[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA, No. 132]

Studies in the Phenanthrene Series. VII. 3-Hydroxyacetylphenanthrenes and Amino Ketones and Alcohols Derived from Them. Hydroxyaminophenanthrenes[1]

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Some of the phenanthrene derivatives which contain the pharmacologically interesting hydroxyethylamino side chain, —CHOH—CH_2—NR_2 (R=H or alkyl),[2] produce in the cat a typical morphine-like excitement, dilatation of the pupils and marked analgesia.[3] Since there is but little doubt that the phenolic hydroxyl group in position 3 in morphine plays an essential role in the physiological action of this alkaloid, it seemed necessary to follow the change in the physiological action which may be expected to result from the introduction of a phenolic hydroxyl group into phenanthrene derivatives of this type.

In a previous communication[1] we described 3-hydroxy-X-acetyl- and 3-methoxy-Y-acetylphenanthrene as starting materials for such substances. In order to decide between positions 6 and 7 for X, the CH_3CO complex has been converted to OH through COOH and NH_2, followed by methylation of the resulting product to a substance identical with 3,6-dimethoxyphenanthrene, prepared according to Fieser.[4] Therefore the X-acetyl compound must be 3-hydroxy-6-acetylphenanthrene.

In order to decide between the probable positions 7 and 9 for Y[5] we made use of the method described above for the 3,6-series to replace the Y-acetyl group by NH_2, obtaining thus a product identical with Werner's 3-methoxy-9(or 10)-aminophenanthrene.[6] Since the 3-methoxy-Y-carboxylic acid was different from 3-methoxy-10-carboxylic acid,[7] Werner's amine is established as 3-methoxy-9-aminophenanthrene and the Y-acetyl compound as 3-methoxy-9-acetylphenanthrene. As an additional proof we prepared, by degradation of the 3-methoxy-10-carboxylic acid, the 3-methoxy-10-aminophenanthrene which proved to be different from Werner's amine.

The reduction of 3-methoxy-9-nitrophenanthrene according to Werner's directions yields, besides the expected amino compound, a chlorinated amine in varying amounts; addition of graphite[8] practically prevents chlorination. The most convenient reducing agent, however, is sodium hyposulfite. The same holds true for the 3-ethoxy-9-nitrophenanthrene[9] and the 3-hydroxy-9-nitrophenanthrene, prepared by nitration of 3-acetoxyphenanthrene and subsequent saponification.

We also prepared, for comparative pharmacological studies, several derivatives of 3-hydroxy-4-amino- and 9-hydroxy-10-aminophenanthrene (Vahlen's "morphigenine").[10] While the alkylation of the N-acetyl derivatives of these hydroxyamines takes a normal course with diazomethane, the reaction with diazoethane proceeds violently. Besides the 9-ethoxy-10-acetylamidophenanthrene (yield 40–50%) a crystalline, unsharply-melting mixture is formed. The yield of 3-ethoxy-4-acetylamidophenanthrene, also, did not exceed 40%, and in this case we were able to identify the by-product (about 30%) as phenanthrene-3,4-methyloxazole by direct comparison with the methyloxazole derivative prepared according to Fieser.[11] We are not able at present to offer an explanation for this surprising difference in the behavior of diazomethane and diazoethane.

The tertiary amino ketones and alcohols derived from 3-methoxy-9-acetyl- and 3-hydroxy-6-acetylphenanthrene were prepared in the same general manner as the ω-aminoacetylphenanthrenes and aminomethylphenanthrylcarbinols.[2] The exchange of the ω-bromine atom with aliphatic amines did not proceed as smoothly as in the phenanthrene derivatives containing no hydroxyl or methoxyl group. The amino ketones were isolated and purified as the perchlorates and

(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., and the Rockefeller Foundation. It is the continuation of Studies in the Phenanthrene Series, III, Hydroxy Aldehydes and Hydroxy Ketones, THIS JOURNAL, **55**, 2981 (1933).

(2) Mosettig and van de Kamp, *ibid.*, **55**, 3448 (1933).

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

(4) Fieser, THIS JOURNAL, **51**, 2471 (1929).

(5) Ref. 1, p. 2983.

(6) Werner, *Ann.*, **321**, 286 (1902). The acetylamido compound which Werner describes as a monoacetyl derivative is an N-diacetyl derivative.

(7) Pschorr, Wolfes and Buckow, *Ber.*, **33**, 174 (1900).

(8) *Cf.* Lassar-Cohn, "Arbeitsmethoden," 5th ed., p. 904.

(9) Henstock, *J. Chem. Soc.*, **89**, 1527 (1906).

(10) *Arch. exp. Path. Pharm.*, **47**, 368–410 (1902); *Ber.*, **35**, 3044 (1902); *Z. physiol. Chem.*, **39**, 97 (1903); *cf.* Pschorr, *Ber.*, **35**, 2729 (1902).

(11) Fieser, THIS JOURNAL, **51**, 1935 (1929).

EXPERIMENTAL

PHENANTHRENE DERIVATIVES

No.	Substituents	Solvent of recrystn.	M. p., °C. (corr.)	Yield, %	Appearance	Formula	Carbon, % Found	Carbon, % Calcd.	Hydrogen, % Found	Hydrogen, % Calcd.	Nitrogen, % Found	Nitrogen, % Calcd.	Chlorine, % Found	Chlorine, % Calcd.
1	3-Methoxy-6-carboxylic acid hydrazide[a]	EtOH	193–194	83	White needles	$C_{16}H_{14}O_2N_2$					10.93	10.53		
2	3-Methoxy-6-ethylurethan[b]	Dil. EtOH	134–135	40	Colorless	$C_{18}H_{17}O_3N$					4.76	4.75		
3	3-Methoxy-6-amino	Dil. MeOH	125		Colorless needles	$C_{15}H_{13}ON$	80.72	80.68	6.16	5.87				
4	3-Methoxy-6-amino hydrochloride	EtOH–ether	263–264 (dec.)		Colorless needles	$C_{15}H_{14}ONCl$					5.30	5.39		
5	3-Methoxy-6-hydroxy[c]	Dil. MeOH	135–136		Colorless	$C_{1}H_{12}O_2$	80.80	80.32	5.52	5.40				
6	3,6-Dimethoxy[d]	Dil. MeOH	104–105		Colorless	$C_{16}H_{14}O_2$	80.50	80.63	5.91	5.93				
7	-Picrate	EtOH	154.5 (dec.)		Deep red	$C_{22}H_{17}O_9N_3$					9.02	9.00		
8	-Picrate[e]	EtOH	153 (dec.)		Deep red	$C_{22}H_{17}O_9N_3$					8.91	9.00		
9	3-Methoxy-9-carboxylic acid hydrazide[a]	EtOH or xylene	234 (dec.)	98	Colorless needles	$C_{16}H_{14}O_2N_2$					10.87	10.53		
10	3-Methoxy-9-ethylurethan	EtOH	147	88	Colorless needles	$C_{18}H_{17}O_3N$					4.91	4.75		
11	3-Methoxy-9-amino[f]	MeOH	117–118		Faintly yellow needles	$C_{15}H_{13}ON$	80.67	80.68	6.09	5.87				
12	3-Methoxy-9-diacetylamido[g]	EtOH	148.5–150		Colorless leaflets	$C_{19}H_{17}O_3N$	73.89	74.23	5.70	5.58	4.67	4.56		
13	3-Methoxy-9-amino-X-chloro[h]	MeOH	128–129	15	Yellow needles	$C_{15}H_{12}ONCl$	69.62	69.89	4.72	4.70	5.54	5.44	13.48	13.77
14	3-Methoxy-9-diacetylamido-X-chloro	EtOH	134–135		Colorless needles	$C_{19}H_{16}O_3NCl$					4.21	4.10	10.16	10.38
15	3-Ethoxy-9-amino-X-chloro	Dil. MeOH	120–123		Yellow needles	$C_{16}H_{14}ONCl$					5.49	5.16	12.19	13.06
16	3-Ethoxy-9-diacetylamido-X-chloro	Dil. MeOH	122		Colorless needles	$C_{20}H_{18}O_3NCl$					4.16	3.93	9.53	9.94
17	3-Acetoxy-9-nitro[i]	Acetone	159	50	Yellow needles	$C_{16}H_{11}O_4N$	67.97	68.30	4.15	3.93				
18	3-Hydroxy-9-nitro[i]	Toluene	188–189	100	Yellow needles	$C_{14}H_9O_3N$	70.45	70.27	4.22	3.80	5.98	5.86		
19	3-Hydroxy-9-amino[k]	EtOH	265–267 (dec.)	80	Colorless	$C_{14}H_{11}ON$					7.12	6.70		
20	3-Hydroxy-9-amino hydrochloride	MeOH–EtOAc		94	Colorless needles	$C_{14}H_{12}ONCl$					5.87	5.66	13.91	14.44
21	3-Methoxy-10-carboxylic acid methyl ester[l]	MeOH	93	100	Colorless needles	$C_{17}H_{14}O_3$	76.92	76.66	5.59	5.30				
22	3-Methoxy-10-carboxylic acid hydrazide[a]	EtOH	243–244		Thin white needles	$C_{16}H_{14}O_2N_2$					11.00	10.53		
23	3-Methoxy-10-ethylurethan	Dil. EtOH	136.5–137.5	90	Colorless needles	$C_{18}H_{17}O_3N$					4.93	4.75		
24	3-Methoxy-10-amino	EtOH	116–116.5	65	Colorless needles	$C_{15}H_{13}ON$	80.72	80.68	6.10	5.87	6.15	6.28		
25	3-Methoxy-10-diacetylamido	Dil. EtOH	122.5–123.5		Colorless	$C_{19}H_{17}O_3N$	74.12	74.23	5.48	5.58	4.63	4.56		
26	9-Acetylamido-10-methoxy[m]	EtOH	249–250		Colorless	$C_{17}H_{15}O_3N$	76.71	76.94	5.56	5.70	5.37	5.28		
27	9-Amino-10-methoxy[n]	Dil. MeOH	68–69	40	Slightly brown	$C_{15}H_{13}ON$					6.74	6.28		
28	9-Acetylamido-10-ethoxy	Dioxane–ether	247		Colorless	$C_{18}H_{17}O_2N$	77.43	77.38	6.35	6.14	5.31	5.02		
29	3-Hydroxy-4-acetylamido[o]	EtOH	197		Colorless needles	$C_{16}H_{13}O_2N$	76.10	76.46	5.40	5.22	5.58	5.55		
30	3-Methoxy-4-acetylamido[p]	EtOH	208–209		Prisms or needles	$C_{17}H_{15}O_2N$					5.52	5.28		
31	3-Ethoxy-4-acetylamido	EtOH	159	34	Colorless leaflets	$C_{18}H_{17}O_2N$	77.51	77.38	6.17	6.14	5.54	5.02		
32	3-Methoxy-9-ω-bromoacetyl[q]	EtOH	115.5–116.5	75	Yellow needles	$C_{17}H_{13}O_2Br$	61.63	62.00	3.83	3.98			(Br) 23.40	24.28
33	3-Methoxy-9-ω-dimethylaminoacetyl perchlorate[r]	Acetone–ether	198–199	40–50	Yellow	$C_{19}H_{20}O_6NCl$					3.84	3.56		
34	3-Methoxy-9-ω-dimethylaminoacetyl hydrochloride	EtOH–ether	190–191 (dec.)		Colorless	$C_{19}H_{20}O_2NCl$					4.27	4.25		
35	3-Methoxy-9-dimethylaminomethylcarbinol hydrochloride[s]	EtOH–ether	207–208 (dec.)	90	Colorless	$C_{19}H_{22}O_2NCl$	68.31	68.75	6.68	6.69	4.39	4.22		
36	-Picrate	EtOH or acetone	229 (dec.)		Yellow needles	$C_{25}H_{24}O_9N_4$					11.06	10.69		
37	-Hydrochloride of benzoate	EtOH–ether	168–170 (dec.)		Colorless	$C_{26}H_{26}O_2NCl$					3.53	3.22		
38	3-Acetoxy-6-ω-bromoacetyl[t]	EtOH	160	84	Colorless	$C_{18}H_{13}O_3Br$							(Br) 22.14	22.38
39	3-Acetoxy-6-ω-diethylaminoacetyl perchlorate	Acetone–ether	199–200.5	66	Sl. yellow needles	$C_{22}H_{24}O_7NCl$					3.49	3.12	7.78	7.89
40	3-Acetoxy-6-diethylaminomethylcarbinol hydrochloride[u]	EtOH–ether	173–174 (dec.)		Colorless	$C_{22}H_{26}O_3NCl$					3.77	3.61	9.09	9.15
41	3-Hydroxy-6-diethylaminomethylcarbinol[v]	Ether–petr. ether	125		Colorless	$C_{20}H_{23}O_2N$	77.55	77.62	7.50	7.50				
42	-Hydrochloride	EtOH–ether	186–187 (dec.)	94	Colorless	$C_{20}H_{24}O_2NCl$	69.02	69.43	7.09	7.00	4.36	4.05	9.82	10.26
43	-Hydrochloride of dibenzoate	EtOH–ether	190–191		Colorless	$C_{34}H_{32}O_4NCl$					2.87	2.53		

[a] The Curtius degradation was carried out essentially according to the directions of Pschorr, Einbeck and Spangenberg [*Ber.*, **40**, 1998 (1907)] for the degradation of 3,4-dimethoxy-8-hydroxyphenanthrene-carboxylic acid.

[b] The main reaction product is a substance of m. p. 117° (found, N, 13.2) which is much less soluble in alcohol than the urethan. Its nature was not established.

[c] Purified by distillation at 160–170°, 1 mm. pressure.

[d] By methylation with diazomethane, purification by distillation. Identified by mixed m. p. with 3,6-dimethoxyphenanthrene prepared by the method of Fieser.[5]

[e] Prepared from Fieser's 3,6-dimethoxyphenanthrene, identical with No. 7 (mixed m. p.).

[f] Identified with Werner's[6] "3-methoxy-9-(or 10) aminophenanthrene" by mixed m. p. The picrate of m. p. 179° (dec.) is unstable. The picrate of Werner's amine exhibits the same instability and gives no depression in mixed m. p.

[g] Identified with Werner's 3-methoxy-9-(or 10)-"monoacetylamido"-phenanthrene (m. p. 151°) by mixed m. p. Prepared like the following diacetylamido derivatives by boiling the amine with acetic anhydride for three hours according to Werner's directions.

[h] Can be dechlorinated by hydrogenation in alcoholic solution with a Pd–$CaCO_3$ catalyst to 3-methoxy-9-aminophenanthrene of m. p. 117–118° (mixed m. p. with No. 11).

[i] Prepared from one part of 3-acetoxyphenanthrene in fifteen volumes of cold acetic acid by dropwise addition of six volumes of nitric acid (*d* 1.5) with stirring. Poured into water after thirty minutes.

[j] By saponification with hot dilute sodium hydroxide for three minutes. Methylation with dimethyl sulfate yielded the methyl ether of m. p. 136°; its mixed m. p. with Werner's 3-methoxy-9-(or 10)-nitrophenanthrene showed no depression.

[k] Prepared by reduction of the nitro compound in 100 parts of dilute sodium hydroxide with three parts of sodium hyposulfite. The reduction is completed after one minute. Purification through the hydrochloride which is freed from greenish by-products by crystallization. The free amine is sensitive to air.

[l] In the preparation of the 3-methoxyphenanthrene-10-carboxylic acid the yield was improved to 88% by diazotization with amyl nitrite [*cf.* Pschorr, *Ber.*, **39**, 3113 (1906)].

[m] From 9 - acetylamido - 10 - hydroxyphenanthrene [Pschorr, *ibid.*, **35**, 2734 (1902)] with diazomethane or dimethyl sulfate.

[n] Prepared according to the directions of Ladenburg [*ibid.*, 9, 1524 (1876)]. Saponification in HCl–AcOH did not give better results. Very soluble in alcohol, ether, benzene, less so in ligroin.

[o] From the diacetyl derivative (Fieser[11]) by saponification with warm dilute sodium hydroxide.

[p] From No. 29 with diazomethane.

[q] Finely divided 3-methoxy-9-acetylphenanthrene was suspended in absolute ether, and the calculated amount of bromine was added with shaking, preferably in direct sunlight. The ketone went into solution, and a red addition product separated out which decomposed after about one-half hour to the bromo ketone and hydrogen bromide.

[r] From the bromo ketone with a 13% benzene solution of dimethylamine (three moles) in a hydrogen atmosphere for three and one-half hours at room temperature. After evaporation of the solvent in a vacuum the yellow residue was extracted with ether, whereby dimethylamine hydrobromide and tarry products remained undissolved. The ethereal solution was precipitated with ethereal perchloric acid. The base was liberated, purified by shaking with charcoal in alcoholic solution under hydrogen, then the hydrochloride was precipitated with ethereal hydrogen chloride.

[s] By hydrogenation of the amino ketone hydrochloride with PtO_2 in absolute alcohol. The velocity of the reduction depends greatly upon the purity of the sample used.

[t] The yield of 3-acetoxy-6-acetylphenanthrene could be increased to 55–60% by isolating from the mother liquors some crude 3-hydroxy-6-acetylphenanthrene through the sodium salt. The bromination was carried out parallel to that of 3-methoxy-9-acetylphenanthrene.

[u] The oily amino ketone was liberated from No. 39 with sodium bicarbonate and hydrogenated in absolute alcoholic solution with PtO_2.

[v] By hydrogenation with PtO_2 of 3-hydroxy-6-diethylaminoacetylphenanthrene which was obtained by saponification of No. 39. Also formed by saponification of No. 40.

hydrochlorides. A high degree of purity is essential for the catalytic reduction to the corresponding amino carbinols. We prepared as the first representatives of this series 3-methoxyl phenanthrene - 9 - dimethylaminomethylcarbino- and 3 - hydroxyphenanthrene - 6 - diethylaminomethylcarbinol. It is intended to complete this series with the synthesis of the aminocarbinols containing a primary and secondary amino group.

We wish to express our thanks to Merck and Co., Rahway, N. J., for the large scale preparation of the barium phenanthrene sulfonates used in this research.

Summary

1. The structure of 3-hydroxy-6-acetylphenanthrene has been proved by its degradation to 3,6-dimethoxyphenanthrene, that of 3-methoxy-9-acetylphenanthrene by its degradation to 3-methoxy-9-aminophenanthrene.

2. A series of hydroxyphenanthrene amines and derivatives of pharmacological interest is described.

3. The synthesis of 3-hydroxyphenanthrene-6-diethylaminomethylcarbinol and of 3-methoxyphenanthrene-9-dimethylaminomethylcarbinol is described.

UNIVERSITY, VIRGINIA RECEIVED MARCH 27, 1934