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A New Method for the Preparation of 17(α)-Hydroxy-20-ketopregnanes

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Two methods[1,2] have been described for the fabrication of 17(α),21-dihydroxy-20-ketopregnanes.[3] Both of these methods suffer from the circumambience involved in total degradation of the sterol or bile acid side chain to a 17-ketone, followed by reassembly of the two carbon side chain. One of these processes comprises five steps, the other seven, with respective yields of about 3.5 and 5%. The present reaction series, however, employs 20-ketopregnanes as starting material and gives yields of 15 to 50%, depending on the nature of the other substituents in the molecule.

Pregnane-3(α)-ol-11,20-dione acetate (I) reacted with hydrogen cyanide in alcohol solution to give 60–80% of a crystalline cyanhydrin (V). The mother liquors consisted of somewhat lower melting crystals, which presumably contained the epimeric cyanhydrin. Some very interesting properties of the pure cyanhydrin and of the lower melting mixture were observed. While both were stable to hot alcohol, to alcohol–pyridine mixtures and to silver acetate in alcohol, they decomposed when eluted from chromatographic alumina. However, the nature of the products depended on how the alumina had been prepared. With acid-washed alumina, dehydration was the principal reaction. A small yield of a mixture of unsaturated nitriles was obtained. With alumina which had not been treated with acid and which therefore was, as is almost invariably the case, alkaline to phenolphthalein, loss of hydrogen cyanide occurred. About 90% of the parent ketone was recovered from the eluate.

The presence of the acetate group at C_3 was found to affect greatly the stability of the C_{20} cyanhydrin group. When pregnane-3(α)-ol-11,20-dione (II) was converted to the corresponding cyanhydrin (VI), the latter rapidly decomposed to the parent ketone in warm alcohol solution, with or without the addition of pyridine. It was, however, perfectly stable to dilute acetic acid and could be smoothly oxidized with chromic acid to the 3-keto derivative (IX). In this compound also the tendency to lose hydrogen cyanide in alcohol or alkaline alumina was marked. Even acid-washed alumina gave 40% of the 20-ketone, together with oily fractions representing dehydration or rearrangement products.

The reactions of the cyanhydrins of 17-ketosteroids have been investigated by Butenandt and Schmidt–Thomé[4] who showed that they can be dehydrated with phosphorus oxychloride in pyridine at 150°. Upon testing the action of this agent with the 20-cyanhydrin of pregnane-3(α)-ol-11,20-dione acetate (V), it was found that the α,β unsaturated nitrile (XI) was produced very smoothly at room temperature. When the C_3 substituent was a keto group, however, the more facile loss of hydrogen cyanide from the cyanhydrin group reflected an increased difficulty in the dehydration reaction. Thus, the 20-cyanhydrin of pregnane-3,11,20-trione (IX) gave only 20% of the unsaturated nitrile (XII). Accompanying, XII, however, there was a considerable quantity of a lower melting mixture, consisting apparently of isomeric nitriles or rearrangement products. When the dehydration of the cyanhydrins was effected by boron trifluoride or acid-washed alumina, similar mixtures, from which no pure compound was isolable, were obtained.

The reaction of the unsaturated XI and XII with osmium tetroxide in benzene was extremely slow, as would be predicted from the presence of the negative cyano group attached to the ethylene linkage. However, a small amount of pyridine[5] accelerated the addition so that formation of the osmate was complete in a few hours. Hydrolysis of the osmate ester proceeded smoothly with sodium sulfite at room temperature but the corresponding 17,20-dihydroxy-20-cyanopregnane (XVII) could not be isolated. The 17(α)-hydroxy-20-ketopregnane derived from it by loss of hydrogen cyanide was indeed the only product. This result is in accord with the previously mentioned instability of 3-hydroxy- and 3-keto-20-cyanhydrins, but it is mildly surprising that the 17(α)-hydroxy-20-ketones are stable in the decidedly alkaline (*p*H 10) hydrolysis medium.

From Δ^{17}-20-cyanopregnene-3,11-dione (XII), pregnane-17(α)ol-3,11,20-trione (XX) was obtained. The latter was identical with the previously described oltrione obtained by oxidation of a pregnane-17,20-diol-3,11-dione.[6] Hence this dioldione also belongs in the 17(α)-hydroxy series. Δ^{17}-20-Cyanopregnene-3(α)-ol-11-one acetate (XI) gave upon hydroxylation a mixture of pregnane-3(α),17(α)-diol-11,20-dione (XVIII) and its 3-acetate (XIX). That the 17-hydroxyl in XVIII and XIX is α was demonstrated by oxidation of XVIII to XX.

The addition of a 21-acetoxy group to the 20-

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[1] Reichstein and von Euw, *Helv. Chim. Acta*, **23**, 1258 (1940); von Euw and Reichstein, *ibid.*, **24**, 1140 (1941).

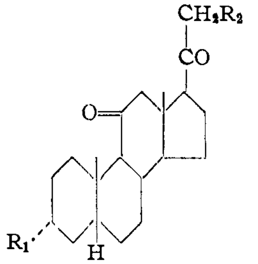
[2] Sarett, *J. Biol. Chem.*, **162**, 601 (1946).

[3] The stereochemical conventions used in this paper are based upon the recent findings of Gallagher and Long [*J. Biol. Chem.*, **162**, 495 (1946)], of Sorkin and Reichstein [*Helv. Chim. Acta*, **29**, 1218 (1946)] and of von Euw and Reichstein, *ibid.*, **30**, 205 (1947)]. The data presented in the last-mentioned contribution show that the configuration of the two carbon side chains in those naturally-occurring pregnane derivatives which bear a hydroxyl group at the 17 position is probably β.

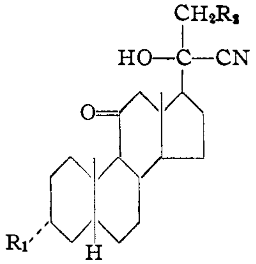
[4] Butenandt and Schmidt-Thomé, *Ber.*, **71**, 1487 (1938); **72**, 182 (1939).

[5] Criegee, Marchand and Wannowius, *Ann.*, **550**, 99 (1942).

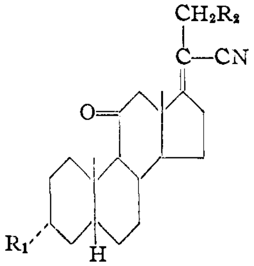
[6] Sarett, THIS JOURNAL, **68**, 2478 (1946).



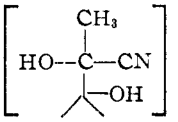
I. R_1 = AcO, R_2 = H
II. R_1 = HO, R_2 = H
III. R_1 = R_2 = OAc
IV. R_1 = HO, R_2 = OAc



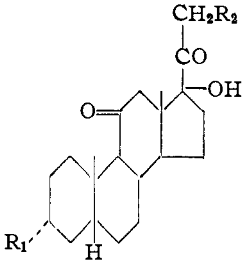
V. R_1 = AcO, R_2 = H
VI. R_1 = HO, R_2 = H
VII. R_1 = R_2 = OAc
VIII. R_1 = HO, R_2 = OAc
IX. R_1 = O=, R_2 = H
X. R_1 = O=, R_2 = OAc



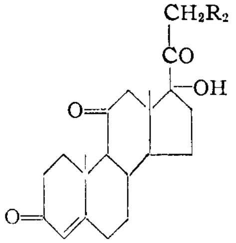
XI. R_1 = AcO, R_2 = H
XII. R_1 = O=, R_2 = H
XIII. R_1 = R_2 = AcO
XIV. R_1 = O=, R_2 = OAc
XV. R_1 = O=, R_2 = OH
XVI. R_1 = R_2 = HO



XVII



XVIII. R_1 = HO, R_2 = H
XIX. R_1 = AcO, R_2 = H
XX. R_1 = O=, R_2 = H
XXI. R_1 = R_1 = HO
XXII. R_1 = R_2 = OAc
XXIII. R_1 = O=, R_2 = OH
XXIV. R_1 = O=, R_2 = OAc



XXV. R_2 = H
XXVI. R_2 = OAc

ketopregnane structures did not materially alter the course of the synthesis. Pregnane-3(α),21-diol-11,20-dione diacetate (III) and the corresponding 21-monoacetate (IV) gave the respective cyanhydrins (VII and VIII). Dehydration of the diacetate cyanhydrin afforded a good yield of the unsaturated nitrile, (XVI), but the 20-cyanhydrin of pregnane-21-ol-3,11,20-trione acetate (X) gave only 20% of the unsaturated compound (XIV). The adverse influence of the 3-keto group on the dehydration is again evident. The hydroxylation of XIV and XV proceeded normally to yield 70–80% of pregnane-3(α),17(α),21-triol-11,20-dione (XXI) and pregnane-17(α),21-diol-3,11,20-trione (XXIII). Treatment with acetic anhydride–pyridine replaced the 21-acetate groups which were removed during the sodium sulfite hydrolysis.

The surprising durability of the side chain permitted conversion of the 3-keto derivatives (XX and XXIV) to the corresponding unsaturated ketones, Δ^4-pregnene-17-ol-3,11,20-trione (XXV) and Δ^4-pregnene-17,21-diol-3,11,20-trione acetate (XXVI, Kendall's compound E acetate).

The assignment of the α or "natural" configuration to the C 17 hydroxyl group in the dioltrione XXIII follows from its conversion into Compound E. Evidence indicates that the other 17-hydroxy-20-ketones described (XVIII, XX and XXII) also belong in the 17(α)-hydroxy series. First, the method of preparation is identical in each case and only one compound is obtained. Second, the rotations fall in the range predicted for 17(α)-hydroxy compounds,[3] the rotations for the 17(β)-hydroxypregnanes being of the order of 100° more toward the *levo* side.

The conversion of Δ^5-pregnene-3(β)-ol-20-one into 17-hydroxyprogesterone was also attempted but the drastic conditions required for hydroxylation of the 17,20 double bond, when conjugated with the 20-cyano group, led to an extensive attack on the $\Delta^{5,6}$ linkage. Oppenauer oxidation of $\Delta^{5,17}$-20-cyanopregnadiene-3(β)-ol gave $\Delta^{4,17}$-20-cyanopregnadiene-3-one but osmium tetroxide in the presence of pyridine appeared to attack both double bonds here also.

Experimental

Rotations were taken in acetone, $c \sim 1.0$. Melting points are corrected.

20-Cyanhydrin of Pregnane-3(α)-ol-11,20-dione Acetate (V).—A solution of 1.70 g. of pregnane-3(α)-ol-11,20-dione acetate (I) in a mixture of 17 cc. of alcohol and 6.4 cc. of acetic acid was cooled to 0° and treated with 6.0 g. of potassium cyanide. The mixture was stirred for one-half hour, then permitted to warm to room temperature. After two hours the solution was diluted with water and the crystalline precipitate was filtered and washed. The wet cake was dissolved in ethyl acetate, excess water removed and the solution concentrated *in vacuo* to a small volume. The addition of petroleum ether gave 1.64 g. of crystals which melted with decomposition at 205–220°. Recrystallization from ethyl acetate gave 1.3 g. of product; m. p. about 221–223° (dec.). A second recrystallization afforded a sample of melting point 217–232° (dec.). Recrystallization from alcohol lowered the melting point to 205–210°.

Anal. Calcd. for $C_{24}H_{35}NO_4$: C, 71.78; H, 8.80. Found: C, 71.50; H, 8.67.

A sample (35 mg.) dissolved in a minimum volume of benzene was put on a column of 1 g. of untreated chromatographic alumina. Elution with 20 cc. of ether gave 29 mg. of pregnane-3(α)-ol-11,20-dione acetate (I); m. p.

and mixed m. p. 135–136°. The experiment was repeated using acid-washed[7] alumina. A crystalline mixture, which melted at 149–170°, was obtained. Repeated recrystallization from methanol yielded a small amount of product of melting point 152–160°.

20-Cyanhydrin of Pregnane-3(α)-ol-11,20-dione (VI).—This cyanhydrin was prepared from II by the procedure given above. From 1.8 g. of ketone, 1.5 g. of recrystallized cyanhydrin, dec. 160–170°, was obtained.

Anal. Calcd. for $C_{22}H_{33}NO_3$: C, 73.49; H, 9.26. Found: C, 73.60; H, 9.51.

20-Cyanhydrin of Pregnane-3(α),21-diol-11,20-dione 21-Acetate (VIII).—This cyanhydrin failed to crystallize readily upon dilution of the alcohol–hydrogen cyanide reaction mixture. The diluted solution was consequently extracted with ethyl acetate, the latter solution washed with water and concentrated *in vacuo* to a small volume. From 2.0 g. of ketone (IV) 1.3 g. of recrystallized cyanhydrin was obtained. It decomposed at 175–185° and lost hydrogen cyanide in alcohol or dilute pyridine solution. A trace of acetic acid appeared to stabilize the compound completely, however.

Anal. Calcd. for $C_{24}H_{35}NO_5$: C, 69.03; H, 8.45; N, 3.35. Found: C, 68.91; H, 8.37; N, 3.60.

Pregnane-3(α),21-diol-11,20-dione Diacetate (III) **and its 20-Cyanhydrin** (VII).—A sample of pregnane-3(α),21-diol-11,20-dione 21-acetate (IV) was warmed on the steam-bath with pyridine–acetic anhydride for ten minutes. The solution was diluted with water and extracted with ether. The ethereal solution was washed with dilute hydrochloric acid, dilute sodium carbonate, finally with water and concentrated to a small volume. The addition of petroleum ether gave crystals of the diacetate, dec. 100–110°, which contained 10% of solvent of crystallization. From benzene–petroleum ether a sample of dec. p. 82–90° was obtained. Conversion of 3.0 g. of this ketone (solvated) to the cyanhydrin gave 2.2 g. of crystals; dec. 148–160°.

Cyanhydrin of Δ^5-Pregnene-3(β)-ol-20-one Acetate.—The usual procedure afforded 88% of a product of melting point 194–198° with decomposition.

Anal. Calcd. for $C_{24}H_{35}NO_3$: C, 74.96; H, 8.92; N, 3.64. Found: C, 74.70; H, 9.05; N, 3.71.

20-Cyanhydrin of Pregnane-3,11,20-trione (IX).—A solution of 1.4 g. of the 20-cyanhydrin of pregnane-3(α)-ol-11,20-dione (VI) in 70 cc. of glacial acetic acid was cooled to 16° and treated over a period of twenty minutes with a solution of 0.9 g. of chromic acid in 7 cc. of acetic acid and 7 cc. of water. After one hour the solution was diluted with water, the precipitate filtered and dissolved in ethyl acetate. Excess water was removed and the solvent was taken off *in vacuo*. The crystalline residue weighed 1.1 g. Recrystallization from ethyl acetate gave 930 mg. of cyanhydrin; dec. 170–180°. For analysis the compound was dried *in vacuo* at room temperature, as with the other cyanhydrins, but, presumably because of solvation, no agreement with theory could be obtained.

20-Cyanhydrin of Pregnane-21-ol-3,11,20-trione Acetate (X).—A solution of 1.2 g. of the 20-cyanhydrin of pregnane-3(α),21-diol-11,20-dione acetate (VIII) in 20 cc. of acetic acid and 2 cc. of water was treated over a period of five minutes with a solution of 600 mg. of chromic acid in 1.2 cc. of water and 11 cc. of acetic acid. After the mixture had stood at room temperature for an hour, water was added and the product worked up as in the preceding oxidation. After purification, 1.0 g. of cyanhydrin, dec. 214–217°, was obtained.

Anal. Calcd. for $C_{24}H_{33}NO_5$: C, 69.36; H, 8.01; N, 3.37. Found: C, 69.31; H, 8.30; N, 3.36.

Samples of this cyanhydrin and of the cyanhydrin IX were treated with alkaline alumina in the manner described above. In both cases the parent ketone was obtained in high yield. Even acid-washed alumina gave 30–40% of the ketone, the remainder of the product being non-crystalline.

Δ^{17}-20-Cyanopregnene-3(α)-ol-11-one Acetate (XI).—A solution of 2.5 g. of the 20-cyanhydrin of pregnane-3(α)-ol-11,20-dione acetate (V) in 8 cc. of pyridine was treated with 1.2 cc. of phosphorus oxychloride. After standing at room temperature overnight, the solution was diluted, the crystalline precipitate filtered and recrystallized from dilute alcohol. The product weighed 1.9 g. and melted at 199–201°. A sample was recrystallized from methanol for analysis and melted at 201.0–201.5°; $[\alpha]^{25}\text{D}$ +40°.

Anal. Calcd. for $C_{24}H_{33}NO_3$: C, 75.15; H, 8.67; N, 4.05. Found: C, 75.10; H, 8.62; N, 4.07.

With crude cyanhydrin the yield of the desired unsaturated nitrile was decreased out of all proportion to the amount of impurities initially present. A sample of cyanhydrin (V) which had been crystallized once from ethyl acetate–petroleum ether (90% of theory, dec. 200–210°) was dehydrated as above. Chromatography of the product gave only 20% of the unsaturated nitrile XI. The remaining crystalline fractions consisted of a mixture, m. p. 172–182°, the properties of which could not be greatly altered by recrystallization and for which the analytical data corresponded most closely to the same empirical formula as the nitrile XI.

Anal. Calcd. for $C_{24}H_{33}NO_3$: C, 75.15; H, 8.67; N, 4.05. Found: C, 75.57; H, 8.33; N, 3.55.

Δ^{17}-20-Cyanopregnene-3,11-dione (XII).—The dehydration of the cyanhydrin IX was carried out in the manner described above. After chromatography of the crude product, 20% of XII was obtained; m. p. 229–237°; $[\alpha]^{25}\text{D}$ +38°.

Anal. Calcd. for $C_{22}H_{29}NO_2$: C, 77.84; H, 8.62. Found: C, 78.05; H, 8.67.

Δ^{17}-20-Cyanopregnene-3(α),21-diol-11-one (XVI).—The dehydration of 2.2 g. of the cyanhydrin VII was carried out in the usual manner. The product was an oil (2.0 g.) which was chromatographed and the portions eluted with petroleum ether–ether mixtures combined. This material, which was presumably XIII, weighed 1.84 g. and failed to show signs of crystallizing. Hence it was saponified by dissolving in a mixture of 10 cc. of benzene and 10 cc. of 1.1 *N* methanolic potassium hydroxide. After ten minutes the solution was acidified with acetic acid, the benzene removed *in vacuo* and the residue crystallized from dilute methanol. The free diol melted at 242–254° and weighed 1.45 g. After recrystallization from acetone and from dilute alcohol it melted at 256–257°; $[\alpha]^{25}\text{D}$ +19.5°.

Anal. Calcd. for $C_{22}H_{33}NO_3$: C, 73.92; H, 8.73; N, 3.92. Found: C, 73.68; H, 8.48; N, 4.22.

Δ^{17}-20-Cyanopregnene-21-ol-3,11-dione Acetate (XIV).—Dehydration of 6.2 g. of the cyanhydrin X according to the usual procedure gave a mixture which was diluted with water and extracted with benzene. The benzene solution was concentrated to dryness and the residue (4.7 g.) was chromatographed. The unsaturated nitrile (XIV) was isolated in 28% yield. Some samples melted at 181–182° with resolidification and remelting at 195–196°, while others only showed the higher melting point; $[\alpha]^{25}\text{D}$ +50°.

Anal. Calcd. for $C_{24}H_{31}NO_4$: C, 72.52; H, 7.85; N, 3.53. Found: C, 72.68; H, 7.85; N, 3.57.

Δ^{17}-20-Cyanopregnene-21-ol-3,11-dione (XV).—Hydrolysis of the acetate (150 mg.) was accomplished by dissolving it in 5 cc. of methanol and adding 2 cc. of water containing 200 mg. of potassium carbonate. The solution was kept at 50° for fifteen minutes, the methanol was then removed *in vacuo* and the crystalline precipitate filtered. Recrystallization from ethyl acetate gave a product of melting point 263–265° (sample introduced at 250°); $[\alpha]^{25}\text{D}$ +36°.

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[7] Chromatographic alumina was suspended in water and sufficient dilute sulfuric acid added to bring the *p*H to 3.0. The alumina was then washed repeatedly with sufficient distilled water to bring the *p*H to 5.5–6.0, then dried at 150°.

Anal. Calcd. for $C_{22}H_{29}NO_3$: C, 74.34; H, 8.22; N, 3.94. Found: C, 74.23; H, 8.00; N, 4.22.

$\Delta^{5,17}$-20-Cyanopregnadiene-3(β)-ol Acetate.—The dehydration of the cyanhydrin of Δ^5-pregnene-3(β)-ol-20-one acetate (900 mg.) in the usual manner gave 60% of a product of melting point 170–172°. This was chromatographed and recrystallized, but this treatment failed to produce an analytically pure sample. Hence, it was converted to the free alcohol.

$\Delta^{5,17}$-20-Cyanopregnadiene-3(β)-ol.—The benzene-methanolic potassium hydroxide method described above was used to hydrolyze $\Delta^{5,17}$-20-cyanopregnadiene-3(β)-ol acetate. Recrystallization of the crude product from dilute methanol gave 85% of the free alcohol; m. p. 176–177°; $[\alpha]^{25}$D −86°.

Anal. Calcd. for $C_{22}H_{31}NO$: C, 81.18; H, 9.60. Found: C, 81.22; H, 9.16.

Attempted hydroxylation of this compound or of the corresponding Δ^5-3-acetoxy derivative by the osmium tetroxide–pyridine procedure described below gave oily products. Milder treatment gave only starting material.

Pregnane-3(α),17(α)-diol-11,20-dione (XVIII) and Its 3-Monoacetate (XIX).—To a solution of 1.65 g. of Δ^{17}-20-cyanopregnene-3(α)-ol-11-one acetate (XI) in 16 cc. of dry benzene was added 1.7 g. of osmium tetroxide and 0.75 cc. of pyridine. After standing at room temperature overnight, the mixture was treated with 50 cc. of water containing 3.0 g. of sodium sulfite. The benzene was then concentrated *in vacuo* to about 5 cc., and the whole was diluted with 50 cc. of alcohol. The mixture was stirred at room temperature for twenty hours, filtered, acidified with a few drops of acetic acid and concentrated *in vacuo* to a small volume. The aqueous mixture was extracted with chloroform, the chloroform solution concentrated to dryness *in vacuo* and the residue crystallized from acetone–ether. The 800 mg. so obtained was recrystallized from dilute alcohol, giving pregnane-3(α),17(α)-diol-11,20-dione; m. p. 207–208°; $[\alpha]^{25}$D +68.5°.

Anal. Calcd. for $C_{21}H_{32}O_4$: C, 72.39; H, 9.25. Found: C, 72.54; H, 9.19.

The mother liquors (850 mg.) consisted of a crystalline mixture of the dioldione and its 3-acetate. It was converted entirely to the latter by dissolving it in 3 cc. of pyridine and 3 cc. of acetic anhydride. The addition of water after three hours gave 850 mg. of crystals; m. p. 206–208°. Recrystallization from dilute alcohol gave the pure 3-acetate (XIX); m. p. 208–209°; $[\alpha]^{25}$D +84°. A mixed melting point with XVIII showed a depression of 30°.

Anal. Calcd. for $C_{23}H_{34}O_5$: C, 70.73; H, 8.79. Found: C, 70.83; H, 8.96.

Pregane-17(α)-ol-3,11,20-trione (XX) from Δ^{17}-20-Cyanopregnene-3,11-dione (XII).—The hydroxylation of XII was carried out according to the procedure described above. A yield of 83% of the oltrione, m. p. 205–206°, was obtained. A mixed melting point with the pregnane-17(α)-ol-3,11,20-trione prepared by oxidation of pregnane-3(α),17(α),20-triol-11-one showed no depression.

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.78; H, 8.81. Found: C, 72.81; H, 8.70.

Pregnane-17(α)-ol-3,11,20-trione (XX) from Pregnane-3(α),17(α)-diol-11,20-dione (XVIII).—A solution of 75 mg. of XVIII in a mixture of 0.8 cc. of acetic acid and 0.2 cc. of water was treated with a solution of 60 mg. of chromic acid in 0.06 cc. of water and 1.14 cc. of acetic acid. After standing at room temperature for ten minutes the solution was diluted with water and extracted twice with chloroform. The washed chloroform solution was concentrated to dryness *in vacuo* and the residue crystallized from ether. Recrystallization from dilute acetone gave the pure oltrione; m. p. and mixed m. p. 205–206°.

Pregnane-3(α),17(α),21-triol-11,20-dione Diacetate (XXII).—The osmium tetroxide–sodium sulfite procedure described above was applied to 1.1 g. of Δ^{17}-20-cyanopregnene-3(α),21-diol-11-one diacetate (amorphous, prepared by acetylation of the pure Δ^{17}-20-cyanopregnene-3(α),21-diol-11-one (XVI) in the usual manner). The crude product was amorphous and presumably consisted of equal amounts of pregnane-3(α),17(α),21-triol-11,20-dione and its 3-monoacetate. In addition, the product was contaminated with some green osmium salts. These were partially removed by dissolving the product in a small volume of acetone and diluting with 100 cc. of absolute ether. The flocculent precipitate was separated, the supernatant yellowish solution was concentrated to dryness and dissolved in a mixture of 5 cc. of pyridine and 5 cc. of acetic anhydride. After standing at room temperature for several hours, the solution was diluted with water and the crystalline precipitate was filtered. Recrystallization from dilute acetone and from alcohol gave 504 mg. of the diacetate; m. p. 233–236°. Additional recrystallization from benzene and from acetone-ether failed to raise the melting point or to remove a trace of greenish discoloration; $[\alpha]^{25}$D +93°.

Anal. Calcd. for $C_{25}H_{36}O_7$: C, 66.94; H, 8.08. Found: C, 66.41; H, 8.08.

Pregnane-17(α),21-diol-3,11,20-trione (XXIII).—One gram of Δ^{17}-20-cyanopregnene-21-ol-3,11-dione acetate (XIV) was treated with osmium tetroxide–pyridine and then hydrolyzed with sodium sulfite in the fashion described above. After concentration of the aqueous-alcoholic solution to a small volume *in vacuo*, it was extracted with four 150-cc. portions of chloroform which were then combined and washed with successive small portions of sodium bicarbonate, dilute hydrochloric acid and water, the washes being back extracted each time. The chloroform solution was then concentrated to dryness *in vacuo* and the residue (861 mg.) crystallized from acetone. A yield of 60% of dioltrione, m. p. 233–235°, was obtained. The pure material was sparingly soluble in chloroform, ethyl acetate and acetone.

Anal. Calcd. for $C_{21}H_{30}O_5$: C, 69.59; H, 8.33. Found: C, 69.45; H, 8.13.

The 21-monoacetate was prepared by treatment of the dioltrione with pyridine–acetic anhydride at room temperature. The initially insoluble starting material dissolved after five to ten minutes of stirring. After an additional five minutes the acetate was precipitated by addition of water. It melted at 228–230°; $[\alpha]^{25}$D +82°.

Anal. Calcd. for $C_{23}H_{32}O_6$: C, 68.29; H, 7.98. Found: C, 68.14; H, 7.91.

Δ^4-Pregnene-17(α)-ol-3,11,20-trione (XXV).—To a solution of 86 mg. of pregnane-17(α)-ol-3,11,20-trione (XX) in 1.0 cc. of acetic acid was added a solution of 41 mg. of bromine in 0.41 cc. of acetic acid. After two minutes the bromine color suddenly disappeared, the solution was poured into water and extracted with chloroform. The chloroform solution was washed with dilute potassium carbonate and water, then concentrated to dryness *in vacuo*. The residue was crystallized from ether to give 71 mg. of crude crystalline 4-bromopregnane-17(α)-ol-3,11,20-trione; dec. *ca.* 185°. This substance was refluxed for five hours in pyridine, the latter removed *in vacuo* and the residue dissolved in ether and dilute hydrochloric acid. The washed ether layer was concentrated to a small volume and the crystalline precipitate (19 mg.) recrystallized twice from methanol. It then melted at 236–239°.

Anal. Calcd. for $C_{21}H_{28}O_4$: C, 73.23; H, 8.18. Found: C, 73.43; H, 7.49.

Δ^4-Pregnene-17(α),21-diol-3,11,20-trione Acetate (XXVI) (Kendall's Compound E Acetate).—A solution of 333 mg. of pregnane-17(α),21-diol-3,11,20-trione 21-acetate (XXIV) in 5.0 cc. of acetic acid was treated with a solution of 132 mg. of bromine in 1.0 cc. of acetic acid. After decolorization had ensued, the solution was worked up as above. Crystallization of the chloroform residue gave 300 mg. of the 4-bromo derivative; dec. 190°. This material was then refluxed with 12 cc. of pyridine for five hours and the mixture then concentrated *in vacuo*, dissolved in chloroform, washed with dilute hydrochloric acid and with water, and concentrated to dryness *in vacuo*. The residue (170 mg.) was crystallized from benzene by the addition of ether, giving 118 mg. of crude crystalline XXVI. This product was dissolved in 2.5 cc. of hot alcohol and the solution permitted to cool slowly to room temperature. It was then kept at −5° for two days at the end of which time the initial precipitate of long dense needles had become contaminated by a small superficial layer of fluffy crystalline balls, apparently containing the saturated dioltrione (XXIV). The needles were easily separated mechanically and after two further recrystallizations from alcohol melted at 236–238°. A total of 83 mg. was obtained; $[\alpha]^{25}\text{D}$ +170°. A mixed melting point with an authentic sample of Compound E acetate gave no depression.

Anal. Calcd. for $C_{23}H_{30}O_6$: C, 68.61; H, 7.52. Found: C, 68.85; H, 7.34.

Acknowledgment.—The author wishes to thank Dr. K. Folkers and Dr. R. T. Major of these laboratories and Dr. E. S. Wallis of Princeton University for their suggestions in connection with this work. The author is indebted to Miss Jean Andrews for assistance. Acknowledgment for microanalyses is made to Messrs. R. Boos, W. H. Humphrey, E. Thornton, J. McGregor and R. Funk.

Summary

A new method for the preparation of 17(α)-hydroxy-20-ketopregnanes is described. A 20-ketopregnane is converted to its cyanhydrin which is then dehydrated to give a Δ^{17}-20-cyanopregnene. With osmium tetroxide followed by aqueous sodium sulfite, the unsaturate nitrile is converted to the 17(α)-hydroxy-20-ketopregnane, hydrogen cyanide being spontaneously eliminated from the hypothetical intermediate, 17,20-dihydroxy-20-cyanopregnane. The method is also feasible for introducing a 17(α)-hydroxy group into a 20-keto-21-acetoxypregnane. This permits the synthesis of Kendall's Compound E.

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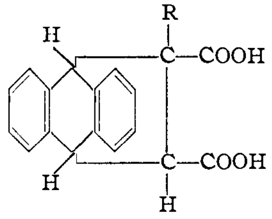
[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

The Reaction of Anthracene with Maleic and Fumaric Acid and their Derivatives and with Citraconic Anhydride and Mesaconic Acid

BY W. E. BACHMANN AND L. B. SCOTT[1,2]

In the present work the addition of seven dienophiles to anthracene is described, the relative rates of reaction are compared, and the effects of changes in some of the reaction variables are noted. By the addition of both the *cis* and *trans* forms of a dienophile, information on the application of the rule of *cis* addition in the Diels–Alder reaction was obtained.

The reaction of maleic anhydride and anthracene to give *cis*-9,10-dihydroanthracene-9,10-endo-α,β-succinic anhydride[3] is well known. We obtained the same anhydride (and not the acid) in high yield from the reaction of maleic acid with anthracene in boiling dioxane. It is not known whether the molecule of water is lost before or after addition, but the latter seems probable in view of the ease with which the *cis*-diacid (I, R = H) is converted to the anhydride (*e.g.*, on recrystallization or on standing in a vacuum desiccator). Diels, Alder and Beckmann[4] prepared the *cis*-dimethyl ester from the anhydride. We have obtained this ester by the addition of dimethyl maleate to anthracene.



I

In spite of the impression that fumaric acid does not engage in the Diels–Alder reaction,[5] we tried its reaction with anthracene and obtained the addition product, the *trans*-acid (I, R = H) in 95% yield. Fumaric acid[6] reacts more slowly (see Table I) than maleic anhydride, requiring days of refluxing in a given solvent to hours for the anhydride. The reaction of anthracene with maleic acid (or maleic anhydride) to give the *cis* adduct and with fumaric acid to give the *trans* acid offers a simple classroom illustration of the

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[3] In this paper the prefixes *cis* and *trans* refer solely to the configuration at the two carbon atoms attached to the carboxyl groups and not to the configuration at the 9,10 positions.

[4] Diels, Alder and Beckmann, *Ann.*, **486**, 191 (1931).

[5] Alder and Stein, *Ann.*, **514**, 203 (1934) mention that fumaric acid does not add to cyclopentadiene. On page 309 of Richter's "Textbook of Organic Chemistry," 2nd ed., John Wiley and Sons, Inc., New York, N. Y. 1943, the following statement appears in the section on the Diels–Alder reaction: "This type of reaction does not occur with the *trans* isomer, fumaric acid."

Dilthey and Henkels, *J. prakt. Chem.*, **149**, 85 (1937), stated that the product obtained from acecyclone and fumaric acid was identical with that obtained with maleic acid (or anhydride) and attributed this result to the addition of maleic acid formed by rearrangement of the fumaric acid. After our work had been completed (1942; publication delayed by the war), Bergmann, Eschinazi and Neenam, *J. Org. Chem.*, **8**, 179 (1943), reported the formation of an amorphous acid adduct from 1,1′-bicyclohexenyl and fumaric acid at 190–200°. The nature of the adduct, which was characterized as a dianilide, was not clearly indicated.

[6] In the paper which follows a Diels–Alder reaction is reported in which fumaric acid was superior to maleic anhydride in that it gave a higher yield of adduct and a lower yield of copolymer.