[Contribution from the Department of Chemistry State University of Iowa]

THE SYNTHESIS OF 9,10-DIHYDRO-9,10-(11-AMINOETHANO)ANTHRACENES

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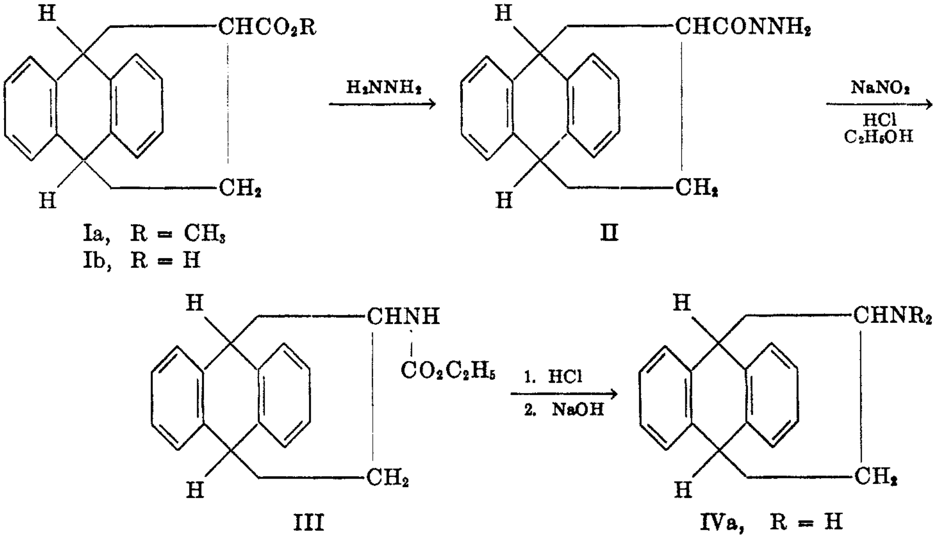
Numerous compounds have been prepared with certain structural features of the morphine molecule in attempts to obtain simpler analgetics (1). One feature which apparently has not been investigated as a possible source of analgetic activity is the three dimensional shape which seems to be unique for this molecule. Such a structure is present in the active N-alkylmorphinans (2) but is difficult to evaluate as far as its contribution towards analgetic activity is concerned since it is present with a quarternary carbon atom which is known to contribute towards such activity (3).

To determine the importance of the three dimensional structure in this field, the simpler amines lacking quarternary carbon atoms, 9,10-dihydro-9,10-(11-aminoethano)anthracene[3] (IVa) and 9,10-dihydro-9,10-(11-dimethylaminoethano)anthracene (IVb) have been synthesized for testing. Work on the preparation of the isomeric compound with the nitrogen in the bridge is in progress.



Ia, R = CH_3
Ib, R = H

II

III

IVa, R = H
IVb, R = CH_3

9,10-Dihydro-9,10-(11-aminoethano)anthracene (IVa) was synthesized from the Diels-Alder adduct from anthracene and methyl acrylate by the steps in-

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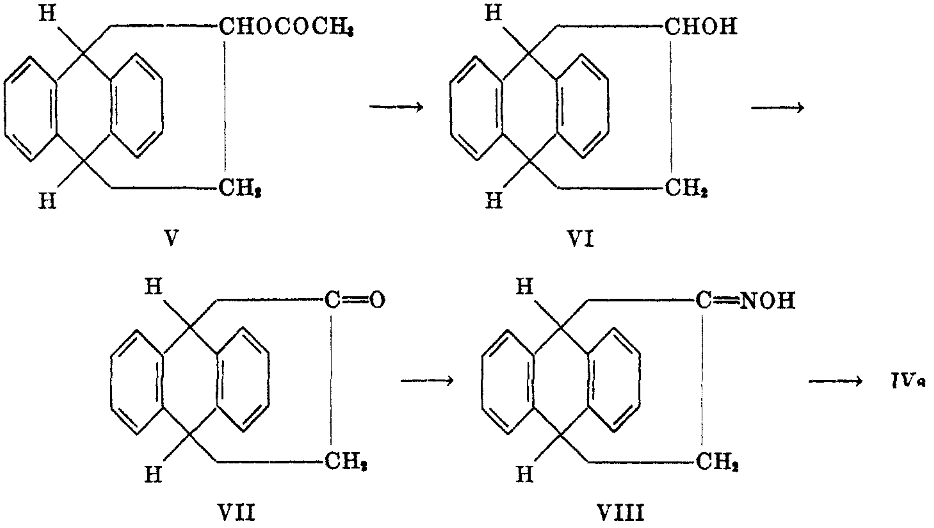
[2] Public Health Research Fellow of the National Institutes of Health, 1951–1952.

[3] The first substituted carbon atom in the bridge is designated as the eleven carbon atom.

dicated below. The conversion of the ester (Ia) to the urethan (III) through the hydrazide (II) proceeded in good yields. The amine (IVa) was prepared by the hydrolysis of the latter compound (III).

The ester (Ia) could also be prepared from the acid (Ib) obtained by the oxidation of the adduct between anthracene and allyl alcohol (4). The acid (Ib) could not be converted into the amine (IVa) by a Schmidt reaction or by a Curtius reaction after conversion to the azide through the acid chloride.



To demonstrate that no change had occurred in the bridge structure during the rearrangement of the azide, the amine (IVa) was synthesized in an independent manner from the Diels-Alder adduct of anthracene and vinyl acetate (5). Transesterification of the ester (V) with methanol gave the alcohol (VI) which could be oxidized by chromic acid or aluminum *tert*-butoxide to the ketone (VII). The latter (VII) readily formed an oxime (VIII) which could be easily reduced with sodium and alcohol to the amine, IVa.

The 9,10-dihydro-9,10-(11-dimethylaminoethano)anthracene (IVb) was prepared by methylating the primary amine (IVa) with formaldehyde and formic acid.

The two amines (IVa, IVb) in preliminary testing have shown no analgetic activity.

EXPERIMENTAL[4]

9,10-Dihydro-9,10-(11-carbomethoxyethano)anthracene (Ia). A mixture of anthracene (89.0 g.) and methyl acrylate (51.5 g.) in xylene (500 ml.) was heated for 12 hours at 210° in a steel bomb. Upon concentration of the solution and cooling, crystalline 9,10-dihydro-9,10-(11-carbomethoxyethano)anthracene (122.2 g.) (93%), was obtained. Crystallization from methanol gave colorless needles melting at 117–118°.

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[4] Melting points are not corrected.

Anal. Calc'd for $C_{18}H_{16}O_2$: C, 81.79; H, 6.10.
Found: C, 81.17; H, 6.08.

A solution of 9,10-dihydro-9,10-(11-carboxyethano)anthracene (Ib) (6.2 g.) in thionyl chloride (45 ml.) after refluxing for 2 hours gave upon removal of the excess thionyl chloride and addition of methanol (60 ml.) at 0° the methyl ester. This compound was isolated by removing the methanol by distillation and recrystallizing the brown residue from methanol after the addition of decolorizing carbon; m.p. 117–118°; yield, 5.3 g. (80%). A mixture with a sample obtained from the Diels-Alder reaction melted at the same point.

Hydrazide of 9,10-dihydro-9,10-(11-carboxyethano)anthracene (II). A mixture of the ester (Ia) (6.8 g.) and hydrazine hydrate (40.0 g.) was refluxed for 15 minutes and then treated with enough ethanol to make a homogeneous solution. The solution after refluxing for 2 hours and removal of the solvent gave a residue which was crystallized from ethanol; m.p. 229–230°; yield, 6.6 g. (97%).

Anal. Calc'd for $C_{17}H_{16}N_2O$: C, 77.24; H, 6.10.
Found: C, 76.71; H, 6.11.

9,10-Dihydro-9,10-(11-carbethoxyaminoethano)anthracene (III). A well-stirred solution of the hydrazide (II) (2.0 g.), 6 *N* hydrochloric acid (5.0 ml.), and acetone (100 ml.) at 0° was treated dropwise with a solution of sodium nitrite (0.5 g.) in water (3.0 ml.) and then kept at this temperature for 30 minutes. To the resulting solution was added ethanol (100 ml.) at 0°. The mixture was stirred further for 15 minutes, filtered, and dried over sodium sulfate at 0° for two hours. The acetone was removed by distillation, ethanol (50 ml.) was added and the solution refluxed for 19 hours. After removal of the solvent, cooling gave a residue which was recrystallized from petroleum ether (b.p. 60–70°); m.p. 155–155.5°; yield, 2.0 g. (95%).

Anal. Calc'd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77.
Found: C, 77.15; H, 6.46; N, 5.09.

9,10-Dihydro-9,10-(11-aminoethano)anthracene (IVa). A solution of the urethan (III) (7.0 g.) in glacial acetic acid (150 ml.) was refluxed for 42 hours. Removal of the solvent at reduced pressure left a residue which was dissolved in water. Addition of potassium hydroxide gave a precipitate which, when recrystallized from petroleum ether (b.p. 60–70°), gave colorless needles melting at 104.5–105°; yield, 4.3 g. (81%).

Anal. Calc'd for $C_{16}H_{15}N$: C, 86.84; H, 6.83; N, 6.33.
Found: C, 86.64; H, 6.99; N, 6.45.

A refluxing solution of the oxime (VII) (1.0 g.) in ethanol (100 ml.) protected from moisture with a calcium chloride tube was treated with sodium (0.5 g.). After the sodium had dissolved the solution was diluted with water and the alcohol removed by distillation. Addition of 6 *N* hydrochloric acid gave a clear solution which, when made alkaline with potassium hydroxide, gave the solid amine. Recrystallization from petroleum ether (b.p. 60–70°) gave a solid which melted at 104.5–105°; yield, 0.3 g. (32%). A mixture with a sample of the amine obtained by hydrolysis of the urethan melted at the same point.

9,10-Dihydro-9,10-(11-hydroxyethano)anthracene (VI). A solution of the Diels-Alder adduct from vinyl acetate and anthracene (V) (60.0 g.) (5), methanol (500 ml.), and sodium methoxide (2.0 g.) was refluxed for 19 hours. Removal of the solvent by distillation and crystallization of the residue from methyl alcohol gave the alcohol (VI) melting at 142–143°; yield, 48.7 g. (96.5%).

9,10-Dihydro-9,10-(11-ketoethano)anthracene (VII). A solution of the alcohol (VI) (20.0 g.) in glacial acetic acid (400 ml.) at 60° was treated with solid chromic anhydride (6.6 g.). The resulting mixture was stirred at room temperature for 2 hours and when poured onto ice gave a precipitate (16.1 g.). Crystallization from petroleum ether (b.p. 60–70°) after treatment with decolorizing carbon gave crystals melting at 152.5–153°; yield (81% crude).

Anal. Calc'd for $C_{16}H_{12}O$: C, 87.24; H, 5.49.
Found: C, 87.29; H, 5.46.

The ketone (VII) was prepared in higher yield and in a much purer state by the Oppenauer oxidation. A solution of the alcohol (VI) (30.0 g.) in cyclohexanone (259 g.) and toluene (1.8 l.) was heated to boiling. When about 500 ml. of distillate had collected in the receiver, a solution of aluminum *tert*-butoxide (97.4 g.) in toluene (675 ml.) was added dropwise over a period of 2.5 hours while the distillation continued. The mixture was cooled and washed in a funnel with 6 *N* hydrochloric acid. Removal of the solvents at reduced pressure gave an oily residue which crystallized upon the addition of petroleum ether (b.p. 60–70°). Recrystallization from petroleum ether (b.p. 60–70°) gave the ketone (VII) melting at 152.5–153°; yield, 21.7 g. (73%). A mixture with the ketone obtained by chromic anhydride oxidation melted at the same point.

The oxime of 9,10-dihydro-9,10-(11-ketoethano)anthracene (VII). A solution of the ketone (VII) (1.0 g.), fused sodium acetate (1.6 g.), and hydroxylamine hydrochloride (1.0 g.) in ethanol (70 ml.) and water (10 ml.) was refluxed for 2.5 hours. Removal of the alcohol and crystallization of the water-insoluble residue from petroleum ether (b.p. 60–70°) gave long colorless needles melting at 214–214.5°; yield, 0.8 g. (75%).

Anal. Calc'd for $C_{16}H_{13}NO$: C, 81.68; H, 5.57; N, 5.95.
Found: C, 81.71; H, 5.44; N, 6.13.

9,10-Dihydro-9,10-(11-dimethylamino)anthracene (IVb). A mixture of the primary amine (IVa) (21.1 g.), 98% formic acid (23.4 g.), and 35% formaldehyde (18.9 g.) was allowed to stand at room temperature for 30 hours and then was heated at 100° for 40 minutes. The resulting solution was treated with 6 *N* hydrochloric acid (25 ml.) and the excess formic acid and formaldehyde were removed by distillation. Filtration of the solution followed by the addition of sodium hydroxide gave the dimethylamino compound (IVb). Crystallization from petroleum ether (b.p. 60–70°) gave a white solid (14.5 g.) melting at 125–127°.

Anal. Calc'd for $C_{18}H_{19}N$: C, 86.70; H, 7.68; N, 5.62.
Found: C, 86.02; H, 7.72; N, 6.08.

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SUMMARY

The synthesis of 9,10-dihydro-9,10-(11-aminoethano)anthracene and 9,10-dihydro-9,10-(11-dimethylaminoethano)anthracene for testing as analgetics is described.

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