The Dehydrogenation of Steroidal $\Delta^{3,5}$-Enol Ethers with Dichlorodicyanoquinone (DDQ)[1]

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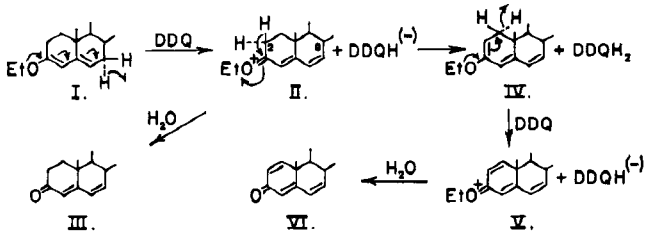
The reaction of dichlorodicyanoquinone (DDQ) with 3-ethoxy $\Delta^{3,5}$-steroids (I) leads, in the absence of water, to 1,4,6-trien-3-ones (VI). The sequence is pictured as proceeding *via* hydride abstraction at C-7, loss of a C-2 proton from the oxonium intermediate (II), followed by hydride loss from C-1. In the presence of water, hydrolysis of the oxonium species (II) is faster than C-2 proton loss leading to a high yield of 4,6-dien-3-one (III).

The quinone-mediated dehydrogenation of steroidal Δ^4-3-ketones has proven to be a reaction of considerable practical application and of intrinsic theoretical interest. Agnello and Laubach[2] found that at elevated temperatures chloranil converted Δ^4-3-keto steroids into the corresponding 6-dehydro steroids and proposed that the reaction proceeded *via* the $\Delta^{3,5}$-enol followed by C-7 hydride ion abstraction. Cited in support of the enol mechanism were the observations that a Δ^5-3-ketone and a $\Delta^{3,5}$-enol ether underwent conversion by chloranil to the $\Delta^{4,6}$-dienone at a much greater rate than was the Δ^4-3-ketone. In contrast to the behavior of chloranil, the closely related but higher potential quinone, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), was found by Burn, Kirk, and Petrow[3] to introduce 1,2 rather than 6 7-unsaturation into Δ^4-3-ketone substrates. Ringold and Turner[4] rationalized the different behavior of the two quinones as oxidation of the kinetically determined enol in the case of DDQ and of the thermodynamically more stable enol in the case of chloranil and demonstrated that in the presence of anhydrous hydrogen chloride, DDQ led to 6,7 dehydrogenation. This latter observation was construed to be evidence for an enol-dependent reaction since in the presence of strong acid the $\Delta^{3,5}$-enol should be the kinetically favored as well as the more stable enol. It was thus of interest to investigate the interaction of DDQ with fixed derivatives of this enol, and, for this purpose the oxidation of a number of 3-ethoxyandrost-3,5-dienes (I), the ethyl enol ethers of Δ^4-3-keto steroids, was studied. This reaction constitutes the subject of the present report.

The slow dropwise addition of 1 equiv. of DDQ dissolved in benzene to a solution of 3-ethoxy-17β-acetoxyandrost-3,5-diene (I) in the same solvent at room temperature led to the immediate precipitation of 2,3-dichloro-5,6-dicyano-1,4-hydroquinone. Separation by thin layer chromatography on silica gel of the steroidal products remaining in the benzene solution established the presence of starting enol ether (I), 4,6-dien-3-one (III), and 1,4,6-trien-3-one (VI) in a ratio of about 0.8:1:1. In addition, alkali-soluble steroidal material which subsequently was characterized as an adduct of the hydroquinone was found. When reaction was carried out in the same solvent by rapid addition of the enol ether to excess (2.5 equiv.) quinone, immediate formation of a gummy black precipitate[5] occurred. The addition of a small volume of acetone to this mixture yielded a homogeneous solution which after work-up was shown to contain 4,6-dien-3-one (III) and 1,4,6-trien-3-one (VI) in a ratio of about 1:9, and again an acidic product was noted. Since neither the 4-en-3-one, the 1,4-dien-3-one, nor the 4,6-dien-3-one (III) react with DDQ under these extremely mild reaction conditions, the formation of III and VI clearly proceed *via* the enol ether and are formulated as shown in Scheme I.

SCHEME I



Abstraction of hydride ion at C-7, probably the axial 7α-hydrogen,[6] leads to the oxonium species (II) and the anion of the hydroquinone, the driving force for this oxidation being provided by the unshared electron pair on the ethereal oxygen and by the allylic position of the C-7 hydrogen atoms. Removal of a proton at C-2[7] by the hydroquinone anion produces the hydroquinone and the 2,4,6-trienol ether (IV) which loses a C-1 hydride ion to another molecule of DDQ forming the oxonium compound (V) as a salt with the hydroquinone anion. Decomposition of the oxonium salt (V) by water then leads to the unsaturated ketone (VI).

While theoretically the oxonium species (II and V) could have lost a proton from C-8 to yield enol ethers with a 7(8) double bond, the 8β-proton is 1,3-diaxially situated with respect to the two angular methyl groups and sterically inaccessible to the approach of base. Therefore, C-2 proton loss occurred from II while V did not undergo further proton loss.

Several points concerned with this reaction sequence deserve further comment. The failure, in the first experiment cited, to detect 2,4,6-trienol ether (IV) demonstrates that this more extensively conjugated enol ether reacts considerably faster with DDQ than

(1) Supported in part by Grant C-4550, U. S. Public Health Service.

(2) E. Agnello and G. Laubach, *J. Am. Chem. Soc.*, **82**, 4293 (1960).

(3) D. Burn, D. N. Kirk, and V. Petrow, *Proc. Chem. Soc.*, 14 (1960).

(4) H. J. Ringold and A. Turner, *Chem. Ind.* (London), 211 (1962).

(5) This complex, which initially contains almost all of the steroid and whose formation appears to depend upon the presence of excess quinone, has resisted characterization due to its extreme instability.

(6) J. A. Campbell and J. C. Babcock [*J. Am. Chem. Soc.*, **81**, 4069 (1959)] demonstrated that the chloranil mediated conversion of Δ^4-3-keto steroids to $\Delta^{4,6}$-dien-3-ones involves the loss of the axial 7α-hydrogen. Mechanistically the two reactions are undoubtedly similar.

(7) Probably the axial 2β-proton whose loss would be favored in this enolization type mechanism.

does enol ether I. In fact, the reaction of I must be the slowest step in the entire sequence.

The second point is the formation of ketones III and VI from oxonium salts II and V, respectively. In nonaqueous medium it appeared possible, *a priori*, that nucleophilic attack of hydroquinone anion on II and IV would lead to the hydroquinone ethyl ether and the steroidal ketones. Not only did attempts to detect this hydroquinone derivative fail but in some experiments the recovery of 2,3-dichloro-5,6-dicyano-1,4-hydroquinone was close to quantitative thus ruling out such a displacement reaction. Species analogous to II and V have long been accepted[8] as intermediates in the hydrolysis of acetals and ketals in aqueous acids. These intermediates react with water in a fast step to give the corresponding aldehydes or ketones. Since the benzene used in the present investigation had not been thoroughly dried, nor had attempts been made to exclude moisture during the reaction, it seemed highly probable that water was implicated in the formation of III from II. When dehydrogenation of the enol ether (I) was carried out in dry benzene and in a moisture-free atmosphere at least seven products could be qualitatively detected by thin layer chromatography which tends to confirm the postulated role of moisture.

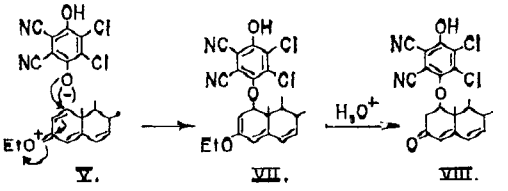
From these experiments it was apparent that the reaction of II with water is a fast step, and it appeared probable that the presence of sufficient water might lead exclusively to III if the addition of water to the oxonium species was faster than the loss of the C-2 proton. This expectation was readily realized in reactions carried out with 2.5 equiv. of DDQ in 95% acetone–5% water which gave 80 to 90% recovery of steroid with the 4,6-dien-3-one (III) as the exclusive product. On a preparative scale the $\Delta^{3,5}$-ethyl enol ethers derived from androst-4-ene-3,17-dione, testosterone acetate, progesterone, and cortisone acetate led to 70–88% yields of the corresponding pure crystalline 4,6-dien-3-ones. Although 4,6-dien-3-ones are available *via* the chloranil[2] or DDQ–hydrogen chloride[4] dehydrogenations of Δ^4-3-ketones, the present aqueous acetone method offers a very mild and rapid procedure which may prove to be of advantage with certain labile steroids.

The reaction of the $\Delta^{3,5}$-enol ethers with DDQ in anhydrous medium was further investigated as a preparative method for the formation of 1,4,6-triene-3-ones. The aforementioned dehydrogenation in benzene with 2.5 equiv. of DDQ led, after the removal of alkali soluble material, to 55–60% recovery of steroid which was shown to be primarily the 1,4,6-trien-3-one (VI), contaminated by small amounts of the 4,6-dien-3-one (III). From this mixture the trienone was readily isolated in pure state in an over-all yield ranging from 40–55%.

In anhydrous acetone (distilled from calcium chloride) the reaction led to products essentially paralleling the benzene case. The addition of 2.5 equiv. of DDQ to an acetone solution of the enol ether led to a transient deep violet color[9] which rapidly changed to light brown. Work-up, either by passage over a column of alumina, or by dilution with water and ether followed by alkaline partition, led only to about a 50% recovery of steroids in the neutral fraction. This material was found to consist of 80–95% 1,4,6-trien-3-one (VI), the balance being the 4,6-dien-3-one (III).

In attempts to isolate the acidic by-products, dehydrogenation was carried out in dry acetone with 1.9 equiv. of DDQ followed by alkaline extraction. Partial separation of the base-soluble steroidal products from the base-soluble hydroquinone was achieved by the addition of saturated salt solution to the alkali extract. A steroidal material separated as a gum, which, after treatment with acid, led to a high-melting solid of composition $C_{27}H_{24}Cl_2N_2O_4$. On the basis of spectral evidence which is detailed in the Experimental section and on mechanistic considerations (Scheme II) the substance is formulated as VIII, which is formally the Michael adduct at C-1 of the hydroquinone and of the 1,4,6-trien-3-one. However, since no adduct formation took place when a mixture of the hydroquinone and trienone were subjected to alkaline conditions, the reaction is pictured in Scheme II as proceeding by hydroquinone anion attack on the oxonium intermediate (V) followed by acid hydrolysis of the resulting enol ether (VII). Cursory examination of the acidic by-product formed with excess DDQ in benzene indicated an identical by-product formation path.

SCHEME II



While the initial oxidation step (Scheme I) and the subsequent steps have been pictured as proceeding by ionic mechanisms these transformations could alternately be accommodated by a radical mechanism although we strongly favor the ionic path. Barnard and Jackman[10] have presented evidence that the quinone dehydrogenation of a number of hydroaromatic substances involve hydride rather than radical abstraction. In subsequent publications we shall present evidence indicating that related steroid dehydrogenations proceed by hydride abstraction and not by radical attack.

Experimental[11]

Preparation of Ethyl Enol Ethers.—A mixture of the Δ^4-3-keto steroid (1 g.), dioxane (10 ml.), ethyl orthoformate (1 ml.), and *p*-toluenesulfonic acid monohydrate (100 mg.) was stirred for 1 hr. at 25°. Pyridine (1 ml.) and water (10 ml.) were added, and the mixture was cooled in ice until solidification occurred. The product was recrystallized from aqueous methanol containing a few drops of pyridine and the constants agreed in each case with the reported values.

Preparative Procedure for $\Delta^{1,4,6}$-Trienones. Androst-1,4,6-triene-3,17-dione. A.—To a stirred solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 120 mg.) in benzene (7.5

(8) M. M. Kreevoy and R. W. Taft, *J. Am. Chem. Soc.*, **77**, 5590 (1955), and earlier references cited therein.

(9) The color may be due to a charge transfer complex between the quinone and enol ether since anisole in acetone gave a similar but permanent violet coloration with DDQ.

(10) J. R. Barnard and L. M. Jackman, *J. Chem. Soc.*, 3110 (1960).

(11) All melting points are uncorrected. The identity of known compounds was confirmed by mixture melting point determination, thin layer chromatography, and infrared spectra comparison with authentic samples. Ultraviolet spectra were determined in ethanol solution and infrared spectra in potassium bromide pellet.

ml.) a solution of 3-ethoxyandrost-3,5-dien-17-one[12] (75 mg.) in benzene (7.5 ml.) was rapidly added through a dropping funnel. The reaction mixture turned greenish black and a dark gummy precipitate appeared. After 3 min. acetone (3 ml.) was added and stirring continued until the precipitate dissolved (1–5 min.). The solution was poured onto a column of alumina (10 g., Woelm neutral alumina, activity grade I) and eluted first with a 1:1 mixture of acetone and benzene (50 ml.) and then with acetone until a colored band moved to the base of the column. Removal of the combined solvents and crystallization from ethyl acetate–pentane gave 37 mg. of pure androst-1,4,6-triene-3,17-dione,[13] m.p. 165–167°; λ_{max} 225 mμ (ε 9800), 257 (9100), and 299 (11,600).

B.—A solution of 3-ethoxyandrost-3,5-dien-17-one[12] (50 mg.) in benzene (5 ml.) was added rapidly from a dropping funnel to a stirred solution of DDQ (82 mg., 2.5 equiv.) in benzene (5 ml.). The initially formed black gummy precipitate became lighter in color and could be filtered after dilution with methylene chloride. Further washing with the latter and exposure to air left a slightly colored precipitate (67 mg.) whose infrared spectrum was indistinguishable from that of 2,3-dichloro-5,6-dicyanohydroquinone. The filtrate and washings were combined and washed with 1% sodium hydroxide, until colorless, and then with water. The removal of solvent gave 30 mg. of neutral steroid which, after separation by thin layer chromatography on silica gel, yielded androst-4,6-diene-3,17-dione (3 mg.) and androst-1,4,6-triene-3,17-dione (22 mg.).

Pregn-1,4,6-triene-3,20-dione.—To a stirred solution of DDQ (80 mg.) in benzene (5 ml.) a solution of 3-ethoxypregn-3,5-dien-20-one[14] (progesterone enol ether, 50 mg.) in benzene (5 ml.) was rapidly added. Following work-up as described in A and crystallization from ethyl acetate–pentane, 24 mg. of pregn-1,4,6-triene-3,20-dione[15] was obtained, m.p. 150–152°; λ_{max} 225 mμ (ε 10,100), 258 (8600), and 301 (11,800).

17β-Acetoxyandrost-1,4,6-trien-3-one.—The treatment of 3-ethoxy-17β-acetoxyandrost-3,5-diene[12] (testosterone acetate enol ether, 50 mg.) with DDQ in benzene as above, followed by crystallization from acetone–hexane, gave 18 mg. of 17β-acetoxyandrost-1,4,6-trien-3-one,[13] m.p. 153–155°; λ_{max} 225 mμ (ε 10,800), 258 (9700), and 300 (12,700).

21-Acetoxy-17α-hydroxypregn-1,4,6-triene-3,11,20-trione.—To a stirred solution of DDQ (120 mg.) in benzene (7.5 ml.) was added rapidly a solution of 3-ethoxy-21-acetoxy-17α-hydroxypregn-3,5-diene-11,20-dione[16] (cortisone acetate enol ether, 75 mg.) in benzene (7.5 ml.). Work-up as above and crystallization from acetone–pentane gave 29 mg. of 21-acetoxy-17α-hydroxypregn-1,4,6-triene-3,11,20-trione,[2] m.p. 224–225°; λ_{max} 234 mμ (ε 9000), 255 (8000), and 296 (10,200).

Preparative Procedure for $\Delta^{4,6}$-Dienones. Androst-4,6-diene-3,17-dione.—To a stirred solution of 3-ethoxyandrost-3,5-diene-17-one (25 mg.) in 95% aqueous acetone (2.5 ml.), a solution of DDQ (19 mg.) in 95% aqueous acetone (0.5 ml.) was added dropwise. After 2 min. more acetone (5 ml.) was added, and the solution was poured onto a column of alumina (2 g., Woelm neutral alumina, activity grade I) and eluted with acetone until a colored band moved to the base of the column. Removal of solvent and crystallization from acetone–pentane gave 18 mg. of pure androst-4,6-diene-3,17-dione,[17] m.p. 169–170°; λ_{max} 283 mμ (ε 24,200).

Pregn-4,6-diene-3,20-dione.—To a stirred solution of 3-ethoxypregn-3,5-dien-20-one (100 mg.) in aqueous acetone (95%, 10 ml.), a solution of DDQ (65 mg.) in aqueous acetone (95%, 2 ml.) was added dropwise. Work-up as above and crystallization from acetone–pentane gave 63 mg. of pregn-4,6-diene-3,20-dione,[2] m.p. 128–130°; λ_{max} 283 mμ (ε 25,400).

17β-Acetoxyandrost-4,6-dien-3-one.—To a stirred solution of 3-ethoxyandrost-3,5-dien-17β-ol acetate (50 mg.) in aqueous acetone (95%, 5 ml.), a solution of DDQ (34 mg.) in aqueous acetone (95%, 1 ml.) was added dropwise. Treatment as above and crystallization from ethyl acetate–pentane gave 40 mg. of 17β-acetoxyandrost-4,6-dien-3-one,[17] m.p. 142–144°; λ_{max} 283 mμ (ε 25,600).

21-Acetoxy-17α-hydroxypregn-4,6-diene-3,11,20-trione.—To a stirred solution of 3-ethoxy-21-acetoxy-17α-hydroxypregn-3,5-diene-11,20-dione (104 mg.) in aqueous acetone (95%, 10 ml.), a solution of DDQ (65 mg.) in aqueous acetone (95%, 2 ml.) was added dropwise. Work-up as above and crystallization from chloroform–pentane gave 69 mg. of pure 21-acetoxy-17α-hydroxypregn-4,6-diene-3,11,20-trione,[2] m.p. 237–240°; λ_{max} 284 mμ (ε 25,700).

Reaction of 3-Ethoxy-17β-acetoxyandrost-3,5-diene with 1 Equiv. of DDQ in Benzene.—To a stirred solution of the enol ether (68 mg.) in benzene (5 ml.) was added dropwise a solution of DDQ (46 mg.) in benzene (5 ml.). A pinkish precipitate which formed on the addition of each drop was allowed to disperse before the addition of the subsequent drop. When the addition was complete the precipitate was filtered and washed with benzene. The combined filtrates were concentrated and adsorbed on a plate of silica gel (1 mm. thick). Development with 23% ethyl acetate in benzene and the spraying of a small strip with dinitrophenylhydrazine reagent indicated the presence of three zones in addition to material remaining at the base line. Each zone was cut out; the steroid was eluted with acetone and characterized by infrared spectra and thin layer chromatography. From the relative intensities in the ultraviolet the ratio of the compounds was estimated. In this manner it was shown that the three zones, in order of polarity, contained the starting enol ether, 17β-acetoxyandrost-4,6-dien-3-one, and 17β-acetoxyandrost-1,4,6-trien-3-one in a ratio of about 0.8:1:1, respectively.

Reaction of 3-Ethoxyandrost-3,5-dien-17-one with 1 Equiv. of DDQ in Benzene.[18]—A stirred solution of the enol ether (19 mg.) in benzene (5 ml.) was treated with a solution of DDQ (15 mg.) in benzene (5 ml.). The initial black precipitate rapidly turned gray. Stirring was continued for an additional 5 min. before the addition of methylene chloride and filtration of the hydroquinone (12 mg.). The filtrate was diluted with ether and extracted with cold 1% sodium hydroxide and then water until colorless. The removal of solvent left a gum (13 mg.). Thin layer chromatography (20% ethyl acetate–80% benzene) showed two spots. The more polar corresponded to the $\Delta^{1,4,6}$-trienone and was identified as such by its ultraviolet maxima at 225, 257, and 299 mμ. The less polar corresponded to Δ^{4}-3,17-dione plus $\Delta^{4,6}$-3,17-dione (inseparable in this system) and showed maxima at 242 (Δ^{4}) and 283 mμ ($\Delta^{4,6}$). The ratio of Δ^{4}:$\Delta^{1,4,6}$:$\Delta^{4,6}$ steroids was estimated by ultraviolet to be about 1:1:0.5.

Reaction of 3-Ethoxy-17β-acetoxyandrost-3,5-diene with 2 Equiv. of DDQ in Dry Benzene.—A stirred solution of DDQ (90 mg., 2 equiv.) in dry benzene (3 ml.) was treated dropwise with a solution of 3-ethoxy-17β-acetoxyandrost-3,5-diene (68 mg.) in dry benzene (0.5 ml.). Benzene dried over sodium was used, and the experiment was carried out under nitrogen. The benzene was removed by blowing nitrogen over the mixture to leave a greenish black solid. This was broken up under fresh dry benzene with a spatula and filtered. Further washings with benzene left the precipitate (91 mg.) as a light green powder whose infrared spectrum was indicative of impure hydroquinone. The filtrates were combined and concentrated. A thin layer chromatogram, developed with 15% ethyl acetate in benzene, indicated the presence of more than seven compounds whose isolation was not attempted.

Reaction of 3-Ethoxyandrost-3,5-dien-17β-ol Acetate with 2.5 Equiv. of DDQ in Dry Acetone.—A stirrred solution of the enol ether (68 mg.) in acetone (3 ml., distilled over calcium chloride) was treated rapidly from a dropping funnel with a solution of DDQ (112 mg., 2.5 equiv.) in acetone (2 ml.). A transient deep violet color changed within seconds to a light brown. After 10 min. the solution was poured onto a column of alumina (Woelm neutral alumina, activity grade I) and eluted with acetone until a colored band moved to the base of the column. Removal of solvent gave a mixture (33 mg.) which appeared as two spots on thin layer chromatography. Estimation by ultraviolet as in the previous experiment indicated that the material was a 9:1 mixture of $\Delta^{1,4,6}$-trienone and $\Delta^{4,6}$-dienone.

The above experiment was repeated but instead of putting the material on the column, the acetone solution was diluted with ether, washed with water, then 2 *N* sodium hydroxide until

(12) A. Serini and H. Koster, *Ber.*, **71B**, 1766 (1938).

(13) C. Djerassi, G. Rosenkranz, J. Romo, St. Kaufmann, and J. Pataki, *J. Am. Chem. Soc.*, **72**, 4531 (1950).

(14) S. Liisberg, W. O. Godtfredsen, and S. Vangedal, *Tetrahedron*, **9**, 149 (1960).

(15) G. O. Weston, D. Burn, D. N. Kirk, and V. Petrow, British Patent 854,343 (1960).

(16) P. L. Julian, E. W. Meyer, W. J. Karpel, and W. Cole, *J. Am. Chem. Soc.*, **73**, 1982 (1951).

(17) C. Djerassi, G. Rosenkranz, J. Romo, St. Kaufmann, and J. Pataki, *ibid.*, **72**, 4534 (1950).

(18) This experiment was initially carried out in these laboratories by Dr. Alan B. Turner, Royal Technical College, Glasgow.

colorless, and again with water. Removal of ether left 33 mg. of neutral steroid.

Attempted Michael Addition of Hydroquinone to 17β-Acetoxyandrost-1,4,6-trien-3-one.—A solution of $\Delta^{1,4,6}$-trienone (62 mg.) and 2,3-dichloro-5,6-dicyano-1,4-hydroquinone (90 mg.) in acetone (5 ml.) was allowed to stand for 10 min. Then ether was added, and the solution was washed with water, 2 *N* sodium hydroxide (three times), and finally with water. Removal of ether left unchanged $\Delta^{1,4,6}$-trienone (56 mg.).

Isolation of the Acidic By-product (VIII).—A stirred solution of 3-ethoxyandrost-3,5-dien-17-one (180 mg.) in acetone (6 ml.; dried over calcium chloride) was treated with a solution of DDQ (227 mg.) in acetone (1 ml.). The acetone was blown off by a rapid stream of nitrogen (10 min.), and the residue was suspended in benzene and filtered. The filtrate was diluted with ether and then washed successively with 0.2 *N* sodium hydroxide and water. Evaporation of the organic phase left 76 mg. of neutral steroid which was shown by thin layer chromatography to be a mixture of $\Delta^{4,6}$- and $\Delta^{1,4,6}$-3-keto steroids.

The alkali extracts were added to a saturated sodium chloride solution, and the resulting yellow gummy precipitate was separated by filtration. It was dissolved in methanol, diluted with water, and acidified with dilute sulfuric acid. Ether extraction gave a gum (67 mg.) which, after repeated crystallizations from ether and methanol–methylene chloride, gave VIII, m.p. 275–277°; ultraviolet spectrum showed $\lambda_{max}^{EtOH-HCl}$ 224 mμ (ε 23,500), 292 (19,400), shoulders 235 (20,500) and 345 (5100); $\lambda_{max}^{EtOH-NaOH}$ 210 mμ (ε 22,500), 254 (22,400), 285 (21,500), and 392 (6,700). The infrared spectrum showed bands at 4.51 (C≡N), 5.85 (17-ketone), 6.05 (3-ketone), and 6.20 μ (C=C); Beilstein test was positive.

Anal. Calcd. for $C_{27}H_{24}Cl_2N_2O_4$: C, 63.41; H, 4.73. Found: C, 63.64; H, 4.89.

Steroids. LXXI.[1,2] The Base-Catalyzed Reaction between Acetone and 20-Keto-16-pregnenes with 12β and 12α Substituents

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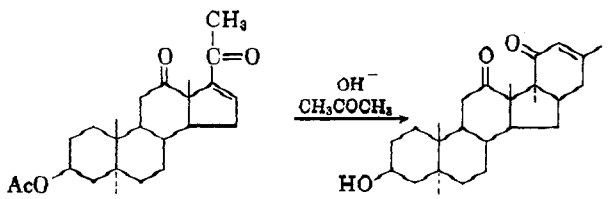
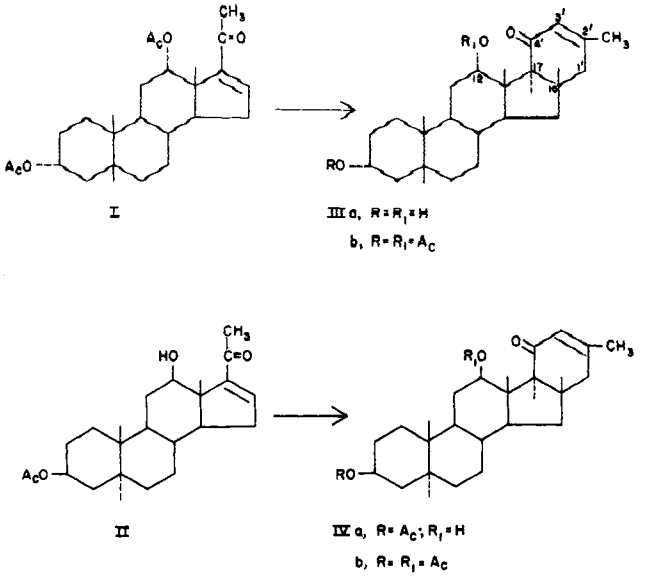
Reaction of 3α,12α-diacetoxy-5β-Δ^{16}-pregnen-20-one (I) or of 3β-acetoxy-12β-hydroxy-5α-Δ^{16}-pregnen-20-one (II) with acetone in the presence of potassium hydroxide gave the respective 16β,17α-cyclo derivatives (III and IV). The stereochemistry of these products are discussed in detail as are the hydrogen-bonding relationships between C-12 and C-20 or C-12 and C-4′ substituents.

Recently we established the structure and stereochemistry of the cyclic product formed by the base-catalyzed reaction of acetone with 3β-acetoxy-5α-Δ^{16}-pregnene-12,20-dione.[3] The reaction was shown to involve Michael addition followed by aldol condensation to give the pentacyclic product indicated below.



We now wish to report that the reactions of acetone with 3α,12α-diacetoxy-5β-Δ^{16}-pregnen-20-one (I) and with 3β-acetoxy-12β-hydroxy-5α-Δ^{16}-pregnen-20-one (II) give after acetylation the analogous cyclization products IIIb and IVa, respectively, although in much lower yield. To date we have been unable to demonstrate a similar reaction with 12-desoxy-16-dehydropregnenes.

The requisite 16-dehydropregnenes were made by slight modifications of literature procedures. The 12α-acetoxypregnene (I) was prepared *via* bromination of commercially available 3α,12α-diacetoxy-5β-pregnan-20-one, followed by treatment with sodium iodide and sodium metabisulfite.[4] The yield of pure I obtained by this procedure was poor (16.5%).[5] The preparation of the 12β-hydroxy-Δ^{16}-pregnene (II) involved slight modification of a preparation already in the literature.[6] Lithium aluminum hydride reduction of 3β-acetoxy-5α-Δ^{16}-pregnene-12,20-dione gave the crude triol, 3β,12β,20-trihydroxy-5α,Δ^{16}-pregnene. Selective oxidation of the allylic hydroxyl group with manganese di-



(1) Previous paper in this series, S. G. Levine, M. E. Wall, and N. H. Eudy, *J. Org. Chem.*, **28**, 1936 (1963).

(2) (a) The research reported in this paper was supported under contract SA-43-ph-4351 of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health; (b) presented at the 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April, 1963.

(3) M. E. Wall, S. Serota, H. Kenney, and G. S. Abernethy, Jr., *J. Am. Chem. Soc.*, **85**, 1844 (1963).

(4) W. J. Adams, D. K. Patel, V. Petrow, and I. A. Stuart-Webb, *J. Chem. Soc.*, 1825 (1954).

(5) This reaction was studied briefly with the aid of thin layer chromatography. Bromination of 3α,12α-diacetoxy-5β-pregnan-20-one with 3 moles of bromine[4] gave a crude tribromo derivative which gave only one spot on thin layer chromatography (silica gel G). After treatment with sodium iodide and metabisulfite, a mixture of the initial pregnan-20-one and the desired Δ^{16}-pregnene (I) was obtained. The mixture was readily resolved on a thin layer chromatogram, and no tribromopregnene (this is much faster moving on t.l.c. than the pregnane or Δ^{16}-pregnene) was obtained.

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