[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA, NO. 156]

Studies in the Phenanthrene Series. VIII. Amino Alcohols Derived from 1,2,3,4,5,6,7,8-Octahydrophenanthrene[1]

BY JACOB VAN DE KAMP AND ERICH MOSETTIG

Pharmacological investigations[2] have shown that some of the phenanthrene derivatives with the side chain $-CHOHCH_2N=$[3] and $-CHOHCHN=$[4] (CH_3) exhibit in the cat a certain resemblance to morphine. Since the fundamental hydrocarbon skeleton of morphine is a hydrogenated phenanthrene nucleus, the synthesis of hydrogenated phenanthrene derivatives carrying these alkamine side chains has been undertaken in the hope of attaining still more active compounds.

Among the known partially hydrogenated phenanthrenes the 1,2,3,4,5,6,7,8-octahydrophenanthrene or "octanthrene"[5] appears especially convenient as starting material for the introduction of substituents. By the Friedel and Crafts reaction with chloroacetyl chloride the 9-ω-chloroacetyloctanthrene of Schroeter[5] can be prepared, in which, however, the halogen atom reacts with secondary amines only slowly. Therefore we prepared the ω-bromoacetyl derivative by bromination of 9-acetyloctanthrene. The bromine is easily exchanged for the dimethylamino, diethylamino and piperidino groups. Attempts to prepare in the same way, with monomethyl- and monoethylamine, the secondary amino ketones were without results. The primary amino ketone is obtained by the reduction of isonitrosoacetyloctanthrene with stannous chloride. In an analogous way, the corresponding homologous amino ketones were prepared from 9-propionyloctanthrene. The exchange of the α-bromine atom with the monomethylamino and monoethylamino group in α-bromopropionyloctanthrene proceeds very well, quite in contrast to the corresponding experiments with ω-bromoacetyloctanthrene.

The catalytic reduction of the amino ketones to the corresponding amino alcohols does not offer any difficulties. Of the propanolamines apparently only one of the possible diastereomeric forms was obtained. Acetyl- and propionyloctanthrene yield on oxidation with sodium hypochlorite the acid known as octanthrene-9-carboxylic acid. This acid is identical with that obtained by catalytic reduction of phenanthrene-9-carboxylic acid. The hitherto assumed 9-position of the carboxyl group in octanthrene-9-carboxylic acid, as well as the position of the chloroacetyl, acetyl and propionyl groups in the octanthrene derivatives here described, is thus demonstrated.

Table I gives a summary of the reactions and compounds dealt with in this paper. It is intended to attempt the preparation of analogous amino alcohols derived from 9,10-dihydro-, 1,2,3,4-tetrahydro- and 1,2,3,4,9,10,11,12-octahydrophenanthrene.

We are indebted to Mr. Lyon Southworth of this Laboratory for many of the analyses appearing in this paper.

Experimental

Preparation of 1,2,3,4,5,6,7,8-Octahydrophenanthrene.—Three hundred and fifty-six grams (2 moles) of phenanthrene,[6] 40 cc. of dry decahydronaphthalene[7] and 10 to 12 g. of Raney nickel catalyst[8] were heated, with constant shaking, in a hydrogen atmosphere at 120° under an initial pressure varying from 1600 to 2100 lb., in the apparatus (contents 750 cc.) described by Adkins and Cramer.[9]

Hydrogen absorption started at 120°. From two to eight days were required for absorption of the amount of hydrogen necessary for the formation of octahydrophenanthrene. Every two days a fresh amount of 10 to 12 g. of catalyst was added. The end of the reduction was evident by a marked drop in the rate of hydrogen absorp-

(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) Nathan B. Eddy, unpublished results.

(3) (a) Mosettig and van de Kamp, THIS JOURNAL, **55**, 3448 (1933); (b) Burger and Mosettig, *ibid.*, **56**, 1745 (1934).

(4) Mosettig and Czerwin, unpublished results.

(5) Schroeter, *Ber.*, **57**, 2025 (1924). The trivial name proposed by Schroeter will be used as a convenient abbreviation.

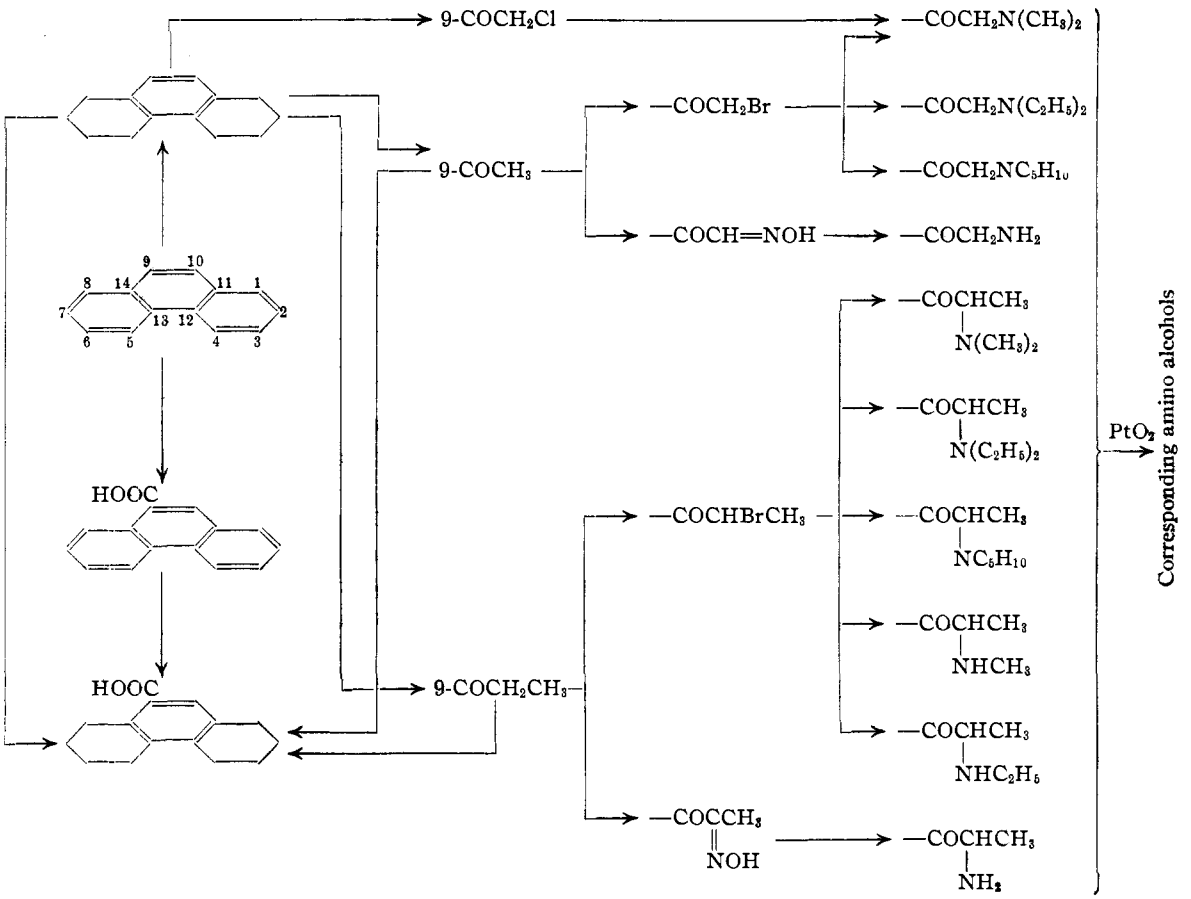
(6) The phenanthrene used in these reductions was a product purified according to Cohen and Cormier, THIS JOURNAL, **52**, 4363 (1930), subsequently heated with sodium at 200° for two hours, and finally distilled.

(7) Mosettig and van de Kamp, *ibid.*, **55**, 2996 (1933), footnote 10.

(8) This catalyst was prepared according to directions of Covert and Adkins, *ibid.*, **54**, 4116 (1932). It was then washed with absolute ethyl alcohol and subsequently with decahydronaphthalene until the latter showed no turbidity. The nickel was kept under dry decahydronaphthalene.

(9) Adkins and Cramer, *ibid.*, **52**, 4349 (1930).

TABLE I



tion.[10] After removal of catalyst and solvent, the reduction product was distilled in an oil pump vacuum and then purified through the sodium sulfonate according to Schroeter.[5] The regenerated hydrocarbon was rectified, b. p. 179–180° (20 mm.), $n^{17}D$ 1.5669.[11] Cooled in ice, it readily crystallized to a mass of colorless needles.[12] In our experiments the yield varied from 70 to 85%, the better yield being obtained at the lower temperature (120°).

Anal. Calcd. for $C_{14}H_{18}$: C, 90.25; H, 9.75. Found: C, 90.31; H, 9.66.

Friedel and Crafts Reactions.—For the preparation of 1,2,3,4,5,6,7,8-octahydrophenanthrene-9-carboxylic acid, 9-ω-chloroacetyl-, 9-acetyl- and 9-propionyl-1,2,3,4,5,6,7,-8-octahydrophenanthrene, the Friedel and Crafts reaction was applied to 1,2,3,4,5,6,7,8-octahydrophenanthrene.

To a solution of 1 part of 1,2,3,4,5,6,7,8-octahydrophenanthrene in 10 parts of carbon disulfide, cooled to −15°, the acid chloride[13] was added, and 2 moles of aluminum chloride was added in small portions in the course of one hour. After this, stirring was continued for five more hours and the temperature maintained at −15°.

The yields of the acid, chloroacetyl-, acetyl- and propionyl- derivative were 87, 89, 98.5 and 97%, respectively. The acid gave no depression in melting point when mixed with a sample of the acid which results from saponification of the product formed by catalytic reduction (4 moles of hydrogen) of phenanthrene-9-carboxylic acid ethyl ester with platinum in glacial acetic acid.

Oxidations of both 9-acetyl- and 9-propionyl-1,2,3,4,-5,6,7,8-octahydrophenanthrene with a 2% sodium hypochlorite solution gave 1,2,3,4,5,6,7,8-octahydrophenanthrene-9-carboxylic acid. This acid and its methyl ester gave no depression in melting points with samples of the acid mentioned above, and its methyl ester, respectively.

The ketones were brominated[14] to the 9-ω-bromoacetyl- and 9-α-bromopropionyl-1,2,3,4,5,6,7,8-octahydrophenanthrene, respectively. The bromine atom in these bromo ketones was exchanged with primary and secondary amines, to form secondary and tertiary amino ketones. From 9-acetyl- and 9-propionyl-1,2,3,4,5,6,7,8-octahydrophenanthrene the isonitroso derivatives[15] were prepared

(10) At temperatures of 140° a satisfactory yield of octahydrophenanthrene was obtained in a shorter time. At 150° the yield was considerably smaller due to the formation of higher hydrogenated products. At 175° only higher hydrogenated products were formed.

(11) Auwers, *Ann.*, **430**, 259 (1930), measured $n^{20}D$ 1.5668 on Schroeter's product.

(12) Schroeter gives the m. p. as 16.7°.

(13) In the case of acetyl-, propionyl- and chloroacetyl chloride, a 10% excess was used, with oxalyl chloride, 100% excess. Schroeter, in the preparation of ω-chloroacetyloctanthrene, heated the hydrocarbon with the acid chloride and a trace of phosphorus pentoxide.

(14) The bromination was carried out in absolute ether as described previously (see reference 3a).

(15) The yield of the isonitroso derivatives varied between 30 and 50% of the theoretical.

TABLE II

Derivatives of 1,2,3,4,5,6,7,8-Octahydrophenanthrene	Solvent	Appearance[a]	M. p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Halogen, % Calcd.	Halogen, % Found
9-Acetyl-*	MeOH	Rectangular plates	58–59	$C_{16}H_{20}O$	84.15	84.00	8.83	8.57				
-Oxime	MeOH	Plates	158.5–159.5	$C_{16}H_{21}ON$					5.76	5.98		
-Semicarbazone	MeOH	Plates	191.5–193	$C_{17}H_{23}ON_3$	71.53	71.49	8.13	8.04				
9-Propionyl-*	MeOH	Prisms	52.5–53	$C_{17}H_{22}O$	84.24	84.35	9.16	9.08				
-Oxime	MeOH	Needles	146–147	$C_{17}H_{23}ON$					5.45	5.67		
9-ω-Bromoacetyl-*	EtOH	Needles	55–56	$C_{16}H_{19}OBr$							Br, 26.03	25.97
9-α-Bromopropionyl-*		Oil		$C_{17}H_{21}OBr$							Br, 24.89	25.01
*-9-Carboxylic acid	EtOH, AcOH	Prisms	241–242	$C_{15}H_{16}O_2$	78.21	78.39	7.88	7.94				
-Methyl ester	MeOH	Prisms	45	$C_{16}H_{20}O_2$	78.64	78.28	8.26	8.35				
9-(2-Amino-1-oxo)-ethyl-* hydrochloride	H_2O	Leaflets	232–234[b] dec.	$C_{16}H_{22}ONCl$							Cl, 12.68	12.71
-Picrate	EtOH	Prisms	215–216 dec.	$C_{22}H_{24}O_8N_4$					11.87	11.73		
9-(2-Amino-1-hydroxy)-ethyl-*	EtOH + H_2O	Needle clusters	103–104	$C_{16}H_{23}ON$	78.31	78.00	9.45	9.42				
-Hydrochloride	EtOH + ether	Leaflets	253.5–254	$C_{16}H_{24}ONCl$					4.97	5.08		
-Picrate	EtOH	Needles	208.5–209.5 dec.	$C_{22}H_{26}O_8N_4$					11.82	11.96		
9-(2-Dimethylamino-1-oxo)-ethyl-* hydrochloride[c]	EtOH + ether	Plates	236–237.5[d] dec.	$C_{18}H_{26}ONCl$							Cl, 11.52	11.51
-Picrate	EtOH	Plates	116–117	$C_{24}H_{28}O_8N_4$					11.20	11.35		
9-(2-Dimethylamino-1-hydroxy)ethyl-*	EtOH	Plates	80–80.5	$C_{18}H_{27}ON$	79.06	79.00	9.96	9.85				
-Hydrochloride	EtOH + ether	Diamonds	217–218	$C_{18}H_{28}ONCl$					4.52	4.62		
-Picrate	EtOH	Plates	193–194	$C_{24}H_{30}O_8N_4$					11.16	11.42		
9-(2-Diethylamino-1-oxo)-ethyl-* perchlorate[c]	EtOH + ether	Plates	165–166	$C_{20}H_{30}O_5NCl$					3.51	3.66		
-Picrate	EtOH	Needles	144.5–145.5	$C_{26}H_{32}O_8N_4$					10.61	10.79		
9-(2-Diethylamino-1-hydroxy)-ethyl-*	EtOH + H_2O	Plates	72.5–73	$C_{20}H_{31}ON$	79.67	79.71	10.37	10.38				
-Hydrochloride	EtOH + ether	Prisms	148–149	$C_{20}H_{32}ONCl$							Cl, 10.50	10.56
-Picrate	EtOH	Rectangular plates	159–160	$C_{26}H_{34}O_8N_4$					10.57	10.85		
9-(2-Piperidino-1-oxo)-ethyl-* perchlorate[c]	Acetone-ether	Needles	220.5–222	$C_{21}H_{30}O_5NCl$					3.40	3.63		
-Picrate	EtOH	Needles	116.5–117	$C_{27}H_{32}O_8N_4$					10.37	10.57		
9-(2-Piperidino-1-hydroxy)-ethyl-[e]*		Needles	86–86.5	$C_{21}H_{31}ON$	80.45	80.12	9.97	9.91				
-Hydrochloride	EtOH	Prisms	227–227.5	$C_{21}H_{32}ONCl$							Cl, 11.32	11.33
-Picrate	EtOH	Blades	164.5–165.5	$C_{27}H_{34}O_8N_4$					10.33	10.52		
9-(2-Amino-1-oxo)-propyl-* hydrochloride	EtOH	Needles	231–233 dec.	$C_{17}H_{24}ONCl$					4.77	4.84		
-Picrate	EtOH	Needles	181–182 dec.	$C_{23}H_{26}O_8N_4$					11.52	11.80		
9-(2-Amino-1-hydroxy)-*n*-propyl-*	EtOH	Plates	164–164.5	$C_{17}H_{25}ON$	78.70	78.57	9.72	9.67				
-Hydrochloride	EtOH + ether	Diamonds	278–279	$C_{17}H_{26}ONCl$							Cl, 11.99	12.12
-Picrate	EtOH	Prisms	224–224.5[f] dec.	$C_{23}H_{28}O_8N_4$					11.48	11.77		
9-(2-Dimethylamino-1-oxo)-propyl-* perchlorate[c]	EtOH + ether	Rectangular plates	198.5–200	$C_{19}H_{28}O_5NCl$					3.63	3.59		
-Picrate	EtOH	Plates	185–186 dec.[g]	$C_{25}H_{30}O_8N_4$					10.90	10.91		
9-(2-Dimethylamino-1-hydroxy)-*n*-propyl-* hydrochloride[h]	EtOH + ether	Hexagonal plates	227–228	$C_{19}H_{30}ONCl$	70.43	70.43	9.34	9.52			Cl, 10.95	11.08
-Picrate	EtOH	Needles	174–174.5	$C_{25}H_{32}O_8N_4$					10.85	10.92		
9-(2-Diethylamino-1-oxo)-propyl-* perchlorate[c]	EtOH + ether	Plates	209–210	$C_{21}H_{32}O_5NCl$					3.39	3.56		
9-(2-Diethylamino-1-hydroxy)-*n*-propyl-[i]*		Oil		$C_{21}H_{33}ON$	79.93	79.86	10.55	10.79				
-Hydrochloride	EtOH + ether	Plates	210–211	$C_{21}H_{34}ONCl$							Cl, 10.08	10.25
9-(2-Piperidino-1-oxo)-propyl-* hydrochloride[c]	EtOH + ether	Blades	181–182	$C_{22}H_{32}ONCl$					3.87	4.01		

TABLE II (*Concluded*)

Derivatives of 1,2,3,4,5,6,7,8-Octahydrophenanthrene	Solvent	Appearance[a]	M. p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Halogen, % Calcd.	Halogen, % Found
9-(2-Piperidino-1-hydroxy)-*n*-propyl-*	EtOH	Plates	126.5–127.5	$C_{22}H_{33}ON$	80.67	80.95	10.16	10.24				
-Hydrochloride	EtOH	Prisms	235–236	$C_{22}H_{34}ONCl$					3.85	4.04	Cl, 9.75	9.95
9-(2-Methylamino-1-oxo)-propyl-* hydrochloride[j]	EtOH + ether	Prisms	223–224.5	$C_{18}H_{26}ONCl$					4.55	4.70		
-Picrate	EtOH	Plates	192–193 dec.[k]	$C_{24}H_{28}O_8N_4$					11.20	11.18		
9-(2-Methylamino-2-hydroxy)-*n*-propyl-*	EtOH	Prisms	129.5–130	$C_{18}H_{27}ON$	79.06	79.04	9.96	9.84				
-Hydrochloride	EtOH + ether	Diamonds	218–219	$C_{18}H_{28}ONCl$							Cl, 11.45	11.45
-Picrate	EtOH	Plates	179–180	$C_{24}H_{30}O_8N_4$					11.16	11.31		
9-(2-Ethylamino-1-oxo)-propyl-* hydrochloride[j]	EtOH + ether	Plates	226–228	$C_{19}H_{28}ONCl$					4.85	4.53		
-Picrate	EtOH	Blades	163–164	$C_{25}H_{30}O_8N_4$					10.90	10.95		
9-(2-Ethylamino-1-hydroxy)-*n*-propyl-**		Prisms	124.5–125	$C_{19}H_{29}ON$	79.38	79.52	10.18	10.33				
-Hydrochloride	EtOH + ether	Rectangular plates	118–119	$C_{19}H_{30}ONCl$					4.33	4.22	Cl, 10.95	10.96

[a] All substances are colorless, with the exception of the picrates which are all yellow. [b] Turns brown at 225°. [c] The exchange of the bromine atom with the amine was effected in ethereal solutions as described in a previous paper, see reference 3a. [d] Sinters at 226°. [e] Sublimed at 0.01 mm. [f] Sinters at 223°. [g] Sinters at 180°. [h] The free base is oily. [i] Distilled at 0.01 mm. [j] The exchange of the bromine atom with the amine was effected by heating a solution of the bromo ketone in dry benzene with the amine in a pressure flask at 50–55°. [k] Sinters at 189°.

according to Claisen and Manasse[16] and were reduced to the corresponding amino ketones with stannous chloride and concentrated hydrochloric acid in the presence of a trace of tin.[17]

The exchange of the bromine atom in ω-bromoacetyl-1,2,3,4,5,6,7,8-octahydrophenanthrene with primary amines has so far failed to give any satisfactory results.

All the amino ketones were reduced catalytically with platinum oxide in ethyl alcohol, either as the free base or preferably as the hydrochloride, to the corresponding amino alcohols.[18]

In Table II the data concerning these compounds are presented. In order to avoid frequent repetition of the name 1,2,3,4,5,6,7,8-octahydrophenanthrene, it is indicated by *.

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

(17) Rupe, *ibid.*, **28**, 251 (1895); Mills, *J. Chem. Soc.*, 1567 (1934).

(18) The method of preparing the secondary and tertiary propanolamines in this series is in principle the same as that first applied by Eberhard, *Arch. Pharm.*, **253**, 62 (1915), more recently by Hyde, Browning and Adams, THIS JOURNAL, **50**, 2287 (1928) in the preparation of ephedrine and its homologs.

Summary

The preparation of a series of amino alcohols derived from 1,2,3,4,5,6,7,8-octahydrophenanthrene is described. From 9-acetyl-1,2,3,4,5,6,-7,8-octahydrophenanthrene derivatives carrying the side chain $-CHOHCH_2NR_2$ (NR_2 being the amino, dimethylamino, diethylamino, or piperidino group) are obtained. From 9-propionyl-1,2,3,4,5,6,7,8-octahydrophenanthrene, derivatives with the side chain $-CHOHCH(CH_3)NR_2$ (NR_2 being the amino, dimethylamino, diethylamino, piperidino, monomethylamino, or monoethylamino group) are obtained.

UNIVERSITY, VA. RECEIVED APRIL 13, 1935