The redistribution of the compound was effected by treating 0.07 mole with 3.5 mole per cent. of aluminum chloride at room temperature for sixty-six hours, followed by extraction of the catalyst with water. The analytical distillation of the product is shown by the open circles of Fig. 1, and its composition is given in Table II.

**Tetramethyl- with Tetraethyltin.**—The redistribution of a mixture of 0.15 mole each of the two tin alkyls with 2.5 mole per cent. of aluminum chloride was carried out in 50 ml. of pentane at the boiling point of the mixture, 60°, for five hours. The catalyst went into solution in the mixture and later there was formed about 1 ml. of heavy yellow oil, from which the product was decanted. After distilling off the solvent, there remained 61 g. of tin alkyls, whose analysis by distillation is given in Table III and Fig. 2.

**Tetraethyl- with Tetrapropylsilicon.**—The redistribution of a mixture of 0.14 mole of tetraethylsilicon and 0.15 mole of tetrapropylsilicon (48% ethyl radicals) with 2.5 mole per cent. of aluminum chloride was carried out at the boiling point of the mixture, 175–180°, for five hours. There was no visible reaction of the catalyst, which finally was extracted with water. The analytical distillation shown in Fig. 3, although not made carefully, showed that redistribution had occurred, and the estimated composition corresponded with the expected equilibrium mixture, as shown in Table IV.

**Dimethyl- with Diethylzinc.**—A mixture of 0.32 mole of dimethylzinc and 0.21 mole of diethylzinc, after refluxing for five hours in an atmosphere of nitrogen, was fractionated into the two original components without evidence of redistribution. After refluxing the same mixture at atmospheric pressure (temperature about 60°) for five hours in the presence of 1.4 mole per cent. of aluminum chloride, followed by vacuum distillation (20–50 mm.) from the catalyst, fractionation again gave only the symmetrical zinc alkyls. Repeating the experiment with the addition of 1.5 mole per cent. of a mixture of methylaluminum chlorides to the aluminum chloride still did not bring about redistribution.

The recovery of products in the above experiments was essentially quantitative, except for normal handling losses incurred during extraction of the catalyst, filtration, transfer, and distillation.

## Summary

The alkyl compounds of mercury, tin and silicon readily undergo the redistribution reaction, yielding random equilibrium mixtures, while the zinc alkyls at 60° failed to react. Methylethylmercury was isolated and found to be stable on standing or distillation, in the absence of redistribution catalysts.

DETROIT, MICHIGAN RECEIVED OCTOBER 9, 1939

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[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA, AND THE NATIONAL INSTITUTE OF HEALTH, WASHINGTON, D. C.]

# Studies in the Phenanthrene Series. XXIV. Phenolic Amino Alcohols and Naphthisoquinolines Derived from 9,10-Dihydrophenanthrene[1]

BY ALFRED H. STUART AND ERICH MOSETTIG

Ethanolamine and propanolamine derivatives of 9,10-dihydrophenanthrene prepared in our laboratory[2] have been found to exhibit a relatively high analgesic activity, which, unfortunately, was accompanied by convulsant and emetic effects of similar or even higher degree.[3] In the hope of finding compounds with a more favorable ratio of desirable and undesirable physiological effects, it was decided to synthesize analogous amino alcohols of the dihydrophenanthrene series, containing besides the alkamine side chain also a phenolic hydroxyl group.

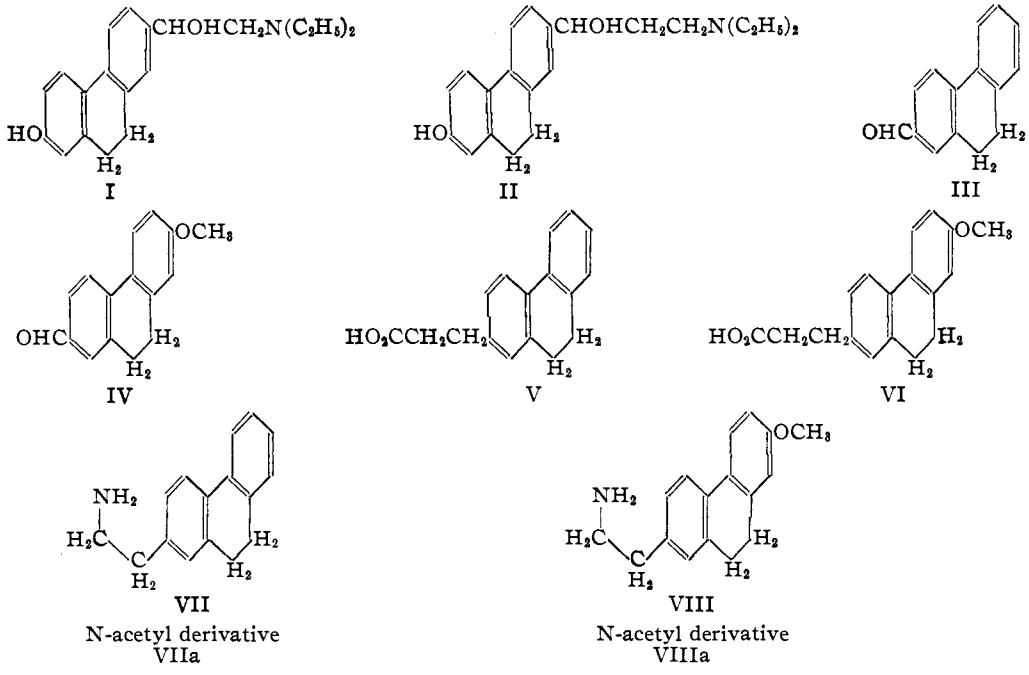
The choice of positions into which the phenolic hydroxyl group can be introduced appears to be limited, and the same holds true for the introduction of a second substituent that can be used for building up alkamine side chains or other desirable groups. Thus, the phenolic hydroxyl group can be conveniently introduced only into position 2 of 9,10-dihydrophenanthrene.[4] Also acyl groups enter chiefly position 2, and position 7 if 2 is already occupied by a phenolic hydroxyl group.[2,4b] We have described recently a practicable method for the preparation of 2-hydroxy-7-acetyl-9,10-dihydrophenanthrene,[4b] and this compound, indeed, became the key substance for the various syntheses described in this communication. The 2-hydroxy-7-[2-(diethylamino)-1-hydroxyethyl]-9,10-dihydrophenanthrene (I) was prepared by bromination of the above-mentioned hydroxy ketone, replacement of the bromine by the di-

(1) This work 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. Publication authorized by the Surgeon General, U. S. P. H. S.

(2) Burger and Mosettig, THIS JOURNAL, **58**, 1857 (1936).

(3) Small, Eddy, Mosettig and Himmelsbach, "Studies on Drug Addiction," Supplement No. 138 to the Public Health reports, pp. 81–83 (1938).

(4) (a) Burger and Mosettig, THIS JOURNAL, **59**, 1302 (1937); (b) Mosettig and Stuart, *ibid.*, **61**, 1 (1939); (c) Krueger and Mosettig, *J. Org. Chem.*, **3**, 340 (1938).




ethylamino group, and subsequent reduction of the resulting amino ketone. Actually, the reactions were carried out on the respective O-acetyl derivatives, with saponification as the last step of the synthesis. Similarly, application of the Mannich amino ketone synthesis to 2-acetoxy-7-acetyl-9,10-dihydrophenanthrene gave 2-acetoxy-7-[3-(diethylamino)-1-oxopropyl]-9,10-dihydrophenanthrene, from which the amino alcohol II was obtained by catalytic reduction. In this procedure, aqueous formaldehyde[5] was employed, the advantage over the use of paraformaldehyde and isoamyl alcohol[6] being that unreacted starting material can be recovered readily.[7]

Encouraged by the favorable reports on the pharmacological effectiveness of an isoquinoline derivative,[8] which was obtained by closing a nitrogen-containing ring onto the phenanthrene nucleus, we decided to synthesize analogous compounds derived from 9,10-dihydrophenanthrene and 2-methoxy-9,10-dihydrophenanthrene. The starting materials in these syntheses were the aldehydes III and IV, which were prepared *via* the corresponding acids by the Rosenmund method.[9] The phenanthroic acids themselves were readily obtained from 2-acetyl- and 2-methoxy-7-acetyl-9,10-dihydrophenanthrene by oxidation with sodium hypochlorite. This detour to the aldehydes was chosen because thereby better results were achieved than by the application of the direct method, involving the action of metal chlorides and hydrogen cyanide on 9,10-dihydrophenanthrene.[4a] Attempts to prepare the hydroxy aldehyde corresponding to IV by modified Gattermann syntheses[10] were unsuccessful. We did not succeed in preparing the β-phenanthrylethylamines VII and VIII by electrolytic reduction of the corresponding nitrovinyl derivatives, a method that we had applied previously to the preparation of other β-phenanthrylamines.[8a] Eventually we were able to synthesize VII and VIII in yields of from 60 to 80% by the Curtius method, starting from β-[2-(9,10-dihydrophenanthryl)]-propionic acid (V) and β-[7-(2-methoxy-9,10-dihydrophenanthryl)]-propionic acid (VI). Acid V had been prepared by us previously.[4a] The analogous preparation of acid VI did not offer any difficulties.

Attempts to produce tetrahydroisoquinoline derivatives by cyclization of the formaldehyde

(5) Mannich, Borkowsky and Wan Ho Lin, *Arch. Pharm.*, **275**, 54 (1937).

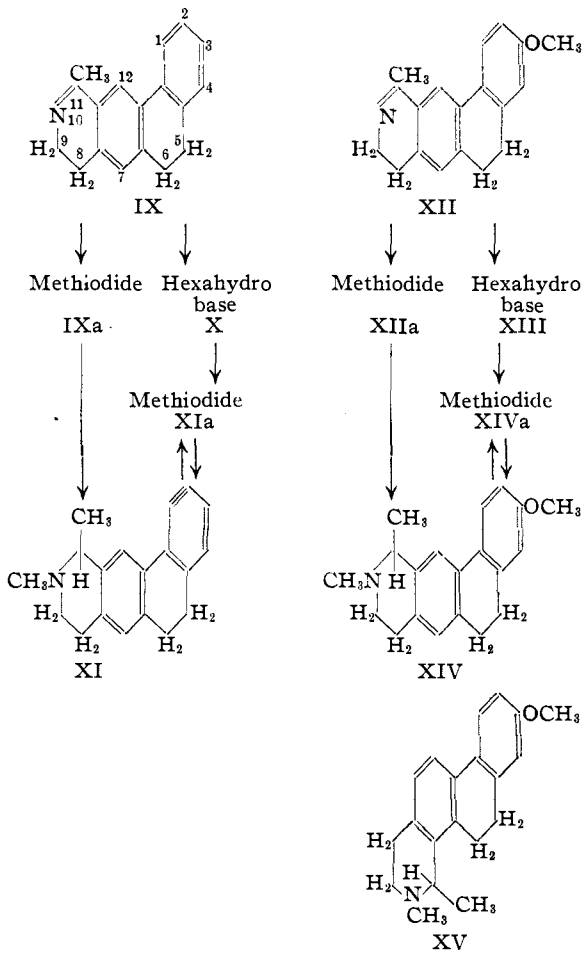
(6) *Cf.* van de Kamp and Mosettig, THIS JOURNAL, **58**, 1568 (1936).

(7) The possibility that the $-CH_2N(C_2H_5)_2$ group has entered a nuclear position activated by the acetoxy group, cannot be entirely excluded [*cf.* Auwers and Dombrowski, *Ann.*, **344**, 280 (1906)]. We had not enough material available to prove the structure of the amino ketone or the corresponding amino alcohol.

(8) (a) Mosettig and May, THIS JOURNAL, **60**, 2962 (1938). (b) Eddy, unpublished results.

(9) See Mosettig and van de Kamp, *ibid.*, **55**, 2995 (1933).

(10) Adams and co-workers, *ibid.*, **45**, 2373 (1923); **46**, 1518 (1924); Hinkel and co-workers, *J. Chem. Soc.*, 2793 (1932); 184, 339 (1936).




condensation products of VII and VIII[11] were completely unsuccessful, variations in experimental conditions leading either to starting material or to amorphous, insoluble, and non-basic condensation products. No satisfactory method for the preparation of the desired isoquinoline derivatives in adequate amounts was devised. Ring closure was effected eventually by the Bischler–Napieralski reaction. After investigating a number of modifications of this method,[12] we found that the best results were obtained by cyclizing the N-acetyl derivatives, VIIa and VIIIa, to the dihydroisoquinoline derivatives IX and XII by the action of phosphorus oxychloride in boiling toluene, in an average yield of less than 30%. In order to transform IX and XII into the corresponding N-methyltetrahydroisoquinoline derivatives XI and XIV, two routes were followed in each series. (a) The methiodides IXa and XIIa respectively were reduced catalytically. (b) The bases IX and XII were reduced catalytically to X and XIII, respectively. The latter two were completely methylated, and the resulting methiodides XIa and XIVa were decomposed by heating in an oil-pump vacuum. In each series, identical end-products, XI and XIV, were obtained by either route.

Because of the large number of steps involved in the synthesis of XI and XIV, and, in particular, on account of the relatively poor yield in the Bischler–Napieralski reaction, we eventually did not have enough material available to attempt a structural proof of the bases XI and XIV. By analogy,[13] we assume structure XI to be correct, *i. e.*, the ring closure of VIIa to have taken place in position 3 of the phenanthrene nucleus. There are no precedents in the 9,10-dihydrophenanthrene series that would justify speculations whether the methoxyl group in the terminal nucleus had any influence on the direction of ring closure of compound VIIIa. Formula XIV, therefore, can be suggested only tentatively, and an alternative structural formula, XV, must also be taken into consideration.

Compounds I, II, and XIV have been submitted to pharmacological investigation. As yet only results obtained with I are available. The analgesic activity of I (10 mg./kg., cat) shows, according to Dr. Eddy, a twofold increase over that of its analog carrying no phenolic hydroxyl group, the 2-[2-(diethylamino)-1-hydroxyethyl]-9,10-dihydrophenanthrene. The former was also more toxic and more convulsant, but the difference in these respects was relatively less.

## Experimental

**2-Acetoxy-7-ω-bromoacetyl-9,10-dihydrophenanthrene.**—A saturated solution of 2-acetoxy-7-acetyl-9,10-dihydrophenanthrene[4b] in absolute ethanol was mixed at 0° in a quartz flask with an ice-cold solution of one molecular equivalent of bromine in absolute ether, and the mixture was exposed to a mercury vapor-lamp for five minutes. The hydrogen bromide formed in the reaction was neutralized with potassium carbonate, and the solution was evaporated to dryness. The product crystallized from ethanol in small white needles that melted at 123–124°.

*Anal.* Calcd. for $C_{18}H_{15}BrO_3$: C, 60.18; H, 4.21. Found: C, 60.68; H, 3.81.

**2-Acetoxy-7-[2-(diethylamino)-1-oxoethyl]-9,10-dihydrophenanthrene.**—A mixture of the above bromo ketone

(11) See ref. 8a and Decker and Becker, *Ann.*, **395**, 342 (1913); Buck, THIS JOURNAL, **56**, 1769 (1934).

(12) Pictet and Kay, *Ber.*, **42**, 1973 (1909); Späth and Mosettig, *Ann.*, **433**, 146 (1923); Haworth, *J. Chem. Soc.*, 2281 (1927); Späth, Berger and Kuntara, *Ber.*, **63**, 134 (1930); Kindler, Peschke and Plüddemann, *Arch. Pharm.*, **277**, 25 (1939).

(13) See ref. 4a and Mosettig and Krueger, *J. Org. Chem.*, **3**, 317 (1938).

and diethylamine (5–6 molecular equivalents) in dry benzene was allowed to stand at room temperature for five hours. The amino ketone was isolated in the customary manner and purified through its perchlorate. It melted at 89–90°.

*Anal.* Calcd. for $C_{22}H_{25}NO_3$: N, 3.99. Found: N, 3.93.

The **perchlorate** was recrystallized from an ethanol–ether mixture. It melted at 165–166°.

*Anal.* Calcd. for $C_{22}H_{26}ClNO_7$: N, 3.10; Cl, 7.84. Found: N, 3.39; Cl, 7.68.

No crystalline hydrochloride could be obtained.

**2-Acetoxy-7-[2-(diethylamino)-1-hydroxyethyl]-9,10-dihydrophenanthrene.**—A mixture of 2 g. of the amino ketone perchlorate, 70 cc. of absolute alcohol, and 0.1 g. of platinum oxide absorbed the calculated amount of hydrogen within six hours. The perchlorate of the resulting amino alcohol and the base itself were oily. The **hydrochloride** was recrystallized from an alcohol–ether mixture and melted at 154–155°.

*Anal.* Calcd. for $C_{22}H_{28}ClNO_3$: N, 3.59; Cl, 9.09. Found: N, 3.55; Cl, 9.32.

**2-Hydroxy-7-[2-(diethylamino)-1-hydroxyethyl]-9,10-dihydrophenanthrene** (I).—The above acetoxy compound was saponified readily. The base itself could be obtained only as an oil. The hydrochloride was recrystallized from an alcohol–ether mixture and melted at 202–203°.

*Anal.* Calcd. for $C_{20}H_{26}ClNO_2$: N, 4.03; Cl, 10.19. Found: N, 4.05; Cl, 10.23.

**2-Acetoxy-7-[3-(diethylamino)-1-oxopropyl]-9,10-dihydrophenanthrene.**—A mixture of 3 g. of 2-acetoxy-7-acetyl-9,10-dihydrophenanthrene, 1.4 g. of diethylamine hydrochloride, and 1.1 cc. of 36% aqueous formaldehyde was stirred mechanically in a nitrogen atmosphere for ten minutes at room temperature, and for one hour at 100°, during which the formaldehyde lost by evaporation was replaced by occasional additions. The mixture was diluted with water, and unchanged starting material was extracted with ether (1.6 g., after crystallization from ethanol). The amino ketone was precipitated in the aqueous layer with ammonia and extracted with ether. The recrystallized **hydrochloride** weighed 1.5 g. and melted at 132–134° (yield, calcd. on the basis of reacting material, 75%).

*Anal.* Calcd. for $C_{23}H_{28}ClNO_3$: Cl, 8.82. Found: Cl, 9.32.

In subsequent runs, the relative amounts of reacting material varied somewhat, but the yield of amino ketone was constant. When the reaction was carried out by boiling a mixture of ketone, diethylamine hydrochloride, and paraformaldehyde in isoamyl alcohol, the yield of crystalline amino ketone hydrochloride was approximately the same, but starting material could be recovered only with difficulty.

**2-Hydroxy-7-[3-(diethylamino)-1-hydroxy-*n*-propyl]-9,10-dihydrophenanthrene** (II).—The above compound, when reduced catalytically, absorbed smoothly one molecular equivalent of hydrogen ($PtO_2$, absolute alcohol), but no crystalline base or salt of the resulting amino alcohol could be obtained. Therefore, the crude reduction product was saponified, whereby a crystalline phenolic amino alcohol of m. p. 178–185° was formed. It crystallized readily from ethyl acetate and melted, after drying in the desiccator, at 129–130°. The analytical data agree approximately with values for a base containing two moles of ethyl acetate

*Anal.* Calcd. for $C_{21}H_{27}NO_2 + 2C_4H_8O_2$: C, 69.42; H, 8.63. Found: C, 70.70; H, 8.34.

When this compound was dried at 100° in an oil-pump vacuum, its m. p. rose to 182–183°. Satisfactory analytical data were obtained only after the base was sublimed in an oil-pump vacuum. It then melted at 185–186°.

*Anal.* Calcd. for $C_{21}H_{27}NO_2$: C, 77.50; H, 8.36. Found: C, 77.41; H, 8.69.

The hydrochloride melted after recrystallization at 180–181°.

*Anal.* Calcd. for $C_{21}H_{28}ClNO_2$: C, 69.69; H, 7.80. Found: C, 69.61; H, 7.68.

By allowing the pyridine solution of the above hydrochloride and the calculated amount of benzoyl chloride to stand for five hours, we obtained a dibenzoyl derivative whose hydrochloride melted unsharply at 157–159° after two crystallizations from an alcohol–ether mixture.

*Anal.* Calcd. for $C_{35}H_{38}ClNO_4$: Cl, 6.22. Found: Cl, 6.58.

**9,10-Dihydrophenanthroyl-2-chloride.**—2-Acetyl-9,10-dihydrophenanthrene[2] was oxidized readily by 1.5% aqueous sodium hypochlorite solution. The dried crude acid was suspended in thionyl chloride and the mixture was boiled under reflux for four hours. The solution was evaporated in a vacuum, and left an oily residue, which was distilled twice in an oil-pump vacuum. The distillate solidified slowly (yield, 95%). The analytical sample was sublimed slowly, and appeared as long, colorless needles, m. p. 50–51°.

*Anal.* Calcd. for $C_{15}H_{11}ClO$: C, 74.23; H, 4.57; Cl, 14.61. Found: C, 73.91; H, 4.51; Cl, 14.49.

**9,10-Dihydrophenanthrene-2-aldehyde** (III).—The acid chloride[14] was converted into the aldehyde by the method of Rosenmund, using an aged palladium–barium sulfate catalyst and decalin as solvent.[9] The yield was 70% (identified as semicarbazone).

**2-Methoxy-9,10-dihydrophenanthroyl-7-chloride.**—This compound was prepared from the corresponding acid[4a] in the manner described above. The crude crystalline residue from evaporation of the reaction mixture was used for catalytic reduction. For analysis, a sample was sublimed twice in an oil-pump vacuum; white needles, m. p. 87–88°.

*Anal.* Calcd. for $C_{18}H_{13}ClO_2$: C, 70.46; H, 4.80. Found: C, 70.84; H, 5.29.

**2-Methoxy-9,10-dihydrophenanthrene-7-aldehyde** (IV).—The catalytic replacement of the chlorine by hydrogen proceeded smoothly, and the aldehyde was formed in a yield of 67% (calculated on the basis of acid). It was recrystallized from methanol and melted at 100°.

*Anal.* Calcd. for $C_{18}H_{14}O_2$; C, 80.65; H, 5.92. Found: C, 80.42; H, 6.22.

(14) The thionyl chloride used in the preparation of the acid chlorides was purified according to the directions of Fieser's "Experiments in Organic Chemistry," 1935.

**2-(2-Nitrovinyl)-9,10-dihydrophenanthrene.**—Aldehyde III (4.5 g.) was condensed[8a,15] with nitromethane (2.6 cc.) in ethanolic solution (300 cc.) in the presence of sodium hydroxide (2.8 g.). When the reaction mixture was poured into 10% hydrochloric acid, the product separated as a yellow oil, which slowly became crystalline. It crystallized from ethanol in bright yellow needles, m. p. 77°; yield, 75%.

*Anal.* Calcd. for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21. Found: C, 76.13; H, 5.43.

The electrolytic reduction according to Slotta and Szyszka,[16] employing 4.1 g. of the compound, 52 cc. of ethanol, 80 cc. of glacial acetic acid, and 12 cc. of concd. hydrochloric acid, proceeded rather rapidly, the yellow color having disappeared within two hours. A large amount of insoluble sludge was produced and the expected amine VII could be isolated in a yield of only 16%. Similar experiences were encountered in the electrolytic reduction of 2-methoxy-7-(2-nitrovinyl)-9,10-dihydrophenanthrene.

**Hydrazide of β-[2-(9,10-Dihydrophenanthryl)]-propionic Acid.**—The acid V was prepared according to Burger and Mosettig[4b] and converted to the methyl ester by diazomethane. The oily methyl ester was heated under reflux in a mixture of 2.4 parts (by volume) of absolute ethanol and 2.4 parts of 42% aqueous solution of hydrazine hydrate for forty-two hours. The white hydrazide separated from the cooled reaction mixture. It was recrystallized from water and melted at 134–135°; yield, 85%.

*Anal.* Calcd. for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81. Found: C, 76.17; H, 6.80.

**2-(2-Aminoethyl)-9,10-dihydrophenanthrene (VII).**—The Curtius reaction was carried out, following in part the technique of Mayer and Schnecko.[17] To a cooled suspension (0 to 3°) of 8.5 g. of hydrazide in 250 cc. of 0.5 *N* hydrochloric acid was added in several portions a solution of 6 g. of sodium nitrite in 25 cc. of water. The mixture was stirred for one hour after the last portion of nitrite had been added. The azide formed was extracted with ether, the ether solution was dried and mixed with 180 cc. of absolute ethanol. The ether was distilled off and the ethanolic solution was kept boiling under reflux for five hours. No attempt was made to isolate the urethan, but a solution of 74 g. of potassium hydroxide in 300 cc. of absolute alcohol was added and the whole was kept boiling for twenty hours. The reaction mixture was concentrated to a small volume, water added, and the oil taken up in ether. The dried ether solution left, after evaporation, the desired amine, which was distilled in an oil-pump vacuum. The distillate consisted of 5.4 g. of colorless oil. A crystalline hydrochloride was obtained and purified in the customary manner; m. p. 229–230°.

*Anal.* Calcd. for $C_{16}H_{18}ClN$: C, 73.97; H, 6.98; Cl, 13.65. Found: C, 73.50; H, 7.08; Cl, 13.36.

Acidification of the aqueous alkaline layer (from the extraction of the amine with ether) yielded 0.8 g. of nearly pure dihydrophenanthrylpropionic acid. Taking this into account, the yield of amine in the Curtius reaction was about 75%.

**Formyl Derivative.**—The formate of VII was precipitated by addition of formic acid to an ethereal solution of the base. Heated at 150° for one-half hour, the salt slowly melted down to a brown oil, which solidified on cooling. It was recrystallized from a mixture of benzene and petroleum ether, and melted at 91°; yield, 80%.

*Anal.* Calcd. for $C_{17}H_{17}NO$: C, 81.24; H, 6.82. Found: C, 80.82; H, 7.38.

**Acetyl Derivative (VIIa).**—A mixture of base VII with half of its weight of acetic acid was heated with stirring at 150° for one hour. After cooling, the mass solidified, and was recrystallized from a benzene–petroleum ether mixture; m. p. 112°, yield 85%.

*Anal.* Calcd. for $C_{18}H_{19}NO$: C, 81.47; H, 7.22. Found: C, 81.08; H, 7.12.

**β-[7-(2-Methoxy-9,10-dihydrophenanthryl)]-acrylic Acid.**—A mixture of 19 g. of the aldehyde IV, 24 g. of malonic acid, 2 cc. of piperidine, and 60 cc. of pyridine was heated on the steam-bath for seventy-five minutes, and then kept boiling for ten minutes in order to complete the reaction. The acrylic acid derivative was purified by crystallization from methyl ethyl ketone; m. p. 192–193°, yield, 87%.

*Anal.* Calcd. for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75. Found: C, 76.53; H, 5.73.

**β-[7-(2-Methoxy-9,10-dihydrophenanthryl)]-propionic Acid (VI).**—This acid was obtained nearly quantitatively by reducing the unsaturated acid catalytically (absolute alcohol, platinum oxide catalyst). It was recrystallized from dilute ethanol, and melted at 177°.

*Anal.* Calcd. for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.00; H, 6.62.

The **methyl ester** was prepared with diazomethane, and was recrystallized from methanol; m. p. 61–62°.

*Anal.* Calcd. for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 76.05; H, 6.70.

**Hydrazide.**—A mixture of crude methyl ester (prepared from 20 g. of the methoxy dihydrophenanthrylpropionic acid), 55 cc. of 42% hydrazine hydrate, and 60 cc. of absolute ethanol was heated under reflux for forty-four hours. The hydrazide precipitated from the cooled solution, and was recrystallized from dilute ethanol; m. p. 155–156°, yield, 90% (calculated on acid).

*Anal.* Calcd. for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80. Found: C, 72.85; H, 6.50.

**2-Methoxy-7-(2-aminoethyl)-9,10-dihydrophenanthrene (VIII).**—Seven and five-tenths grams of the hydrazide was degraded in the manner described for the analog without the methoxyl group. The end-product was distilled in an oil-pump vacuum, yielding 3.8 g. of a pale yellow oil, which partly solidified. The hydrochloride melted over a wide range, beginning to sinter at 240°.

*Anal.* Calcd. for $C_{17}H_{20}ClNO$: C, 70.45; H, 6.96. Found: C, 70.33; H, 6.75.

The **acetyl derivative** (VIIIa) was prepared like its methoxy-free analog. After crystallization from a benzene–petroleum ether solution, it melted at 125-126°.

(15) *Cf.* also Lange and Hambourger, THIS JOURNAL, **53**, 3865 (1931).

(16) Slotta and Szyszka, *J. prakt. Chem.*, [2] **137**, 339 (1933).

(17) Mayer and Schnecko, *Ber.*, **56**, 1408 (1923); *cf.* also Mayer and Krieger, *ibid.*, **55**, 1659 (1922).

*Anal.* Calcd. for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17. Found: C, 76.57; H, 7.58.

**Ring Closure Experiments.**—(a) According to the method of Decker and Becker. Numerous attempts were made to cyclize the formaldehyde condensation products of the amines VII and VIII. Condensation with formaldehyde took place readily with both, but no ring closure products could be obtained by heating the resulting products with hydrochloric acid. Variations in conditions of condensation extended from use of slightly more than one molecular equivalent of formaldehyde to use of a large excess of this reagent, and from five minutes to one hour of heating. The residues remaining after the removal of the excess of formaldehyde in each case were heated with 23% hydrochloric acid for times varying from five minutes to four hours. Under the mildest conditions, amine VII was isolated almost unchanged. When only one molecular equivalent of formaldehyde was used and the time of heating the condensation product did not exceed thirty minutes, small amounts of unchanged amine VII still remained. Under stronger conditions, and when using amine VIII under all conditions, only amorphous white products were obtained, which were insoluble in acids as well as in organic solvents.

(b) According to the method of Bischler–Napieralski. Attempts to bring about ring closure of the formyl derivatives of VII by the action of phosphorus pentoxide were unsuccessful. No reaction occurred in boiling benzene, while in xylene and in tetralin only tarry products were produced. In subsequent experiments the N-acetyl derivatives VIIa and VIIIa were used. Small amounts of IX were obtained by the action of phosphorus pentoxide on the acetyl derivative VIIa in boiling toluene or xylene. The use of phosphorus oxychloride as condensing agent in xylene gave similar results. The use of phosphorus oxychloride in boiling toluene appeared to be relatively most favorable.

**11-Methyl-5,6,8,9-tetrahydronaphth[2,1-g]isoquinoline (IX).**[18]—A typical reaction was carried out by boiling a solution of 1.6 g. of the N-acetyl derivative VIIa and 1.6 cc. of phosphorus oxychloride in 40 cc. of dry toluene for thirty-five minutes. After two minutes the solution became cloudy and oily material slowly began to separate. The isoquinoline derivative was isolated by extracting the reaction mixture repeatedly with small portions of 5 *N* hydrochloric acid. The base was liberated, extracted with ether, and reconverted to the hydrochloride. The salt melted at 230–232°.

*Anal.* Calcd. for $C_{18}H_{18}ClN$: Cl, 12.50. Found: Cl, 12.44.

**Methiodide (IXa).**—On addition of methyl iodide to an acetone solution of the base IX, the methiodide precipitated rapidly. It crystallized from absolute ethanol in long, pale yellow needles, m. p. 267–268°.

*Anal.* Calcd. for $C_{19}H_{20}IN$: I, 32.60. Found: I, 32.67.

(18) The nomenclature policy of *Chemical Abstracts* has been followed in numbering the naphthisoquinoline derivatives. Formula-pictures of IX, XI, XII, and XIV have been oriented accordingly. For the sake of emphasizing the direction of ring closure, formula XV (a naphth[1,2-*h*]isoquinoline derivative) has been oriented incorrectly (see also ref. 8a).

**11-Methyl-5,6,8,9,10,11-hexahydronaphth[2,1-g]isoquinoline (X).**—The hydrochloride of base IX, dissolved in absolute ethanol, absorbed readily one molecular equivalent of hydrogen when reduced catalytically (platinum oxide catalyst). The hydrochloride of the reduction product was recrystallized from an ethanol–ether mixture and melted at 239–241°.

*Anal.* Calcd. for $C_{18}H_{20}ClN$: C, 75.64; H, 7.05. Found: C, 75.06; H, 7.05.

**Methiodide of 10,11-Dimethyl-5,6,8,9,10,11-hexahydronaphth(2,1-g)isoquinoline (XIa).**—To a solution of 0.25 g. of base X in 3 cc. of acetone was added 0.15 g. of powdered potassium hydroxide and 0.4 cc. of methyl iodide. A white methiodide precipitated rapidly. It was filtered off, washed with water (0.3 g.) and recrystallized from absolute ethanol; m. p. 231°.

*Anal.* Calcd. for $C_{20}H_{24}IN$: I, 31.31. Found: I, 29.81.

**10,11-Dimethyl-5,6,8,9,10,11-hexahydronaphth[2,1-g]-isoquinoline (XI).**—(a) The methiodide IXa was reduced catalytically (absolute ethanol, platinum oxide). The oily base of the reduction product was liberated and distilled in an oil-pump vacuum. Its **hydrochloride** melted at 234–236°.

*Anal.* Calcd. for $C_{19}H_{22}ClN$: C, 76.11; H, 7.40; Cl, 11.83. Found: C, 75.39; H, 7.39; Cl, 11.80.

A sample of the base was dissolved in acetone, and methyl iodide was added. The white methiodide which precipitated immediately was identical (melting point, and mixture melting point) with the methiodide (XIa) that was obtained from 11-methyl-5,6,8,9,10,11-hexahydronaphth[2,1-g]isoquinoline (X), as described above.

(b) The methiodide XIa (from either source) decomposed smoothly when heated above 200° in an oil-pump vacuum. The oily base thus formed was redistilled and converted to the hydrochloride which melted at 232–235°. The mixture melting point with the hydrochloride of the base obtained in the catalytic reduction of methiodide IXa was 233–236°.

**3-Methoxy-11-methyl-5,6,8,9-tetrahydronaphth[2,1-g]-isoquinoline-(?)(XII).**—A solution of 2 g. of the acetyl derivative VIIIa and 2 cc. of phosphorus oxychloride in 50 cc. of dry toluene was boiled for thirty-five minutes. The reaction product was extracted with 5 *N* hydrochloric acid. The base was liberated and purified by crystallization of the hydrochloride (28%). The salt melted at 249–250°.

*Anal.* Calcd. for $C_{19}H_{20}ClNO$: Cl, 11.30. Found: Cl, 10.96.

**Methiodide (XIIa).**—This was precipitated from an acetone solution of the base by addition of methyl iodide. It was recrystallized from absolute ethanol, in which it is but slightly soluble; yellow, m. p. 287–288°.

*Anal.* Calcd. for $C_{20}H_{22}INO$: I, 30.27. Found: I, 30.43.

**3-Methoxy-11-methyl-5,6,8,9,10,11-hexahydronaphth-[2,1-g]isoquinoline (XIII).**—The hydrochloride of XII was hydrogenated rapidly in absolute ethanol solution (platinum oxide). The hydrochloride was precipitated with ether from the filtered solution, and melted at 261–263° after recrystallization from an ethanol–ether mixture.

*Anal.* Calcd. for $C_{19}H_{22}ClNO$: Cl, 11.23. Found: Cl, 11.73.

**Methiodide of 3-Methoxy-10,11-dimethyl-5,6,8,9,10,11-hexahydronaphth[2,1-g]isoquinoline (XIVa).**—The base from 0.2 g. of the above hydrochloride was dissolved in 3 cc. of acetone, and 0.3 cc. of methyl iodide and 0.1 g. of powdered potassium hydroxide were added. After one hour the white methiodide was filtered, and washed free of alkali with cold water. It was recrystallized from absolute ethanol; m. p. 256–258°.

*Anal.* Calcd. for $C_{21}H_{26}INO$: I, 29.15. Found: I, 29.47.

**3-Methoxy-10,11-dimethyl-5,6,8,9,10,11-hexahydronaphth[2,1-g]isoquinoline (XIV).**—(a) The methiodide XIIa (m. p. 287–288°) absorbed one mole of hydrogen rapidly when catalytically reduced. After removal of the catalyst, the ethanol solution was concentrated, and a white **hydriodide** was precipitated by addition of ether. It was recrystallized from ethanol, and melted at 236–238°.

*Anal.* Calcd. for $C_{20}H_{24}INO$: I, 30.12. Found: I, 29.75.

The **base** was liberated with ammonium hydroxide and slowly distilled at about 100° in an oil-pump vacuum; m. p. 97–98°.

*Anal.* Calcd. for $C_{20}H_{23}NO$: C, 81.87; H, 7.90. Found: C, 81.70; H, 7.72.

The **hydrochloride** was prepared and purified in the usual way, and melted at 200–202°.

*Anal.* Calcd. for $C_{20}H_{24}ClNO$: C, 72.82; H, 7.33. Found: C, 72.71; H, 7.53.

Addition of methyl iodide to an acetone solution of the base precipitated the quaternary methiodide, XIVa, identical (melting point, mixture melting point) with that obtained by the action of methyl iodide and potassium hydroxide on 3-methoxy-11-methyl-5,6,8,9,10,11-hexahydronaphth[2,1-g]isoquinoline (XIII).

(b) Base XIV was also obtained by heating the methiodide XIVa to 250° in an oil-pump vacuum. It was identified by melting point and mixture melting point.

## Summary

The synthesis of two new phenolic amino alcohols, 2-hydroxy-7-[2-(diethylamino)-1-hydroxyethyl]-9,10-dihydrophenanthrene and 2-hydroxy-7-[3-(diethylamino)-1-hydroxy-*n*-propyl]-9,10-dihydrophenanthrene, is described.

The synthesis of two isoquinoline derivatives of the 9,10-dihydrophenanthrene series, 10,11-dimethyl-5,6,8,9,10,11-hexahydronaphth[2,1-g]isoquinoline and 3-methoxy-10,11-dimethyl-5,6,8,-9,10,11-hexahydronaphth[2,1-g]isoquinoline (?), is described.

The starting materials, 9,10-dihydrophenanthrene-2-aldehyde and 2-methoxy-9,10-dihydrophenanthrene-7-aldehyde, were obtained by the Rosenmund method from the corresponding phenanthroic acid chlorides, while the intermediate products, 2-(2-aminoethyl)-9,10-dihydrophenanthrene and 2-methoxy-7-(2-aminoethyl)-9,10-dihydrophenanthrene, were prepared by the Curtius reaction from the corresponding β-dihydrophenanthrylpropionic acids.

WASHINGTON, D. C. RECEIVED FEBRUARY 23, 1940

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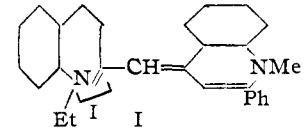
[JOINT CONTRIBUTION FROM THE KODAK RESEARCH LABORATORIES AND THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

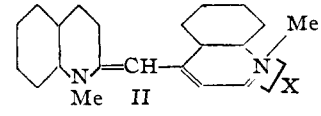
# Color and Constitution. I. Halochromism of Anhydronium Bases Related to the Cyanine Dyes[1]

BY L. G. S. BROOKER, R. H. SPRAGUE, C. P. SMYTH AND G. L. LEWIS

In their work on the structure of the isocyanines, Kaufmann and Vonderwahl[2] brought forward evidence which they interpreted as indicating the static configuration I for 1-ethyl-1′-methyl-2′-phenyl-2,4′-cyanine iodide. They heated the dye in a high vacuum and obtained ethyl iodide and a base having the composition of a methylphenylquinolylidenequinaldine, and this was considered to prove that the iodine atom was attached to the nitrogen atom of the quinaldine nucleus.




I




II

On the other hand, as a result of their experiments on the oxidation of 1,1′-dimethyl-2,4′-cyanine acetate, Mills and Wishart[3] felt that it was justifiable to accept II as the formula of this substance rather than the alternative structure in

(1) Communication No. 755 of the Kodak Research Laboratories. Presented in part before the Organic Section of the American Chemical Society at the September, 1937, meeting at Rochester, New York.

(2) Kaufmann and Vonderwahl, *Ber.*, **45**, 1407 (1912).

(3) Mills and Wishart, *J. Chem. Soc.*, **117**, 579 (1920).