condensation is that the reaction proceeds much quicker, whereas in ethyl alcohol, the solvent used by Mannich, the condensation takes place very slowly. By prolonged boiling in ethyl alcohol, furthermore, the yield of the expected amino ketone is considerably lowered, on account of the formation of by-products. These are both neutral and basic in nature and in part crystalline. In the preparation of most of the piperidino and tetrahydroisoquinolino ketones the hydrochlorides crystallized out after five to ten minutes. They were filtered off from the cooled reaction mixture and recrystallized. In the cases where the hydrochlorides did not precipitate, the reaction mixture was cooled, after having been kept boiling for fifteen to twenty minutes. After the addition of a few drops of concentrated hydrochloric acid, in order to depolymerize unchanged paraformaldehyde, unreacted ketone and formaldehyde were taken up in ether. The aqueous layer was alkalified and extracted with ether and the residue left from evaporation of the ether was warmed slightly in a vacuum in order to remove aliphatic amines. The amino ketones subsequently were purified through the hydrochlorides.

The amino ketones were reduced in the form of the hydrochlorides, in 50–70% ethyl alcohol, using platinum oxide as a catalyst. In two cases where the free amino ketones were reduced, namely, in the cases of the 3-dimethylamino ketone and the 9-(1,2,3,4-tetrahydroisoquinolino) ketone, two moles of hydrogen were absorbed, and in the case of the 2-dimethylamino ketone, approximately three moles of hydrogen were taken up. The reduction of the 3-(1,2,3,4-tetrahydroisoquinolino) ketone was effected with good results either by hydrogenating the free base in 95% ethyl alcohol, or by reducing the hydrochloride in 60% ethyl alcohol.

Summary

1. A series of amino ketones of the type $C_{14}H_9COCH_2CH_2NR_2$ (NR_2 representing the dimethylamino-, the diethylamino-, the piperidino- and tetrahydroisoquinolino group) has been prepared by the Mannich method from 2-, 3- and 9-acetylphenanthrene.

2. By catalytic hydrogenation the corresponding amino alcohols $C_{14}H_9CHOHCH_2CH_2NR_2$ have been prepared. These substances will be investigated to determine the result pharmacologically of lengthening the carbon chain of amino alcohols of the phenanthrene series.

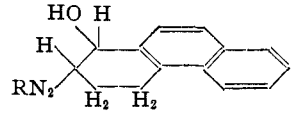
UNIVERSITY, VIRGINIA RECEIVED JUNE 22, 1936

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

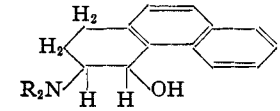
Studies in the Phenanthrene Series. XII.[1] Amino Alcohols Derived from 1,2,3,4-Tetrahydrophenanthrene[2]

BY ALFRED BURGER AND ERICH MOSETTIG

Among the synthetical substances which have been prepared in this Institution in the attempt to find morphine substitutes, 2-piperidino-1-hydroxy-1,2,3,4-tetrahydrophenanthrene (type I), and 3-(1,2,3,4-tetrahydroisoquinolino)-4-hydroxy-1,2,3,4-tetrahydrophenanthrene (type II) proved to have the strongest analgesic action (minimal effective doses administered orally to cats, 20 and 15 mg. per kilogram, respectively, comparable with doses of 20 mg. for pseudocodeine, 10 mg. for codeine, and 1 mg. for morphine).[2] Experiments are under way to resolve these compounds and eliminate or "muzzle" their alcoholic hydroxyl in the hope of increasing their physiological activity.[3]

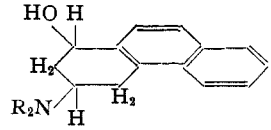


I

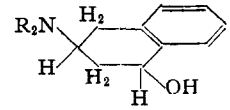


II

We are reporting in the present communication the preparation of compounds which differ from those of types I and II principally through the position of the nitrogen group. Compounds which may be represented by type formulas III and IV, analogs of the propanolamines reported in the foregoing communication, are obviously not readily accessible.



III

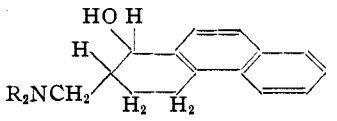


IV

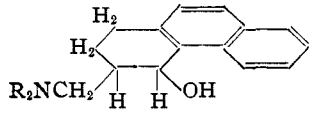
(1) The work reported in this paper is part of a unification of effort by a number of agencies having responsibility for the solution of the problem of drug addiction. The organizations taking part are: The Rockefeller Foundation, the National Research Council, the U. S. Public Health Service, the U.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

(2) First communication on amino alcohols derived from 1,2,3,4-tetrahydrophenanthrene, Mosettig and Burger, THIS JOURNAL, **57**, 2189 (1935).

(3) Elimination and muzzling of the alcoholic group in morphine and its derivatives produce generally a marked increase in analgesic action. Eddy, *J. Pharmacol.*, **55**, 127 (1935); Eddy and Howes, *ibid.*, **55**, 257 (1935).



V



VI

The compounds of type V and VI, however, carrying the nitrogen group in the same relative position to the alcoholic hydroxyl group as in the propanolamines and in types III and IV could be conveniently prepared, essentially by the Mannich method,[4] that is, by the action of the hydrochlorides of secondary amines (dimethylamine, diethylamine, piperidine and tetrahydroisoquinoline) and paraformaldehyde on 1- and 4-ketotetrahydrophenanthrenes, and subsequent reduction of the amino ketones.[5]

We have not proved experimentally formulas V or VI for the new amino alcohols described in this communication, but the formation of the corresponding amino ketones by the method of Mannich hardly leaves any doubt as to the constitution of the amino alcohols, since the formulas of the amino ketones prepared by Mannich and Braun[4,6] from cyclohexanone, amine hydrochloride and formaldehyde appear to be well established. In the reduction of our amino ketones to the amino alcohols, only one of the possible diastereomeric forms is obtained.

It was observed that two of the amino alcohols (V and VI, NR_2 represents the diethylamino- and tetrahydroisoquinolino group) split off water with ease when an attempt was made to acetylate them with acetic anhydride in pyridine. This loss of water also takes place under the influence of alcoholic hydrogen chloride. The resulting unsaturated amine readily can be reduced catalytically. We have not sufficient experimental data to make any conjecture concerning the structural features upon which the tendency to split out water is dependent. This question will be investigated in another connection.

The 1- and 4-tetanthrenones are also convenient starting materials for the synthesis of 1- and 4-aminotetanthrenes, which are obtained in good yields by reduction of the corresponding ketoximes.

(4) Mannich and Braun, *Ber.*, **53**, 1874 (1920).

(5) By employing 1,2,3,4-tetrahydroquinoline no definite reaction could be initiated. The same observation was made by Mannich in the case of aryl methyl ketones [Mannich and Lammering, *Ber.*, **55**, 3510 (1922)]. It should be recalled that it was impossible to obtain definite reaction products in the attempt to exchange the bromine in the bromotetanthrenones with tetrahydroquinoline.[2]

(6) See also Bodendorf and Koralewski, *Arch. Pharm.*, **271**, 101 (1933).

Experimental

Preparation of Amino Ketones.—A mixture of 1- or 2-ketotetrahydrophenanthrene (1 mole), the amine hydrochloride (1.2 moles), and paraformaldehyde (2.5 moles) in isoamyl alcohol was heated under reflux for ten to fifteen minutes. Generally portions of 5 to 10 g. of ketone in 50 to 100 cc. of isoamyl alcohol were used. A clear solution resulted after two or three minutes. The excess of paraformaldehyde was depolymerized by addition of a few drops of alcoholic hydrogen chloride. The solution was cooled, diluted with ether and extracted with dilute aqueous hydrochloric acid. The amino ketones were liberated, extracted into ether and purified by crystallization or in the form of their salts. The secondary amines used in the reaction were dimethylamine, diethylamine, piperidine and tetrahydroisoquinoline. No definite reaction was observed with tetrahydroquinoline. In the case of the two tetrahydroisoquinolino ketones, the hydrochlorides crystallized directly from the reaction mixtures. They were filtered and washed with a little cold water.

Preparation of Amino Alcohols.—The amino ketones were hydrogenated as hydrochlorides in solution in 90% alcohol, using a platinum oxide catalyst. In most of the cases the reductions stopped when one mole of hydrogen had been absorbed.

1,2-Dihydro-3-[(1,2,3,4-tetrahydroisoquinolino)-methyl]-phenanthrene.—In the attempt to acetylate 4-hydroxy-3-[(1,2,3,4-tetrahydroisoquinolino)-methyl] - 1,2,3,4-tetrahydrophenanthrene with acetic anhydride and pyridine at room temperature, the unsaturated amine was formed. The same substance was obtained by allowing 4-hydroxy-3-[(1,2,3,4-tetrahydroisoquinolino)-methyl] - 1,2,3,4-tetrahydrophenanthrene to stand with alcoholic hydrogen chloride overnight. The base crystallized from dilute alcohol; m. p. 81–82°.

Anal. Calcd. for $C_{24}H_{23}N$: C, 88.56; H, 7.13; N, 4.31. Found: C, 88.55; H, 7.39; N, 4.40.

The hydrochloride was crystallized from alcohol–ether and melted at 227–228°.

Anal. Calcd. for $C_{24}H_{24}NCl$: C, 79.62; H, 6.69; N, 3.87. Found: C, 79.41; H, 6.84; N, 4.09.

The hydrochloride readily absorbs one mole of hydrogen (platinum oxide catalyst).

3,4-Dihydro-2-[(diethylamino)-methyl]-phenanthrene.—1 - Keto-2 - [(diethylamino) - methyl] - 1,2,3,4 - tetrahydrophenanthrene hydrochloride readily absorbed one mole of hydrogen, but neither the free amino alcohol nor any of its derivatives could be obtained in a crystalline state. On treatment with either acetic anhydride or alcoholic hydrogen chloride as described above, a colorless hydrochloride was obtained; recrystallized from alcohol–ether, m. p. 231–232°.

Anal. Calcd. for $C_{19}H_{24}NCl$: C, 75.58; H, 8.02; N, 4.64. Found: C, 75.88; H, 8.52; N, 4.88.

The free base from the hydrochloride was oily. The hydrochloride absorbed one mole of hydrogen on catalytic reduction.

TABLE I

Derivatives of 1,2,3,4-tetrahydrophenanthrene	Appearance	Solvent	Yield, %	M. p., °C.,	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1-Keto-2-((dimethylamino)-methyl)-	Colorless blades	Pet. ether		66–82	$C_{17}H_{19}ON$					5.53	5.22
Hydrochloride	Colorless	EtOH	65	199–200	$C_{17}H_{20}ONCl$					4.84	4.87
1-Keto-2-((diethylamino)-methyl)-	Leaflets	Pet. ether		60–61	$C_{19}H_{23}ON$					4.98	4.44
Hydrochloride	Colorless	EtOH-Et_2O	59	137–138	$C_{19}H_{24}ONCl$					4.41	4.49
Picrate	Yellow	EtOH		163–164	$C_{25}H_{26}O_8N_4$					10.98	11.08
1-Keto-2-(piperidinomethyl)-	Leaflets or needles	MeOH	40	97–98	$C_{20}H_{23}ON$					4.78	5.11
Hydrochloride	Colorless	EtOH-Et_2O		170–220	$C_{20}H_{24}ONCl$					4.25	4.26
1-Keto-2-((1,2,3,4-tetrahydro-isoquinolino)-methyl)-	Colorless needles	MeOH		121–123	$C_{24}H_{23}ON$					4.11	4.37
Hydrochloride	Shining leaflets	EtOH-Et_2O	61	148–150	$C_{24}H_{24}ONCl$					3.71	3.76
4-Keto-3-((dimethylamino)-methyl)--HCl	Shining leaflets	EtOH	77	178–179	$C_{17}H_{20}ONCl$					4.84	4.85
4-Keto-3-((diethylamino)-methyl)--HCl	Colorless	EtOH-Et_2O	51	153–154	$C_{19}H_{24}ONCl$					4.41	4.38
Picrate	Yellow	EtOH		149–151	$C_{25}H_{26}O_8N_4$					10.98	11.28
4-Keto-3-(piperidinomethyl)-	Yellow leaflets	Dil. acetone	37	106–107	$C_{20}H_{23}ON$					4.78	4.90
Perchlorate	Colorless	EtOH		163–164	$C_{20}H_{24}O_5NCl$					3.56	3.88
4-Keto-3-((1,2,3,4-tetrahydro-isoquinolino)-methyl)-.HCl	Glitt. prisms	EtOH-Et_2O	34	159–161	$C_{24}H_{24}ONCl$					3.71	3.80
1-Hydroxy-2-((dimethyl-amino)-methyl)-	Colorless	MeOH		146–147	$C_{17}H_{21}ON$	79.94	80.29	8.30	8.33	5.49	5.63
Hydrochloride	Colorless	EtOH-Et_2O	70	236	$C_{17}H_{22}ONCl$					4.80	4.87
1-Hydroxy-2-(piperidino-methyl)-	Fine needles	MeOH		133–134.5	$C_{20}H_{25}ON$	81.30	81.31	8.54	8.59	4.75	4.87
Hydrochloride	Needles	EtOH-Et_2O		227–228	$C_{20}H_{26}ONCl$					4.22	4.27
1-Hydroxy-2-((1,2,3,4-tetra-hydroisoquinolino)-methyl)-	Colorless	EtOH		159–160	$C_{24}H_{25}ON$	83.91	83.67	7.34	7.53	4.08	4.28
Hydrochloride	Colorless	EtOH-Et_2O		217	$C_{24}H_{26}ONCl$					3.69	3.80
4-Hydroxy-3-((dimethylamino)-methyl)--HCl	Colorless	EtOH-Et_2O		186–187	$C_{17}H_{22}ONCl$	69.95	69.66	7.61	7.74	4.80	4.85
4-Acetoxy-3-((dimethylamino)-methyl)--HCl	Colorless	EtOH-Et_2O		200	$C_{19}H_{24}O_2NCl$					4.20	4.32
4-Hydroxy-3-((diethylamino)-methyl)--HCl	Colorless	EtOH-Et_2O	86	172–173	$C_{19}H_{26}ONCl$	71.32	71.42	8.20	8.39	4.38	4.52
Picrate	Yellow	EtOH		177–179	$C_{25}H_{28}O_8N_4$					10.94	11.26
4-Hydroxy-3-(piperidino-methyl)--HCl	Colorless	Acetone	71	178–179	$C_{20}H_{26}ONCl$	72.36	72.51	7.90	8.14	4.22	4.20
4-Hydroxy-3-((1,2,3,4-tetra-hydroisoquinolino)-methyl)-	Colorless	Dil. MeOH		149.5–151	$C_{24}H_{25}ON$	83.91	83.92	7.34	6.92		
Hydrochloride	Colorless	EtOH-Et_2O		181–182	$C_{24}H_{26}ONCl$	75.85	75.50	6.90	6.76		
1-Amino-[a]	Colorless		86	61–63	$C_{14}H_{15}N$					7.07	7.23
Hydrochloride	Colorless	EtOH-Et_2O		256–257	$C_{14}H_{16}NCl$	71.92	71.81	6.90	6.90	6.00	6.09
Benzal 1-amino-[b]	Colorless	EtOH		103–105	$C_{21}H_{19}N$					4.91	4.96
1-(Methylamino)--HCl[b]	Colorless	EtOH-Et_2O	54	258	$C_{15}H_{18}NCl$	72.70	72.31	7.33	7.31	5.66	5.84
Hydriodide[b]	Glitt. leaflets	EtOH		243	$C_{15}H_{18}NI$					4.13	4.25
1-(Dimethylamino)--HCl[c]	Colorless	EtOH-Et_2O		216	$C_{16}H_{20}NCl$	73.39	73.47	7.71	7.82		
Picrate	Yellow	EtOH		177–178	$C_{22}H_{22}O_7N_4$					12.34	12.59
4-Amino--HCl[d]	Colorless	EtOH-Et_2O		267–268	$C_{14}H_{16}NCl$	71.92	71.70	6.90	7.00	6.00	5.96
4-(Dimethylamino)--HCl[c]	Colorless	EtOH-Et_2O		202	$C_{16}H_{20}NCl$	73.39	73.46	7.71	8.05		

[a] Prepared by reduction of 1-tetanthrenone oxime [Schroeter, Müller and Huang, *Ber.*, **62**, 645 (1929)] with 2.5% sodium amalgam in alcohol solution, acidified with acetic acid, or with aluminum amalgam in moist ether. [b] Prepared by the method of Decker, *Ann.*, **395**, 362 (1913). [c] Prepared by heating the primary amine with methyl iodide and sodium acetate at 100° for five hours and separating the reaction mixture by the Hinsberg method. [d] Prepared by reduction of 4-tetanthrenone oxime with aluminum amalgam in moist ether.

Summary

1. The synthesis of a series of amino alcohols derived from 1,2,3,4-tetrahydrophenanthrene is described. The synthesis is effected by condensing 1-keto-1,2,3,4-tetrahydrophenanthrene and 4-keto-1,2,3,4-tetrahydrophenanthrene, respectively, with paraformaldehyde and the hydrochlorides of dimethylamine, diethylamine, piperidine and 1,2,3,4-tetrahydroisoquinoline, respectively, by the method of Mannich, and subsequent catalytic hydrogenation of the resulting amino ketones.

2. By reduction of the oximes of the above-mentioned tetanthrenones with sodium amalgam or aluminum amalgam, 1- and 4-aminotetanthrene can be prepared in satisfactory yields. The amino alcohols will be investigated for comparison of their physiological action with that of the next lower homologs.

UNIVERSITY, VIRGINIA RECEIVED JUNE 22, 1936