alcohol was satisfactory but best results were obtained with absolute ethyl alcohol saturated with the rare earth salt.

It was found best to cool the reaction tube with tap water since heat is developed by the reaction and at the higher temperature the tendency toward decomposition of the amalgam increases.

Potassium amalgams reacted with the anhydrous rare earth chlorides similarly to the sodium amalgams but were not as satisfactory. Barium amalgam gave partial displacement of the cerium group elements but did not react at all with the yttrium chlorides.

Yttrium amalgam was readily decomposed by heating in an evacuated Pyrex distilling bulb, the product being a pyrophoric powder which contained a small amount of mercury. Attempts to obtain yttrium metal entirely free from mercury have thus far been unsuccessful. The removal of all the mercury from the amalgams of the cerium group metals was successfully accomplished by placing the amalgams in an alundum crucible which had a lining of rare earth oxides and heating in a steel vacuum chamber by means of an electric furnace.

Summary

1. Amalgams of cerium, neodymium, didymium and yttrium have been prepared by displacement from the alcohol solution of their chlorides by sodium amalgam.

2. The most successful runs were made by suspending powdered sodium amalgam, containing 2–2.5% sodium, in a saturated alcoholic solution of the rare earth chlorides. The mixture was thoroughly agitated; the time required varied with the rare earth used.

3. This method takes much less time than the electrolytic method and gives a considerably more concentrated amalgam in the case of yttrium. The amalgams always retain a trace of sodium.

4. Metals of the cerium group were obtained free from the mercury by heating their amalgams in an evacuated chamber. This method did not yield yttrium which was entirely free from mercury.

URBANA, ILLINOIS RECEIVED AUGUST 12, 1935

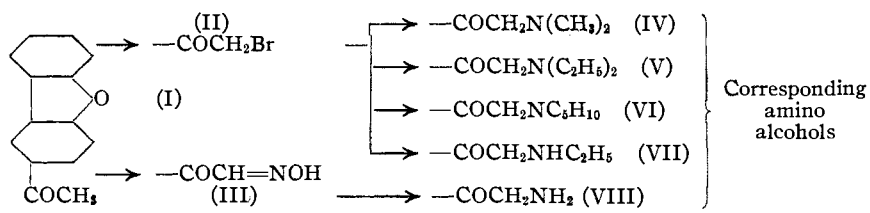
[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

Amino Alcohols Derived from Dibenzofuran[1]

BY ERICH MOSETTIG AND RICHARD A. ROBINSON

The structural similarity of dibenzofuran to 4,5-phenanthrylene oxide has led us to the study of dibenzofuran derivatives[2] as a part of our search for morphine substitutes. The present communication deals with dibenzofuran alkamines containing the characteristic side chain —CHOH—CH_2—NR_2; these compounds were selected for comparison with amino alcohols of the phenanthrene series which have been found to resemble morphine somewhat in physiological action.[3] Such comparison of dibenzofuran and phenanthrene analogs may yield information as to whether the phenanthrene nucleus contributes an essential part to the total physiological action of morphine, or whether it can be replaced by another polynuclear system.

Starting from the known 2-acetyldibenzofuran, the synthesis of the alkamines was accomplished as outlined in the diagram.



The tertiary amino ketones IV, V and VI were prepared by a method similar to that used for the synthesis of their respective phenanthrene analogs.[3] The primary amino ketone VIII was obtained by reduction of the isonitroso compound III according to the method of Hartung and Munch.[4]

The exchange of the bromine atom in II with ethylamine yields only about 30% of the expected ethylamino ketone VII. The yield of the corresponding monomethylamino ketone does not exceed 5%. In the latter case a small amount of

(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) Mosettig and Robinson, THIS JOURNAL, **57**, 902 (1935).

(3) (a) Mosettig and van de Kamp, *ibid.*, **55**, 3448 (1933); (b) unpublished results by Eddy and co-workers, University of Michigan.

(4) Hartung and Munch, *ibid.*, **51**, 2262 (1929).

DIBENZOFURAN DERIVATIVES

No.	Substituent	Solvent	M. p., °C. (corr.)	Formula	Carbon, % Found	Carbon, % Calcd.	Hydrogen, % Found	Hydrogen, % Calcd.	Nitrogen, % Found	Nitrogen, % Calcd.	Halogen, % Found	Halogen, % Calcd.
1	*-2-ω-Bromoacetyl-[a]	Bz.–lig.	105–106	$C_{14}H_9O_2Br$							Br, 27.64	27.66
2	2-[2-(Dimethylamino)-1-oxo]-ethyl[b]	Dil. EtOH	82–83	$C_{16}H_{15}O_2N$	75.82	75.85	5.93	5.97				
	-Hydrochloride[c]	.....	212–235	$C_{16}H_{16}O_2NCl$					4.84	4.84	Cl, 12.03	12.25
3	*2-[2-(Diethylamino)-1-oxo]-ethyl-(hydrochloride)[d]	EtOH or dil. HCl	200–212	$C_{18}H_{20}O_2NCl$							Cl, 11.32	11.17
4	2-(2-Piperidino-1-oxo)-ethyl-[e]	Dil. EtOH		$C_{19}H_{19}O_2N$	77.63	77.77	6.58	6.53				
	*-Hydrochloride[f]	Dil. HCl	255–265	$C_{19}H_{20}O_2NCl$					4.34	4.22	Cl, 10.75	10.76
5	2-[2-(Ethylamino)-1-oxo]-ethyl-(hydrochloride)[g]	MeOH	254–256 (dec.)	$C_{16}H_{16}O_2NCl$					5.04	4.84	Cl, 12.45	12.25
6	2-(2-Amino-1-oxo)-ethyl-(hydrochloride)[h]	Dil. HCl	245–255 (dec.)	$C_{14}H_{12}O_2NCl$					5.48	5.36	Cl, 13.52	13.56
7	2-[2-(Dimethylamino)-1-hydroxy]-ethyl-[i]	Dil. EtOH	88–89	$C_{16}H_{17}O_2N$	75.46	75.25	6.76	6.72	5.59	5.49		
	-Hydrochloride[j]	EtOH	173–174	$C_{16}H_{18}O_2NCl$							Cl, 12.29	12.16
	-Benzoic acid ester[k]	EtOH	99–100	$C_{23}H_{21}O_3N$					3.92	3.90		
8	2-[2-(Diethylamino)-1-hydroxy]-ethyl-[l]	MeOH	75–76	$C_{16}H_{21}O_2N$	75.93	76.28	7.33	7.47				
	*-Hydrochloride[m]	EtOH–Et_2O	157–159	$C_{16}H_{22}O_2NCl$					4.36	4.38	Cl, 11.22	11.13
9	*2-(2-Piperidino-1-hydroxy)-ethyl-[n]	EtOH	116.5–117.5	$C_{19}H_{21}O_2N$	77.06	77.24	7.21	7.17	4.68	4.75		
	*-Hydrochloride[o]	H_2O	250–251	$C_{19}H_{22}O_2NCl$							Cl, 10.90	10.70
	-Benzoic acid ester[p]	EtOH	119	$C_{26}H_{25}O_3N$					3.67	3.50		
10	2-[2-(Ethylamino)-1-hydroxy]-ethyl[q]	Bz.–lig.	99.5–101	$C_{16}H_{17}O_2N$	75.07	75.25	6.89	6.72	5.42	5.49		
	-Hydrochloride[r]	MeOH	219–219.5	$C_{16}H_{18}O_2NCl$							Cl, 12.32	12.16
11	2-(2-Amino-1-hydroxy)-ethyl-[s]	Dil. EtOH	132	$C_{14}H_{13}O_2N$					6.08	6.17		
	-Hydrochloride[t]	H_2O	261 (dec.)	$C_{14}H_{14}O_2NCl$	63.57	63.74	5.56	5.35	5.44	5.31	Cl, 13.51	13.45
12	2-(1-Hydroxy)-ethyl-[u]	Dil. EtOH	63–64	$C_{14}H_{12}O_2$	78.84	79.21	5.63	5.70				
13	2-Propionyl-[v]	95% EtOH	101.5–102.5	$C_{15}H_{12}O_2$	79.92	80.32	5.36	5.40				
	-Semicarbazone	Benzene	184–186	$C_{16}H_{15}O_2N_3$					14.62	14.95		
14	2-[2-(Methylamino)-1-oxo]-ethyl- (hydrochloride)?[w]	Dil. HCl	225–250	$C_{15}H_{14}O_2NCl$					4.89	5.08	Cl, 12.19	12.87
15	Methyl-bis-[(2-dibenzofuroyl)methyl]-amine hydrochloride?[x]	EtOH	235–245	$C_{29}H_{22}O_4NCl$					2.91	2.90	Cl, 6.91	7.33

[a] Prepared by bromination of 2-acetyldibenzofuran in absolute ether at 0°. The bromo ketone was purified by recrystallization from benzene–ligroin mixture or from acetic acid. The yield of pure substance was 55%; soluble in benzene. The residue, a lower-melting fraction, could not be greatly purified by further recrystallization and probably consisted of nuclear bromination products. In order to prove that the bromine atom was located in the side chain, the bromo ketone was oxidized with sodium hypochlorite to dibenzofuran-2-carboxylic acid. The 2-acetyldibenzofuran was prepared by the method of Friedel and Crafts.[5] The reaction was carried out at room temperature with nitrobenzene as the solvent (duration of reaction, forty-eight hours). The crude ketone was purified by vacuum distillation (pressure approximately 1 mm.). The unchanged dibenzofuran can be easily separated in this way but the acetyl derivative so isolated is contaminated with about 5% of a compound of m. p. 148–149° that cannot be removed efficiently by distillation. This compound is probably identical with the 2,8-diacetyldibenzofuran reported by Borsche and Schacke.[5] The separation of this impurity from the 2-acetyldibenzofuran is best effected by several crystallizations from ether or isopropyl ether; yield of pure 2-acetyldibenzofuran, 32%, m. p. 82°; in addition, 24% of practically pure substance (m. p. 74–79°).

[b] Five grams of (1), finely pulverized and thoroughly dried, was suspended in 25 cc. of absolute ether and mixed immediately with a solution of 2.2 g. of dimethylamine in 60 cc. of absolute ether (temperature approximately 0°). The powdered bromo ketone, which gradually dissolves, is replaced by a precipitate of dimethylamine hydrobromide. The transformation is complete in one hour. The amino ketone was worked up as the hydrochloride, yield 90%. The free base is moderately stable but becomes colored on long standing or in ethereal solution.

[c] Soluble in water; precipitates almost quantitatively from dilute hydrochloric acid as white needles containing one mole of water of crystallization. *Anal.* Calcd. for $C_{16}H_{16}O_2NCl \cdot H_2O$: H_2O, 5.85. Found: H_2O, 6.57.

[d] Prepared from diethylamine and the bromo ketone by the method given for (2); yield, 97%; soluble in water and ethanol. The transformation is complete in one hour, and coloration of the products can be avoided by working up immediately at this point. With dimethylamine and piperidine there is very little tendency for the reaction products to become colored. The free diethylamino ketone base is a colorless oil. K. and P prepared this substance from chloroacetyldibenzofuran and state as melting point for the hydrochloride 204–206°.

[e] Prepared from piperidine and the bromo ketone by the method given for (2); yield, 96%. The free base is moderately stable but becomes yellow on long standing. It softens at 97–100° and melts over a wide range.

(5) Galewsky, *Ann.*, **264**, 187 (1891); Borsche and Schacke, *Ber.*, **56**, 2498 (1923).

Moderately soluble in water; K. and P. give m. p., 270–271°.

[g] Prepared from ethylamine and the bromo ketone by the method given for (2). The transformation is complete in one and one-half hours and the reaction mixture always becomes highly colored. The amino ketone was extracted from the filtered ether solution with dilute acetic acid and precipitated as the hydrochloride by the addition of concd. hydrochloric acid to the acetic acid solution; yield, 30%, difficultly soluble in water and alcohol. From 5 g. of bromo ketone, 0.5–1 g. of dibenzofuran-2-carboxylic acid was found as a by-product. The remainder of the material was a highly sensitive substance. The freshly precipitated free base soon turns pink. It melts at 65–75°.

[h] Prepared by reducing 2-isonitrosoacetyldibenzofuran by the method of Hartung.[4] The solvent was prepared by mixing 150 cc. of methanol with 40 cc. of concentrated hydrochloric acid. The amino ketone hydrochloride precipitates after about 90% of the calculated amount of hydrogen has been absorbed and absorption stops completely at this point; yield, 64%. The salt is sparingly soluble in alcohol, moderately soluble in water. It turns pink in warm alcohol or water, but is stable in dilute hydrochloric acid. The free base becomes pink immediately when liberated from the hydrochloride. The isonitroso compound was obtained from 2-acetyldibenzofuran by the method of Claisen and Manasse[6] in a yield of 60%. It is soluble in alcohol and benzene, and was crystallized once from dilute alcohol and reduced without further purification. It decomposes over a wide temperature range starting at 171°.

[i] Prepared by reducing (2) (free base or hydrochloride) in absolute alcohol solution with platinum oxide catalyst; yield, 90%, soluble in alcohol.

[j] Soluble in alcohol and water.

[k] Prepared by the method of Schotten–Baumann.

[l] This compound could not be obtained by reducing the free base of (3). The amino ketone solution became colored during preparation and would not reduce. In two cases the hydrochloride was successfully reduced in absolute ethanol. Exactly one mole of hydrogen was absorbed and the expected compound obtained. In other experiments, when reduced in absolute ethanol, the hydrochloride absorbed 2 to 3 moles of hydrogen, yielding about 25% of unchanged amino ketone hydrochloride and an oily hydrochloride which became colored. By using 70% ethanol we were able to obtain consistently, with the absorption of one mole of hydrogen, the desired amino alcohol in a yield of 80–90%. It is soluble in ethanol and benzene. This amino alcohol and its hydrochloride as well as all other members of this series are, in contrast to the amino ketones, very stable compounds.

[m] Very soluble in ethanol and water. K. and P. give m. p. 137°.

[n] Obtained from (4) (free base) by reducing in absolute ethanol with platinum oxide catalyst; yield 90%; moderately soluble in ethanol. K. and P. state m. p. 103–104°.

[o] Sparingly soluble in water, moderately soluble in alcohol. K. and P. give m. p. 242°.

[p] Prepared by the method of Schotten–Baumann.

[q] Obtained by reducing (5) (hydrochloride) in dry methanol with platinum oxide catalyst; soluble in benzene and alcohol.

[r] Moderately soluble in ethanol, soluble in methanol and water.

[s] Obtained from (6) (hydrochloride) by reduction in dry methanol; yield 90%, soluble in ethanol. If traces of free hydrochloric acid are present (originally added to suppress coloring of the hydrochloride solution) 2 to 6 moles of hydrogen are absorbed. The addition of water in this case does not stop the reduction at one mole of hydrogen.

[t] Soluble with difficulty in water and alcohol.

[u] Obtained from 2-acetyldibenzofuran by reduction in absolute ethanol with platinum oxide catalyst; yield, 90%, soluble in benzene and alcohol. *Anal.* Calcd. for $C_{14}H_{12}O_2$: hydroxyl, 8.02. Found: hydroxyl, 10.3.

[v] A solution of 35 g. of aluminum chloride in 75 cc. of anhydrous nitrobenzene was added slowly at room temperature to a solution of 20 g. of dibenzofuran and 12.5 g. of propionyl chloride in 25 cc. of anhydrous nitrobenzene. The mixture was allowed to react at room temperature for sixty hours and was then worked up in the usual way. For purification the crude ketone was distilled in a vacuum of about 5 mm. and then recrystallized from 95% ethanol; yield of pure substance, 11 g.; moderately soluble in ethanol. For constitutional proof the propionyldibenzofuran was oxidized by means of sodium hypochlorite to dibenzofuran-2-carboxylic acid.

[w] Soluble in water.

[x] Soluble in water and alcohol with difficulty.

Compounds 5, 6, 10, 11, 14 and 15 were extremely difficult to burn even when mixed with copper oxide.

(6) Claisen and Manasse, *Ber.*, **20**, 2194 (1887).

the tertiary amine, methyl-bis-[-(2-dibenzofuroyl)-methyl]-amine, formed by the reaction of one mole of methylamine with two moles of the bromo ketone, could be isolated. In both cases 2-dibenzofurancarboxylic acid could be separated from the reaction products. Its formation in the reaction is as yet unexplained. Attempts to increase the yield of the secondary amino ketones by variation of experimental conditions failed. The amino ketones IV, V and VI were obtained in almost quantitative yield.

While the dimethylamino and piperidino ketones IV and VI can be reduced without any complications, the amino and diethylamino ketones VIII and V absorb two to six moles of hydrogen unless certain conditions are strictly observed.

Dibenzofuran shows as little physiological activity as phenanthrene; with the introduction of simple groups such as $-COCH_3$, COC_2H_5, mild depressant action becomes apparent. The amino alcohols do not give a morphine-like picture in the cat, but are generally more analgesic and more toxic than the corresponding amino alcohols in the phenanthrene series.[3b]

Experimental Part

The compounds marked with an asterisk have been recently prepared by Kirkpatrick and Parker.[7] We have included descriptions of them here because of some differences in physical properties. The authors will be referred to as K. and P.

(7) Kirkpatrick and Parker, THIS JOURNAL, **57**, 1123 (1935).

Summary

The preparation of a series of amino alcohols derived from dibenzofuran is described. From 2-acetyldibenzofuran derivatives carrying the side chain —CHOH—CH_2NR_2 (NR_2 being the amino, dimethylamino, ethylamino, diethylamino and piperidino group) are obtained.

UNIVERSITY, VIRGINIA RECEIVED JULY 1, 1935

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

Studies in the Phenanthrene Series. IX. Amino Alcohols Derived from 1,2,3,4-Tetrahydrophenanthrene[1]

BY ERICH MOSETTIG AND ALFRED BURGER

Morphine and most of its derivatives may be considered essentially as amino alcohols having the secondary alcoholic hydroxyl and the tertiary nitrogen attached to a partially hydrogenated phenanthrene nucleus. This consideration has led us in the past few years to the synthesis of a series of derivatives of phenanthrene and of partially hydrogenated phenanthrene carrying the side chains

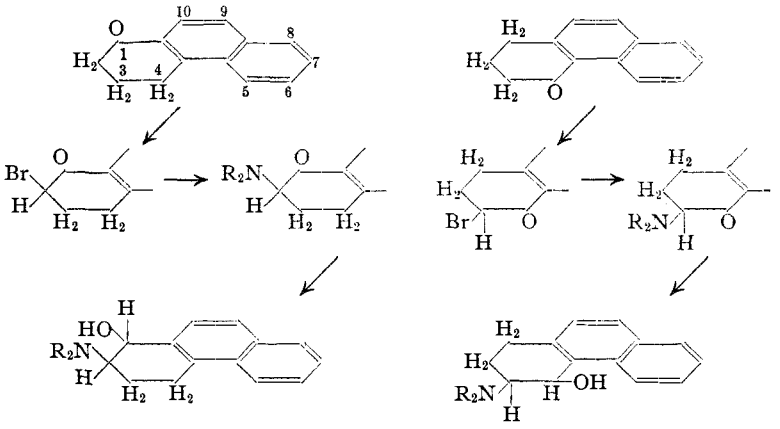
—CHOH—CH_2N= and —CHOHCH(—CH_3)—N=[2]

Some of the amino alcohols of this type show a decided pharmacological resemblance to morphine.[3]

This communication deals with a series of amino alcohols which differ principally from those mentioned above in that the alcoholic hydroxyl and the nitrogen are not located in a side chain, but are attached directly to carbon atoms of the phenanthrene nucleus itself, which must necessarily be hydrogenated in the ring carrying the substituents. It is apparent that the amino alcohols of this type are structurally somewhat more closely related to morphine and hence might be expected to show a morphine-like effect more pronounced than that of the open-chain amino alcohols.

The known 1-keto-1,2,3,4 - tetrahydrophenanthrene ("1-tetanthrenone"[4]) and the 4-isomer are convenient starting materials for the synthesis of a series of these new amino alcohols. The synthesis is outlined in the diagram.

The bromination of the tetanthrenones proceeds smoothly. The dimethylamino- and piperidino- ketones are formed in yields of over 80%,



NR_2 = dimethylamino-, diethylamino-, piperidino- and 1,2,3,4-tetrahydroisoquinolino-.

the corresponding tetrahydroisoquinolino compounds in yields of 60–70%. It is noteworthy that all attempts to exchange the bromine in the bromotetanthrenones with tetrahydroquinoline were without much success. In the reaction with diethylamine, whether carried out at room temperature or at elevated temperatures, the expected

(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) Mosettig and van de Kamp, THIS JOURNAL, **55**, 3448 (1933); van de Kamp and Mosettig, *ibid.*, **57**, 1107 (1935); Burger and Mosettig, *ibid.*, **56**, 1745 (1934).

(3) Unpublished results by Eddy and co-workers, University of Michigan.

(4) Trivial names introduced by G. Schroeter, *Ber.*, **57**, 2025 (1924).