dry benzene, in the manner described for preparation of esters of thiazoline phenols, although in this case elaborate precautions against hydrolysis are not necessary. The filtered benzene solution was evaporated to dryness and the product extracted with boiling water to remove any unreacted mercaptothiazoline, then with 10% sodium carbonate solution to remove any *p*-nitrobenzoic acid, and finally again with water. The compound was crystallized from benzene in large lemon-yellow crystals or from 95% ethyl alcohol in fine yellow needles (Xb).

The 4-nitrobenzoyl ester was reduced by the method of Babcock and Adams using iron powder and concentrated hydrochloric acid. The benzene extracts of the reduction mixture were combined, dried, filtered, and saturated with dry hydrogen chloride gas. The precipitated hydrochloride was purified by extraction with boiling water, with the use of decolorizing carbon, as white crystals, soluble in hot water, less soluble in cold water (Xc).

Physiological Properties.—Some of the thiazolinephenols thus far prepared were examined for physiological action. It was found that these thiazolinephenols, the hydrochlorides of which are all water soluble, are not toxic and have little bactericidal action, their phenol coefficients being less than one. Then it was found that these sulfur–nitrogen–heterocyclic phenols possess local anesthetic action some to a higher and others to a lesser degree. The best thus far found is the 5-methylthiazoline-*m*-cresol. Little difference in local anesthetic action was found between a 1% cocaine solution and a solution of this compound of equal strength. The toxicity of this compound as compared with cocaine was found to be as shown in the table.

5-Methylthiazoline-*m*-cresol			Cocaine	
Dose, mg. per kg. body weight	No. of mice	% dead	No. of mice	% dead
50	5	0	15	0
100	5	0	15	87
200	5	0	15	100
300	20	5		
400	20	15	(1% solution injected	
500	10	60	intraperitoneally)	

The methyl ether of this compound is about 2–3 times as effective as either cocaine or procaine, but all the compounds, tested as hydrochlorides, upon parenteral injection or topical application, produced severe irritations lasting for more than twenty-four hours. The tartrates, however, are non-irritating.

The above physiological tests were carried out by the Merck Institute of Therapeutic Research.

Acknowledgment.—The authors desire to thank Merck and Co., Inc., Rahway, N. J., for a research fellowship, without which this investigation would have been impossible.

Summary

Several new 5-methyl- and 5,5-dimethylthiazolinephenols have been described, together with a number of derivatives. Physiological tests have been conducted upon several of these compounds, indicating local anesthetic properties and a relatively low toxicity.

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[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

Amino Ketones Derived from Tetrahydrobenzo[b]naphtho[2,3-d]furan[1]

BY RICHARD A. ROBINSON[2] AND ERICH MOSETTIG

In previous communications[3] we have described the synthesis of amino alcohols of the type $R\text{-}CHOHCH_2NR_2$ derived from dibenzofuran and tetrahydrodibenzofuran, respectively. These amino alcohols proved to be slightly more analgesic than the corresponding compounds of the phenanthrene series.[4] Since the most potent synthetic analgesics were found among amino alcohols having the hydroxyl and the nitrogen-containing group directly attached to a hydrogenated benzene nucleus of phenanthrene[5] as indicated in formula I, it appeared desirable to prepare analogous amino alcohols derived from dibenzofuran. We expected that from ketones of formula III or IV such compounds should be obtainable through the series of reactions used for the synthesis of the above mentioned "cyclic amino alcohols" of the phenanthrene series.

When γ-[2-dibenzofuryl]-*n*-butyric acid was cyclized by means of phosphoric acid, a mixture of III and IV was obtained in nearly quantitative yield. Its separation was effected by fractional crystallization, whereby ketone III was isolated

(1) (a) 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. (b) This communication includes also the description of experiments pertaining to a previous note entitled "Amino Alcohols Derived from 1,2,3,4-Tetrahydrodibenzofuran."[3b]

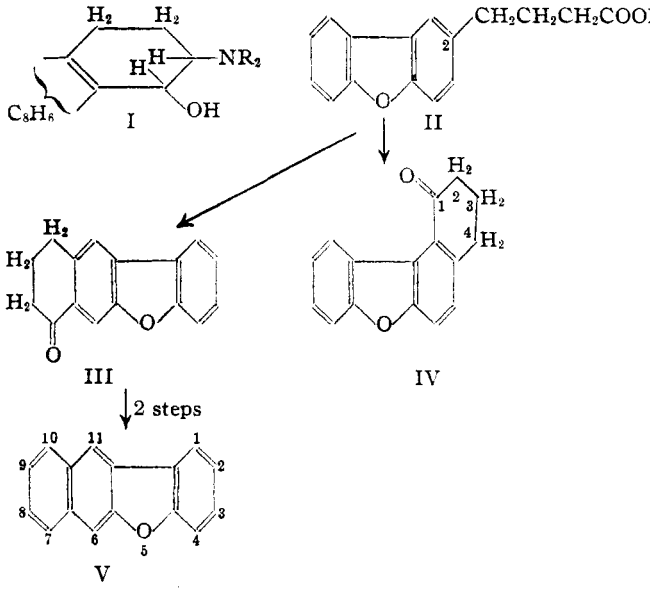
(2) Merck Fellow in Alkaloid Chemistry 1935–1936.

(3) (a) Mosettig and Robinson, THIS JOURNAL, **57**, 2186 (1935); (b) *ibid.*, **58**, 688 (1936).

(4) Small, Eddy, Mosettig and Himmelsbach, "Studies on Drug Addiction," Supplement No. 138 to the Public Health Reports, pp. 99, 102 (Washington, D. C., 1938).

(5) (a) See pp. 88, 90 of ref. 4; (b) Mosettig and Burger, THIS JOURNAL, **57**, 2189 (1935).

quite readily and in pure form, in a yield of about 50%. The purification of the isomer IV proved to be more difficult, yielding only 3–4% of the homogeneous compound. We believe, however, that IV was present in the original mixture in a much greater amount. The structure of ketone III was determined by converting it into the known benzo[b]naphtho[2,3-d]furan[6] (brazan) (V), whose structure appears well established.



We confirmed its identity by direct comparison with an authentic sample of brazan of the Gesellschaft für Teerverwertung, m. b. H., Duisburg-Meiderich,[7] and comparison of the quinones prepared from both samples. This structural proof of ketone III is obviously also an indirect proof for the structure of ketone IV, since the latter can have only the alternative structure.

The bromination of ketone III did not offer any difficulties. The exchange of the bromine atom in the resulting bromo ketone with the dimethylamino, piperidino, and tetrahydroisoquinolino group was effected readily in benzene solution. The amino ketone hydrochlorides, however, were rather unstable compounds and could be purified only with considerable loss. As by-products in these reactions were obtained, in varying amounts, the original ketone III and, in very small amounts, a phenolic product which is very probably 7-hydroxybrazan.[8] Attempts to reduce the dimethylamino and piperidino ketones to the corresponding amino alcohols were without success and did not warrant further experiments in this direction.

Owing to a misunderstanding no experimental data were supplied in the previous communication[3b] describing amino alcohols derived from tetrahydrodibenzofuran. The preparation of these compounds proceeded quite normally, with the exception of the last step, the reduction of the amino ketones to the corresponding amino alcohols, in which unusual difficulties were encountered. In spite of a number of experimental variations in the catalytic reduction, we were not able to obtain the diethylamino alcohol.

We wish to express our thanks to the Gesellschaft für Teerverwertung m. b. H., Duisburg-Meiderich, for furnishing us with a generous sample of brazan.

Experimental

7 - Keto - 7,8,9,10 - tetrahydrobenzo[b]naphtho-[2,3-d]-furan (III) and 1-Keto-1,2,3,4-tetrahydrobenzo[b]naphtho[1,2-d]furan (IV).—Ten grams of γ-[2-dibenzofuryl]-*n*-butyric acid (m. p. 110–112°),[9] 125 cc. of commercial 85% phosphoric acid, and 20 g. of phosphorus pentoxide were well mixed and heated, with mechanical stirring, to 170° for one hour. The cooled reaction mixture was decomposed with ice and extracted with ether. On evaporation of the ethereal solution which had been washed with dilute alkali, 10 g. of a brown solid remained, which by distillation at 206–210° at 5 mm. yielded a colorless crystalline product. When a hot benzene solution of this product was cooled, the less soluble ketone III precipitated in practically pure form. One crystallization from benzene yielded 4–4.5 g. of pure ketone III as colorless needles (or prisms) melting at 137–138°. After some concentration of the mother liquor, another small crop of ketone III precipitated. On further concentration of the mother liquor, a mixture of the two isomeric ketones (III and IV), melting at 80–90°, was obtained. It was redissolved in a very small volume of hot benzene, or, better, in hot methanol, from which the isomers crystallized side by side. They could be separated mechanically, or by washing ketone III out of the mixture with hot methanol in which IV is much less soluble than III. Ketone IV crystallized in thick, short, colorless prisms, melting at 112–113°. From ten combined cyclization experiments about 3–4 g. of pure ketone IV was obtained.[9a]

7,8,9,10 - Tetrahydrobenzo[b]naphtho[2,3-d]furan.—A mixture of 1.0 g. of ketone III, 1.2 cc. of hydrazine hydrate,

(6) Nomenclature according to index of *C. A.*, **31**, 9590 (1937). The parent substance of IV is benzo[b]naphtho[1,2-*d*]furan.

(7) See Kruber, *Ber.*, **70**, 1556 (1937).

(8) Analogous by-products have been observed in the reaction of amines on bromotetanthrenones, see ref. 5b, also Burger, THIS JOURNAL, **60**, 1533 (1938).

(9) Mayer and Krieger, *Ber.*, **55**, 1659 (1922); Mosettig and Robinson, THIS JOURNAL, **57**, 902 (1935).

(9a) Our attention has been called to the fact that the 1-keto-1,2,3,4-tetrahydro-β-(or γ)-brazan mentioned by Parker [*Iowa State Coll. J. Sci.*, **12**, 148 (1937); *C. A.*, **32**, 2937 (1938)] probably is identical with III.

No.	Name of compound	Solvent	M. p., °C.	Formula	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found	Nitrogen, % Calcd.	Found
1	7-Keto-7,8,9,10-tetrahydrobenzo[b]naphtho[2,3-*d*]furan	EtOH or Bz	137–138	$C_{16}H_{12}O_2$	81.32	81.36	5.13	5.18		
2	-Semicarbazone	Pyridine or Bz	260–265 (dec.)	$C_{17}H_{15}O_2N_3$					14.34	14.06
3	1-Keto-1,2,3,4-tetrahydrobenzo[b]naphtho[1,2-*d*]furan	MeOH	112–113	$C_{16}H_{12}O_2$	81.32	81.35	5.13	5.54		
4	-Oxime	EtOH	200–203	$C_{16}H_{13}O_2N$					5.58	5.51
5	7,8,9,10-Tetrahydrobenzo[b]naphtho[2,3-d]furan	EtOH	75–77	$C_{16}H_{14}O$	86.45	86.26	6.35	6.61		
6	-Picrate	EtOH	139–141	$C_{22}H_{17}O_8N_3$					9.31	9.38
7	Benzo[b]naphtho[2,3-d]furan (brazan)	EtOH or AcOH	208–209	$C_{16}H_{10}O$	88.04	87.97	4.62	5.04		
8	-Quinone	AcOH	245–246	$C_{16}H_8O_2$	77.39	77.23	3.25	3.05		
9	8-Bromo-7-keto-7,8,9,10-tetrahydrobenzo[b]naphtho[2,3-d]furan[a]	Benzene	207 (dec.)	$C_{16}H_{11}O_2Br$	Br, 25.37	25.18				
10	8-Dimethylamino-7-keto-7,8,9,10-tetrahydrobenzo[b]-naphtho[2,3-d]furan hydrochloride[b]	EtOH-Et_2O	208–212 (dec.)	$C_{18}H_{18}O_2NCl$	Cl, 11.24	11.68			4.44	4.28
11	8-Piperidino-7-keto-7,8,9,10-tetrahydrobenzo[b]naphtho-[2,3-d]furan hydrochloride[c]	MeOH-Et_2O	235–237 (dec.)	$C_{21}H_{22}O_2NCl$	9.97	10.21			3.94	3.86
12	8-Tetrahydroisoquinolino-7-keto-7,8,9,10-tetrahydrobenzo-[b]naphtho[2,3-d]furan hydrochloride[d]	MeOH-Et_2O	206–210 (dec.)	$C_{28}H_{22}O_2NCl$	8.78	8.80			3.47	3.63

[a] To an ice-cold suspension of no. 1 in absolute ether was added all at once an ethereal solution of one molecular equivalent of bromine. The bromo ketone (felted needles) was formed, in nearly quantitative yields, through the usually observed orange-red intermediate product. [b] Four grams of no. 9 was added to a solution of 2.3 g. of anhydrous dimethylamine in 100 cc. of dry benzene. The mixture was heated in a pressure bottle at 100° for nine hours. The filtered benzene solution was washed with water and dried over sodium sulfate. The amino ketone hydrochloride was precipitated as a brown powdery solid (2.6 g.) by the addition of ethereal hydrogen chloride solution. It is soluble in dilute hydrochloric acid and can be purified with considerable loss from methanol–ether mixture. The solution turns pink immediately and the crystalline hydrochloride cannot be obtained colorless. The benzene filtrate of the crude hydrochloride was evaporated and the residue, 1.2 g. of a white crystalline substance, was boiled with dilute alkali. The alkali-insoluble part was practically pure no. 1 (melting point and mixture melting point), while from the alkaline solution, a very small amount of a phenolic product, presumably 7-hydroxybrazan of m. p. 208–212° (felted needles), could be precipitated by acidification. (Not enough of this material could be collected for satisfactory purification.) [c] A mixture of compound no. 9 and piperidine (four molecular equivalents) in benzene solution was boiled gently under reflux for two hours. The amino ketone hydrochloride is moderately soluble in water and alcohol and was purified by recrystallization from methanol–ether; yield 60–80%. Compound no. 1 mixed with traces of the phenolic by-product was found in quantities ranging from 10–20%. [d] A mixture of 4 g. of no. 9 and 4 g. of tetrahydroisoquinoline in 50 cc. of benzene was heated in a pressure bottle at 100° for nine hours. The tetrahydroisoquinoline hydrobromide was filtered off and the amino ketone and the excess tetrahydroisoquinoline were precipitated as hydrochlorides. The precipitate was washed with water and recrystallized (yield 50–60%). The solutions of the amino ketone hydrochloride are rather unstable and in spite of several recrystallizations the substance can be obtained only as a light brown crystalline powder. In this reaction, compound no. 1 with traces of the hydroxy compound was formed in a yield of approximately 25%.

and a solution of sodium ethoxide (0.5 g. of sodium in 10 cc. of absolute alcohol) was heated in a sealed tube at 160–170° for five hours. The resulting oil (0.4 g.) was distilled in an oil-pump vacuum and the distillate (0.25 g.) yielded by crystallization from alcohol nearly colorless prisms, melting at 75–77°. The picrate was obtained in brick-red prisms, by mixing the components in hot alcoholic solution.

The tetrahydro compound also could be obtained by the Clemmensen reduction, but only in yields of 5–10%. The chief product (40–50%) in this reaction, fine, nearly colorless needles from benzene, melted unsharply at 190–210° and was not investigated further.

Benzo[b]naphtho[2,3-d]furan (Brazan) (V).—A mixture of 1 g. of the above tetrahydro compound and 7 g. of selenium was heated with a luminous flame for thirty to forty-five minutes. The reaction mixture was extracted with benzene, and the benzene residue was sublimed in an oil-pump vacuum. Crystallization from alcohol, in which the product is sparingly soluble, yielded lustrous leaflets, melting at 205–208° (0.52 g.). After resublimation and recrystallization from alcohol or glacial acetic acid the compound melted at 208–209° (sintering at 207°). A mixture of 0.1 g. of the compound (m. p. 205–208°) in 3 cc. of glacial acetic acid and 0.25 g. of chromic acid in a few drops of water and 2 cc. of glacial acetic acid was heated to boiling for about ten minutes. The quinone thus obtained (0.06 g.) melted at 240–243° with sintering at 235°. After sublimation in an oil-pump vacuum and re-

crystallization from glacial acetic acid, the product melted at 245–246° (sintering at 239°). The brazan of the Gesellschaft für Teerverwertung, after sublimation and recrystallization from glacial acetic acid melted at 208–209° (sintering at 207°), and the quinone prepared from it melted at 245–246° (sintering at 239°). The mixture melting point of the two samples of brazan was 208–209° (sintering at 207°), that of the two samples of brazanquinone was 242.5–243° (sintering at 242°).[10] No picrate of brazan could be obtained by heating equal amounts of the components in alcoholic solution.

Experimental Part to the Note of Robinson and Mosettig: Amino Alcohols Derived from 1,2,3,4-Tetrahydrodibenzofuran[1b,3b]

7 - ω - Bromoacetyl - 1,2,3,4 - tetrahydrobenzofuran.—The bromination of the methyl ketone was carried out in absolute ethereal solution at −15° (bromine in an excess of 8%). The resulting colorless solution was washed with water and dried. The ether was distilled off in a vacuum at 0°. The residue consisted of about two parts of crystalline bromo ketone and one part of oily material. The latter could be removed with cold methanol. For the final purification, the bromo ketone was recrystallized from ethanol or benzene–ligroin; yield 40–45%. The compound was converted to the corresponding carboxylic acid of m. p. 252–255° (methyl ester, m. p. 77–78°)[11] by the method of Fuson and Tullock.[12]

Amino Ketones.—A solution of the bromo ketone and the secondary amine (2.5 molecular equivalents of dimethylamine, diethylamine, piperidine, or tetrahydroisoquinoline) in anhydrous benzene (20–40 cc. per gram of bromo ketone) was heated for one hour at 60–80°. The reaction with piperidine proceeded equally well at room temperature. The hydrobromide of the secondary amine was filtered off, and the benzene solution, if necessary diluted with ether, was washed with water in order to remove the excess of secondary amine. The amino ketone was then precipitated from the benzene solution with ethereal hydrogen chloride and the salt was recrystallized from alcohol–ether. The tetrahydroisoquinolino ketone hydrochloride is sparingly soluble in water, which permitted an easy separation from tetrahydroisoquinoline hydrochloride. It was recrystallized from dilute alcohol.

Amino Alcohols.—The free bases of the dimethylamino ketone and the piperidino ketone were reduced in absolute alcoholic solution, using a platinum oxide catalyst (0.05 g. for 2 g. of base). Generally the reduction had to be interrupted after one mole of hydrogen had been absorbed, although it slowed down at that point. In some instances, the hydrogen absorption of the dimethylamino ketone came to a standstill at one mole. The amino alcohols are easily isolated and purified in the form of the hydrochlorides (average yield, 80%). The dimethylamino alcohol is an oil, the piperidino alcohol crystallizes from alcohol as flat needles, melting at 129–131°.

Anal. Calcd. for $C_{19}H_{25}O_2N$: N, 4.68. Found: N, 4.80.

The reduction of the free tetrahydroisoquinolino ketone (obtained by treating the aqueous suspension of the hydrochloride with alkali and washing thoroughly the precipitate) in absolute alcoholic suspension proceeded very slowly and stopped after one mole of hydrogen had been taken up. The amino alcohol was purified by recrystallization from alcohol; lustrous leaflets, m. p. 144.5–145.5°.

Anal. Calcd. for $C_{23}H_{25}O_2N$: N, 4.03. Found: N, 4.08.

The hydrochlorides of the amino alcohols were recrystallized from alcohol–ether.

Summary

By cyclization of γ-[2-dibenzofuryl]-*n*-butyric acid two cyclic ketones were obtained, whose structures were established by converting one of them into brazan.

By exchanging the bromine in 8-bromo-7-keto-7,8,9,10 - tetrahydrobenzo[b]naphtho[2,3-d]furan with tertiary amino groups, amino ketones were obtained which were rather unstable and could not be reduced to the corresponding amino alcohols.

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(10) The brazanquinone is described in the literature as yellow needles, melting at 239–240°; French Patent 779,214; *C. A.*, **29**, 4774 (1935).

(11) This acid and ester have been described by Gilman, Smith and Cheney, THIS JOURNAL, **57**, 2095 (1935).

(12) Fuson and Tullock, *ibid.*, **56**, 1638 (1934).