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

Studies in the Anthracene Series. V. A Novel Rearrangement in the Reaction of Halomethyl Ketones with Secondary Amines

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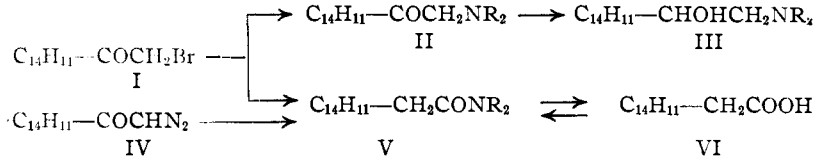
This investigation was undertaken with the purpose of synthesizing, for biological testing, alkamines in which the chain —$CHOHCH_2NR_2$ is attached to the *meso* position of 9,10-dihydroanthracene.

When 9-ω-bromoacetyl-9,10-dihydroanthracene (I) was allowed to react with secondary aliphatic amines, the expected amino ketones (II) were formed in yields of 30–40%. In addition, the isomeric 9-(9,10-dihydroanthryl)-acetamides (V) were obtained in yields of 40–50%.[1] It appears that a rearrangement has taken place similar to that of diazomethyl ketones to the corresponding homo-acid amides in the presence of amine and catalyst.[2]

The amides of type V proved to be exceedingly resistant to hydrolysis, but prolonged acid treatment ultimately gave the acid VI from which V ($R = C_2H_5$) was resynthesized. It was also obtained from 9,10-dihydro-9-anthroic acid in the Arndt–Eistert procedure *via* the diazomethyl ketone IV. A few attempts to convert IV directly to an amino ketone of type II failed. The amino ketones II ($R = C_2H_5$, C_3H_7, C_5H_{11}) were readily hydrogenated (platinum oxide) to the corresponding amino alcohols (III).



$C_{14}H_{11}$ = 9-(9,10-dihydroanthracyl), R = C_2H_5, C_3H_7, C_5H_{11}

Fig. 1.

In the course of this work we developed two convenient methods for the preparation of 9,10-dihydro-9-anthroic acid.[3] In the first, 9-cyanoanthracene[4] was saponified to the acid amide, which was reduced with hydriodic acid and phosphorus to the corresponding dihydro amide. Hydrolysis of the latter gave the acid in a yield of 82%, based on nitrile (70% based on anthracene). Secondly, reduction of 9-anthroic acid with sodium amalgam gave the dihydro acid in a yield of 80%. Reduction of 9-anthroic acid with hydriodic acid and phosphorus led to the desired acid in a yield of only 20%.

The amino alcohols III (R—C_2H_5, C_5H_{11}) were ineffective in blood-inoculated *gallinaceum* malaria.[5]

Acknowledgment.—The microanalyses were carried out by the microanalytical Laboratory of this Institute under the direction of C. A. Kinser. We are indebted to H. George Latham, Jr., for technical assistance.

Experimental[6]

9-Anthramide.—A mixture of 18.8 g. of 9-cyanoanthracene,[4] 17 g. of potassium hydroxide, 10 cc. of water and 75 cc. of ethylene glycol monoethyl ether (Cellosolve) was refluxed for two and one-half hours and diluted with water to give 20.5 g. of amide, m. p. 212–215°. It crystallized from aqueous ethanol in pale yellow needles, m. p. 215–216°.

Anal. Calcd. for $C_{15}H_{11}NO$: C, 81.4; H, 5.0. Found: C, 81.4; H, 5.3.

9,10-Dihydro-9-anthroic Acid.[3] **(a) From 9-Anthramide.**—A mixture of 20.5 g. of 9-anthramide, 5.6 g. of red phosphorus, 14 cc. of 57% hydriodic acid and 150 cc. of acetic acid was refluxed for seven hours, filtered hot, and diluted with twice its volume of water. The precipitate was washed with water and refluxed for two hours with 120 cc. of acetic acid and 60 cc. of concentrated hydrochloric acid. After dilution to 450 cc. with water and ice-cooling, the acid was collected and digested with an excess of dilute, boiling sodium carbonate. Filtration and acidification of the filtrate gave 17 g. (82%) of the dihydro acid of m. p. 199–202°.

(b) By Sodium Amalgam Reduction of 9-Anthroic Acid.—To a stirred mixture of 8.8 g. of 9-anthroic acid,[7] 2.4 g. of sodium carbonate and 100 cc. of water was added during forty-five minutes 200 g. of 2.5% sodium amalgam. The temperature was kept at 10°. After an additional ninety minutes the solution was decanted, treated with decolorizing carbon (Norit), filtered hot, and acidified; yield of acid 7.3 g., m. p. 201.5–203.5°.

N,N-Diethyl-9,10-dihydro-9-anthramide.—A mixture of 0.5 g. of 9,10-dihydro-9-anthroic acid and 1 cc. of thionyl chloride was refluxed for one hour and evaporated to dryness *in vacuo*. The residue, in dry ether, was treated slowly with 1 cc. of diethylamine. After filtration, the filtrate was evaporated to dryness to give a residue which crystallized from aqueous ethanol in long prisms of m. p. 99.5–100.5°; yield 0.5 g. (81%).

Anal. Calcd. for $C_{19}H_{21}NO$: C, 81.7; H, 7.6. Found: C, 81.5; H, 7.9.

9,10-Dihydro-9-anthroylguanidine (NIH 2932).[8]—To a stirred, ice-cooled mixture of 2 g. of guanidine hydrochloride, 2.1 g. of sodium hydroxide, 4 cc. of water and 4 cc. of acetone was added during thirty to forty minutes 4 g. of 9,10-dihydro-9-anthroyl chloride[3] in 16 cc. of acetone. After an additional one-half hour of stirring at

(1) Amide V (R = C_2H_5) was also obtained from 9-ω-chloroacetyl-9,10-dihydroanthracene. Piperidine, the only heterocyclic amine allowed to react with I, gave the homo-acid amide in a yield of only 15%.

(2) "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 38.

(3) See Paper IV of this series, May and Mosettig, THIS JOURNAL **70**, 688 (1948).

(4) Fieser and Hartwell, *ibid.*, **60**, 2555 (1938).

(5) Coatney and Cooper, unpublished results.

(6) All melting points given are uncorrected.

(7) For a convenient preparative method for 9-anthroic acid see the following paper of this series.

(8) This compound was found to be inactive in avian malaria. Compounds tested are designated by an NIH number.

room temperature, the mixture was diluted with water. The precipitate was recrystallized from ethanol to give 2.2 g. (50%) of rods, m. p. 200–201.5° (d.).

Anal. Calcd. for $C_{16}H_{15}N_3O$: C, 72.4; H, 5.7. Found: C, 72.3; H, 5.6.

N,N-Diethyl-9,10-dihydro-9-anthrylacetamide (V, R = C_2H_5).—A mixture of 5.0 g. of I,[3] 5 cc. of diethylamine, and 40 cc. of dry ether was shaken for one-half hour (slight cooling is necessary at first), diluted with about 20 cc. of ligroin (b. p. 30–60°) and cooled in ice to give 4.4 g. of precipitate which, when digested with water, yielded 2.2 g. (45%) of amide, m. p. 133–135°. It crystallized from methanol in long prisms of m. p. 134–135°.

Anal. Calcd. for $C_{20}H_{23}NO$: C, 81.9; H, 7.9; N, 4.8. Found: C, 81.4; H, 7.8; N, 4.7.

9-(2-Diethylamino-1-oxoethyl)-9,10-dihydroanthracene (II, R = C_2H_5) **Picrate.**—The filtrate from the 4.4 g. of precipitate above was washed three times with water, dried, and acidified with hydrogen chloride gas to give 1.5 g. of hydrochloride, m. p. 198–202°, after recrystallization from absolute ethanol–ether. A small sample was treated with aqueous alcoholic picric acid. The resulting picrate crystallized from 95% ethanol in yellow prisms, m. p. 127–129°.

Anal. Calcd. for $C_{26}H_{26}N_4O_8$: C, 59.8; H, 5.0. Found: C, 60.2; H, 5.2.

9-(2-Diethylamino-1-hydroxyethyl)-9,10-dihydroanthracene (III, R = C_2H_5) **Hydrochloride** (NIH 2874).—A mixture of 1.5 g. of the hydrochloride of II (R = C_2H_5), 0.05 g. of platinum oxide and 10 cc. of methanol absorbed one mole of hydrogen in three-fourths of an hour. The filtered solution was concentrated to about 3 cc. and diluted with ether to give 1.3 g. of the amino alcohol hydrochloride; prisms from methanol–ether, m. p. 200–202°.

Anal. Calcd. for $C_{20}H_{26}ClNO$: C, 72.4; H, 7.9. Found: C, 72.1; H, 7.8.

Synthesis of V (R = C_2H_5) **by the Arndt-Eistert Reaction.**—A solution of 1.7 g. of 9,10-dihydro-9-anthroyl chloride in 25 cc. of dry ether was added dropwise to 25 cc. of an ice-cooled, stirred ether solution of diazomethane (from 2.5 g. of nitrosomethylurea). After stirring for fifteen minutes in ice and for two hours at room temperature, the mixture was concentrated and diluted with ligroin to give 1.2 g. of IV, m. p. 104–106.5° (frothing). This diazo ketone (0.4 g.) in 4 cc. of dioxane was treated at 50–60° with a mixture of 0.5 cc. of diethylamine, 0.7 cc. of 10% silver nitrate, and 0.5 cc. of water. After refluxing for fifteen minutes the solution was filtered, diluted with a little water and cooled to give 0.3 g. (66%) of V (R = C_2H_5) of m. p. 132–134°. Recrystallized from methanol, it melted at 134–135°; the m. p. was not depressed by amide prepared as described above.

Hydrolysis of V (R = C_2H_5) **to 9,10-Dihydro-9-anthrylacetic Acid (VI).**—A mixture of 1 g. of the amide, 8 cc. of concentrated hydrochloric acid, and 2 cc. of acetic acid was refluxed vigorously for one week. During this time 4 cc. of concentrated hydrochloric acid and 1 cc. of acetic acid were added. The mixture was diluted with water, cooled, filtered, and the precipitate digested with boiling, dilute sodium carbonate. Filtration gave 0.15 g. of starting material. Acidification of the filtrate gave 0.6 g. (90% based on used amide) of VI, m. p. 165–168°. It crystallized from methanol–water in oblong plates of m. p. 168–169.5°. It appears to be oxidized slowly in air.

Anal. Calcd. for $C_{16}H_{14}O_2$: C, 80.7; H, 5.9. Found: C, 80.5; H, 6.2.

The acid VI was converted to the oily acid chloride with thionyl chloride. This acid chloride, in ether, was treated with diethylamine to give V (R = C_2H_5) in a yield of 90%.

9-(ω-Chloroacetyl)-9,10-dihydroanthracene.—To 0.3 g. of IV in ether was added dropwise 15% alcoholic hydrogen chloride until gas evolution had ceased. Dilution of the mixture with ligroin (b. p. 30–60°) gave 0.3 g. of needles. The analytical sample, from methanol, melted at 113–114°.

Anal. Calcd. for $C_{16}H_{13}ClO$: C, 74.9; H, 5.1. Found: C, 75.2; H, 5.2.

When this chloro ketone, in ether, was allowed to react with diethylamine, V (R = C_2H_5) was obtained in a yield of 45%.

9-(2-Dipropylamino-1-hydroxyethyl)-9,10-dihydroanthracene Hydrochloride (III, R = C_3H_7).—A mixture of 2 g. of I, 1.4 g. of dipropylamine and 15 cc. of dry ether was shaken for one-half hour, cooled in ice and filtered. The filtrate was shaken with three portions of dilute hydrochloric acid, dried, and the ether evaporated to give 1.2 g. of oily amide (V, R = C_3H_7) which was hydrolyzed to VI as described above. The combined aqueous fractions were basified with aqueous ammonia and the resulting oil dried in ether. The ethereal solution was acidified with 15% alcoholic hydrogen chloride to give, after recrystallization from acetone–ether, 0.6 g. of hydrochloride. This in 15 cc. of methanol with 0.01 g. of platinum oxide absorbed one mole of hydrogen during one hour. The filtered solution was evaporated to dryness *in vacuo*. The residue crystallized from acetone–ether in a yield of 0.5 g., m. p. 160–167°. The analytical sample melted at 171–172.5° after drying in a vacuum desiccator.

Anal. Calcd. for $C_{22}H_{30}ClNO$: C, 73.4; H, 8.4. Found: C, 73.6; H, 8.7.

The picrate crystallized from ethanol in yellow hexagons, m. p. 182–184°.

Anal. Calcd. for $C_{28}H_{32}N_4O_8$: C, 60.9; H, 5.8. Found: C, 61.0; H, 5.9.

9-(2-Diamylamino-1-hydroxyethyl)-9,10-dihydroanthracene (III, R = C_5H_{11}) **Hydrochloride** (NIH 2885).—A mixture of 3 g. of I, 3.3 g. of diamylamine and 25 cc. of dry ether was shaken for one-half hour, cooled in ice and filtered. The filtrate was acidified to congo red with hydrogen chloride gas, diluted with ligroin (b. p. 30–60°) and filtered. The 2 g. of solid was recrystallized from acetone–ether to give 1.6 g. of a mixture of II (R = C_5H_{11}) and diamylamine hydrochloride. This in 15 cc. of methanol with 0.05 g. of platinum oxide absorbed 0.85 mole of hydrogen in three-fourths hour. The filtered solution was evaporated to dryness *in vacuo*. The residue was triturated with ether–ethyl acetate to give 0.3 g. of diamylamine hydrochloride. Slight dilution of the filtrate with ligroin gave 1.0 g. of III (R = C_5H_{11}) hydrochloride. It crystallized from acetone–ether in triangles, m. p. 113–115.5°.

Anal. Calcd. for $C_{26}H_{38}ClNO \cdot {}^1/_2CH_3OH$: C, 73.7; H, 9.3; CH_3OH, 3.7. Found: C, 73.8; H, 9.2; loss in wt. (97° at 1 mm.), 4.5.

After the loss-in-weight determination, the sample was analyzed for carbon and hydrogen.

Anal. Calcd. for $C_{26}H_{38}ClNO$: C, 75.0; H, 9.2. Found: C, 74.6; H, 9.0.

The picrate crystallized from ethanol in yellow crusts of m. p. 143–145°.

Anal. Calcd. for $C_{32}H_{40}N_4O_8$: C, 63.1; H, 6.6. Found: C, 63.1; H, 6.5.

The ether–ligroin filtrate from the 2 g. of II (R = C_5H_{11}) above was washed with water, dried and evaporated to dryness. The residual oily amide (V, R = C_5H_{11}), hydrolyzed as described above, gave VI in a yield of 37%.

9,10-Dihydro-9-anthrylacetpiperidide (V, NR_2 = piperidino).—A mixture of 1.0 g. of I and 15 cc. of dry ether was swirled while adding 1 cc. of piperidine. The mixture was shaken vigorously for fifteen minutes and extracted three times with water. The dried ether solution was acidified with dry hydrogen chloride. The resulting semi-solid was recrystallized from methanol–ether to give 0.9 g. of a precipitate which was digested with water and filtered. The crystals (0.15 g., m. p. 109–110.5°) were

recrystallized from methanol–water to give the amide in long prisms, m. p. 108–110°.

Anal. Calcd. for $C_{21}H_{23}NO$: C, 82.6; H, 7.6. Found: C, 82.4; H, 7.6.

This compound was also prepared from VI as described above for V (R = C_2H_5).

9-(2-Piperidino-1-oxoethyl)-9,10-dihydroanthracene Hydrochloride.—The aqueous filtrate from the 0.15 g. of amide above was basified with aqueous ammonia and the liberated base dried in ether. The ethereal solution was acidified with 1.7 cc. of 15% alcoholic hydrogen chloride. Enough acetone and absolute ethanol were added to dissolve the precipitated oil. The amino ketone salt crystallized in a yield of 0.5 g., m. p. 221–223°; flakes from methanol–ether, m. p. 222–224° (d.).

Anal. Calcd. for $C_{21}H_{24}ClNO$: C, 73.8; H, 7.1. Found: C, 74.0; H, 7.1.

Summary

In the reaction of 9-ω-bromoacetyl-9,10-dihydroanthracene with secondary aliphatic amines, the 9-(2-dialkylamino-1-oxoethyl)-9,10-dihydroanthracenes and the corresponding amides of 9-(9,10-dihydroanthryl)-acetic acid were obtained in nearly equal amounts.

Two convenient methods for the preparation of 9,10-dihydro-9-anthroic acid are described.

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Studies in the Anthracene Series. VI. Derivatives of 1,2,3,4-Tetrahydroanthracene

BY H. GEORGE LATHAM, JR., EVERETTE L. MAY AND ERICH MOSETTIG

As a key substance for further synthetic work, 9-bromo-1,2,3,4-tetrahydroanthracene was needed in quantity. Bachmann and Cronyn[1] have shown that the bromination of tetrahydrophenanthrene gives exclusively and in good yield, the 9-bromo derivative. When tetrahydroanthracene was similarly treated,[2] 9-bromo-1,2,3,4-tetrahydroanthracene (VIII) was formed in a yield of *ca.* 30%. In addition, varying amounts of a dibromo-1,2,3,4-tetrahydroanthracene (IX) could be isolated.

The position of the bromine atom in VIII was established in the following way: VIII was converted, with cuprous cyanide, to the nitrile VI, which was also synthesized from 9-anthroic acid (I) *via* II and III as shown in Fig. 1. Furthermore, we hydrolyzed VI to amide V which, again, was obtained in the catalytic hydrogenation of IV. The dibromo derivative IX appears to be identical with the compound cursorily described by Schroeter[3] as the only bromination product of tetrahydroanthracene. Since it can also be prepared from VIII, one of its bromine atoms must be located in position 9.

The conversion of VI into ketone X constitutes additional evidence for the structure of the latter[4] and supports the formula assigned to the oily acetyltetrahydroanthracene, obtained together with the 6 isomer in the Friedel–Crafts reaction on tetrahydroanthracene.[5]

9-Anthroic acid was conveniently prepared in a yield of 60–70% by heating under reflux, anthracene and oxalyl chloride in nitrobenzene.[6] When 9-bromoanthracene was treated under the same conditions, carboxylation took place to the extent of only 12%. The acid is obviously identical with the 9-bromo-10-anthroic acid of Beyer and Fritsch,[7] since it can be readily oxidized to 9,10-anthraquinone.

Acknowledgment.—We are indebted to Edward A. Garlock, Jr., for much of the preliminary work on the bromination of tetrahydroanthracene and the hydrogenation of 9-anthroic acid.

Experimental[8,9]

9-Anthroic Acid (I).—A mixture of 50 g. of anthracene,[10] 30 cc. of oxalyl chloride, and 150 cc. of dry nitrobenzene in a one-liter flask was heated in a metal-bath. A gentle reflux was maintained by raising the temperature of the bath from 120 to 240° during five to six hours. After steam-distillation of the nitrobenzene, 100 cc. of 10 *N* sodium hydroxide and enough water to make the total volume 700 cc. were added, and the mixture was refluxed for one-half hour. Insoluble material (11 g. of anthracene after purification)[11] was collected. The filtrate was washed with ligroin (b. p. 30–60°), treated with decolorizing carbon (Norit), filtered hot, and the Norit washed with 2 *N* sodium carbonate. Acidification of the combined filtrate and washings gave 41.6 g. (67%) of I, m. p. 208–212°.

9-Bromo-10-anthroic Acid.[7]—This acid was prepared from VIII, as described for I (reaction time twenty-five hours), in a yield of 12%, m. p. 263–266° (dec.). The

(1) Bachmann and Cronyn, *J. Org. Chem.*, **8**, 456 (1943).

(2) The preliminary experiments of the bromination were carried out by E. A. Garlock, Jr.

(3) Schroeter, *Ber.*, **57**, 2014 (1924).

(4) See Paper III of this series, May and Mosettig, THIS JOURNAL, **70**, 686 (1948).

(5) Garlock and Mosettig, THIS JOURNAL, **67**, 2255 (1945).

(6) We were unable to duplicate the experiments of Liebermann and Zsuffa [*Ber.*, **44**, 208 (1911)] who obtained 9-anthroic acid in yields of 70–80% by heating anthracene and oxalyl chloride in a sealed tube at 160–170°. In our hands the experiment yielded only 15–20% of 9-anthroic acid. Furthermore, Nenitzescu, *et al.* [*Ann.*, **491**, 210 (1931)] prepared 9-benzoylanthracene in nearly quantitative yields by refluxing a solution of anthracene and benzoyl chloride in nitrobenzene. In repeated attempts to reproduce the results of these authors, anthracene was hardly attacked and was recovered nearly quantitatively.

(7) Beyer and Fritsch, *Ber.*, **74**, 494 (1941).

(8) All melting points given are uncorrected.

(9) The microanalyses were carried out by the microanalytical Laboratory of this Institute under the direction of C. A. Kinser.

(10) See Garlock and Mosettig[5] for the grade of anthracene used.

(11) During some preliminary work on this reaction, appreciable amounts of a yellow solid, m. p. 260–262°, were encountered.

Anal. Calcd. for $C_{28}H_{18}O$: C, 91.1; H, 4.7. Found: C, 90.8; H, 5.0.

This analysis indicates that the compound might be 9,9'-dianthryl ketone.