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

The Synthesis of 3-Hydroxy-16-equilenone, a Structural Isomer of Equilenin[1]

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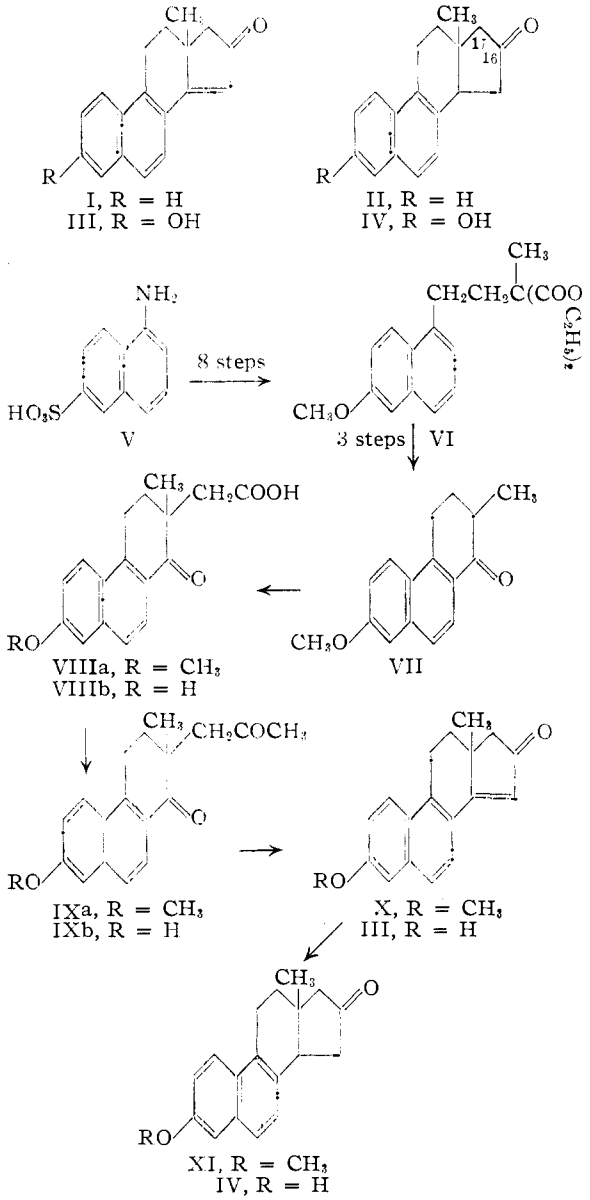
Several years ago Wilds and Beck[3] developed a method for synthesizing the unsaturated ketone I and its reduction product 16-equilenone (II). The present paper describes the extension of this synthesis to compounds having a 3-hydroxyl group, leading to the phenolic ketone IV, which is a structural isomer of the female sex hormone equilenin having the carbonyl group in the 16- rather than the 17-position.



An improved synthesis for the necessary intermediate, 1-keto-2-methyl-7-methoxytetrahydrophenanthrene (VII), was developed from 1-naphthylamine-6-sulfonic acid (V) by a modification of the method employed by Bachmann, Cole and Wilds[4] for the lower homolog lacking the 2-methyl group.

For introducing an acetic acid residue into the 2-position of the ketone VII, the enolate was prepared using triphenylmethylsodium or sodium amide and alkylated with methyl bromoacetate. The yield of the acid VIIIa after hydrolysis was 72–82% This acid was converted to the methyl ketone by condensing the acid chloride with sodiomalonic ester followed by hydrolysis and decarboxylation with hydrochloric and acetic acids.[3] When a short time (1.25 hours) was employed for the hydrolysis step the crystalline methoxy diketone IXa resulted in 80% yield. When the period of hydrolysis was long, the yield was lowered and considerable amounts of the phenolic ketone IXb were obtained. The latter was best prepared by demethylation of the crystalline methoxy diketone.

Marked differences in ease of cyclization to the unsaturated cyclopentenophenanthrene ketone were observed between the hydroxy diketone IXb, the methoxy diketone IXa and the desoxy analog, with the hydroxy diketone the most difficult to cyclize and the methoxy compound intermediate.[5] Under sufficiently drastic conditions, however, these could be cyclized in good yield to the ketones III and X. The phenolic ketone III was best prepared, in 94% yield, by demethylation of X with a mixture of hydrobromic and acetic acids. The ultraviolet absorption spectra of these unsaturated ketones were reported earlier.[6]

With the desoxy unsaturated ketone I it had been found that selective reduction of the double bond with palladium–charcoal catalyst gave predominantly one isomer of the ketone II.[3] Recently this was shown to belong to the β-equilenane series (presumably *trans*),[7] which probably has the same stereochemical configuration at the C:D ring juncture as equilenin. A similar reduction of the methoxy ketone X gave a mixture of

(1) Supported in part by the Research Committee of the Graduate School from funds supplied by the Wisconsin Alumni Research Foundation.

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(3) Wilds and Beck, THIS JOURNAL, **66**, 1688 (1944).

(4) Bachmann, Cole and Wilds, *ibid.*, **62**, 824 (1940).

(5) These interesting differences in reactivity can be rationalized on the basis of the electronic conjugation of the 7-methoxyl (or hydroxyl) group with the 1-keto group. The resulting polarization would partially neutralize the ketonic reactivity of carbon atom 1 and cause the observed decreased reactivity in the aldol-like cyclization. The 7-hydroxyl group as the phenoxide ion would have an even more adverse effect on the cyclization.

(6) Wilds, Beck, Close, Djerassi, J. A. Johnson, T. L. Johnson and Shunk, THIS JOURNAL, **69**, 1985 (1947).

(7) Wilds, Beck and Johnson, *ibid.*, **68**, 2161 (1946).

isomers which could be separated only with difficulty. From an initial run a small amount (5%) of what appears to be one of the two stereoisomers of the reduced ketone XI, m.p. 185–186°, could be isolated in addition to some of the unreduced ketone. In another run using a 25% excess of hydrogen, the second isomer of XI was isolated in 24% yield, m.p. 169.5–171°. Selective reduction also was carried out with the phenolic ketone III. Again a mixture of steroisomers was obtained, from which one pure isomer, m.p. 265–266°, could be separated in 15% yield by fractional crystallization. The same phenolic ketone was obtained by demethylation of the 169.5–171° isomer of the reduced methoxy ketone (XI). Further work is now in progress to determine the effect of various reagents and catalysts on the stereochemical course of these hydrogenations.

In tests for estrogenic activity, for which we are indebted to Drs. J. A. Leighty and E. D. Campbell of Eli Lilly and Co., 30γ of this stereoisomer of 3-hydroxy-16-equilenone (IV) was equivalent to one mouse unit of estrone (0.066γ). Under similar conditions one mouse unit of *dl*-equilenin was about 10γ. Thus, if the two compounds belong to the same stereochemical series,[7a] the activity is reduced to about one-third by shifting the carbonyl group from the 17- to the 16-position. The acetate of the unsaturated ketone III was somewhat less active (50γ = 1 m.u.). The methyl ester of the phenolic acid VIIIb showed weak activity (1 m.u. = about 800γ; VIIIb itself inactive at 100γ) as did the phenolic diketone (1 m.u. = 1050γ).

Experimental[8]

The synthesis of 1-keto-2-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene was patterned after the method used by Bachmann, Cole and Wilds[4] for 1-keto-7-methoxytetrahydrophenanthrene, which in turn was based upon earlier work by Butenandt and Schramm[9] and Cohen, Cook, Hewett and Girard.[10] Since the intermediate compounds are of considerable importance in a number of syntheses, more detailed directions are included here than are available in previous publications, along with improvements in certain of the steps.

1-Acetylamino-6-naphthol.—The fusion of Cleve's acid was carried out in a cylindrical iron pot (24 cm. in diameter and 24 cm. deep) equipped with a removable iron cover which was fitted with a metal paddle-type stirrer, a thermometer well and an opening for introducing reagents. To a mixture of 3300 g. of potassium hydroxide and 880 g. of sodium hydroxide, heated to 255°, was added 2000 g. of 1-naphthylamine-6-sulfonic acid (Cleve's acid, Eastman Kodak Co. technical grade) over a ten-minute period and heating was resumed to maintain the temperature at 290–300° for forty to fifty minutes.

The black molten mass was poured into shallow pans, allowed to cool and then placed in flasks with a total of 5 liters of water. The material was slowly acidified to congo red with concentrated hydrochloric acid (hood), brought to a boil with frequent stirring, more acid added if necessary (congo red), and filtered. The insoluble tar was washed thoroughly by boiling with several portions of water in order to leach out all of the aminonaphthol hydrochloride. To the combined filtrates (about 20 liters) was added 3 liters of concentrated hydrochloric acid, then the mixture was cooled in ice for several hours until crystallization of the salt was complete, and filtered.

The solid was dissolved in 8 liters of boiling water, treated with Norit and filtered, and the amber-colored filtrate was distributed between five 5-liter flasks, cooled to room temperature and each portion was acetylated by adding simultaneously 90 cc. of acetic anhydride and a solution of 100 g. of sodium acetate in 400 cc. of water; the stoppered flask was shaken vigorously and at intervals of about ten minutes two additional 20-cc. portions of acetic anhydride were added. After about one hour the material was filtered and allowed to dry. The yield in a number of runs varied from 800 to 876 g. (44–49%). The melting point of the crude product varied from 193–205° to 203–212°.

1-Acetylamino-6-methoxynaphthalene.—A solution of 300 g. of the crude acetylaminonaphthol in 2400 cc. of water containing 72 g. of sodium hydroxide was cooled to 10° and shaken vigorously with 60 cc. of dimethyl sulfate. At ten-minute intervals two 60-cc. portions of dimethyl sulfate were added and after one hour an additional 20 cc As necessary 10% sodium hydroxide solution was added to keep the mixture alkaline to litmus. After two hours some ammonium hydroxide was added to destroy any remaining dimethyl sulfate and the product was filtered. The yield of the dried dark brown to gray solid varied from 281 to 302 g. (88–94%); the m. p. varied from 115–125° to 123–130°. By dissolving in hot alcohol, filtering and allowing to crystallize, a light gray product, m. p. 140–142°, was obtained. The yield of this material was dependent upon the quality of the original Cleve's acid used. In the present case it amounted to 166–202 g. (52–63%).

6-Methoxy-1-naphthylamine Hydrochloride.—Hydrolysis[4] of 245 g. of the methoxy acetyl derivative (m. p. 140–142°) gave 224 g. (94%) of light gray salt (this decomposed at about 255° with previous softening).

Some additional material could be obtained from the filtrate, which was conveniently combined with the material obtained by hydrolysis of the oily methoxy acetylamino compound. Thus, in one case from 2 kg. of Cleve's acid 448 g. of hydrochloride was obtained from the recrystallized methoxy acetyl derivative (490 g.). The oil in the filtrate from the recrystallization was hydrolyzed by boiling with 375 cc. of hydrochloric acid and 300 cc. of water, combined with the filtrate from hydrolysis of the purified material, made basic with 20% sodium hydroxide solution and extracted with benzene. The fraction (65 g.) boiling at 160–190° (0.2 mm.) gave 53 g. of solid hydrochloride, making the total yield 501 g. (63% from the crude methoxy acetylamino compound or 27% over-all yield from Cleve's acid).

1-Iodo-6-methoxynaphthalene.—The following procedure gave an improved yield over that of the earlier workers,[9,10] which in our hands gave only 48% of the iodo derivative. A solution of 175 g. of the amine hydrochloride in 2 liters of hot water was filtered into a 5-liter, round-bottomed flask and cooled in an ice–salt-bath with stirring. At room temperature 80 cc. of concentrated sulfuric acid in 250 cc. of water was added. At 0° an ice-cold solution of 63 g. of sodium nitrite in 250 cc. of water was added all at once to the vigorously stirred (Hershberg stirrer) suspension. After stirring at 0–5° for ten minutes, 8 g. of urea in 50 cc. of water was added. After another five minutes some ether was added to decrease subsequent foaming and a solution of 145 g. of potassium iodide in 250 cc. of water was added over a fifteen-minute period.[11]

(7a) We expect to determine whether or not this is the case by elimination of the keto group (*cf.* ref. 7).

(8) All melting points are corrected, unless otherwise noted. Those marked vac. were determined in sealed Pyrex capillaries evacuated to at least 0.5 mm. For temperatures above 250° a copper block was used.

(9) Butenandt and Schramm, *Ber.*, **68**, 2083 (1935).

(10) Cohen, Cook, Hewett and Girard, *J. Chem. Soc.*, 653 (1934); 445 (1935).

(11) The yield was lowered considerably if the diazonium solution was added to a sulfuric acid–potassium iodide mixture, or if a larger excess of the latter was employed.

The reaction mixture was covered with a layer of benzene and allowed to stand for two hours after reaching room temperature. Considerable foaming occurred, but it was readily controlled. Then it was warmed gently on the steam-bath to about 40° during a ten-minute period and finally to about 60° for a total of twenty to thirty minutes. The mixture was cooled to room temperature, filtered to remove a large portion of the tarry by-product, which was washed with benzene, and the benzene layer of the filtrate was washed with water, sodium bisulfite solution, dilute sodium hydroxide and again water. By distillation, collecting material in the fraction b. p. 145–155° (0.3 mm.), 140–150 g. (59–63%) of the iodo derivative was obtained as an orange to red oil. In one run using amine hydrochloride prepared from distilled amine, the yield was 68%.

β-(6-Methoxy-1-naphthyl)-ethyl alcohol was prepared from 171 g. of the iodo compound as described by Bachmann, Cole and Wilds,[4] except that after addition of the ethylene oxide gas and warming, the mixture was recooled to 5° and an additional 30 g. of ethylene oxide gas was introduced. After one hour at room temperature and one hour at reflux, the mixture was worked up as described previously, giving 100–104 g. (82–85%) of the alcohol boiling in the range 130–190° (0.2 mm.).

α-Methyl-γ-(6-methoxy-1-naphthyl)-butyric Acid.—β-(6-Methoxy-1-naphthyl)-ethyl bromide was prepared[4,10] from the alcohol in 82% yield and condensed with sodiomalonic ester as described previously.[4] Instead of saponifying, however, the substituted malonic ester was isolated (84% yield) by distillation, b. p. 180–220° (0.2 mm.). This ester (40 g.) was methylated as described previously in the desoxy series.[3] After the second methylation treatment, the reaction mixture was extracted with benzene and washed with water to remove a small amount of the unmethylated malonic acid. The residue from the benzene layer was then hydrolyzed and decarboxylated as described[3] and the distilled product was crystallized from petroleum ether (b. p. 60–68°) giving a total of 23.8–24.0 g. (79–80%) of acid, m. p. 84–87°. Another recrystallization raised the m. p. of the acid to 86–87° (reported,[12,13] 87°, 89°). The remainder of the material was oily. When less pure malonic ester derivative was used (prepared from the crude rather than the recrystallized 1-acetylamino-6-methoxynaphthalene) the yield of crystalline acid was lower (70%) and more of the oily acid resulted. The latter appeared to contain some of the 7-methoxy derivative resulting from the isomeric 1,7-Cleve's acid.

1-Keto-2-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene (VII).—The acid was cyclized by treating 25 g. with approximately 250 g. of anhydrous hydrogen fluoride at 0° for one and one-half hours.[14] Then the reagent was evaporated and the residue treated with saturated sodium bicarbonate solution, extracted with ether, washed and the product crystallized from methanol containing a small amount of acetone. The total yield was 21.9–22.7 g. (94–98%), m. p. 108.5–110°. Further recrystallization raised the m. p. of the colorless leaflets to 109–110° (reported,[4] 109–110°).

1-Keto-2-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene-2-acetic Acid (VIIIa). (a) Triphenylmethylsodium Procedure.—Following a procedure developed by Thomas L. Johnson for the compound without the methoxy group, a solution of 5 g. of the ketone in 50 cc. of dry benzene was treated at 0° with a 10% excess of triphenylmethylsodium solution (0.42 *N* in ether) under a nitrogen atmosphere. After standing at 0° for five minutes, 20 cc. of methyl bromoacetate in 20 cc. of benzene was added all at once, and the now yellow mixture was refluxed for one and one-half hours. The solvent was evaporated and the residue hydrolyzed by refluxing for sixteen hours with a mixture of 75 cc. of 45% potassium hydroxide and 150 cc. of methanol. Most of the methanol was evaporated, the residue diluted with water and neutral material extracted with ether (or filtered first to remove solid, then extracted). After acidification of the aqueous layer the oil was taken up in ether and the acidic material extracted with several portions of sodium bicarbonate solution. Acidification and extraction of the latter gave an oily solid which was crystallized from benzene to give a total of 5.17 g. of the solid acid. This material contained benzene of crystallization; as a result the m. p. had a wide range and was dependent upon the rate of heating. After drying the solid at 80°, the m. p. was 140–145° (gas). A sample which had been recrystallized several times from benzene and allowed to dry at room temperature was found to contain one-half molecule of benzene of crystallization, m. p. 125–138° (gas).

Anal. Calcd. for $C_{18}H_{18}O_4 \cdot {}^1/_2C_6H_6$: C, 74.8; H, 6.3. Found: C, 75.0; H, 6.4.

The yield of product (5.17 g.) corrected for benzene corresponded to 4.57 g. (74%). An analytically pure, solvent-free sample was obtained by drying the solid containing benzene at 80° and 0.3 mm. for twelve hours and recrystallizing from methanol. The colorless prisms melted at 146–148°.

Anal. Calcd. for $C_{18}H_{18}O_4$: C, 72.5; H, 6.1. Found: C, 72.6; H, 5.9.

From the ether extract after washing with bicarbonate (see above) a small amount (about 300 mg. or 6%) of a crude phenolic solid was obtained, m. p. 117–145°. By evaporative distillation at 170–190° (0.1 mm.) and crystallization from benzene 30 mg. of colorless solid, m. p. 172–174°, was obtained. Further recrystallization raised the m. p. of the solid to 174–175°. The analysis suggested that this material was probably 2-methyl-7-methoxy-1-phenanthrol.

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

None of the starting ketone could be recovered as the semicarbazone from the neutral fraction.

(b) Sodium Amide Procedure.—The following modification of the procedure of Wilds and Beck[3] was found to be more satisfactory in the present case. Sodium amide was prepared from 3.5 g. of sodium, 75 cc. of liquid ammonia and 0.25 g. of ferric nitrate and the ammonia was replaced by 100 cc. of dry toluene, finally heating at 60° while passing a stream of nitrogen through the system. Then 10 g. of finely powdered ketone was added and the mixture was stirred and heated at 55–60° for twenty to twenty-two hours. After cooling in ice 21 cc. of methyl bromoacetate was added all at once and when the intial reaction was over the mixture was heated at 90° for four hours. The subsequent treatment was similar to that described previously.[3]

Recrystallization of the crude solid acid (12.8 g.) from benzene gave 10.2 g. (73% yield) of the acid containing solvent; after drying at 80° the m. p. was 140–144°. In other runs (2–20 g. scale) the yields were 76–82%.

The neutral fraction amounted to 1.15 g. from which a total of 1.05 g. (11%) of the original ketone could be recovered, m. p. 98–102°.

The methyl ester of 1-keto-2-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene-2-acetic acid, prepared with diazomethane in ether, was obtained in 91% yield as colorless clumps of needles from methanol, m. p. 99.5–100°.

Anal. Calcd. for $C_{19}H_{20}O_4$: C, 73.1; H, 6.5. Found: C, 73.2; H, 6.3.

1-Keto-2-methyl-7-hydroxy-1,2,3,4-tetrahydrophenanthrene-2-acetic Acid (VIIIb).—The methoxy acid (1.0 g. containing benzene of crystallization) was demethylated by heating for four hours under nitrogen with 20 cc. of acetic acid and 20 cc. of 42% hydrobromic acid. After dilution, extraction with ether and crystallization from benzene–acetone, a total of 798 mg. (95%) m. p. 196–200°, of tan solid was obtained. Further recrystallization gave nearly colorless hydroxy acid, m. p. 199–201° (vac.).

Anal. Calcd. for $C_{17}H_{16}O_4$: C, 71.8; H, 5.7. Found: C, 71.9; H, 5.8.

The methyl ester of the hydroxy acid, prepared in 91% yield using diazomethane, was obtained either as large

(12) Burnop, Elliot and Linstead, *J. Chem. Soc.*, 727 (1940).

(13) Haberland and Blanke, *Ber.*, **70**, 170 (1937).

(14) See W. S. Johnson, "Organic Reactions," John Wiley and Sons, New York, N. Y., 1944, Vol. II, p. 158.

colorless prisms from petroleum ether–methanol, m. p. 150–151°, or as clumps of fine needles from petroleum ether–benzene, m. p. 157–158°. When the melt of the lower melting form was seeded at 150° with the higher melting form, it resolidified and remelted at 157–158°.

Anal. Calcd. for $C_{18}H_{18}O_4$: C, 72.5; H, 6.1. Found: C, 72.3; H, 6.2.

1-Keto-2-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene-2-acetone (IXa).—Sodiomalonic ester was prepared from 10 cc. of malonic ester and 1 g. of sodium powder in 100 cc. of dry ether, by heating and stirring for six hours. The acid chloride was prepared from 5 g. of the product containing benzene of crystallization, 10 cc. of thionyl chloride and 1 drop of pyridine in 50 cc. of dry ether. As the mixture was swirled the acid went into solution and in a short time the acid chloride began to precipitate. After one hour at room temperature, the mixture was evaporated to dryness under reduced pressure, the solid residue was stirred with 10 cc. of dry benzene and again evaporated at reduced pressure. The solid acid chloride was added to the sodiomalonic ester suspension, using 10 cc. of benzene to complete the transfer, the mixture was stirred overnight at room temperature and finally refluxed gently for two hours.

After cooling, 3 cc. of acetic acid was added followed by water, and the ether extract was concentrated. The residual oil was hydrolyzed and decarboxylated by heating for one and one-quarter hours under nitrogen with 50 cc. of concentrated hydrochloric acid, 50 cc. of acetic acid and 20 cc. of water. The mixture was diluted, extracted thoroughly with ether and washed several times each with water, 5% sodium bicarbonate, 10% sodium hydroxide and finally water. From the dried ether layer was obtained by slow crystallization from methanol a total of 3.48 g. (80%) of colorless solid, m. p. 80–83°.

From the bicarbonate extract was recovered 0.39 g. (8%) of acidic oil which yielded 0.15 g. (3%) of the starting acid, m. p. 135–143° (gas). The sodium hydroxide washes gave 0.35 g. (8%) of phenolic oil, from which 0.16 g. (4%) of the crude phenolic diketone (IXb) was obtained, m. p. 167–175°.

Purification of the methoxy diketone by evaporative distillation (180–200° at 0.5 mm.) and repeated recrystallization from methanol did not sharpen the m. p. of 80.5–83.5°.

Anal. Calcd. for $C_{19}H_{20}O_3$: C, 77.0; H, 6.8. Found: C, 77.0; H, 6.8.

When longer periods of time were used in the hydrolysis–decarboxylation step the amount of phenolic material was increased at the expense of the neutral product, as indicated by the following data: two hours, 68% methoxy diketone, 14% phenolic oil; seven hours, 39% neutral oil (of which only 21% crystallized) and 35% of phenolic diketone, m. p. 181–184°; twenty-two hours, 20% of solid methoxy diketone, 54% of phenolic diketone, m. p. 183–185°.

1-Keto-2-methyl-7-hydroxy-1,2,3,4-tetrahydrophenanthrene-2-acetone (IXb).—This was best prepared by demethylation of the methoxy diketone as follows: 200 mg. of diketone, 10 cc. of hydrochloric acid, 10 cc. of acetic acid and 4 cc. of water were refluxed under nitrogen for twenty-two hours, the reaction mixture was diluted, extracted thoroughly with ether and the latter washed well with 10% sodium hydroxide. The oil obtained from the alkaline extracts was evaporatively distilled at 180–210° (0.05 mm.) and recrystallized from benzene to give a total of 158 mg. (83%), m. p. 183–185°. Further recrystallization from benzene–acetone raised the m. p. of the short fine needles to 184.5–185.5° (vac.).

Anal. Calcd. for $C_{18}H_{18}O_3$: C, 76.6; H, 6.4. Found: C, 76.8; H, 6.4.

The yield was less satisfactory (57%) when hydrobromic acid was used instead of hydrochloric acid (refluxed four hours), due to the formation of tarry condensation products.

$\Delta^{1,1'}$-2'-Keto-2-methyl-7-methoxy-3,4-dihydro-1,2-cyclopentenophenanthrene (X).—A mixture of 6 g. of the methoxy diketone, 120 cc. of methanol and 24 cc. of 45% potassium hydroxide was refluxed for eighteen hours under nitrogen; the diketone gradually went into solution and after about an hour the cyclic ketone started to crystallize. At the end of the reflux period, the mixture was cooled in ice and filtered to give 5.26 g. of nearly colorless flakes, m. p. 203–206°. From the filtrate by dilution, extraction with ether and crystallization of the residual oil upon evaporation, an additional 0.08 g. of ketone, m. p. 200–203°, was obtained, bringing the total yield to 95%. By recrystallization from benzene colorless needles, m. p. 205–206°, were obtained.

Anal. Calcd. for $C_{19}H_{18}O_2$: C, 82.0; H, 6.5. Found: C, 82.0; H, 6.5.

The **oxime**, prepared in 98% yield using hydroxylamine hydrochloride and pyridine in absolute alcohol, crystallized from alcohol as a solid melting at 236–240° (dec.). The melting point was not improved by further recrystallization.

Anal. Calcd. for $C_{19}H_{19}O_2N$: C, 77.8; H, 6.5. Found: C, 77.9; H, 6.3.

The long period of reflux in the above cyclization was necessary in order to achieve complete reaction. When the time was reduced to six hours the yield was lowered to 78%; with a three-hour heating period the yield of satisfactory material was only 51%. Using 5% aqueous potassium hydroxide at reflux with efficient stirring for sixteen hours, 70% of satisfactory cyclic ketone was obtained, the remainder being uncyclized material. Without stirring the yield dropped to 18%. Thus, this diketone was much less readily cyclized than the corresponding compound without the methoxyl group.[3]

$\Delta^{1,1'}$-2'-Keto-2-methyl-7-hydroxy-3,4-dihydro-1,2-cyclopentenophenanthrene (III). (a) **By Demethylation.**—Two grams of the methoxy ketone X, 40 cc. of 42% hydrobromic acid and 40 cc. of acetic acid were refluxed under nitrogen for four hours. Cooling and diluting the intensely red solution resulted in a light tan solid, 1.83 g., m. p. 243–253° (dec.). By recrystallization from alcohol a total of 1.78 g. (94%) of the phenolic ketone, m. p. 254–257° (dec., uncor.) was obtained.

(b) **By Cyclization of the Hydroxy Diketone (IXb).**—A mixture of 200 mg. of the diketone IXb and the solution of sodium ethoxide from 0.5 g. of sodium and 10 cc. of absolute alcohol was refluxed for forty-six hours under nitrogen. The sodium salt of the product was dissolved by adding warm water, the clear yellow solution was cooled, acidified and filtered, giving 185 mg. of tan solid, m. p. 225–252°. The low melting point suggests that cyclization was not complete even in this length of time. Recrystallization from alcohol gave a total of 151 mg. (81%) of yellow needles, m. p. 256–259° (uncor., dec.).

The use of potassium hydroxide in methanol for cyclization as for the methoxy diketone, gave incomplete reaction here. Thus, after sixteen hours of heating only 23% of satisfactory cyclic ketone was obtained. Heating the remainder of the material an additional forty-eight hours brought the total yield to 60%.

The product from either (a) or (b) could be purified by continued recrystallization from alcohol or acetone, using Norit,[15] to give cream-colored leaflets, m. p. 262–263° (vac., uncor.).

Anal. Calcd. for $C_{18}H_{16}O_2$: C, 81.8; H, 6.1. Found: C, 81.7; H, 6.2.

The **acetate** was prepared by heating 100 mg. of the phenol with 2 cc. of acetic anhydride and 2 cc. of pyridine at gentle reflux for one-half hour. After cooling and diluting, 116 mg. of solid, m. p. 135–139°, was obtained. A solution of the acetate in ether was washed with 10% sodium hydroxide and the neutral material was recrystallized from alcohol, giving a total of 84 mg. (72%) of material which melted originally at 140–143°, resolidified and remelted at 152–154°, indicating the existence of two polymorphic modifications. After evaporative distillation

(15) Part of the phenol was strongly absorbed on the Norit and recovered only with difficulty.

(180–210° at 0.5 mm.) and further recrystallization, the colorless solid melted at 151–152° with previous softening; however, when the melt was allowed to resolidify slowly, it remelted sharply at 154–155°.

Anal. Calcd. for $C_{20}H_{18}O_3$: C, 78.4; H, 5.9. Found: C, 78.3; H, 5.8.

3-Methoxy-16-equilenone (XI).—A mixture of 500 mg. of the methoxy ketone X (purified by evaporative distillation at 200–220° and 0.05 mm. and recrystallization from benzene–acetone), 30 cc. of purified dioxane and 200 mg. of 30% palladium–charcoal catalyst[16] was stirred with hydrogen at room temperature and atmospheric pressure until the uptake corresponded to 1.07 moles (fourteen hours). By repeated fractional crystallization of the product from methanol–acetone a total of 18% of the starting ketone was recovered, m. p. 203–206°, and from the filtrates by recrystallization from benzene was obtained 24 mg. (5%) of colorless leaflets, m. p. 185–186°. This appears to be one of the two *dl*-mixtures of the reduced ketone, **3-methoxy-16-equilenone (isomer A)**.

Anal. Calcd. for $C_{19}H_{20}O_2$: C, 81.4; H, 7.2. Found: C, 81.0, 81.4; H, 7.2, 7.3.

For a second reduction the ketone was purified by refluxing in alcohol with Raney nickel catalyst and then recrystallizing; 600 mg. of ketone, 300 mg. of palladium–charcoal catalyst and 30 cc. of dioxane were used. After two hours an additional 150 mg. of catalyst was added. The reaction was allowed to proceed until the equivalent of 1.25 moles of hydrogen had been absorbed (twenty-eight hours). By repeated fractional crystallization first from benzene and then from methanol–acetone, 100 mg. of the second racemate, **3-methoxy-16-equilenone (isomer B)**, m. p. 169.5–171°, was obtained as colorless needles. The m. p. was depressed to 156–168° when this compound was mixed with the 186° isomer.

Anal. Calcd. for $C_{19}H_{20}O_2$: C, 81.4; H, 7.2. Found: C, 81.4; H, 7.3.

By treating the material in the filtrates with Girard reagent P and recrystallizing the ketonic fraction many times from benzene and then from methanol–acetone, it was possible to isolate an additional 47 mg., m. p. 168–170°, bringing the total yield of isomer B to 24%. None of the pure isomer A was isolated from this run.

3-Hydroxy-16-equilenone (IV). (a) By Reduction.—A suspension of 500 mg. of the unsaturated phenolic ketone and 200 mg. of 30% palladium–charcoal in 35 cc. of pure dioxane was stirred at room temperature and atmospheric pressure. After three hours an additional 40 cc. of dioxane was added to effect complete solution of the compound and 100 mg. of catalyst was added. Hydrogenation was continued for a total of twenty-six hours (50 mg. of catalyst added after twenty-two hours) until the hydrogen uptake was equivalent to 1.25 moles. By repeated fractional crystallization from alcohol 72 mg. (14%) of one of the isomers, **3-hydroxy-16-equilenone (isomer B)** was obtained as colorless needles, m. p. 264–266° (vac., uncor.). This material showed no depression in melting point when admixed with the sample of phenolic ketone obtained in (b).

Anal. Calcd. for $C_{18}H_{18}O_2$: C, 81.2; H, 6.8. Found: C, 81.2; H, 6.9.

(b) By Demethylation.—A mixture of 47 mg. of isomer B of 3-methoxy-16-equilenone (m. p. 168–170°), 4 cc. of 42% hydrobromic acid and 4 cc. of acetic acid was heated under nitrogen for three hours. After dilution and extraction with ether, the phenolic fraction was removed by repeated extraction with sodium hydroxide solution. Upon acidification 31 mg. (70%) of nearly colorless solid, m. p. 260–263° (dec.) was obtained. By recrystallization from alcohol, using Norit, cream colored leaflets, m. p. 265–266° (vac., uncor.), were obtained.

(16) Linstead and Thomas, *J. Chem. Soc.*, 1130 (1940).

Summary

3-Hydroxy-16-equilenone, a structural isomer of the sex hormone equilenin having the keto group at C-16 instead of C-17, has been synthesized from 1-keto-2-methyl-7-methoxytetrahydrophenanthrene. An improved method of preparation is described for the latter.

MADISON 6, WIS. RECEIVED JUNE 21, 1947

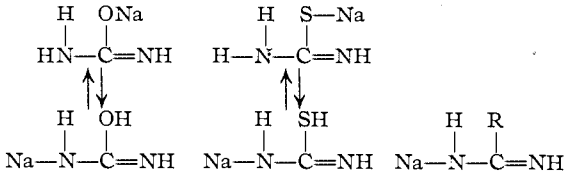
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF DELAWARE]

Condensations of α-Alkyl-α-carbethoxy-γ-butyric Lactones

BY GLENN S. SKINNER, ARTHUR STOKES[1] AND GEORGE SPILLER[1a]

The discovery that α-alkyl-α-carbethoxy-γ-butyric lactones[1b] can be substituted for malonates in the preparation of barbituric acid derivatives immediately suggested that thiourea and amidines could be used in place of urea.

It has long been the belief of many chemists that the tautomeric forms of these reagents are the most reactive ones. With sodium ethoxide the driving force of the reaction is evidently the capacity of sodium to displace hydrogen with the ultimate formation of a compound that has still greater capacity of neutralizing the sodium ethoxide. Amidines, however, can compete with the alcohol for the sodium only by substitution for the hydrogen linked to nitrogen. According to the application of the above view to this reaction the concentration of the intermediates would be less in the case of amidines and the reaction should be expected to proceed less easily. This has been found to be the case. As indicated by yields from the lactone esters at the lowest practical reaction temperature the relationship is thiourea > urea > benzamidine.



The lactone esters in common with numerous other ring systems possess the structural characteristic for increased reactivity at position 3 in

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(1b) Last previous report of this series: Skinner and Mitchell, THIS JOURNAL, **67**, 1252 (1945).