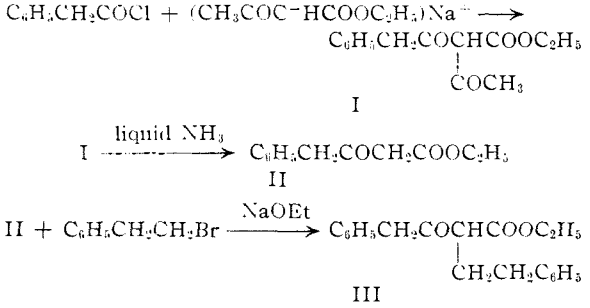
[CONTRIBUTION FROM THE ORGANIC RESEARCH DEPARTMENT, ABBOTT LABORATORIES]

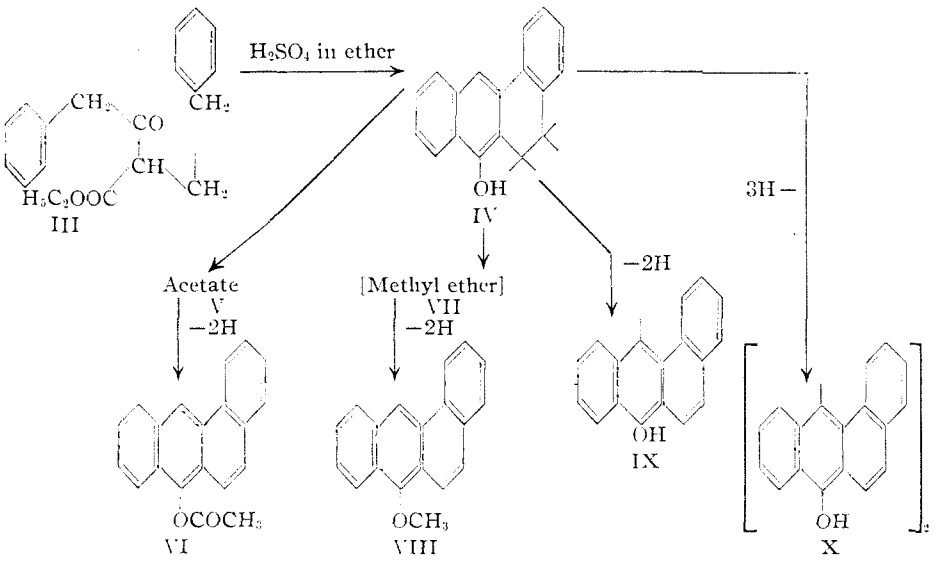
A Synthesis of 3,4-Dihydro-10-hydroxy-1,2-benzanthracene and Derivatives

BY HAROLD E. ZAUGG

In a recent publication Latif and Soliman[1] described a novel ring-closure reaction in which ethyl α-benzyl-γ-phenylacetoacetate, treated with concentrated sulfuric acid, produced 1-hydroxy-2,3-benzfluorene in a yield of 52%. Since it has been found[2] that "some monomethoxy-derivatives of polycyclic aromatic hydrocarbons strongly inhibit the growth of tumors," the importance of the new ring-closure reaction in this connection renders it worthy of further development.

In the present work the following series of reactions has been carried out with the double purpose of finding optimum conditions for the primary steps and of indicating the extent of further possible application of the ring-closure reaction.





Published methods[3,4] for the synthesis of ethyl γ-phenylacetoacetate (II) suffer from obvious disadvantages for the preparation of relatively large quantities. A modification of the general method of Bouveault and Bongert[5] was finally adopted for this purpose. The diketo-ester I was purified through its copper chelate and added directly (in ether solution) to excess liquid ammonia. In this way γ-phenylacetoacetic ester (II) was obtained in a 30% over-all yield from acetoacetic ester.

The alkylation of II with phenylethyl bromide was carried out in the usual manner[1] to give the β-keto-ester III in a 65% yield. Treatment of III with concentrated sulfuric acid[1] gave the dihydrobenzanthracene derivative IV in poor yield, as did treatment of III with anhydrous hydrogen fluoride. However, when the concentrated sulfuric acid was diluted with half its volume of ether a 70% yield of IV was produced.

Compound IV formed a crystalline benzoate and an acetate V which was obtained in two polymorphic forms. The methyl ether VII could not be crystallized but was dehydrogenated directly to VIII. Dehydrogenations of compounds IV, V and VII to IX, VI and VIII, respectively, were carried out in refluxing (175°) *p*-cymene using 10–20% palladium-on-charcoal as catalyst. The three last named compounds have been reported[6] and the identities of the acetate VI and the methyl ether VIII were established by mixed melting points with authentic samples kindly supplied by Dr. Fieser.

Compound X was formed by dehydrogenation of IV at 230–240° in the absence of a solvent. The structure indicated is tentative and is based only on microanalytical results, high melting point and low solubility. Molecular weight determinations were inconclusive because of an apparent tendency to decompose in the camphor solvent.

All attempts to oxidize compound IV directly to benzanthraquinone using chromium trioxide or hydrogen peroxide as oxidants were unsuccess-

(1) Latif and Soliman, *J. Chem. Soc.*, 56 (1944).

(2) Cook and Schoental, *ibid.*, 288 (1945); *cf.* "20th Annual Report of the British Empire Cancer Campaign," 20 (1943).

(3) Sonn and Litten, *Ber.*, **66**, 1512 (1933).

(4) Breslow, Baumgarten and Hauser, THIS JOURNAL, **66**, 1286 (1944).

(5) Bouveault and Bongert, *Bull. soc. chim.*, [3] **27**, 1088 (1902).

(6) Fieser and Hershberg, THIS JOURNAL, **59**, 1028 (1937).

ful. Likewise, numerous experiments directed toward formation of benzanthracene and dihydrobenzanthracene, by zinc dust cleavage[7] of compounds VI and IV, respectively, were fruitless.

Experimental

Ethyl γ-Phenylacetoacetate (II).—In a 12-liter three-necked flask fitted with a stirrer and reflux condenser (calcium chloride tube) were placed 6 liters of dry benzene and 400 g. (3.08 moles) of acetoacetic ester. To this solution was added 69 g. of sodium in small pieces. The mixture was then stirred and refluxed overnight. The suspension of sodium salt was cooled to room temperature and 636 g. (4.1 moles) of phenylacetyl chloride was added dropwise with stirring. The mixture was again refluxed overnight, cooled and poured into ice-water. The organic layer was separated and the benzene removed by distillation. The residual dark oil weighed 858 g.

This oil was poured with vigorous stirring into a 4-liter beaker containing a copper ammonium sulfate solution previously prepared by dissolving 500 g. of copper sulfate in 2 liters of water and adding 550 cc. of concentrated ammonium hydroxide. The copper chelate began to precipitate almost at once. Vigorous stirring, preferably with a high-velocity propeller-type mixer, was continued for fifteen minutes and the blue-green product was filtered off. The filter-cake was suspended in 1200 cc. of 95% ethanol, stirred for a few minutes and allowed to stand overnight. The insoluble blue precipitate was filtered from the green solution, washed with liberal quantities of alcohol, and resuspended in 800 cc. of fresh alcohol. After stirring for a few minutes and allowing to stand for one hour the mixture was filtered again, washed with more alcohol and dried. There was obtained 515 g. (60%) of light blue product of m. p. 179–181°. The reported[8] melting point of the pure copper chelate is 182–183°. In several smaller runs, yields of copper derivative varied between 60 and 70% (based on acetoacetic ester).

To a well-cooled (5–10°) solution of 110 cc. of concentrated sulfuric acid in 600 cc. of water was added 1500 cc. of ether followed by the 515 g. of copper derivative. The mixture was stirred vigorously with continued cooling until all of the copper salt was decomposed. The blue aqueous layer (containing some crystallized copper sulfate) was drawn off and the ether solution was washed with water and saturated sodium bicarbonate, and dried over anhydrous calcium chloride. Filtration and removal of the ether by distillation gave 438 g. (96% from the copper chelate) of a yellow oil pure enough for use in the next step. Distillation of a sample gave analytically pure ethyl α-phenylacetylacetoacetate, (I) b. p. 135–137° (0.5 mm.), $n^{24}D$ 1.5354.

To a stirred solution of 400 g. of liquid ammonia in 450 cc. of dry ether was added over a period of ten minutes a solution of 228 g. of the above undistilled ester (I) in 300 cc. of dry ether. The temperature of the solution rose from −30 to −25° during the addition. The mixture was then stirred for an hour and allowed to stand overnight at room temperature in a well-ventilated hood.

The mixture was cooled in ice and any insoluble material (mainly phenylacetamide) was filtered off. The ethereal filtrate was washed with ice-cold 3 *N* hydrochloric acid, 10% sodium carbonate solution and water, and dried over anhydrous calcium chloride. Filtration and distillation of the ether gave an oil which was distilled through a 15 cm. helix-packed column. After a definite forerun (20 g.) there was obtained 87 g. (46% based on undistilled ester I) of colorless ethyl γ-phenylacetoacetate (II) b. p. 118–123° (0.6 mm.), $n^{25}D$ 1.5066.

The product was identified by analysis, by conversion to the phenylpyrazolone,[9] m. p. 131–132°, and by formation of the copper chelate, light green needles from methylcyclohexane, m. p. 128–129°.[10] Repeated crystallization did not result in any improvement in the carbon analysis over that shown.

Anal. Calcd. for $C_{24}H_{26}O_6Cu$: Cu, 13.41; C, 60.81; H, 5.53. Found: Cu, 13.41, 13.54, 13.40; C, 61.61, 61.57, 61.54; H, 5.59, 5.59, 5.57.

Ethyl γ-Phenyl-α-(2-phenylethyl)-acetoacetate (III).—To a warm solution of sodium ethoxide (5.88 g., 0.255 g.-atom Na) in 250 cc. of absolute alcohol was added 52.5 g. (0.255 mole) of ethyl γ-phenylacetoacetate (II) in one portion with stirring. The mixture was heated to reflux and 70.8 g. (0.383 mole) of freshly distilled β-phenylethyl bromide was added dropwise with stirring over a period of twenty minutes. Refluxing and stirring was continued for fifteen hours after which the mixture was cooled and poured into ice water containing a little hydrochloric acid. The oil was extracted with ether, washed with water and dried over anhydrous calcium chloride.

Distillation gave, after a considerable forerun, 51 g. (65%) of product, b. p. 168–174° (0.3 mm.), $n^{27}D$ 1.5379. Redistillation of a sample for analysis gave b. p. 162–164° (0.2 mm.), $n^{23}D$ 1.5387.

Anal. Calcd. for $C_{26}H_{22}O_3$: C, 77.39; H, 7.15. Found: C, 77.60; H, 7.01.

3,4-Dihydro-10-hydroxy-1,2-benzanthracene (IV).—To a solution of 57 g. of the alkylated β-keto-ester III in 285 cc. of dry ether cooled to 5–10° in an ice-bath was added, dropwise with stirring, 570 cc. of cold concentrated sulfuric acid. The temperature was kept below 20° and after addition was complete, stirring was continued for an hour.

After standing overnight at room temperature the mixture was poured into three liters of ice-water and extracted with ether. The ethereal solution was washed with bicarbonate and water and dried over anhydrous magnesium sulfate. Filtration and evaporation of the ether gave 31 g. (70%) of pink solid, m. p. 120–123°. Recrystallization from 700 cc. of methylcyclohexane gave 27 g. of cream-colored needles of m. p. 124–126°. For analysis, a sample was recrystallized from benzene to give fluffy needles, m. p. 126–127°.

Anal. Calcd. for $C_{18}H_{14}O$: C, 87.78; H, 5.73. Found: C, 88.07; H, 5.60.

The bicarbonate washings, on standing, deposited 3.1 g. of a sodium salt which crystallized from aqueous alcohol in shiny colorless needles analyzing for a sodium sulfonate (monohydrate) derivative of IV.

Anal. Calcd. for $C_{18}H_{13}O_4SNa \cdot H_2O$: C, 59.01; H, 4.13; S, 8.75. Found: C, 59.40; H, 3.94; S, 8.86.

Benzoate of IV.—Treatment of compound IV with benzoyl chloride in pyridine gave the benzoate, which crystallized from Skellysolve C in rosets, m. p. 124–126°.

Anal. Calcd. for $C_{25}H_{18}O_2$: C, 85.69; H, 5.18. Found: C, 85.88; H, 5.23.

3,4-Dihydro-1,2-benzanthracene-10-acetate (V).—Acetylation of IV, using acetic anhydride and fused potassium acetate in the usual manner, gave 95% of the acetate V, which crystallized from 95% ethanol in elongated prisms, m. p. 111–113°.

Anal. Calcd. for $C_{20}H_{16}O_2$: C, 83.31; H, 5.59. Found: C, 83.40; H, 5.70.

A second preparation of the acetate V in exactly the same manner gave an almost quantitative yield of product which crystallized from 95% ethanol in prisms, m. p. 137.5–138.5°.

Anal. Calcd. for $C_{20}H_{16}O_2$: C, 83.31; H, 5.59. Found: C, 83.68; H, 5.59.

A mixture of the 112° acetate and the 138° acetate melted at 138°, indicating polymorphism.

1,2-Benzanthracene-10-acetate (VI).—Two grams of the acetate V was refluxed for forty hours in 50 cc. of *p*-

(7) Clar, *Ber.*, **72**, 1646 (1939).

(8) Bülow and Haider, *ibid.*, **35**, 929 (1902).

(9) Metzner, *Ann.*, **298**, 382 (1897).

(10) Sonn and Litten (ref. 3) reported a light blue compound of m. p. 176–178° for this copper derivative, but gave no analysis. Apparently theirs was an impure sample of the much less soluble blue copper derivative, m. p. 182–183°, of the uncleaved ester (I).

cymene with 0.8 g. of 10% palladium-on-charcoal. The warm solution was filtered from catalyst, and on cooling colorless needles of VI slowly crystallized: yield 0.7 g.; m. p. 158–160°. Recrystallization from acetic acid diluted with a little water, or from 95% ethanol, gave needles of m. p. 162–163°. The identity of the product was demonstrated by analysis and by mixed melting point with an authentic sample.[6]

10-Methoxy-1,2-benzanthracene (VIII).—Two grams of compound IV was methylated in methanolic alkali, using dimethyl sulfate as alkylating agent. The oil obtained in this manner could not be crystallized so it was refluxed in 50 cc. of *p*-cymene with 1.0 g. of 20% palladium-on-charcoal for twenty-four hours. The catalyst was filtered off and the filtrate concentrated to dryness. The residue was triturated with Skellysolve B and several successive 50-cc. portions of Skellysolve B were distilled from the product, which solidified to give 0.45 g. of yellow crystals of m. p. 104–106°. Two recrystallizations from Skellysolve B gave colorless platelets of m. p. 109.5–110.5°. The identity of this product was established by analysis and by mixture melting point with an authentic specimen.[6]

10-Hydroxy-1,2-benzanthracene (IX).—Two grams of compound IV was heated with a mixture of 2 g. of sodium chloride, 10 g. of zinc chloride and 4 g. of zinc dust at 270–300° for twenty minutes, according to the method of Clar.[7] The product could not be purified so it was refluxed for twenty-four hours in 20 cc. of *p*-cymene with 1.5 g. of 10% palladium-on-charcoal. Filtration and cooling gave 0.3 g. of yellow crystals of m. p. 148–154°. Two recrystallizations from benzene gave golden yellow leaflets, m. p. 153–155° (lit.[8] m. p. 154–155.5°).

Direct dehydrogenation of compound IV in refluxing *p*-cymene, without previous zinc dust treatment, gave IX (in a much poorer yield) contaminated with a large amount of the bimolecular dehydrogenation product X.

The Bimolecular Dehydrogenation Product X.—Two grams of compound IV was heated in an oil-bath at 230–240° for three hours with 0.3 g. of 10% palladium-on-charcoal. The cooled residue was taken up in 100 cc. of 95% ethanol and filtered. The filtrate was concentrated to dryness to give a solid residue, consisting of a mixture of a deep green and a colorless product. Recrystallization did not result in purification so the solid was sublimed at a bath temperature of 145° and under a vacuum of 0.2 mm. The sublimed, dark colored material could not be purified but the non-volatile residue consisted of 0.3 g. of colorless material of m. p. 230–235° (dec.). Recrystallization from 50 cc. of 95% ethanol gave fine colorless needles of m. p. 241–244° (dec.).

Anal. Calcd. for $C_{36}H_{22}O_2$ (compound X): C, 88.86; H, 4.56. Found: C, 88.90; H, 4.71.

Acknowledgments.—The help of Dr. William Sidon in the preparation of starting materials is gratefully acknowledged. For the microanalyses, the author is indebted to Mr. E. F. Shelberg, chief microanalyst, Abbott Laboratories.

Summary

The application of a novel cyclization reaction to the synthesis of oxygenated benzanthracene derivatives has been studied. A modification in the preparation of the important intermediate, ethyl γ-phenylacetoacetate, is reported.

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Some N-(2-Diethylaminoethyl)-anilines[1]

BY MARK A. STAHMANN AND ARTHUR C. COPE

Most antimalarial drugs contain one or more relatively weakly basic groups and in addition an alkylamino side chain which is more strongly basic. For example, 8-aminoquinolines of the Plasmochin type, similarly substituted 4-aminoquinolines, and Atebrin have a strong basic center in the side chain and weaker basic centers provided by the heterocyclic nitrogen and the secondary amino group attached to the heterocyclic nucleus. These common structural features suggest that the presence of these basic centers is associated with the antimalarial activity of the compounds. Some evidence in this direction is furnished by the observation that the toxic effects of Atebrin and quinine to certain microörganisms may be overcome or antagonized by small amounts of several polybasic amines, notably spermine and spermidine.[2] In such experiments the basic centers of the polybasic amines presumably compete with those of the antimalarial drugs for the same enzyme surface, and provide the enzyme with some degree of protection from inactivation by combination with the drugs. It appears possible, therefore, that the antimalarial drugs function by inactivating an essential enzyme of the malaria parasite by combining with the enzyme, and that the basic groups of the drugs are involved in this combination. Enzymatic processes are known which depend upon combination of the enzyme with basic centers in the substrate. For example, the hydrolysis of peptides by aminopeptidases depends upon the presence of a basic center (the α-amino group) in the peptide.[3] Such a process might be blocked by a basic antimalarial drug which could combine with and inactivate the enzyme.

As part of a study of the relationship of chemical structure to antimalarial activity directed along the lines indicated above, we have prepared a series of N-(2-diethylaminoethyl)-anilines (I) and N,N-bis-(2-diethylaminoethyl)-anilines (II). These

$ArNHCH_2CH_2N(C_2H_5)_2$ (I) $ArN(CH_2CH_2N(C_2H_5)_2)_2$ (II)

compounds were investigated to determine whether such simple aromatic amines with alkylamino side chains have antimalarial properties. They

(1) The work described in this paper was done under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Massachusetts Institute of Technology.

(2) Silverman and Evans, *J. Biol. Chem.*, **154**, 521 (1944).

(3) See Johnson and Berger, *Advances in Enzymol.*, **2**, 69 (1942).