catalyzed cyclization of the resulting half-ester, followed by acid hydrolysis affords 3'-keto-3,4-dihydro-1,2-cyclopentenonaphthalene in 52–54% over-all yield from tetralone-1.

Acetic–hydrochloric acid hydrolysis of the half-ester effects the loss of the carbethoxyl group to produce β-(3,4-dihydro-1-naphthyl)-propionic acid and the corresponding lactone. These substances can be cyclized by the zinc chloride method also to give the cyclopentenonaphthalene derivative. Hydrogen fluoride, in contrast, promotes ring closure mainly into the aromatic nucleus to give perinaphthanone derivatives.

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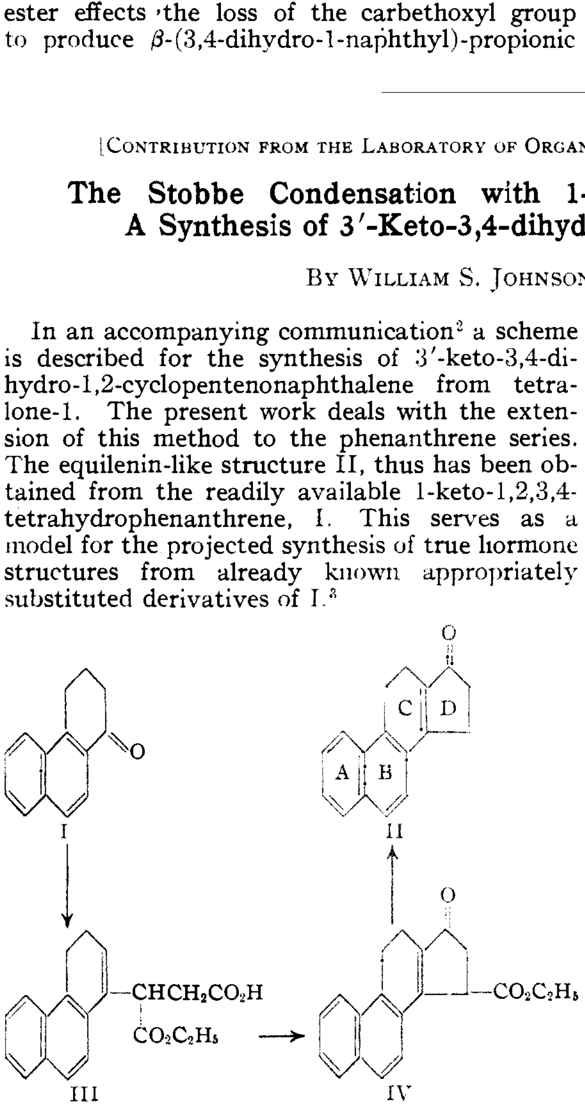
[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

The Stobbe Condensation with 1-Keto-1,2,3,4-tetrahydrophenanthrene. A Synthesis of 3'-Keto-3,4-dihydro-1,2-cyclopentenophenanthrene[1]

BY WILLIAM S. JOHNSON AND JACK W. PETERSEN

In an accompanying communication[2] a scheme is described for the synthesis of 3'-keto-3,4-dihydro-1,2-cyclopentenonaphthalene from tetralone-1. The present work deals with the extension of this method to the phenanthrene series. The equilenin-like structure II, thus has been obtained from the readily available 1-keto-1,2,3,4-tetrahydrophenanthrene, I. This serves as a model for the projected synthesis of true hormone structures from already known appropriately substituted derivatives of I.[3]



Like tetralone-1,[2] 1-keto-1,2,3,4-tetrahydrophenanthrene condensed readily with diethyl succinate in the presence of potassium *t*-butoxide.[4] The yield of crystalline half-ester was 88%, and the structure III is suggested by analogy to the probable structure of the corresponding half-ester in the naphthalene series.[2] Cyclization with zinc chloride in acetic acid and acetic anhydride afforded a keto ester, probably IV (position of double bond uncertain), which on acid hydrolysis, readily lost the carbethoxyl group to give 3'-keto-3,4-dihydro-1,2-cyclopentenophenanthrene, II. Without isolation of the keto ester the over-all yield of II from the half-ester III was 50%. This ketone is probably identical with the one obtained by Bardhan[5a] (in unspecified yield) through the Bougault cyclization of the keto ester Va followed by pyrolytic ring closure of the resulting dicarboxylic acid; and with the product prepared by Robinson and Thompson[5b] (in 15% yield) from the keto ester Vd; and also with the ketone synthesized by Bachmann, Gregg and Pratt[5c] through Bougault cyclization (in 15–23% yield) of Vc followed by decarboxylation and Dieckmann cyclization of the dicarboxylic ester. Although the yields of II obtained by the previous methods[5] are low in comparison with those realized in the present work, it should be noted that the cyclization of keto esters like V is generally improved by the activating influence of a methoxyl group in the 6 position of the naphthalene nucleus.[5c] The melting points reported for the various specimens of II are 210,[5a] 212–213°,[5b] and 214–216°.[5c] The ketone obtained in the present work melted at 222.5–223.3° (cor.), the semicarbazone at 316–317°, and the oxime at 254.5–255°.

Nitric acid oxidation of the semicarbazone of IV gave benzene-1,2,3,4-tetracarboxylic acid, evidently arising from ring B, thus indicating that the ring closure had taken place into the alicyclic rather than into the aromatic nucleus. Conclusive proof of the nuclear structure was afforded by the degradation which Bardhan[5a] used, namely, Clemmensen reduction followed by dehydrogenation to give the known 1,2-cyclopentenophenanthrene. The ultraviolet absorption spectrum of the ketone has been obtained by Dr. A. L. Wilds and his collaborators.[6] The results of this work which will be published in the near future indicate beyond reasonable doubt that the double

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(1) This work was assisted, in part, by a grant from the Wisconsin Alumni Research Foundation.

(2) W. S. Johnson, H. C. E. Johnson and Petersen, THIS JOURNAL, **67**, 1360 (1945).

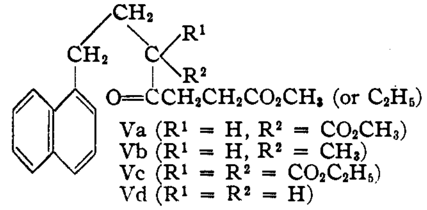
(3) The preliminary results of work in progress on some of these derivatives of I are promising.

(4) *Cf.* Johnson, Goldman and Schneider, THIS JOURNAL, **67**, 1357 (1945).

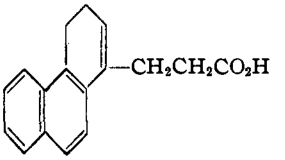
(5) (a) Bardhan, *J. Chem. Soc.*, 1848 (1936); (b) Robinson and Thompson, *ibid.*, 1739 (1939); (c) Bachmann, Gregg and Pratt, THIS JOURNAL, **65**, 2314 (1943).

(6) Wilds, Beck, Close, Djerassi, J. A. Johnson and T. L. Johnson.

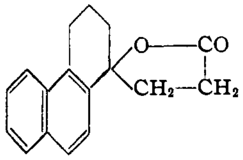
bond is conjugated both with the carbonyl group and with the naphthalene nucleus. This places the unsaturation between rings C and D (formula II).



Va (R^1 = H, R^2 = CO_2CH_3)
Vb (R^1 = H, R^2 = CH_3)
Vc (R^1 = R^2 = $CO_2C_2H_5$)
Vd (R^1 = R^2 = H)



VI



VII

As in the naphthalene series,[2] hydrochloric-acetic acid hydrolysis of the half-ester III gave an excellent yield of a mixture of the unsaturated acid VI (position of double bond uncertain) and the corresponding lactone VII. The proportion of unsaturated acid VI to lactone VII was found to vary markedly with the conditions of hydrolysis. Thus the ratio of VI to VII was about 3 to 1 when the crude half-ester was heated for one and one-half hours in a mixture composed of acetic acid, concentrated hydrochloric acid and water in the proportion 10 to 5 to 1 (by volume). In striking contrast, the ratio of VI to VII was about 1 to 5 when the proportion of solvents was 7 to 3.5 to 5. This phenomenon is being studied further, and will be considered in a future communication.

Both the unsaturated acid VI and the lactone VII could be cyclized by the zinc chloride-catalyzed method to give the ketone II in 53 and 32% yields, respectively. In the naphthalene series, the corresponding cyclizations proceeded in 76% yield from the unsaturated acid and in 62% yield from the lactone.[2] It is noteworthy that in both cases the lactones were cyclized in lower yields than the unsaturated acids, which suggests that ring closure of the lactones may actually proceed via the unsaturated acid. This is a plausible hypothesis since these lactones can undergo acid-catalyzed isomerization to the corresponding unsaturated acids, a phenomenon which will be considered also in a future communication. Cyclization of the lactone VII with phosphorus pentoxide[7] afforded the crude ketone II in 32% yield.

Haberland and his co-workers[8] have prepared unsaturated acids and lactones comparable to VI and VII, both through the cyclization of keto esters (Vb) and also through the Reformatsky reaction of a β-halopropionic ester with ketones like I. Neither of these approaches gave good over-all yields. The German workers also investigated the cyclization of the chlorides of the unsaturated acids by the Darzens method with stannic chloride, but the direction of ring closure is as yet uncertain, particularly in view of the observation that the course of such a cyclization may be altered profoundly by changing the method of ring closure.[2]

Experimental[9]

β-Carbethoxy-β-(3,4-dihydro-1-phenanthryl)-propionic Acid (III).—To a solution of 0.86 g. of potassium in 16 cc. of *t*-butyl alcohol were added 3.92 g. of 1-keto-1,2,3,4-tetrahydrophenanthrene[10] (m. p. 93–95°) and 5.22 g. of diethyl succinate. An additional 4 cc. of *t*-butyl alcohol was used to transfer the ketone and ester. From this point the procedure (b) for the Stobbe condensation of tetralone-1[2] was followed, except that the mixture was allowed to reflux for fifty minutes (solution was not complete until after twenty minutes) and 1 *N* ammonium hydroxide was used for extraction of the half-ester, because the alkali-metal salts proved to be sparingly soluble. Acidification of the ammonia extracts afforded 5.72 g. (88% yield) of pale yellow crystalline half-ester, m. p. 142–148°. A sample recrystallized from methanol was obtained as colorless rods, m. p. 148.2–149.3°.

Anal. Calcd. for $C_{20}H_{20}O_4$: C, 74.05; H, 6.22. Found: C, 74.32; H, 6.35.

Lactone (VII) of β-(1-Hydroxy-1,2,3,4-tetrahydro-1-phenanthryl)-propionic Acid.—The decarbethoxylation of 1.00 g. of the crude half-ester III (m. p. 142–148°) was effected with 10 cc. of acetic acid, 5 cc. of concentrated hydrochloric acid and 1 cc. of water. After refluxing for one and one-half hours the solution was concentrated under reduced pressure and the residue taken up in ether. Extraction with 1 *N* ammonium hydroxide solution gave after acidification 0.125 g. of crude unsaturated acid VI, m. p. 157–170°. A single recrystallization from benzene raised the m. p. to 178–179°. Mixed m. p. determinations showed this to be identical with the unsaturated acid VI described below. Evaporation of the dried (over anhydrous sodium sulfate) neutral ether solution afforded 0.585 g. (a 75% yield) of crude colorless lactone, m. p. 111–118° Recrystallization from methyl alcohol gave a total of 0.520 g. (67% yield) of colorless leaflets, m. p. 125–126°. A sample prepared for analysis by further recrystallization melted at 126.5–127°.

Anal. Calcd. for $C_{17}H_{16}O_2$: C, 80.92; H, 6.39. Found: C, 80.77, 80.72; H, 6.06, 6.39.

The lactone was cleaved readily with warm aqueous sodium hydroxide. Acidification of the alkaline solution gave a mixture of lactone and unsaturated acid. The hydroxy acid was not isolated even when the acidification was carried out in the cold with acetic acid.

β-(3,4-Dihydro-1-phenanthryl)-propionic Acid (VI).—When the decarbethoxylation of 1.00 g. of the crude half-ester was effected by refluxing for two hours with 7 cc. of acetic acid, 3.5 cc. of concentrated hydrochloric acid and 5 cc. of water, the reaction mixture remained heterogeneous. On working up the products as described in the preceding experiment the crude lactone amounted to 0.115 g., m. p. 103–110°. Recrystallization of this fraction usually afforded about 85% recovery of material melting at 127–128°. The acid fraction afforded 0.610 g. (79% yield) of VI, m. p. 173–178°. Recrystallization from benzene gave 0.560 g. of material melting at 178–179°. A sample recrystallized to constant melting point was obtained as thin colorless blades, m. p. 181.8–182.9°.

Anal. Calcd. for $C_{17}H_{16}O_2$: C, 80.92; H, 6.39. Found: C, 81.20; H, 6.39.

Ethyl 3′-Keto-3,4-dihydro-1,2-cyclopentenophenanthrene-1′-carboxylate (IV).—A 1.00-g. sample of the crude

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(7) *Cf.* Frank, Arvan, Richter and Vanneman, THIS JOURNAL, **66**, 4 (1944).

(8) Haberland and Kleinert, *Ber.*, **71**, 470 (1938); Haberland and Heinrich, *ibid.*, **72**, 1222 (1939); Haberland, *ibid.*, **76**, 621 (1943).

(9) Unless otherwise indicated, all melting points are corrected.

(10) Prepared by the procedure of Wilds, THIS JOURNAL, **64**, 1421 (1942).

half-ester (m. p. 142–148°) was cyclized with a mixture of 10 cc. of acetic anhydride and 5 cc. of a solution of acetic acid containing 20 mg./cc. of anhydrous zinc chloride. After refluxing for four and one-half hours in an atmosphere of nitrogen, the solution was treated with water to decompose the anhydride, and the volatile acids were removed under reduced pressure. The residue was taken up in ether, washed with 1 *N* ammonium hydroxide, and dried over anhydrous sodium sulfate. The oily residue obtained on evaporation was submitted to evaporative distillation at 150° (0.1 mm.). Crystallization of the light yellow oily distillate from methanol afforded a total of 0.455 g. (a 48% yield) of pale yellow crystals, m. p. 93–94.5°. Further recrystallization gave colorless lozenge-shaped blades m. p. 95.2–96.3°.

Anal. Calcd. for $C_{20}H_{18}O_3$: C, 78.41; H, 5.92. Found: C, 78.12, 78.55; H, 5.97, 5.79.

The **semicarbazone** of the above keto ester was prepared from crude IV by the conventional procedure using alcohol, semicarbazide hydrochloride and pyridine. The product was obtained as small, pale yellow needles from acetic acid, m. p. 270.5–271.3° (dec., introduced in bath at 266°).

Anal. Calcd. for $C_{21}H_{21}O_3N_3$: C, 69.40; H, 5.83. Found: C, 69.43; H, 5.62.

3′-Keto-3,4-dihydro-1,2-cyclopentenophenanthrene (II). (*a*) *From the Half-Ester* (*III*).—A cyclization was carried out exactly as described in the preceding experiment for the preparation of IV. After the refluxing was completed, the cooled solution was treated with 10 cc. of water and 6 cc. of concentrated hydrochloric acid, and refluxing was then continued for one hour. The residue obtained upon removal of the solvents under reduced pressure was heated on the steam-bath for thirty minutes with about 40 cc. of 5% potassium hydroxide to hydrolyze any lactone. The solid which remained undissolved was filtered, and sublimed at 160° (0.1 mm.). The pale, yellow, crystalline ketone amounted to 0.36 g. (a 50% yield), m. p. 217.5–220.5°.

(*b*) *By Cyclization of the Unsaturated Acid VI.*—A mixture of 0.500 g. of the unsaturated acid VI, 2.5 cc. of acetic acid, 5 cc. of acetic anhydride and 2.5 cc. of a solution of acetic acid containing 20 mg./cc. of anhydrous zinc chloride was allowed to reflux for four and one-half hours during which the solution turned very dark. The acetic anhydride was destroyed with methanol, and the mixture was evaporated under reduced pressure. The residue was heated on the steam-bath for thirty minutes with about 40 cc. of 5% potassium hydroxide, and the insoluble material was separated and sublimed as in procedure (a) above; yield 0.245 g. (53%), m. p. 218–220.5°.

(*c*) *By Zinc Chloride-Catalyzed Cyclization of the Lactone VII.*—A 0.500-g. sample of the lactone VII (m. p. 125–127°) was cyclized by exactly the same procedure as described for the unsaturated acid under (b) above. The yield of sublimed ketone was 0.150 g. (32%), m. p. 218–221°.

(*d*) *Cyclization of the Lactone VII with Phosphorus Pentoxide.*—A solution of 0.200 g. of the lactone (m. p. 127–128°) in 5 cc. of benzene was treated with 0.400 g. of phosphorus pentoxide and 0.400 g. of filter-cel. After refluxing for two and one-half hours the dark mixture was cooled, treated with water, washed with 5% potassium hydroxide solution, and concentrated. The residue was heated on the steam-bath for two and one-half hours with about 15 cc. of 10% potassium hydroxide. The undissolved material amounted to 0.060 g. (32% yield) of crude dark ketone, m. p. 205–210° with previous softening. After two recrystallizations from benzene it melted at 219–221°. When toluene was used in place of benzene and the refluxing period was reduced to one and one-half hours the yield was lower (20%, m. p. 205–214°).

An analytical sample of 3′-keto-3,4-dihydro-1,2-cyclopentenophenanthrene was prepared from the product obtained in (a) above by recrystallization from chloroform-acetone. It was obtained in the form of pale, yellow diamond-shaped plates, m. p. 222.5–223.3°. Mixed melting point determinations were made with the samples obtained by the various procedures, and no depressions were observed.

Anal. Calcd. for $C_{17}H_{14}O$: C, 87.15; H, 6.02. Found: C, 87.03, 87.35; H, 6.02, 5.95.

The **semicarbazone** of II was prepared by heating a mixture of 50 mg. of ketone, 25 mg. of semicarbazide hydrochloride and 3 drops of pyridine in 10 cc. of ethanol at 75° for one hour. The derivative separated as small needles as it formed and was best purified by trituration with boiling water and then with hot chloroform. The product thus obtained was almost colorless and melted at 316–317° (dec., uncor., introduced at 312°). The m. p. in an evacuated tube was 317–318° (dec.).

Anal. Calcd. for $C_{18}H_{17}ON_3$: C, 74.20; H, 5.88. Found: C, 74.09; H, 5.65.

The above material was very sparingly soluble in most solvents. It could be crystallized from glacial acetic acid, but this operation was attended by considerable decomposition. The dark yellow product thus obtained had an indefinite m. p. and a low percentage of carbon.

The **oxime** of II crystallized from methanol in the form of almost colorless needles, m. p. 253–254° (dec. with softening at 252°, introduced in bath at 250°). In an evacuated tube it melted at 254.5–255° (dec., with softening at 253.5°).

Anal. Calcd. for $C_{17}H_{15}ON$: C, 81.90; H, 6.06. Found: C, 81.88; H, 5.89.

The conversion of II to 1,2-cyclopentenophenanthrene was carried out according to the procedure of Wilds[10] for the conversion of $\Delta^{1,1'}$-2′-keto-3,4-dihydro-1,2-cyclopentenophenanthrene to the same hydrocarbon. From 0.300 g. of ketone there was finally obtained after sublimation 0.170 g. of colorless product, m. p. 115–123°. A single crystallization from acetic acid afforded 0.09 g. of colorless needles, m. p. 131–132.5°. On admixture with authentic 1,2-cyclopentenophenanthrene (m. p. 130–132°) kindly supplied by Dr. Wilds the m. p. was 130–132°. The residue from the mother liquor of the recrystallization was converted to the trinitrobenzene complex which after recrystallization from ethanol amounted to 0.07 g.; m. p. 164.5–166°, not depressed on admixture with an authentic specimen (m. p. 165–166.5°).

Nitric Acid Oxidation of the Semicarbazone of IV.—A mixture of 0.190 g. of the semicarbazone of IV, 3 cc. of water and 4 cc. of concentrated nitric acid was heated in a sealed tube at 200–210° for eighteen hours. The residue obtained on evaporation of the filtered solution was recrystallized from 3 cc. of concentrated nitric acid. Thus was obtained 0.022 g. of acid, m. p. 227–228° (dec.). This material was converted to the methyl ester with diazomethane, which after recrystallization from methanol melted at 128.5–129.7°. On admixture with an authentic specimen of tetramethyl benzene-1,2,3,4-tetracarboxylate (m. p. 130–131°)[11] the m. p. was 128.5–131°.

Summary

The Stobbe condensation between 1-keto-1,2,3,4-tetrahydrophenanthrene and diethyl succinate proceeds in 88% yield in the presence of potassium *t*-butoxide. Zinc chloride-catalyzed cyclization of the resulting half-ester followed by acid hydrolysis affords the equilenin-like structure, 3′-keto-3,4-dihydro-1,2-cyclopentenophenanthrene in 50% yield. This ketone is also produced by cyclization of the unsaturated acid or lactone obtained by acid-catalyzed decarbethoxylation of the half-ester.

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[11] Preparation described by Johnson and Goldman, THIS JOURNAL, **66**, 1030 (1944).