C–H bond of an alcoholic group, giving two configurationally unstable radicals. They stabilize by disproportionation or dimerization.

The significance of the results for the photochemical behavior of ergosterol is discussed.

REHOVOTH, PALESTINE RECEIVED MARCH 12, 1938

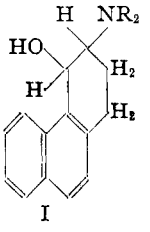
[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

Studies in the Phenanthrene Series. XVII. Amino Alcohols Derived from 9-Hydroxy-1,2,3,4-tetrahydrophenanthrene[1]

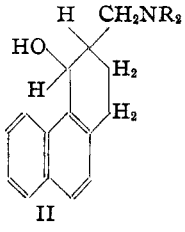
BY ALFRED BURGER

Some of the amino alcohols of types I and II derived from 1,2,3,4-tetrahydrophenanthrene[2] have been found to possess relatively favorable pharmacological properties.[3]

The 1,2,3,4-tetrahydroisoquinolino derivative of type I, for example, approaches codeine and pseudocodeine in analgesic action. The corresponding derivative of type II is weaker in analgesic effect, but does not exhibit any convulsant and emetic action. In morphine, the phenolic hydroxyl group is undoubtedly an important factor influencing the high analgesic effect of this alkaloid,[4] and therefore it appeared desirable to synthesize amino alcohols of types I and II carrying a phenolic hydroxyl group in one of the aromatic nuclei. The synthesis of the



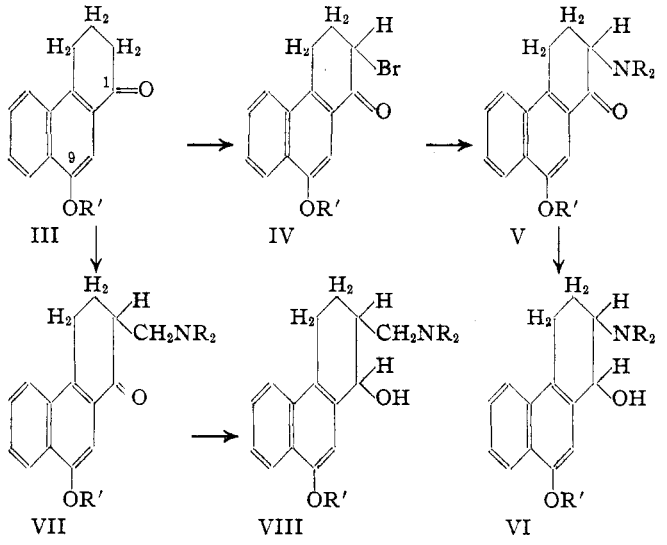
I



II

first group of amino alcohols with these structural features was planned as shown.

The starting materials for these syntheses, III (R′ = H, CH_3, CH_3CO) are relatively easily accessible.[5]



III IV V VII VIII VI

The preparation of IV (R′ = H, CH_3) did not offer any difficulties; only monobromo compounds were obtained. Attempts to exchange the bromine atom in IV (R′ = H) with secondary amines were without success. With R′ = CH_3, however, the reaction resulted in the expected amino ketones in yields that varied according to the secondary amine used. With piperidine the corresponding amino ketone V (R_2 = C_5H_{10}) was obtained in a yield of about 60%, while 1-hydroxy-9-methoxyphenanthrene appeared as a by-product. When diethylamine was used the amino ketone was formed in yields of about 30%; in this instance the formation of 1-hydroxy-9-methoxyphenanthrene by loss of hydrogen bromide and subsequent aromatization seems to be a main reaction, perhaps accompanied by the simultaneous formation of III.[6]

Unfortunately, catalytic hydrogenation under various experimental conditions did not furnish the corresponding amino alcohols VI, since the hydrogen absorption would not stop at this stage.

(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) (a) Mosettig and Burger, THIS JOURNAL, **57**, 2189 (1935); (b) Burger and Mosettig, *ibid.*, **58**, 1570 (1936).

(3) Mosettig, Eddy and co-workers, "Attempts to Synthesize Substances with Central Narcotic and, in Particular, Analgesic Action," Supplement to the U. S. Public Health Reports, in press.

(4) Edmunds, Eddy and Small, *J. Am. Med. Assoc.*, **103** 1417 (1934).

(5) Kon and Ruzicka, *J. Chem. Soc.*, 187 (1936).

(6) Compare footnotes 5 and 6 of Ref. 2a.

An excess of one to four moles of hydrogen was absorbed, and it was impossible to isolate any homogeneous reaction products.

The amino ketones of type VII were obtained by the Mannich method[7] in yields varying from 20–70%, depending on the nature of NR_2 and R′ (CH_3 or CH_3CO). Catalytic hydrogenation yielded the corresponding amino alcohols VIII. In each case only one of the two possible diastereoisomeric forms was obtained.

Further experiments that should lead to isomeric phenolic amino alcohols of types VI and VIII are in progress.

Experimental Part

Derivatives of 1-Keto-9-hydroxy-1,2,3,4-tetrahydrophenanthrene.—The reduction of β-[1-(4-methoxynaphthoyl)]-propionic acid[8] was carried out by the technique of Martin.[9] Five per cent. of glacial acetic acid by volume was added to the reaction mixture.[10] Commercial mossy zinc proved to be superior to other grades. The properties of the γ-[1-(4-methoxynaphthyl)]-butyric acid, obtained in a yield of 50%, agreed with those described by Martin[9] and by Kon and Ruzicka.[5]

It was hoped that the yield of the butyric acid derivative could be improved by reducing the methyl ester of β-[1-(4-methoxynaphthoyl)]-propionic acid catalytically. This ester was prepared from the acid with diazomethane in ether solution, or by the action of dimethyl sulfate in sodium hydroxide solution. It was recrystallized from dilute methanol, giving colorless needles, m. p. 42–43°.

Anal. Calcd. for $C_{18}H_{17}O_4$: C, 70.29; H, 6.28. Found: C, 70.46; H, 5.96.

In alcoholic solution, using a 16% palladium–charcoal catalyst, this ester absorbed more than two moles of hydrogen very slowly. Forty per cent. of the starting material was recovered unchanged, and the remaining acid, obtained by saponification of the mother liquors, was oily.

Hydrogen under high pressure at 100° in the presence of a chromite catalyst did not attack the ester in four hours. In other experiments (156, 185 and 210° for six hours, respectively) a mixture was obtained that melted from 104–108°. Repeated crystallization from methanol raised the m. p. to 120–122°. This substance appears in colorless leaflets, but is not entirely pure. Its behavior in alkaline solution and its analyses indicate that it represents a methoxytetrahydronaphthyl-γ-butyrolactone. No further efforts in this direction were made.

1 - Keto - 9 - acetoxy - 1, 2, 3, 4 - tetrahydrophenanthrene.—Ten grams of 1-keto-9-hydroxy-1,2,3,4-tetrahydrophenanthrene[5] was allowed to react with acetic anhydride (15 ml.) in pyridine solution (30 ml.) for forty-eight hours. Large crystals separated and were filtered. The mother liquor was evaporated in a vacuum, and the residue was combined with the crystals. The product was purified by distillation in a high vacuum, and recrystallization.

1 - Keto - 2 - bromo - 9 - methoxy - 1,2,3,4 - tetrahydrophenanthrene.—Ten grams of 1-keto-9-methoxy-1,2,3,4-tetrahydrophenanthrene was dissolved in 250 ml. of absolute ether, and 2.4 ml. of bromine was added. Two milliliters of a saturated ethereal solution of hydrogen chloride was added to initiate decoloration which was complete after about five minutes. The bromo ketone crystallized out, was filtered, washed with methanol and water, and purified by crystallization.

1 - Keto - 2 - diethylamino - 9 - methoxy - 1,2,3,4 - tetrahydrophenanthrene.—Eight grams of 1-keto-2-bromo-9-methoxy-1,2,3,4-tetrahydrophenanthrene was boiled under reflux with 20 g. of diethylamine in 80 ml. of benzene for five hours. A crystalline precipitate separated out after some time. Water was added to the reaction mixture, and the free diethylamino ketone was obtained by the addition of alkali to the aqueous solution. The crude diethylamino ketone melted at 90–95°. It was converted to the hydrochloride in acetone solution. From the benzene layer, 1-hydroxy-9-methoxyphenanthrene was obtained as described below.

1 - Hydroxy - 9 - methoxyphenanthrene.—The benzene layer (see above) was evaporated in a vacuum, and the residue was boiled with a 5% methyl alcoholic potassium hydroxide solution for ten minutes. The solvent was evaporated in a vacuum, the residue was dissolved in water and the filtered solution was acidified. The 1-hydroxy-9-methoxyphenanthrene precipitated as an oil which soon solidified (1.9 g.). It was purified by distillation in an oil-pump vacuum and crystallization from benzene–petroleum ether. Colorless needles were obtained, m. p. 131–132°.

Anal. Calcd. for $C_{15}H_{12}O_2$: C, 80.32; H, 5.40. Found: C, 80.76; H, 5.66.

1-Acetoxy-9-methoxyphenanthrene.—One and nine-tenths grams of 1-hydroxy-9-methoxyphenanthrene was boiled with 30 ml. of acetic anhydride and 2 g. of anhydrous sodium acetate for three hours. The mixture was decomposed with water, and the acetylation product was purified by distillation at 5 mm. pressure and crystallization from alcohol; fine, colorless needles, m. p. 154.5–155.5°; yield 2 g.

Anal. Calcd. for $C_{17}H_{14}O_3$: C, 76.66; H, 5.30. Found: C, 76.52; H, 5.04.

Attempts to oxidize this compound to 1-acetoxy-9,10-phenanthrenequinone failed.

1,9-Dihydroxyphenanthrene.—One part of 1-acetoxy-9-methoxyphenanthrene was boiled under reflux with twenty parts of a mixture of 48% hydrobromic acid and glacial acetic acid (1:1) for one hour. The reaction mixture was poured into water, and a pink crystalline precipitate separated out. It was dissolved in cold dilute potassium hydroxide solution which contained some sodium sulfite. The dihydroxy compound obtained by acidification was purified by distillation in a high vacuum and recrystallization from benzene. The compound was obtained as light brown plates which sinter at 181° and melt at 184–185° (evac. tube).

(7) Mannich and co-workers, *Ber.*, **53**, 1874 (1920); **55**, 3510 (1922); *Arch. Pharm.*, **255**, 261 (1917); **275**, 54 (1937); Bodendorf and Koralewski, *ibid.*, **271**, 101 (1933).

(8) Fieser and Hershberg, THIS JOURNAL, **58**, 2314 (1936).

(9) Martin, *ibid.*, **58**, 1438 (1936).

(10) Private communication by Dr. E. B. Hershberg.

TABLE I

No.	Derivatives of 1,2,3,4-tetrahydrophenanthrene	Solvent	Appearance	Yield, %	M. p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	1-Keto-9-acetoxy-	*n*-Butanol	Colorless needles	83	159–160	$C_{16}H_{14}O_3$	75.56	75.15	5.55	5.34		
2	1-Keto-2-bromo-9-methoxy-	*n*-Butanol	Yellow plates	88	174–175	$C_{16}H_{13}BrO_2$	59.01	59.53	4.30	4.26		
3	1-Keto-2-bromo-9-hydroxy-[a]	Methanol	Yellow leaflets		Above 330	$C_{14}H_{11}BrO_2$	57.73	56.99	3.81	3.72		
4	1-Keto-2-diethylamino-9-methoxy—HCl	Alcohol–ether	Colorless light needles	27	128–138 (dec.)	$C_{19}H_{24}ClNO_2$					Cl, 10.63	10.27
5	1-Keto-2-piperidino-9-methoxy—HCl[b]	Alcohol–ether	Colorless	63	Sinters 246 258–261 (dec.)	$C_{16}H_{24}ClNO_2$	69.43	69.45	7.00	7.14	4.05	4.32
6	1-Keto-2-(1,2,3,4-tetrahydroisoquinolino)-methyl-9-methoxy—HCl	Methanol–ether	Yellow spears	46	176–177 (dec.)	$C_{25}H_{26}ClNO_2$					3.44	3.76
7	-Perchlorate[c]	Methanol–ether	Yellow		135–150 (dec.)	$C_{25}H_{26}ClNO_6$					2.97	3.12
8	1-Hydroxy-2-(1,2,3,4-tetrahydroisoquinolino)-methyl-9-methoxy-	Methanol	Colorless needles		137–138[d]	$C_{25}H_{27}NO_2$	80.38	80.63	7.29	7.32		
9	-Hydrochloride	Alcohol–ether	Colorless	90	211	$C_{25}H_{28}ClNO_2$	73.22	73.07	6.89	6.99		
10	1-Acetoxy-2-(1,2,3,4-tetrahydroisoquinolino)-methyl-9-methoxy—HCl	Alcohol–ether	Colorless		200–201 (dec.)	$C_{27}H_{30}ClNO_3$	71.73	71.98	6.70	6.41		
11	1-Keto-2-(1,2,3,4-tetrahydroisoquinolino)-methyl-9-acetoxy-[e]	Methanol	Almost colorless needles		144	$C_{26}H_{25}NO_3$	78.15	77.86	6.31	6.33		
12	-Hydrochloride	Alcohol–ether	Colorless rhombic plates	72	167–168 (dec.)	$C_{26}H_{26}ClNO_3$					3.22	3.21
13	1-Hydroxy-2-(1,2,3,4-tetrahydroisoquinolino)-methyl-9-acetoxy—HCl	Methanol–ether	Colorless prisms	90	234–235 (dec.)	$C_{26}H_{28}ClNO_3$	71.28	71.00	6.45	6.35		
14	1-Hydroxy-2-(1,2,3,4-tetrahydroisoquinolino)-methyl-9-hydroxy-[f]	Methanol	Colorless		213(dec.)(vac.)	$C_{24}H_{25}NO_2$	80.17	79.96	7.02	7.03		
15	-Hydrochloride[g]	Alcohol	Crystal powder	75	225–227 (dec.)	$C_{24}H_{26}ClNO_2$	72.79	72.63	6.62	6.56		
16	1-Keto-2-diethylaminomethyl-9-methoxy-	Methanol	Colorless prisms	41	83	$C_{20}H_{23}NO_2$	77.12	77.38	8.10	8.22	4.50	4.68
17	-Hydrochloride	Alcohol–ether	Colorless prisms		160–161	$C_{20}H_{26}ClNO_2$					4.03	3.97
18	1-Hydroxy-2-diethylaminomethyl-9-methoxy—HCl	Alcohol–ether	Colorless square plates	86	190 (dec.)	$C_{20}H_{28}ClNO_2$	68.63	68.48	8.07	7.92		
19	1-Acetoxy-2-diethylaminomethyl-9-methoxy—HCl	Alcohol–ether	Glittering prisms		165–166 (dec.)	$C_{22}H_{30}ClNO_3$	67.40	67.67	7.72	7.57		
20	1-Keto-2-diethylaminomethyl-9-acetoxy—HCl[h]	Alcohol–ether	Colorless prisms	20	146–147	$C_{21}H_{26}ClNO_3$					3.73	3.76

[a] Bromination of 1-keto-9-hydroxy-1,2,3,4-tetrahydrophenanthrene was carried out as in the case of no. 2. A mixture of chloroform and ether (5:1) was used as a solvent. The bromo compound turned dark at 190°, the light color returned at 210° and the sample did not melt below 330°. [b] Prepared analogously to no. 4. The free piperidino ketone, prepared from the hydrochloride, was recrystallized from methanol: brown needles which darken rapidly in air, m. p. 112–113°. Also in this case, 1-hydroxy-9-methoxyphenanthrene was obtained as a by-product in the preparation of the piperidino ketone. [c] Prepared from the free base with ethereal perchloric acid. [d] After drying at 100° in a high vacuum. [e] Prepared from no. 12 with dilute ammonium hydroxide solution. [f] Prepared by making the acid mother liquors of the crude no. 15 alkaline with sodium bicarbonate solution and extraction into ether. The pure substance melted at 195–196° (decomp.) in an open tube. Methylation with diazomethane in alcohol–ether solution yielded the methyl ether, m. p. 129–131°, identical (mixed m. p.) with no. 8. [g] One part of no. 13 was heated with 3 parts of an 8% methyl alcoholic potassium hydroxide solution for a few minutes, the solution was diluted with water and acidified with hydrochloric acid. The tarry hydrochloride precipitated out. It was separated from the mother liquor by decanting, and it crystallized on treatment with acetone. [h] The mother liquors from the preparation of this salt contained dark basic and non-basic by-products of elevated m p.

Anal. Calcd. for $C_{14}H_{10}O_3$: C, 79.97; H, 4.80. Found: C, 80.13; H, 5.08.

1,9-Diacetoxyphenanthrene.—A sample of 1,9-dihydroxyphenanthrene was allowed to react with acetic anhydride in pyridine solution overnight. The diacetoxy compound was purified by distillation in the vacuum of an oil pump and crystallization from dilute alcohol, resulting in fine, colorless needles, m. p. 154–155°.

Anal. Calcd. for $C_{18}H_{14}O_4$: C, 73.44; H, 4.80. Found: C, 72.87; H, 4.80.

1,9-Dimethoxyphenanthrene.—One and six-tenths milliliters of dimethyl sulfate was added dropwise to a mixture of 0.3 g. of 1-hydroxy-9-methoxyphenanthrene, 1.45 ml. of 60% potassium hydroxide solution and 10 ml. of acetone, with vigorous stirring in the course of ten minutes.[11] After another ten minutes, the dimethoxy compound was precipitated with water and purified by distillation in an oil-pump vacuum and crystallization from methanol; colorless oblong plates resulted, m. p. 113–114°. The yield was nearly quantitative.

Anal. Calcd. for $C_{16}H_{14}O_2$: C, 80.63; H, 5.93. Found: C, 80.68; H, 6.38.

Preparation of Amino Ketones by the Mannich Reaction.—One mole of 1-keto-9-methoxy- or 1-keto-9-acetoxy-1,2,3,4-tetrahydrophenanthrene was boiled with 1.2 to 1.4 moles of the hydrochloride of the respective secondary amine and 3 moles of para-formaldehyde in 4 to 7 parts of isoamyl alcohol for four to five minutes. The hydrochlorides of the amino ketones precipitated as oils on addition of ether. These oily salts either solidified and could be filtered out, or, as in the case of the easily soluble diethylamino derivatives, they were extracted into water. The amino ketones were liberated and purified by crystallization or by conversion to a crystalline salt. The hydrochlorides of the less soluble amino ketones often can be separated from some unchanged hydrochloride of the respective secondary amine by their insolubility in cold water. Washing with acetone frequently removes colored impurities.

Preparation of Amino Alcohols.—The hydrochlorides of the amino ketones were hydrogenated, using a platinum oxide catalyst in methanol solution. One mole of hydrogen was absorbed in two to sixteen hours. The catalyst was filtered, and the solution concentrated in a vacuum. The hydrochlorides of the amino alcohols crystallized directly from the solution, or after addition of ether, and were purified by recrystallization.

The acetyl derivatives of the amino alcohols were obtained by allowing the free alkamines or their hydrochlorides to react with acetic anhydride in pyridine solution overnight. The solutions were then evaporated in a vacuum and the acetyl derivatives were converted into the hydrochlorides in the usual way.

Oxime of 1-Keto-9-methoxy-1,2,3,4-tetrahydrophenanthrene.—Ten grams of 1-keto-9-methoxy-1,2,3,4-tetrahydrophenanthrene, 6 g. of hydroxylamine hydrochloride, and 7.5 g. of barium carbonate in 170 ml. of alcohol were boiled for four hours. The barium salts were filtered from the hot solution, and the oxime was allowed to crystallize from the filtrate; yield, 9.7 g. of shining needles (from alcohol), m. p. 174–175°.

Anal. Calcd. for $C_{16}H_{15}NO_2$: N, 5.81. Found: N, 6.08.

1 - Amino - 9 - methoxy - 1, 2, 3, 4 - tetrahydrophenanthrene.—A solution of 9.5 g. of the oxime of 1-keto-9-methoxy-1,2,3,4-tetrahydrophenanthrene in 500 ml. of moist ether was allowed to react with 30 g. of aluminum amalgam for forty-eight hours. The mixture was filtered and the aluminum sludge was washed repeatedly with warm ether. The ethereal solution was extracted with dilute hydrochloric acid. An insoluble yellow hydrochloride (5.8 g.) precipitated and was filtered off. The clear aqueous solution was made alkaline, the oily amine was extracted into ether, and converted to the hydrochloride (1.1 g.) in the customary way. It was recrystallized from methanol as colorless needles, m. p. 291° (dec., evac. tube).

Anal. Calcd. for $C_{16}H_{18}ClNO$: C, 68.28; H, 6.88; N, 5.31. Found: C, 68.42; H, 7.39; N, 5.33.

The insoluble hydrochloride could be recrystallized from 400 parts of alcohol. It appeared as a poorly crystalline material that turned yellow on drying.

Summary

The synthesis of several tertiary 1-hydroxy-2-aminomethyl-1,2,3,4-tetrahydrophenanthrenes, carrying in position 9 a phenolic hydroxyl, a methoxy or acetoxy group, is described. A number of derivatives of 1,9-dihydroxyphenanthrene were obtained from 1-hydroxy-9-methoxyphenanthrene, which is formed in a side reaction in the exchange of the bromine atom of 1-keto-2-bromo-9-methoxy-1,2,3,4-tetrahydrophenanthrene with secondary amines.

UNIVERSITY, VIRGINIA RECEIVED MAY 9, 1938

(11) *Cf.* Stevens and Tucker, *J. Chem. Soc.*, **123**, 2140 (1923).