydrochloric acid, from which a solid crystalline mass precipitated on addition of alkali; yield, 84 g. from 80 g. of amino compound. Crystallization from 95% alcohol gives a rough separation, the benzofuro-[3,2-g]-quinoline (B) being considerably less soluble than the benzofuro-[2,3-f]-quinoline (A). The filtrate may then be treated with alcoholic hydrogen chloride, and the hydrochloride of A thus precipitated almost quantitatively. The hydrochloride of B, being considerably more soluble in hot alcohol than the hydrochloride of A, can be completely removed by washing the precipitate with hot alcohol. The purification is completed by vacuum distillation and recrystallization of the free bases from alcohol; yield 28% of pure A and 32% of pure B, calculated on 3-aminodibenzofuran. Usually no unchanged starting material is found. If so it can be easily removed, since its sulfate is much less soluble in water than the sulfates of the two quinoline compounds.

Degradation of the N-Methyl-tetrahydrobenzofuroquinolines by the Method of Emde.—Three parts of III or IV methiodide, suspended in water, was stirred for an hour with five parts of freshly precipitated silver chloride on the steam-bath. After removal of the silver halide and evaporation of the water, the crystalline, water-soluble methochloride was obtained quantitatively and worked up without any further purification. Ten grams of methochloride was dissolved in 100 cc. of water and refluxed with a large excess of 5% sodium amalgam. The base began to separate immediately; refluxing was continued for four hours, and the mixture then extracted with ether. The yield was 7–8 g. Salts prepared from this product can be purified only with great difficulty; therefore the base was slowly distilled in an oil pump vacuum at 110–120°, whereby about one-third remained undistilled. This residue was soluble in ether and acid, and was not further investigated. The distilled base, a colorless oil, forms pure salts readily. It is evident that reductive fission takes place to about 30% in other directions.

Synthesis of 2-[γ-(Dimethylamino)-n-propyl]-dibenzofuran.—A finely ground mixture of 30 g. of dibenzofuran and 10 g. of succinic anhydride was added in small portions to a solution of 50 g. of aluminum chloride in 150 cc. of nitrobenzene (cooling under the tap). The reaction mixture was then allowed to stand at room temperature for twenty-four hours and worked up in the usual way. The yield was 25 g. of β-[2-dibenzofuroyl]-n-propionic acid of m. p. 178–185°, m. p. after recrystallization from alcohol 185–187°. Mayer and Krieger[6] give the m. p. 184–185° but do not describe the preparation of the acid. The following notes to the Mayer and Krieger procedure seem necessary. (1) The γ-[2-dibenzofuryl]-n-butyric acid was purified by distillation of the ethyl ester in an oil pump vacuum and by crystallization of the potassium salt from alcohol, m. p. 114–115°, yield 80–90%. (2) We were not able to bring the melting point of the hydrazide up to 122–123° (M. and K.); for the preparation of the azide a hydrazide melting unsharply at 118–120° was diazotized in 40% acetic acid solution. (3) From 15 g. of hydrazide, 9.8 g. of urethan, m. p. 72–74° was obtained.

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(9) Prepared according to Borsche and Bothe (Ref. 7b). In the nitration of dibenzofuran, chloroform was used instead of acetic acid, and the temperature was kept below 10°. The dibenzofuran used melted at 82–84° ("diphenylene oxide, pure" Ges. f. Teerverwertung, Duisburg-Meiderich).

When the azide was taken up in ether, a sparingly soluble by-product separated crystalline from benzene, m. p. 220–222°. A second by-product (140–160°) is found in the crude oily urethan. (4) The urethan yields 96% of 2-[γ-amino-n-propyl]-dibenzofuran hydrochloride, m. p. 228–231°, corr. (M. and K., 219–220°).

One gram of 2-[γ-amino-n-propyl]-dibenzofuran hydrochloride, 1 g. of 99–100% formic acid, and 10 g. of 37% aqueous formaldehyde were heated in a sealed tube for fifteen hours at 130–160°. After treatment of the basic reaction products with benzene sulfonyl chloride, 0.45 g. of the hydrochloride of 2-[γ-(dimethylamino)-n-propyl]-dibenzofuran, m. p. 190–193° was obtained, and purified by repeated crystallization.

Summary

1. The synthesis of benzofuro-[3,2-g]-quinoline and benzofuro-[2,3-f]-quinoline from 3-amino-dibenzofuran is described.

2. The tetrahydro and N-methyltetrahydro compounds of the benzofuroquinolines were prepared.

3. The constitution of the benzofuro-quinolines has been proved through the Emde degradation products of the N-methyltetrahydrobenzofuro-quinolines.

UNIVERSITY, VIRGINIA   RECEIVED FEBRUARY 23, 1935

The Preparation of Aromatic Alcohols by the Crossed Cannizzaro Reaction with Formaldehyde

BY DAVID DAVIDSON AND MARSTON TAYLOR BOGERT

Introduction

The conversion of aldehydes to esters or their hydrolytic products (Cannizzaro reaction) may be brought about by alkalies (hydroxides or alkoxides).[1,2,3,4,5,6,7]

$$RCHO + RCHO \longrightarrow RCH_2OCOR \xrightarrow{H_2O} RCH_2OH + RCOOH$$

Nord and others have shown that aluminum ethoxide effects a crossed Cannizzaro reaction, converting binary mixtures of anhydrous aldehydes into unsymmetrical esters.[8] Crossed Cannizzaro reactions may also be assumed to occur in the formation of polyhydric alcohols by the action of alkalies on mixtures of aliphatic aldehydes; e. g., the production of pentaerythritol from a mixture of acetaldehyde and formaldehyde.[9]

The action of alkali on mixtures of aromatic aldehydes and formaldehyde does not appear to have been studied previously.[10] It has now been found that a crossed Cannizzaro reaction occurs

which leads to the formation of formic acid and the aromatic alcohol

$$RCHO + CH_2O + H_2O \longrightarrow RCH_2OH + HCOOH$$

This offers a particularly convenient method of preparing certain aromatic alcohols, such as anisyl, piperonyl, and veratryl alcohols, of which the corresponding aldehydes are readily available.

Experimental

Into a 2-liter three-necked flask equipped with dropping funnel, efficient mercury-sealed mechanical stirrer, and reflux condenser are introduced one mol of aromatic aldehyde, 200 cc. of methanol, and 100 cc. (1.3 mols) of formalin. The mixture is heated to 65° and then surrounded by cold water while a solution of 120 g. (3 mols) of sodium hydroxide (or 168 g. of potassium hydroxide) in 120 cc. of water is added rapidly through the dropping funnel, the internal temperature being maintained between 65 and 75°. The reaction mixture is then heated at 70° for 40 minutes and finally refluxed for 20 minutes. The product is isolated by cooling the reaction mixture, diluting with 300 cc. of water, separating the oil, extracting the aqueous layer four times with 150-cc. portions of benzene, washing the combined oil and extracts with water, clearing the benzene solution with sodium sulfate, and distilling in vacuum; yield, 85–90%.

About 2–5% of the aromatic acid may be recovered from the aqueous layer by blowing out the benzene and acidifying with hydrochloric acid.

Summary

The action of alkali on mixtures of aromatic aldehydes and formaldehyde results in the practically complete conversion of the aromatic aldehydes to the corresponding alcohols.

NEW YORK, N. Y.   RECEIVED FEBRUARY 28, 1935

(1) Wöhler and Liebig, Ann., 3, 254 (1832).

(2) Cannizzaro, ibid., 88, 129 (1853).

(3) Kohn and Trantom, J. Chem. Soc., 75, 1158 (1899).

(4) Lachman, THIS JOURNAL, 45, 2356 (1923).

(5) Elderfield, J. Chem. Ed., 7, 594 (1930).

(6) Tischtschenko, Chem. Zentr., 77, II, 1309, 1554, 1556 (1906).

(7) Child and Adkins, THIS JOURNAL, 47, 799 (1925).

(8) (a) Nord, Biochem. Z., 106, 275 (1920); (b) Beiträge Physiol., 2, 301 (1924); (c) Nakai, Biochem. Z., 152, 258 (1924); (d) Chusetsu Endoh, Rec. trav. chim., 44, 866 (1925); (e) Orloff, Bull. soc. chim., [4] 35, 360 (1924).

(9) "Organic Syntheses," Coll. Vol. I, 1932, p. 417.

(10) Van Marle and Tollens, Ber., 36, 1347 (1903), reported that no solids were formed by the action of barium or calcium hydroxides on mixtures of benzaldehyde and formaldehyde.