

[CONTRIBUTION FROM THE DIVISION OF PHYSIOLOGY, NATIONAL INSTITUTE OF HEALTH]

Studies in the Anthracene Series. III. Amino Ketones Derived from 9-Acetylanthracene

BY EVERETTE L. MAY AND ERICH MOSETTIG

This investigation was undertaken with the purpose of preparing anthracene-9-alkamines of the types $-\text{CHOHCH}_2\text{NR}_2$ and $-\text{CHOHCH}_2\text{CH}_2\text{NR}_2$ which could be expected to show anti-malarial activity in view of the marked action of analogous 9-derivatives in the phenanthrene series.¹

By the bromination of 9-acetylanthracene (V), 9- ω -bromoacetylanthracene (III), the desired intermediate for the preparation of the ethanolamine derivatives, was obtained in a yield of 50%. The bromo ketone III, however, failed under a variety of conditions to react normally with secondary amines.² The inertness of the bromine atom made its location in the side-chain appear somewhat doubtful, but eventually III could be obtained also by the Friedel-Crafts reaction of anthracene with bromoacetyl bromide, although only in yields of 2-3%. Aluminum isopropoxide reduction of III did not give the expected bromohydrin. In one instance, a 25% yield of a bromine-free compound, tentatively designated 9-(β -hydroxyethyl)-anthracene (IV),^{3,4} was isolated, but usually only amorphous products were obtained. The product IV was shown by direct comparison to be different from 9-(α -hydroxyethyl)-anthracene.⁵ Hydrogenation of the bromo ketone III with palladium-charcoal catalyst yielded readily 9-acetylanthracene.

By condensing, according to Mannich, 9-acetylanthracene, paraformaldehyde, and morpholine, 9-(3-morpholino-1-oxopropyl)-anthracene (VI) was obtained in a yield of 50%. The amino ketone VI, as hydrochloride, absorbed approximately two moles of hydrogen (platinum oxide), and 9-(3-morpholino-1-oxopropyl)-1,2,3,4-tetrahydroanthracene (VIII)⁶ was obtained as the main product. As a by-product was isolated a small quantity of 9-propionyl-1,2,3,4-tetrahydroanthracene (IX) which increased in amount as the hydrogen absorption was allowed to proceed beyond two moles. When VI was reduced as base, three moles of hydrogen was absorbed and IX was isolated in a yield of 74%. Finally, amino ketone

VIII slowly absorbed one mole of hydrogen, yielding ketone IX.

In the hydrogenation of 9-propionylanthracene, two moles of hydrogen was absorbed, and the resulting product was found to be identical with the ketone IX obtained in the reductive fission of the amino ketones VI and VIII. Moreover, we were able to prepare VIII by subjecting 9-acetyl-1,2,3,4-tetrahydroanthracene (VII) (formed by catalytic reduction of V) to the Mannich condensation with paraformaldehyde and morpholine. Chromic acid oxidation of the ketones VII and IX gave 1,2,3,4-tetrahydro-9,10-anthraquinone (X).

The outlined series of reactions establishes the structure of the amino ketone VIII and the alkyl ketones VII and IX.⁷ Obviously, owing to steric hindrance, the carbonyl group attached to the *meso* position of anthracene is resistant to catalytic hydrogenation, and one of the terminal benzene rings is attacked. This observation corroborates the failure of V and II to form, under standard conditions, semicarbazones, the failure of the bromo ketone III to react with secondary amines, and the resistance of 9-anthramide to hydrolysis.⁸

Recently Horeau and Jacques⁹ found that the hydrogenation (Raney Nickel) of 9-benzoylanthracene yields in a ratio of about 1:5, 9,10-dihydroanthryl-9-phenylcarbinol and a product to which they assign the structure of 9-benzoyl-1,2,3,4-tetrahydroanthracene. Our study appears to support the conclusions of these authors.

Acknowledgment.—We are indebted to H. George Latham, Jr., of this Laboratory for the preparation of 9-acetyl- and 9-propionylanthracenes. The microanalyses were carried out by C. A. Kinser and Betty Mount of this Institute.

Experimental¹⁰

9-Acetylanthracene (V) was prepared by the method of Lüttringhaus and Kačer¹¹ who quote the melting point *ca.* 80°. Our material melted at 74-76°.

9-Propionylanthracene (II).—It was found necessary to modify slightly¹² the directions of Lüttringhaus and Kačer¹¹ in the preparation of II. To a mixture of 50 g. of anthracene, 132 g. of propionyl chloride and 320 cc. of benzene, cooled to -5° , was added, with stirring, 75 g. of aluminum chloride at such a rate that the temperature did not rise above 0°. The temperature was maintained

(1) May and Mosettig, *J. Org. Chem.*, **11**, 10, 105 (1946).
 (2) See Eisleb, *Med. u. Chemie Abhandl. Med.-Chem. Forschungstälten I. G. Farbenind.*, **3**, 48 (1936), for an analogous instance in the acridine series.
 (3) Cf. Winstein, Jacobs, Henderson and Florsheim, *J. Org. Chem.*, **11**, 150 (1946).
 (4) Cf. "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 193.
 (5) Fieser and Hartwell, *THIS JOURNAL*, **60**, 2555 (1938).
 (6) Compound VIII was originally believed to be 9-(3-morpholino-1-hydroxypropyl)-9,10-dihydroanthracene, and was entered as such (SN 1820) in Wiselogle, "Survey of Antimalarial Drugs, 1941-1945," Vol. II, J. W. Edwards, Ann Arbor, 1946, p. 358.

(7) Ketone VII has also been synthesized from 9-cyanotetrahydroanthracene. See a later paper of this series.

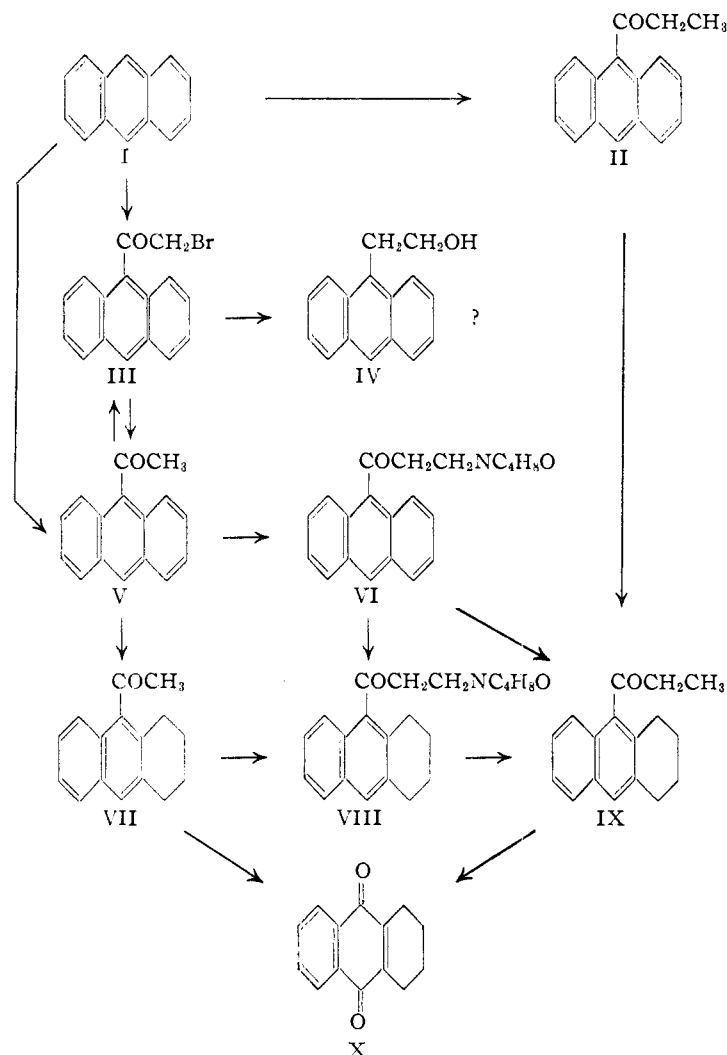
(8) See Karrer and Zeller, *Helv. Chim. Acta*, **2**, 485 (1919); see also a later paper of this series.

(9) Horeau and Jacques, *Bull. soc. chim.*, 71 (1946).

(10) All melting points given are uncorrected.

(11) Lüttringhaus and Kačer, German Patent 493,688; *C. A.*, **24**, 2257 (1930).

(12) The modified procedure was developed by H. George Latham, Jr., of this Laboratory.



at 0° for one and one-half hours, and allowed to rise to 10° during an additional hour (stirring). The complex was filtered, washed with cold benzene and decomposed in ice-hydrochloric acid. The resulting solid was extracted with ether, the ether was washed with 2 *N* sodium carbonate, dried over sodium sulfate and evaporated to give an oil which was digested with methanol. Insoluble material was filtered, the filtrate was evaporated to dryness, and the residue distilled in a high vacuum. The distillate was recrystallized from methanol to give 7.0 g. of II, m. p. 71–75°. A second crop weighed 8.3 g. and melted at 69–73°.

9- ω -Bromoacetyl anthracene (III). (a) **By Bromination of V.**—To an ice-cooled solution of 5 g. of V in 50 cc. of dry ether was added 1.1 cc. of bromine during one hour. After stirring for an additional hour, 2.5 g. of solid was collected. The ethereal filtrate was concentrated and diluted with ligroin (b. p. 30–60°) to give a second fraction of 1.5 g. The two fractions were combined and recrystallized from benzene–ligroin; yield 3.2 g. (50%), m. p. 104.5–107°. The analytical sample melted at 107–108.5°; pale yellow prisms.

Anal. Calcd. for $\text{C}_{16}\text{H}_{11}\text{BrO}$: C, 64.2; H, 3.7. Found: C, 63.8; H, 3.8.

(b) **By the Friedel-Crafts Reaction.**—A mixture of 10 g. of anthracene, 65 cc. of benzene and 27 cc. of bromoacetyl bromide, stirred and cooled to –25°, was treated

with 15 g. of aluminum chloride during ten minutes. The mixture was allowed to warm to 0° during one hour and decomposed in ice-hydrochloric acid. The benzene layer was diluted with ether and washed with dilute potassium hydroxide. It was dried over sodium sulfate and concentrated to a small volume to give, after cooling, 4.5–6.5 g. of anthracene. The filtrate was diluted to 200 cc. with ligroin (b. p. 30–60°), kept in the ice-box overnight, and decanted from some oil and crystals. On further dilution of the decantate to 300 cc., seeding, and cooling in the ice-box for forty hours, 0.2–0.4 g. (3–4% based on used anthracene) of prisms, m. p. 104.5–107°, separated. Mixed with the III from (a), they melted at 105–107.5°.

Debromohydrogenation of III.—A mixture of 1.0 g. of III, from either (a) or (b), 0.4 g. of palladium charcoal (5% Pd), and 50 cc. of absolute ethanol absorbed one mole of hydrogen in about one hour. After removal of catalyst, the filtrate was concentrated to 10 cc. to give, after ice-cooling, 0.5 g. (65%) of V, m. p. 74–76°.

Aluminum Isopropoxide Reduction of III.—One gram of III was reduced for four hours with 5 cc. of 1 *M* aluminum isopropoxide. The mixture was evaporated to dryness and the residue partitioned between benzene and dilute hydrochloric acid. The benzene layer was dried and concentrated to 4–6 cc. After addition of ligroin (b. p. 30–60°), 0.2 g. (25%) of leaflets (IV?), m. p. 105–107°, separated.

Anal. Calcd. for $\text{C}_{16}\text{H}_{14}\text{O}$: C, 86.5; H, 6.4. Found: C, 86.5; H, 6.3.

In subsequent experiments, attempts to isolate this compound failed.

9-(3-Morpholino-1-oxopropyl)-anthracene (VI).—A mixture of 25 g. of V, 15 g. of morpholine hydrochloride, 10 g. of paraformaldehyde and 125 cc. of absolute ethanol was refluxed for about twenty hours. After evaporation of solvent *in vacuo*, the residue was triturated with acetone to give 6 g. of morpholine hydrochloride. From the filtrate 12.5 g. of the hydrochloride of VI, m. p. 140–143°, was obtained. Upon recrystallization from absolute ethanol–ether it was converted to another crystalline form of m. p. 167–168.5°. Either form gave, with dilute ammonium hydroxide, VI which crystallized from methanol in prisms, m. p. 116–117.5°. Ten grams of V was recovered.

Anal. Calcd. for $\text{C}_{21}\text{H}_{21}\text{NO}_2$: C, 79.0; H, 6.6. Found: C, 78.9; H, 6.6.

9-(3-Morpholino-1-oxopropyl)-1,2,3,4-tetrahydroanthracene (VIII).—A mixture of 3.0 g. of VI hydrochloride (m. p. 167–168.5°), 0.1 g. of platinum oxide, and 40 cc. of methanol absorbed two moles of hydrogen during 6.5 hours. Absorption was then constant at about 20 cc. per hour. The mixture was warmed to solution, filtered, concentrated *in vacuo*, and diluted with ether to give 1.9 g. (62%) of hydrochloride. Dilute ammonium hydroxide-alcohol converted it to the base which crystallized from alcohol–water in cubes, m. p. 103–104°.

Anal. Calcd. for $\text{C}_{21}\text{H}_{23}\text{NO}_2$: C, 78.0; H, 7.8. Found: C, 77.8; H, 7.6.

The hydrochloride crystallized from 95% ethanol in prisms of m. p. 202.5–203°.

Anal. Calcd. for $\text{C}_{21}\text{H}_{26}\text{ClNO}_2$: C, 70.1; H, 7.3. Found: C, 70.1; H, 7.6.

9-Propionyl-1,2,3,4-tetrahydroanthracene (IX). (a) **From the Reduction of VI Hydrochloride.**—The filtrate from the 1.9 g. of VIII hydrochloride above was evapo-

rated to dryness and the residue partitioned between water and ether. The ether-soluble material was dried and evaporatively distilled in a high vacuum to give a small amount of oil which crystallized from methanol in plates of m. p. 58.5–59.5°.

Anal. Calcd. for $C_{16}H_{16}O$: C, 85.7; H, 7.6. Found: C, 85.4; H, 7.6.

(b) **From VI (base).**—A mixture of 1.1 g. of VI (m. p. 115–117°), 0.05 g. of platinum oxide, and 25 cc. of methanol absorbed three moles of hydrogen in twenty-five hours. After filtration of catalyst and evaporation of solvent, the residue was recrystallized from methanol to give 0.6 g. (74%) of IX, m. p. 56–58°.

(c) **From VIII.**—The base VIII (0.2 g.) absorbed one mole of hydrogen (platinum oxide) to give 0.1 g. of IX, m. p. 56.5–58°.

(d) **By Hydrogenation of 9-Propionylantracene.**—A mixture of 1.0 g. of II (m. p. 72–75°), 0.04 g. of platinum oxide, and 20 cc. of methanol absorbed two moles of hydrogen during fifteen to twenty-five hours. After filtration, concentration of the filtrate and ice-cooling, 0.6 g. (60%) of IX, m. p. 57.5–59° was obtained. It gave no depression when mixed with any of the samples of IX obtained as described above.

The semicarbazone of IX could not be obtained (boiling ethanol). Ketone IX was recovered.

9-Acetyl-1,2,3,4-tetrahydroanthracene (VII).—As described under (d) above, VII was obtained in a yield of 74%. It crystallized from methanol in prisms, m. p. 74.5–75.5°.

Anal. Calcd. for $C_{16}H_{16}O$: C, 85.7; H, 7.2. Found: C, 85.2; H, 7.2.

In an attempt to prepare the semicarbazone (four hours in refluxing ethanol) VII was recovered quantitatively.

Preparation of VIII from VII.—The Mannich reaction using 0.7 g. of VII, 0.5 g. of morpholine hydrochloride, 0.3 g. of paraformaldehyde, and 7 cc. of absolute ethanol yielded as described for the preparation of VI, 0.2 g. (21%) of VIII, m. p. 102.5–103°. The m. p. was not depressed by mixture with VIII described above. Two-tenths gram of VII was recovered.

1,2,3,4-Tetrahydro-9,10-anthraquinone (X). (a) **From VII.**—To a stirred mixture of 1.0 g. of VII and 10 cc. of acetic acid was added during one-half hour, 2.0 g. of chromic acid in 1 cc. of water and 5 cc. of acetic acid. After three and one-half hours stirring, water was added and the mixture was cooled in ice; yield of X, 0.25 g. (27%), m. p. 145–153°. After one recrystallization from alcohol it melted at 152–154°, m. p. not depressed by authentic material.

(b) **From IX.**—One gram of IX in 20 cc. of acetic acid gave, as above, 0.2 g. (22%) of X.

Summary

Attempts failed to prepare, by standard methods, the alkamines $—CHOHCH_2NR_2$ and $—CH_2OHCH_2CH_2NR_2$ derived from anthracene and carrying the side chain in position 9. 9- ω -Bromoacetylanthracene does not react with secondary amines. In the catalytic reduction of 9-(3-morpholino-1-oxopropyl), 9-acetyl and 9-propionylantracenes the carbonyl group is not attacked while one of the terminal benzene rings adds two moles of hydrogen.

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[CONTRIBUTION FROM THE DIVISION OF PHYSIOLOGY, NATIONAL INSTITUTE OF HEALTH]

Studies in the Anthracene Series. IV. *Meso*-Substituted 9,10-Dihydroanthracene Derivatives

BY EVERETTE L. MAY AND ERICH MOSETTIG

In the foregoing communication¹ we have shown that the catalytic hydrogenation of 9-(3-morpholino-1-oxopropyl)-anthracene hydrochloride (VIII), with the absorption of two moles of hydrogen, yields chiefly 9-(3-morpholino-1-oxopropyl)-1,2,3,4-tetrahydroanthracene. Originally, we had assumed this reduction product to be 9-(3-morpholino-1-hydroxypropyl)-9,10-dihydroanthracene (XIII). Analogously, alkyl 9-anthryl ketones gave the corresponding alkyl 9-tetrahydroanthryl ketones and not the expected alkyldihydroanthrylcarbinols. In order to study the chemistry and some biological aspects of the 9-substituted 9,10-dihydroanthracene derivatives, we elaborated their synthesis together with structural proofs.

9-Acetyl-9,10-dihydroanthracene (VI) was first prepared by Nenitzescu and co-workers² through the Friedel-Crafts reaction on 9,10-dihydroanthracene with acetyl chloride. On repeating this remarkable reaction,³ we obtained, in modifying the isolation procedure, the oily ketone VI and

small but varying amounts of 2-acetylanthracene. In a similar manner we prepared 9-propionyl-9,10-dihydroanthracene (II). The dihydro ketones could also be obtained in satisfactory yields in the hydriodic acid-phosphorus reduction⁴ of 9-acetyl- and 9-propionylantracenes. Moreover, VI was synthesized from 9,10-dihydro-9-anthroic acid (IX) via the diazo and bromo ketones. Acid IX was obtained in a yield of 27% in the Beckmann rearrangement of the stereochemically heterogeneous oxime of 9-benzoyl-9,10-dihydroanthracene, along with anthracene (26%) and a nitrogen-containing compound (17%) to which we assign tentatively formula XII. Anthracene has been formed, very likely, from the intermediate 9-amino-9,10-dihydroanthracene, unstable under the conditions of hydrolysis following rearrangement.⁵

The Mannich condensation on ketone VI, employing morpholine as the base, gave the morpholino ketone X which was readily hydrogenated (platinum oxide) to 9-(3-morpholino-1-hydroxypropyl)-9,10-dihydroanthracene (XIII). The

(1) May and Mosettig, *THIS JOURNAL*, **70**, 686 (1948).

(2) Nenitzescu, Gavát and Cocora, *Ber.*, **72**, 819 (1939).

(3) See also Cook, Robinson and Roe, *J. Chem. Soc.*, 266 (1939).

(4) This reductive method was employed by Cook, *J. Chem. Soc.*, 1677 (1926), in the preparation of 9-benzoyldihydroanthracene.

(5) Goldmann, *Ber.*, **23**, 2522 (1890).