Summary

The procedure involving adsorption of the antineuritic vitamin upon fuller's earth and subsequent extraction, benzoylation and acetone precipitation has yielded, without the use of any precipitating agents, final products the most active of which was curative in 0.03-mg. doses, by the Smith rat method. This is an activity about one-fourth greater than that of the Jansen and Donath crystals. It is more than twice as great on the nitrogen basis. Products of somewhat lower activity were obtained in considerably larger yields. Apparently small variations of conditions at certain stages of the process may affect greatly the quantity and quality of the final product. Especial attention has been given to the effect of variation of ratio of the benzoylating reagents and of the temperature of the reaction upon the quality and yield of the final concentrate.

WASHINGTON, D. C.

[CONTRIBUTION NO. 75 FROM THE COBB CHEMICAL LABORATORY OF THE UNIVERSITY OF VIRGINIA]

NEW ALKAMINES IN THE TETRAHYDRONAPHTHALENE SERIES[1]

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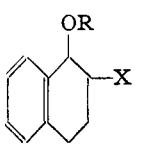
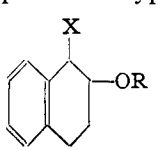
In the classic investigations of partially hydrogenated naphthalene derivatives carried out by Bamberger[2] over forty years ago, the fact was established that alicyclic β-tetrahydronaphthylamine and its derivatives exert to a considerable degree a specific pharmacological action. After studying a number of compounds, Bamberger stated the rule that this property is exhibited only when the substituted nucleus is hydrogenated, and only when the basic substituent occupies the β-position. In more recent years, this observation was confirmed through the investigations of von Braun[3] on alicyclic amino alcohol derivatives of tetrahydronaphthalene. He was able to show that only compounds of type I have pharma-



I



II

X = NH_2, $HNCH_3$, $N(CH_3)_2$, etc. R = H or alkyl

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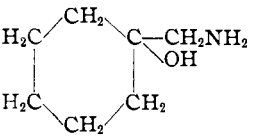
[1] This investigation was supported by a grant from the Committee on Drug Addiction of the National Research Council from funds provided by the Bureau of Social Hygiene, Inc.

[2] E. Bamberger and W. Filehne, *Ber.*, **22**, 777 (1889).

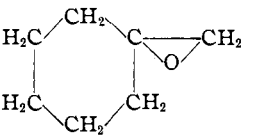
[3] Von Braun, Braunsdorf and Kirschbaum, *ibid.*, **55**, 3648 (1922); v. Braun and Weissbach, *ibid.*, **63**, 3052 (1930); *cf.* Strauss and Rohrbacher, *ibid.*, **54**, 40 (1921).

cological properties resembling those of alicyclic β-tetrahydronaphthylamine, whereas derivatives of type II are comparatively inactive. The β-position of the basic group in these cases is likewise the deciding factor.

In an earlier paper[4] we described attempts to synthesize hydroaromatic alkamines of type III which had their starting point in the oxide IV,



III



IV

but which as practicable synthetic methods were unsuccessful, since the reaction of diazomethane on cyclohexanone, used for the preparation of IV, ran chiefly to ring enlargement, giving cycloheptanone and cyclooctanone. At that time the surmise was made that the corresponding naphthalene derivatives, α- and β-ketotetrahydronaphthalene, because of the linkage of the hydrogenated ring to an aromatic nucleus, would show far less tendency to undergo ring enlargement.

Of the isomeric ketotetrahydronaphthalenes, only β-tetralone can be induced to react with diazomethane; α-tetralone is indifferent toward this reagent. This is in general accord with the observations of von Braun and others[3] on the remarkable differences in the activity of the two tetralones. We need mention here only the relative instability of β-tetralone, and the unexplained blue color which results when this compound is exposed to atmospheric oxygen in the presence of alkali.[5] The behavior of the two ketones toward sodium bisulfite differs also; only the β-isomer gives a bisulfite compound. We believe that an analogy for this is to be found in the case of mixed aliphatic–aromatic ketones. Whereas ketones of the type $ArCOCH_3$ do not, in general, give bisulfite addition products, benzyl methyl ketones, the so-called β-ketones of the type $ArCH_2COCH_3$, in most cases do so. In a recent investigation of ketones of this type[6] the conclusion was drawn that if a ketone forms a bisulfite compound it may be expected to react with diazomethane. The behavior of α- and β-tetralone toward diazomethane and sodium bisulfite gives additional support to this conclusion.

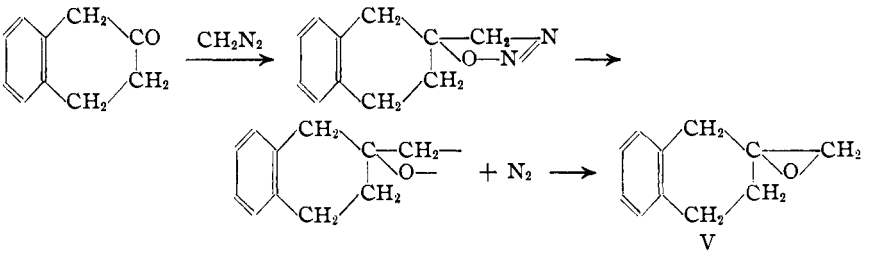
When carefully purified β-tetralone is acted upon by diazomethane in ether–methanol mixture, a product containing an additional $-CH_2-$ group and showing none of the properties of a ketone results. It is characterized as an ethylene oxide derivative by its facile conversion to amino alcohols. Arndt, Meerwein and Mosettig (for a bibliography, see the paper

[4] Mosettig and Burger, THIS JOURNAL, **52**, 3456 (1930).

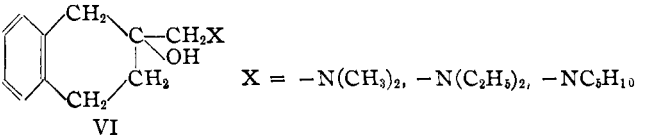
[5] We have found that this color appears also in the presence of ammonia and amines, as dimethylamine, diethylamine or piperidine.

[6] Mosettig and Jovanovič, *Monatsh.*, **53** and **54**, 427 (1929).

of Mosettig and Burger, Ref. 4) have investigated thoroughly in recent years the reaction of diazomethane with carbonyl compounds, and according to their formulation the reaction under discussion may be represented as

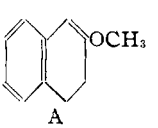


where Formula V depicts the oxide obtained as the end-product. Reasoning from analogy and from the general rule that addition of amines to ethylene oxides results in an hydroxyl group on the carbon atom carrying the least hydrogen, we believe that the amino alcohols formed by addition of amines to V must have the formula VI.



The oxide (V) derived from β-tetralone could not be purified for analysis, and the dimethylamino-, diethylamino- and piperidino alcohols from it, which do not crystallize, were characterized and analyzed as the well-crystallized hydrochlorides, perchlorates and platinichlorides. It is possible that isomers of these amino alcohols, formed by addition of the amines to the oxide in the alternative way, are present in the reaction mixture, and the formation of homologs, from a theoretically possible homologous oxide, is not excluded. The mother liquors from the crystalline salts of all of these amino alcohols yielded oily fractions in considerable quantity, but in only one case (that of the dimethylamino alcohol) could a second amino alcohol be isolated in the form of well-defined salts.

In addition to the oxide (V), the reaction of diazomethane with β-tetralone gives about a 30% yield of a yellow oil which has the properties of neither a ketone nor an ethylene oxide. The substance is free from nitrogen and is monomolecular, but analytical values, which do not correspond to any plausible empirical formula, are not significant, since in spite of the narrow boiling range observed we cannot be sure that only one compound is present. The oil has an agreeable odor, recalling that of β-naphthol methyl ether. The methoxyl determination and hydrogenation experiments were negative, which together with the high boiling point, 137–139° (1 mm.), excludes the possibility that the indifferent compound is the methyl ether



of the enolic form of β-tetralone, b. p. 136° (15 mm.) (A), which has been prepared by von Braun.[7] We are at present able to make no conjecture as to the nature of the indifferent by-product.

The reaction of diazoethane with β-tetralone proceeds much more vigorously than that of diazomethane, but yields nevertheless more than half of the β-tetralone unchanged. The rest of the reaction mixture consists of a high-boiling, rather unstable, strongly colored oil, which could not be purified. The crude reaction mixture, which was believed to contain an ethylene oxide type, was treated with piperidine in an unsuccessful attempt to isolate amino alcohols. In this experiment the interesting observation was made that β-tetralone forms an addition product with piperidine on gentle warming. The addition compound is unstable and decomposes slowly on standing into its components, β-tetralone and piperidine. The decomposition, which also takes place in dilute hydrochloric acid solution, is accelerated by heating.

α-Tetralone does not give such an addition product with piperidine.

The new alicyclic alkamines from tetrahydronaphthalene described in this paper have been prepared preliminary to an extension of the synthetic method to analogous compounds involving higher ring systems. According to Bamberger's rule mentioned above, the amino alcohols prepared from β-tetralone should have a marked pharmacological action. The pharmacological report on these substances will be published (C. W. Edmunds and N. B. Eddy) from the Medical School of the University of Michigan.

Experimental Part

β-Tetralone (1,2,3,4-Tetrahydro-2-ketonaphthalene) and Diazomethane.—β-Tetralone was prepared by heating the methiodide of 1-dimethylamino-2-hydroxy-1,2,3,4-tetrahydronaphthalene according to the directions of von Braun.[8] The product obtained gave a semicarbazone which melted at 194–195° on rapid heating, 189–191° on slow heating (v. Braun gives m. p. 190–191°).

The β-tetralone, which cannot be kept unchanged for any length of time, was converted to the bisulfite compound, which was washed with ether and kept in a glass-stoppered bottle. The free ketone was liberated from the bisulfite compound with sulfuric acid, just before using.

Twenty-five grams of β-tetralone was prepared by decomposition of the bisulfite compound and distilled in a vacuum, b. p. 142° (15 mm.). It was added to a solution of 15.2 g. of diazomethane (*i. e.*, a little over two molecular equivalents) in 660 cc. of ether at −5°. After addition of 200 cc. of absolute methyl alcohol, the mixture was allowed to stand at room temperature and soon began to evolve nitrogen vigorously. After the solution had stood for thirty-six hours, the ether was removed on a steam-bath and the methyl alcohol was distilled off under reduced pressure at 25–30°. The residue was purified by distillation in a vacuum. It boiled between 123–140° at 1 mm. pressure, the main portion distilling at 137–138°. The distillate consisted of 24 g. of a yellow oil. The residue from the distillation was a reddish-brown resinous tar.

[7] Von Braun and Weissbach, *Ber.*, **63**, 3055 (1930).

[8] Von Braun, Braunsdorf and Kirschbaum, *ibid.*, **55**, 3659 (1922).

In another run with 74 g. of β-tetralone and 47 g. of diazomethane in 2560 cc. of ether and 500 cc. of methyl alcohol, 68 g. of the yellow distillate was obtained, of which 63 g. boiled from 135–145° at 6 mm. pressure. In this case relatively more of the non-distillable resinous substance remained in the flask.

The yellow oil gave neither a semicarbazone nor a bisulfite compound. It showed a more or less pronounced color reaction when treated with a dilute solution of alkali or strong amines. The solution turned blue although no β-tetralone could be shown to be present in the mixture. The oxide (V) formed about two-thirds of this oil, from which it could be removed by treating with amines as described below. The indifferent part (35 to 36% of the whole weight of the oil) was purified by repeated distillation. The final distillate was a yellow oil of b. p. 137–139° (1 mm.).

Anal. Subs., 0.0690, 0.0829, 0.0799: CO_2, 0.2062, 0.2477, 0.2392; H_2O, 0.0496, 0.0589, 0.0571. Found: C, 81.50, 81.49, 81.65; H, 8.04, 7.95, 8.00. *Mol. wt.* Subs., 0.3121: 13.05 g. of benzene; Δt, 0.680°. Calcd. for $C_{11}H_{12}O$: mol. wt. 160. Found: 179.

Amino Alcohols from the Oxide V

General Preparative Method.—These amino alcohols were prepared by heating the crude oxide with 10% more than the calculated amount of the amines (dimethylamine, diethylamine, piperidine, respectively) and the same weight of water in a sealed tube at 95–100° for five hours. The reaction mixtures were taken up in ether and washed with water to remove most of the unchanged amine. The amino alcohols were extracted with dilute hydrochloric acid from the ethereal solution, precipitated with alkali and taken up again in ether. The ethereal solution was dried and the solvent evaporated. The residues distilled in a vacuum as almost colorless oils. The original ethereal layer contained the indifferent oil mentioned above.

The oily amino alcohols were dissolved in a little ether and an ethereal solution of perchloric acid was added in small portions. An oil precipitated out which soon crystallized. The addition of perchloric acid was continued until the precipitated salt began to separate as a viscous mass. It was collected on a filter and recrystallized from alcohol–ether. The yield was about half of that expected. These perchlorates were decomposed with a solution of sodium hydroxide, and the free alkamines were taken up in ether. The dried ethereal solution was treated with ethereal hydrochloric acid and the crystalline hydrochloride recrystallized from a mixture of alcohol and ether.

The procedure outlined above was used to obtain pure dimethyl- and diethylamino alcohols, but in the case of the piperidino alcohol it was found advisable to precipitate the hydrochloride first with ethereal hydrogen chloride, interrupting the precipitation as soon as the hydrochloride no longer separated well crystallized. The mother liquors resulting from the perchlorate precipitations described above yielded a further precipitate of an oily perchlorate with more ethereal perchloric acid.[9] Only in the case of the dimethylamino alcohol could this second precipitated fraction be obtained crystalline, and from it other well-crystallized salts of the unidentified (apparently homologous) dimethylamino alcohol, which is listed second in the table, could be prepared.

β-Tetralone and Piperidine.—Four grams of β-tetralone and a solution of 3.2 g. of piperidine in an equal amount of water was heated in a sealed tube to 100° for four hours. The reaction mixture was shaken with ether and the latter washed with water until the aqueous extracts were but faintly blue. The ethereal layer was then rapidly extracted with dilute hydrochloric acid twice. This absolutely clear acid solution becomes turbid after some time. When the acid solution was warmed to 30°, 3 g. of an oil separated

[9] The piperidino alcohol hydrochloride mother liquors were made alkaline, extracted with ether, and the extract treated with perchloric acid.

TABLE I

CONSTANTS AND ANALYTICAL DATA

Compound	B. p. (or m. p.), °C.	Formula	Calcd., %	Found, %
Dimethylamino alcohol[a]	(b.) 116–118 (1 mm.)	(8 g. of the crude oxide yielded 6.5 g.)		
Hydrochloride[b]	(m.) 175–176	$C_{13}H_{20}ONCl$	Cl, 14.68	14.69
Perchlorate[c]	(m.) 158–159	$C_{13}H_{20}O_5NCl$	Cl, 11.60	11.55
Platinum salt	(m.) 197–198 (dec.)	$C_{26}H_{40}O_2N_2PtCl_6$	Pt, 23.80	23.84
Dimethylamino alcohol (homolog?)				
Hydrochloride	(m.) 196–198	$C_{14}H_{22}ONCl$	Cl, 13.87	13.24
Perchlorate	(m.) 184	$C_{14}H_{22}O_5NCl$	Cl, 11.09	11.17
Platinum salt	(m.) 197–198	$C_{28}H_{44}O_2N_2PtCl_6$	Pt, 23.12	22.87
Diethylamino alcohol	(b.) 135–137 (1 mm.)	(6 g. of the crude oxide yielded 5.2 g.)		
Hydrochloride	(m.) 125–126[d]	$C_{15}H_{24}ONCl\cdot H_2O$	H_2O, 6.26	6.25
		$C_{15}H_{24}ONCl$	Cl, 13.15	13.09
Perchlorate	(m.) 155–156	$C_{15}H_{24}O_5NCl$	Cl, 10.63	10.53
Platinum salt	(m.) 190 (dec.)	$C_{30}H_{48}O_2N_2PtCl_6$	Pt, 22.27	22.41
Piperidino alcohol	(b.) 146–148 (1 mm.)	(8 g. of the crude oxide yielded 8.3 g.)		
Hydrochloride	(m.) 200–200.5	$C_{16}H_{24}ONCl$	Cl, 12.59	12.34
Perchlorate	(m.) 147.5–148	$C_{16}H_{24}O_5NCl$	Cl, 10.26	10.06
Platinum salt	(m.) 205–206.5 (dec.) slow heating; 214–216 (dec.) fast heating	$C_{32}H_{48}O_2N_2PtCl_6$	Pt, 21.68	21.58

[a] The same yields were obtained when the dimethylamino alcohols were prepared by heating the oxide with a benzene solution of dimethylamine. [b] All hydrochlorides were analyzed by direct precipitation with silver nitrate. [c] All perchlorates were analyzed by the method of Hofmann, *Ber.*, **43**, 1080 (1910), fusion with sodium carbonate and determination of halogen. [d] The hydrochloride of the diethylamino alcohol crystallizes from a mixture of ordinary alcohol and ether with one molecule of water of crystallization, which is given off at 92°. The halogen analysis was carried out after drying the substance at 90–95° in a vacuum.

out which was extracted into ether and was identified as pure β-tetralone (semicarbazone, m. p. 189–190°). The acid solution contained only piperidine.

It was not possible to distil the unstable supposed addition compound under the same conditions as the piperidino alcohols described above, and no analysis could be carried out because of the rapid decomposition which took place even at ordinary temperatures. On distillation the addition compound decomposed into the components, β-tetralone and piperidine.

Summary

A series of new alkamines derived from tetrahydronaphthalene has been prepared for pharmacological study.

The alkamines of Formula $C_{10}H_{10}\begin{matrix}CH_2X\\OH\end{matrix}$ (X = $-N(CH_3)_2$, $-N(C_2H_5)_2$, $-NC_5H_{10}$) are formed through addition of secondary amines, as dimethylamine, diethylamine or piperidine, to the ethylene oxide type of compound $C_{10}H_{10}CH_2O$ which results from the action of diazomethane on β-tetralone.

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