thick yellow oil. Rechromatography of this fraction with grade 2 alumina and elution with benzene–hexane (1:1) and benzene gave 243 mg of the desired compound as a colorless solid contaminated by a compound with lower R_f as shown by tlc. Final purification of the compound was achieved by two preparative tlc procedures. In the final procedure, 96 mg of the mixture was placed on two preparative tlc plates (20 × 20 × 1 mm silica gel G plates containing fluorescein dye). The plates were developed continuously for 6 hr (hexane–acetone–ether, 9:0.5:0.5). Elution of the top uv zone from each plate gave a combined yield of 44 mg of colorless solid. Recrystallization of the solid from methanol gave 21.6 mg of colorless crystalline clusters, mp 108–112°. A second recrystallization from methanol gave 17.3 mg (X): mp 112–113.5°; $[\alpha]^{20}D$ −45.3°; infrared spectrum 3618, 1470, 1385, 1114, 1068, 1032, 1020, 918, 832 cm^{-1}; nmr spectrum (δ) 5.25 (m, olefin), 1.26 (s, C-19 methyl), 0.67 (s, C-18 methyl).

Further elution of the BH-3 column with benzene–hexane (1:1) gave 997 mg of impure compound R_f 0.44 (13% of total). The material was then rechromatographed two times on alumina. The final procedure on elution with benzene and ether–benzene (1:9) (grade 2 alumina) gave a combined yield of 325 mg of product highly enriched in the desired compound, but not crystalline. The material was therefore applied to three preparative tlc plates (1-mm plates containing fluoroscein dye). After continuous development for 3 hr and uv lamp inspection of the plates, the lower portion of the top uv zone was eluted with acetone to give a combined yield of 147 mg. The product was recrystallized from petroleum ether to give two crops of colorless crystals, 20.7 mg, mp 122–123°, and 61.0 mg, mp 125–125.5°. The combined crops were recrystallized from petroleum ether to give 68.4 mg of 4-hydroxy-2-methyl-19-norcholesta-1,3,5(10)-triene (IV), as colorless crystals, mp 124.5–125.5°. The compound was identical with IV obtained from the irradiation experiment as shown by mmp 125–126.5° and infrared and ultraviolet spectra.

Fraction BH-4 (2.11 g) was subjected to column chromatography on alumina (grade 1, 63 g). Elution with 0.1, 0.25 and 0.5% methanol in ether gave 1.03 g of combined material containing the desired compound, R_f 0.36 (45% of total reaction mixture), accompanied by minor impurities. The material was then rechromatographed two more times on alumina, the final procedure (17 g, grade 3) after elution with benzene–hexane (1:1) gave 220 mg of pure product. Recrystallization from petroleum ether gave colorless fine needles, mp 126.5–127.5°. A second recrystallization from the same solvent gave pure 3-hydroxy-1-methyl-19-norcholesta-1,3,5(10)-triene (III), mp 128–128.5°. The compound was identical with III obtained from the irradiation experiment with regard to infrared spectrum and mmp 126.5–127.5°.

Registry No.—I, 566-91-6; II, 19202-72-3; III, 17605-79-7; IV, 19202-74-5; V, 19202-75-6; VI, 19202-76-7; IX, 2603-79-4; sodium borohydride, 1303-74-8.

Steroids. LXXX.[1] The Effect of C-12 Substitution on the Reactivity of Δ^{16}-20-Keto Steroids toward 1,4-Nucleophilic Addition[2,3]

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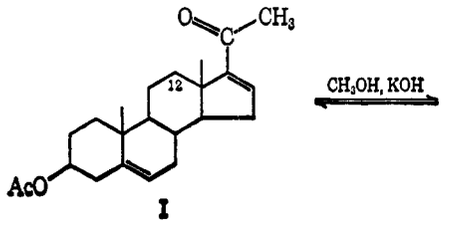
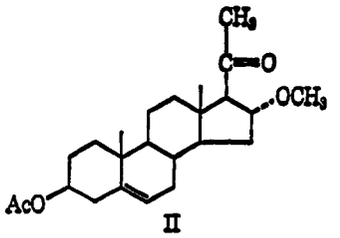
The presence of a ketone function at C-12 has a marked rate accelerating effect on 1,4 additions to Δ^{16}-20-keto steroids. The rates of the base-catalyzed 1,4 addition of methanol to a wide variety of 12-substituted Δ^{16}-20-keto steroids have been measured. On the basis of nmr and ultraviolet spectral data it is concluded that the rapid rate of reaction exhibited by the 12-keto steroids is anomalous. A mechanism is proposed to explain the unexpected rate of 1,4 addition displayed by Δ^{16}-12,20-diketo steroids. This effect is shown to be applicable to a number of nucleophiles, some of which undergo further reaction to produce polycyclic derivatives.

In 1951, Fukushima and Gallagher[4] characterized the product obtained from the action of methanolic potassium hydroxide on Δ^{16}-pregnenolone acetate (I) as the methanol 1,4-addition product II.



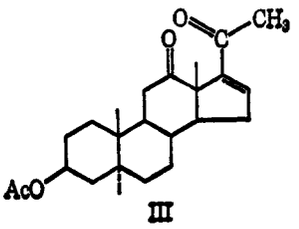
I

CH_3OH, KOH



II

Mueller, *et al.*,[5] have shown that the presence of a ketone at C-12 greatly increases the rate of this reaction. Adams, *et al.*,[6] have also observed this effect and attributed the increased reactivity to the polar effect of the 12-ketone on the adjacent conjugated system. In an earlier publication[7] we reported the facile base-catalyzed 1,4 addition of acetone to the 12-keto compound III.[8] The 12-deoxy analog I[9] failed to



III

react with acetone under the same conditions. It occurred to us that the increased reactivity of III could

(1) Previous paper in this series (Steroids. LXXIX): C. E. Cook, R. C. Corley, and M. E. Wall, *J. Org. Chem.* **33**, 2789 (1968).

(2) (a) The research 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 19th Southeastern Regional Meeting of the American Chemical Society, Atlanta, Ga., Nov, 1967.

(3) Taken from the M.S. Thesis of G. S. Abernethy, Jr., North Carolina State University, 1967.

(4) D. F. Fukushima and T. F. Gallagher, *J. Amer. Chem. Soc.*, **73**, 196 (1951).

(5) G. P. Mueller, R. E. Stobaugh, and R. S. Winniford, *ibid.*, **75**, 4888 (1953).

(6) W. J. Adams, D. N. Kirk, D. K. Patel, V. Petrow, and I. A. Stuard-Webb, *J. Chem. Soc.*, 2209 (1954).

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

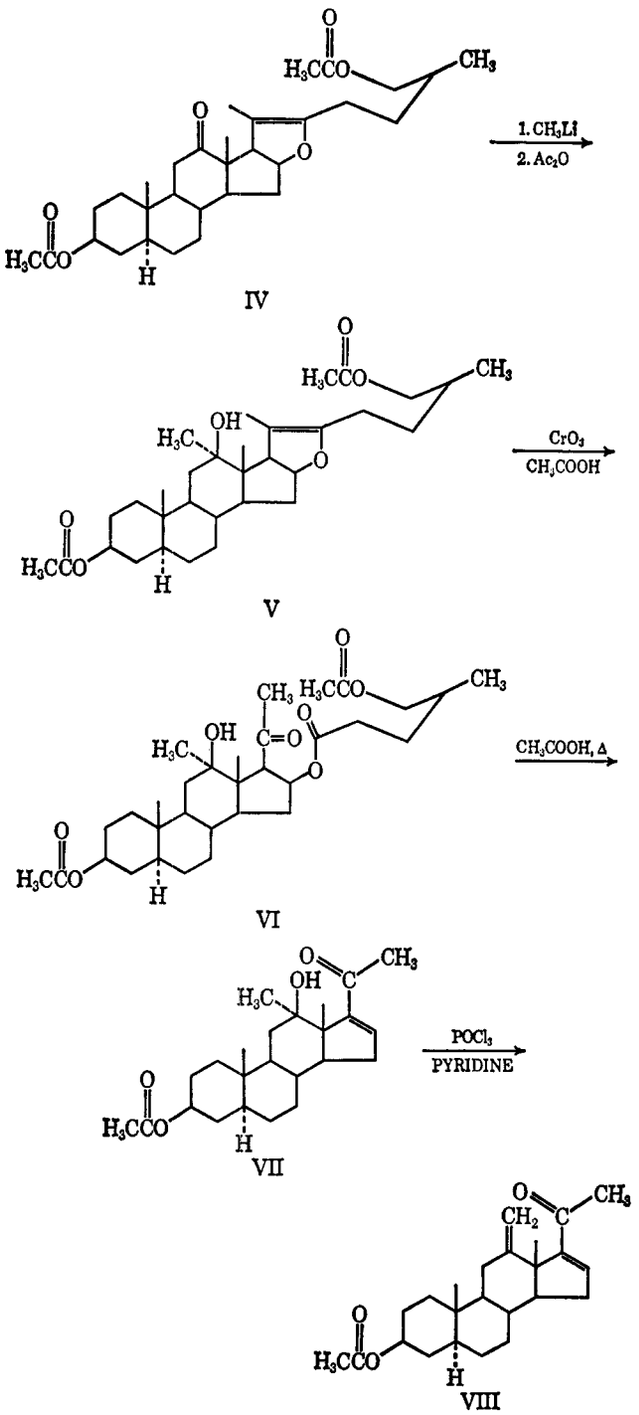
(8) R. B. Wagner, J. A. Moore, and R. F. Forker, *ibid.*, **72**, 1856 (1950).

(9) D. H. Gould, H. Staeudle, and E. B. Hershberg, *ibid.*, **74**, 3685 (1952).

be attributed to ring strain imposed by sp^2 hybridization at C-12 added to that already present in the Δ^{16}-20 keto moiety.

With this in mind, we undertook the synthesis of the 12-methylene analog. This moiety incorporates the steric requirements of III while lacking the polar contributions of the ketone. After several unsuccessful attempts employing the Wittig reaction, a successful synthesis was accomplished as outlined in Scheme I.

SCHEME I



Treatment of pseudohecogenin diacetate (IV)[5] with methyllithium[10] and reacetylation gave 12β-hydroxy-12α-methylpseudotigogenin diacetate (V). Low temperature chromic acid oxidation led to the formation of triester VI. The side chain was cleaved in refluxing acetic acid to give 3β-acetoxy-12β-hydroxy-12α-methyl-5α-pregn-16-en-20-one (VII). The structure of VII and the stereochemistry of the 12β-hydroxy-12α-methyl moiety rests on the evidence, which includes (1) method of preparation; (2) correct analysis for the calculated molecular formula; (3) λ_{max} 242 mμ (ϵ 8250) in accord with postulated Δ^{16}-20 keto moiety; (4) the infrared spectrum indicating strong intramolecular hydrogen bonding (of the 12β-hydroxy and the C-20 carbonyl groups) identical with that observed with the known 12β-hydroxy-12α-methoxy and 12β-hydroxy Δ^{16}-20-ketone compounds.[11] This establishes the configuration at C-12. The nmr spectrum is in accord with the proposed structure showing the presence of five methyl groups and an olefinic proton appearing at δ 6.95. Treatment of the tertiary alcohol with phosphorus oxychloride in pyridine afforded the desired product, 3β-acetoxy-12-methylene-5α-pregn-16-en-20-one (VIII). The structure of VIII derives from its method of preparation[12] and correct analytical values. In particular the presence of the C-12 methylene moiety is shown by the nmr spectrum which shows two singlets at δ 4.38 and 4.63. Molecular models explain the nonequivalency of the C-12 methylene protons as one of them is in close proximity to the C-20 carbonyl.

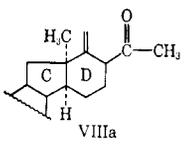
The rates of 1,4 addition of the various steroids were compared by treating the steroid (10^{-4} *M*) with 0.1 *N* methanolic potassium hydroxide. Because of the large excess of methoxide ion employed pseudo-first-order kinetics are observed. The reaction rates were measured by observing the rate of decrease of the ultraviolet absorption maxima. The specific first-order rate constants of a variety of Δ^{16}-20-keto steroids are listed in Table I. These values must be regarded as approximate due to slight variations in temperature.

It is seen that the 12-methylene steroid VIII reacts at

(10) The reaction of methyllithium with steroidal 12-ketones was first described by P. Bladon [*J. Chem. Soc.*, 2191 (1960)] and G. Just [*Can. J. Chem.*, **39**, 548 (1961)].

(11) (a) M. E. Wall and S. Serota, *Tetrahedron*, **10**, 238 (1960); (b) W. J. Adams, D. N. Kirk, D. K. Patel, V. Petrow, and I. A. Stuart-Webb, *J. Chem. Soc.*, 870 (1955).

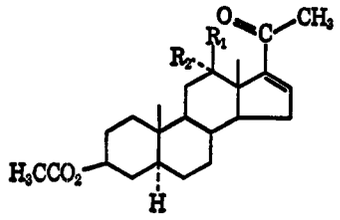
(12) One of the referees has suggested that an alternative structure VIIIa, a C-nor-D-homo product, is not excluded by the data presented. It is indeed



difficult *via* the physical data (ir, uv, nmr, and C and H analysis) to differentiate VIII and VIIIa, particularly since appropriate model compounds are lacking. S. G. Levine and M. E. Wall [*J. Amer. Chem. Soc.*, **82**, 391 (1960)] characterized the 12-methyl-12-hydroxy epimers produced by Grignard reaction of methylmagnesium bromide with the 12-ketosapogenin, hecogenin. On dehydration of the epimers with thionyl chloride in pyridine, *a method closely analogous* to that used in our procedure, a separable mixture of *endo* and *exo* olefins was obtained. Treatment of the *exo* olefin with osmium tetroxide followed by periodate oxidation gave the starting product *hecogenin in 65% yield.* Hence, the methylene group must be at position 12 in the product of Levine and Wall and by close analogy is placed similarly in our compound VIII. It can be stated parenthetically that the C-nor-D-homo rearrangement is characteristically observed on solvolysis of 12β-mesylates or -tosylates (an excellent review of this rearrangement is found in N. L. Wendler, "Molecular Rearrangements," Part II, Paul de Mayo, Ed., John Wiley & Sons, Inc., New York, N. Y., 1964, Chapter 16). In these compounds only the C-13–C-14 bond is located in an appropriate position to participate in this reaction, whereas in dehydration of the 12β-hydroxy-12α-methyl tertiary alcohol VIII, the formation of the *exo*-methylene would (from the data of Levine and Wall) be favored [*cf.* D. H. R. Barton, A. Campus-Neves, and R. C. Cookson, *J. Chem. Soc.*, 3500 (1956), for similar *exo*-methylene formation by dehydration of 3β-hydroxy-3α-methylcholestane].

TABLE I

FIRST-ORDER SPECIFIC RATE CONSTANTS FOR THE REACTION OF Δ^{16}-20-KETO STEROIDS WITH 0.1 *M* METHANOLIC POTASSIUM HYDROXIDE

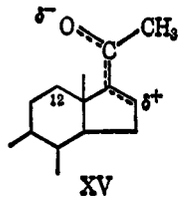


Compd no.	C-12 substituents	Specific rate constant, min^{-1}
IX	R_1 = OH, R_2 = H	0.30[a]
X	R_1R_2 = O=, $\Delta^{9(11)}$	0.072
XI	R_1 = R_2 = H, 11-ketone	0.043
III	R_1R_2 = O=	0.028
XII	R_1 = H, R_2 = OH	0.0075
I	R_1 = R_2 = H, Δ^5	0.0055
XIII	R_1 = R_2 = H	0.0051
VIII	R_1R_2 = H_2C=	0.0027
VII	R_1 = OH, R_2 = CH_3	0.0013
XIV	R_1R_2 = 	0.00066

[a] Minimum value.

a rate slower than either of the 12-unsubstituted analogs I and XIII. Thus the rapid reaction rate exhibited by the 12,20-diketo-Δ^{16}-pregnenes cannot be attributed to sp^2 hybridization at C-12.

The Electrostatic Effect.—The reaction of Δ^{16}-20-keto steroids with a nucleophile requires the development of a partial positive charge at C-16. This positive center is attained through a number of resonance forms which may be summarized as the resonance hybrid (XV).



XV

In order to determine the nature of the effect of substituents at C-12 on the susceptibility of the conjugated system to nucleophilic attack, it was desirable to obtain a measurement of the relative electron densities at C-16. It was found that this information could be obtained by observing the chemical shift of the C-16 proton in the nmr spectra of these compounds. These data are presented in Table II. If the 12-unsubstituted moieties, I and XIII[13] are taken as reference compounds, it is evident that the presence of an ethylene ketal at C-12 (compound XIV)[14] produces a shielding effect on the olefinic C-16 proton. This indicates a relatively high electron density at C-16 in XIV. We believe that this shielding is due to electrostatic repulsion between the ketal oxygens and the C-20 carbonyl which inhibits the formation of the resonance hybrid XV. This effect is similar to that of a 12β-acetoxy group on the Δ^{16}-20-ketone system discussed by Snatzke and Schwinum.[15]

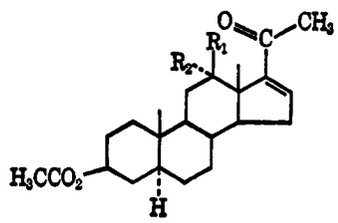
(13) P. A. Plattner, L. Ruzicka, H. Heusser, and E. Angliker, *Helv. Chim. Acta.*, **30**, 385 (1947).

(14) The preparation and physical constants of this compound are given in the Experimental Section.

(15) G. Snatze and E. Schwinum, *Tetrahedron*, **22**, 761 (1966).

TABLE II

NMR CHEMICAL SHIFT OF THE C-16 PROTON IN Δ^{16}-20-KETO STEROIDS[a]



Compd no.	C-12 substituents	Chemical shift of proton, ppm (δ)
XIV	R_1R_2 =	6.55
III	R_1R_2 = O=	6.62
X	R_1R_2 = O=, $\Delta^{9(11)}$	6.62
XIII	R_1 = R_2 = H	6.72
I	R_1 = R_2 = H, Δ^5	6.74
VIII	R_1R_2 = H_2C=	6.75
XII	R_1 = H, R_2 = OH	6.76
XI	R_1 = R_2 = H, 11-ketone	6.80
VII	R_1 = OH, R_2 = CH_3	6.95
IX	R_1 = OH, R_2 = H	6.98

[a] Spectra were obtained in deuteriochloroform solution using a Varian spectrometer operating at 60 Mc and calibrated against internal tetramethylsilane.

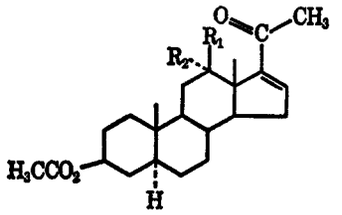
As these data predict, XIV exhibits a very slow rate of 1,4 addition as shown in Table I. The two 12-keto moieties III and X[16] also show a high field shift of the 16-proton. In analogy to the ketal XIV, this observation can be attributed to oxygen–oxygen repulsion between the C-12 and C-20 ketones. In view of these data, III and X would be expected to display a relatively slow rate of 1,4 addition. However, as shown in Table I both of the 12-keto moieties react very rapidly with methanolic potassium hydroxide. The chemical shift of the 16 proton in the 12-methylene derivative VIII and 12α- (axial) hydroxy analog[14] approximates those of the 12-unsubstituted compounds I and XIII. Table I shows that XII reacts slightly faster than the dihydro compounds while VIII reacts at a slower rate. The 11-keto moiety XI[17] shows a slight shift of the 16 proton to lower field indicating a relatively low electron concentration in this region. This observation provides an explanation for the rapid rate of 1,4 addition displayed by XI as shown in Table I. The olefinic protons of the 12β-hydroxy-12α-methyl compound VII and the 12β-hydroxy analog IX exhibit the greatest downfield shift, indicating an electron-deficient center at C-16. This observation can be explained by the strong intramolecular hydrogen bond[15] between the 12β- (equatorial) hydroxyl and the C-20 carbonyl which would stabilize the resonance hybrid XV. These data predict that VII and IX would undergo 1,4-nucleophilic addition at a very rapid rate. This prediction is realized in the case of the 12β-hydroxy compound IX (Table I) while the 12β-hydroxy-12α-methyl derivative VII reacts at a slow rate. Molecular models indicate that the 12α- (axial) methyl function of VII offers considerable steric interaction with the α face of C-16. This interaction could effectively hinder the rear-side attack of a

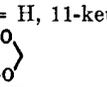
(16) D. Rosenthal and J. P. Gratz, *J. Org. Chem.*, **34**, 409 (1969).

(17) E. M. Chamberlain, W. V. Ruyle, A. E. Erickson, J. M. Chemerda, L. M. Aliminosa, R. L. Erickson, G. E. Sita, and M. Tishler, *J. Amer. Chem. Soc.*, **73**, 2396 (1951).

TABLE III

ULTRAVIOLET ABSORPTION MAXIMA OF Δ^{16}-20-KETO STEROIDS

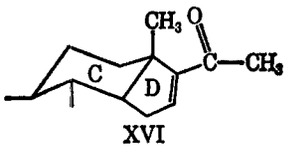


Compd no.	C-12 substituents	λ_{max}, mμ	ϵ_{max}, M^{-1} cm^{-1}	Ref
III	R_1R_2 = O=	227–230	8,510	8
X	R_1R_2 = O=, $\Delta^{9(11)}$	229[a]	17,000[a]	16
XI	R_1 = R_2 = H, 11-ketone	234.5	9,050	17
XIV	R_1R_2 = 	236	7,500	
VIII	R_1R_2 = H_2C=	237	7,800	
XII	R_1 = H, R_2 = OH	237.5	8,850	
I	R_1 = R_2 = H, Δ^5	239	9,100	4
XIII	R_1 = R_2 = H	240	10,000	13
IX	R_1 = OH, R_2 = H	242	8,800	*b*
VII	R_1 = OH, R_2 = CH_3	242	8,250	

[a] ϵ_{max} of the Δ^{16}-20-ketone chromophore is taken as 8500. [b] M. E. Wall, F. I. Carroll, and G. S. Abernethy, Jr., *J. Org. Chem.*, **29**, 604 (1964).

nucleophile at C-16 and thus decrease the rate of reaction. The nmr data correlate well with the reaction rates in Table I with the exception of the 12-keto moieties I and X. The reaction rates of these compounds seem to be anomalous.

The Steric Effect.—Mueller, *et al.*,[5] have demonstrated that Δ^{16}-20-keto steroids exist predominantly in the *s-trans* conformation (XVI). The most stable



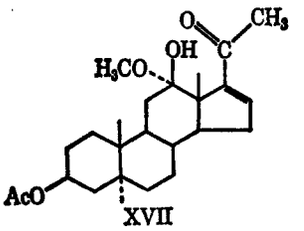
XVI

conformation is that in which the 16,17 double bond and the C-20 carbonyl are coplanar. This conformation allows maximum π-orbital overlap which is necessary for the formation of the resonance hybrid (XV). Any factor which disrupts the planarity of the conjugated system will effectively inhibit the formation of the resonance hybrid by decreasing the π-orbital overlap. Molecular models indicate that the spacial proximity of an equatorial substituent at C-12 to the C-20 carbonyl of a Δ^{16}-20-keto steroid in the *s-trans* coplanar conformation is sufficient to cause considerable steric interaction between the two functions.

Braude, *et al.*,[18] found that this deviation from planarity of a conjugated system may be measured by ultraviolet spectroscopy. A structural change which causes the conjugated system to twist slightly from planarity results in a decrease in absorption with little change in wavelength. A more severe twist in the chromophore results in a decrease in absorption accompanied by a shift to shorter wavelength. The ultraviolet spectral parameters for the steroids studied are listed in Table III. It has been shown by circular dichroism measurements[15] that the conjugated enone system of the 12β-hydroxy compound IX is essentially *s-trans* and coplanar. If this compound is taken as a reference, the degree of steric distortion of the conjugated system of the remaining steroids can be estimated. The 12-ethylenedioxy compound XIV and the 12-methylene analog VIII shows a distinct decrease in absorption indicating a slight out of plane distortion of the enone system. Accordingly, Table I shows that these compounds undergo 1,4 addition at a slower rate than does the 12β-hydroxy moiety. The 12-keto steroids III and X exhibit a hyposchromic shift accompanied by a slight decrease in absorption. This indicates a rather severe distortion of the conjugated system and predicts a slow rate of 1,4 addition. However, both 12-keto steroids display a rapid rate of 1,4 addition as shown in Table I.

The reactivity of the 12-keto steroids is thus apparently anomalous. The nmr spectra indicate a relatively high electron density at C-16 which is not conducive to nucleophilic addition. Also the ultraviolet spectra indicate a severe distortion of the conjugated system which inhibits the development of a positive center at C-16; yet these compounds display a rapid rate of nucleophilic addition.

Proposed Mechanism for 1,4 Addition to Δ^{16}-12,20-Diketo Steroids.—Bearing in mind the rapid reaction rate displayed by the 12β-hydroxy compound IX (Table I), a possible mechanism occurred to us. Wall and Serota[11] have isolated the hemiketal XVII from a methanolic solution of diketone III.



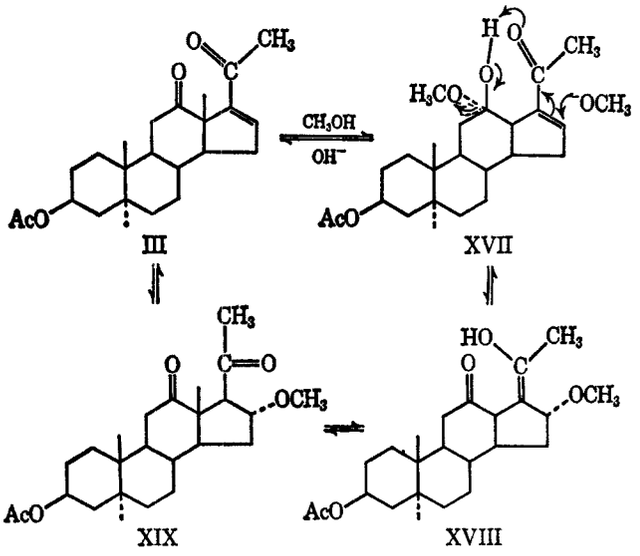
XVII

It was impossible to measure effectively the rate of 1,4 addition of methanol to XVII owing to rapid decomposition to diketone III in the strong basic media. This observation does not preclude the existence of XVII in basic solution, although its concentration is undoubtedly low.

(18) E. A. Braude, E. R. H. Jones, H. P. Koch, R. W. Richardson, F. Sondheimer, and J. B. Toogood, *J. Chem. Soc.*, 1890 (1949).

In view of these considerations, we can rationalize the apparently anomalous rate of 1,4 addition displayed by Δ^{16}-12,20-diketo steroids by Scheme II. The first step involves solvolysis of the 12-ketone to form hemiketal XVII. Attack of methoxide ion at C-16 is followed by abstraction of the hydrogen from the 12β-hydroxyl group. This leads to the expulsion of the 12α-methoxyl group to yield enol XVIII. This enol can rapidly

SCHEME II

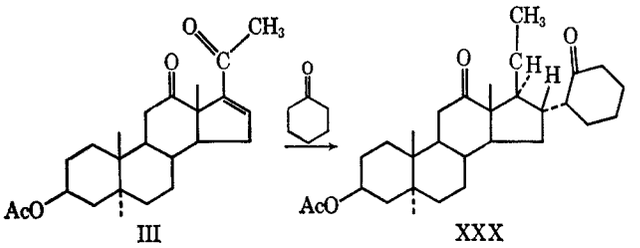


ketonize to form the expected 1,4-addition product XIX.[19] In consideration of the data presented thus far, it is unlikely that XIX is formed directly from III to an appreciable extent.

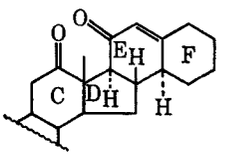
Consideration of certain physical data makes this mechanism more attractive. The strong intramolecular hydrogen bond of the hemiketal XVII should stabilize the resonance hybrid XV, producing a region of low electron density at C-16 and making this moiety more susceptible to nucleophilic attack. The C-16 proton of XVII appears at δ 6.96 in the nmr spectrum, indicating a relatively low electron concentration in this region (see Table II).

The Reaction of Δ^{16}-20-Keto Steroids with Various Nucleophiles.—The addition of nucleophiles to Δ^{16}-20-keto steroids to give 16α-substituted steroids has been reported by many authors.[4,7,20,21] In the previous section we have presented data which explain the greater reactivity of Δ^{16}-12,20-diketopregnenes toward attack by methoxide ion. In this section we wish to show that this is a *general* reaction with applicability to a variety of nucleophiles. As substrates we have chosen the readily available 3β-acetoxy-pregna-5,16-dien-20-one (I) and 3β-acetoxy-5α-pregn-16-ene-12,20-dione (III). In the previous section we have shown that steroids with a Δ^5 or 5α fusion had identical first-order rate constants with respect to the addition of methoxide ion to C-16. Hence I and III should be reasonably comparable in regard to the rate of nucleophilic attack on the conjugated system. If appropriate reaction conditions are selected, the increased reactivity of III becomes evident as shown in Table IV. It is seen that both substrates react with strong nucleophiles such as cyanide ion, ethylenimine and benzyl mercaptide anion under mild conditions. Under comparable conditions in the presence of a quaternary ammonium hydroxide, nitromethane, nitroethane, acetylacetone, ethyl cyanoacetate, cyclohexanone, and cyclopentanone react only with the 12-keto moiety. Cycloheptanone also reacted with III under these conditions, but the product was not crystalline. It is interesting to note that Mazur and Cella[21b] were able to effect the addition of acetylacetone and ethyl cyanoacetate to the 12-deoxy analog I by employing a stronger base. Similarly, as shown in Table IV, nitromethane and cyclohexanone react with I under more stringent conditions.

Reaction of I and III with cyclohexanone has led to some novel polycyclic compounds containing two rings fused at C-16 and C-17 in addition to the tetracyclic steroid nucleus. Cyclohexanone under mild basic conditions reacts with III to give the normal Michael adduct XXX. The stereochemistry at C-16,C-17 is



based on analogy with many previous similar studies.[20,21] In the presence of a stronger base such as sodium methoxide, XXX smoothly undergoes an aldol condensation to yield XXXIII. The structure and



XXXIII

stereochemistry is postulated on the following grounds: (1) agreement of analytical values with the postulated structure; (2) the presence of a conjugated carbonyl as shown by the ultraviolet spectrum, λ_{max} 240 mμ; (3) the infrared spectrum showing strong bands at 1735, 1712, and 1685 cm^{-1} in accord with the presence of the expected acetate, 12-ketone, and conjugated ketone moieties; (4) the nmr spectrum (*cf.* Experimental Section), also in accord with the proposed structure. The ring fusion at C-16,C-17 is based on analogy to a

(19) *A priori* this mechanism may seem to be precluded by the slow rate of 1,4 addition displayed by the 12β-hydroxy-12α-methyl moiety VII which was attributed to steric inhibition of the rear-side attack of methoxide ion at C-16 by the 12α-methyl group. The 12α-methoxyl group in XVII might be expected to hinder the axial attack in a similar fashion. However, molecular models indicate that a 12α-methyl group offers considerably more steric interaction with the α face of C-16 than does a 12α-methoxyl group. This observation is supported by the work of R. W. Taft, Jr. [*J. Amer. Chem. Soc.*, **74**, 3120 (1952)], who found that the rate of acid-catalyzed hydrolysis of *o*-methoxybenzamide is considerably faster than that of *o*-methylbenzamide. It is stated that this effect is steric in nature, and that polar effects are negligible.

(20) (a) J. Romo, M. Romo, C. Djerassi, and G. Rosencrantz, *ibid.*, **73**, 1528 (1951); (b) G. P. Mueller and B. Riegel, *ibid.*, **76**, 3686 (1954).

(21) (a) D. Gould, E. L. Shapiro, L. E. Finckenor, F. Gruen, and E. B. Hershberg, *ibid.*, **78**, 3158 (1956). (b) R. H. Mazur and J. A. Cella, *Tetrahedron*, **7**, 130 (1959). (c) P. F. Beal and J. E. Pike, *J. Org. Chem.*, **26**, 3887 (1961). (d) J. E. Pike, M. A. Rebenstorf, G. Slomp, and F. A. Mackellar, *ibid.*, **28**, 2499 (1963). (e) F. Schneider, J. Hamsher, and R. E. Beyler, *Steroids*, **8**, 553 (1966).

TABLE IV

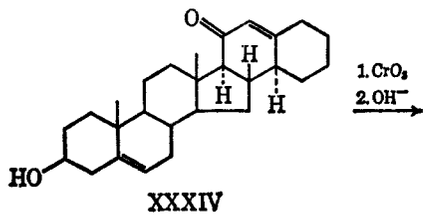
COMPARISON OF THE REACTIVITY OF 12-DEOXY AND 12-KETO-Δ^{16}-20-KETO STEROIDS WITH VARIOUS NUCLEOPHILES

Reactant	Reaction conditions[a]	Product, 16α substituent: 12-Deoxy	12-Keto
Sodium cyanide	A	XX, -CN	XXI, -CN
Ethylenimine	B	XXII,	XXIII,
Benzyl mercaptan	C	XXIV,	XXV,
Nitromethane	C	NR[b]	XXVI, $-CH_2NO_2$
Nitroethane	C	NR	XXVII, $-CH(CH_3)NO_2$
Acetylacetone	C	NR	XXVIII, $-CH(COCH_3)C(=O)CH_3$
Ethyl cyanoacetate	C	NR	XXIX, $-CH(CN)COC_2H_5$
Cyclohexanone	C	NR	XXX,
Cyclopentanone	C	NR	XXXI,
Nitromethane	D	XXXII, $-CH_2NO_2$	
Cyclohexanone	D	XXXIV,	

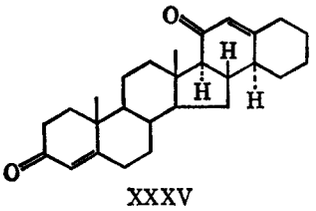
[a] A, 95% ethanol, heat; B, triethylamine catalyst; C, $R_4N^+OH^-$, tetrahydrofuran, heat; D, $(CH_3)_3CO^-K^+$ in $(CH_3)_3COH$. [b] NR, no appreciable reaction.

similar reaction of III with acetone[7] in which the stereochemistry was carefully determined. The assignment of the fusion of rings E and F is based on the fact that the reaction product is thermodynamically controlled. Thus the stable chair form of rings E and F would be predicted by conformational analysis.

As described previously, cyclohexanone failed to react with I under mild conditions. Under more rigorous conditions with potassium *t*-butoxide, Michael addition and aldol cyclization took place to give XXXIV. The physical properties are in accord with



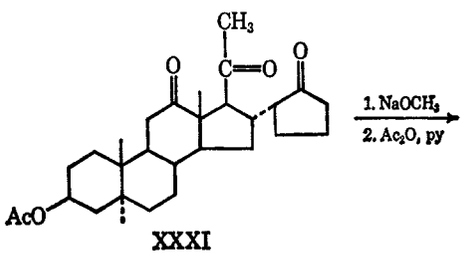
XXXIV



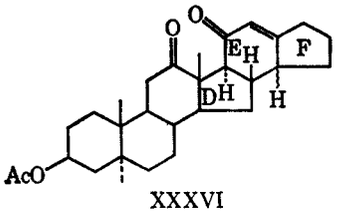
XXXV

the assigned structure. The stereochemistry is assigned on the same basis as described for XXXIII above.

Jones oxidation as described by Djerassi[22] gave the Δ^5-3-ketone which was not isolated, but was isomerized under basic conditions to XVIII, λ_{max} 240 mμ (ϵ 28,900). Cyclopentanone failed to react with I under mild conditions, but formed the Michael adduct XXXI when treated with III. Aldol cyclization of XXXI to XXXVI proceeded in poor yield presumably because of the ring strain involved in the fusion of a five-membered and a six-membered ring. The stereochemistry of the fusion of rings D and E is based on arguments previously



XXXI



XXXVI

(22) C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

cited. The fusion of rings E and F cannot be firmly predicted on the basis of the evidence at hand.

Experimental Section[23]

3β-Acetoxy-12β-hydroxy-12α-methyl-5α-pregn-16-en-20-one (VII).—To 119 ml of a 5.2% solution of methyllithium in ether was added dropwise with stirring a solution of 10.29 g of pseudohecogenin diacetate[5] in 200 ml of dry ether. The resulting mixture was stirred at room temperature for 48 hr and 300 ml of water and 200 ml of ethyl acetate were added. The phases were separated and the aqueous layer was extracted several times with an ether–ethyl acetate solution. After drying the combined organic extracts over sodium sulfate, evaporation of the solvent under reduced pressure gave 8 g of a colorless solid. The infrared spectrum shows a very weak carbonyl absorption.

This solid was dissolved in a solution of 30 ml of pyridine and 20 ml of acetic anhydride. After standing at room temperature overnight, the liquid was removed *in vacuo* to give 10.9 g of a glassy residue. This material was dissolved in methylene chloride and the solution was washed with successive portions of 10% hydrochloric acid solution, 10% sodium bicarbonate solution and water. After drying over anhydrous magnesium sulfate, the solvent was evaporated, leaving 10.1 g of a solid residue. The infrared spectrum of this material showed a weak hydroxyl band at 3600 cm^{-1} and a strong carbonyl absorption at 1720 cm^{-1}. To a stirred solution of 10 g of this material in 50 ml of ethylene dichloride and 50 ml of acetic acid at −5° was added dropwise a precooled solution of 5 g of chromium trioxide in 50 ml of 90% acetic acid. After the addition was complete, the solution was stirred at −5° for 1 hr and 50 ml of a 10% aqueous sodium metabisulfite solution was added. The temperature was maintained below 0° during the addition. The organic layer was separated, and the aqueous layer was extracted several times with methylene chloride. The combined extracts were washed with water and with sodium bicarbonate solution until neutral. After drying over sodium sulfate, evaporation of the solvent afforded 9.3 g of a green glass. The infrared spectrum shows a strong carbonyl absorption at 1730 cm^{-1} with a shoulder at 1700 cm^{-1}.

An 8-g sample of this residue was dissolved in 120 ml of glacial acetic acid and the solution was heated under reflux for 2 hr. The hot solution was poured into a large volume of water, and the resulting suspension was extracted several times with methylene chloride. The combined extracts were washed with water and with sodium bicarbonate solution until neutral. After drying, the solvent was removed *in vacuo* to give 6 g of a brown, glassy residue. This material was chromatographed on 300 g of activity III neutral alumina using a gradient elution system consisting of benzene and a solution of 10% ether in benzene. A fraction weighing 2.01 g crystallized from heptane to give 1.93 g of the desired product: mp 164–166; $[\alpha]D$ +40°; λ_{max} 242 mμ (ε 8250); $\nu_{max}^{CS_2}$ 3050, 1728, 1650, 1375, 1248, 1025, 822 cm^{-1}; nmr ($CDCl_3$) δ 0.87, 0.93, 1.16, 2.02, 2.37 (singlets, 3 H each), 4.71 (multiplet, 1 H), 6.97 (multiplet, 1 H).

Anal. Calcd for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 74.26; H, 9.73.

3β-Acetoxy-12-methylene-5α-pregn-16-en-20-one (VIII).—A solution of 1.5 g of VII in 60 ml of dry pyridine and 1.35 ml of phosphorus oxychloride was allowed to stand at room temperature overnight. The solution was cooled to 0° and 7.5 ml of water was added. After removal of the liquid under reduced pressure, water was added to the residue and the resulting suspension was extracted with several portions of ether. After washing with sodium bicarbonate solution and drying, the solvent was evaporated to give 1.25 g of a solid. Crystallization from 95% ethanol afforded 0.87 g of needles which melted at 151–155.5°. An analytical sample crystallized from 95% ethanol: mp 156–157°; $[\alpha]D$ +164°; λ_{max} 237 mμ (ε 7800); $\nu_{max}^{CS_2}$ 3085, 3045, 1728, 1670, 1245, 1030, 885, 822 cm^{-1}; nmr ($CDCl_3$) δ 0.90, 1.12, 2.02, 2.33 (singlets, 3 H each), 4.38, 4.63 (singlets, 1 H each), 4.60 (multiplet, 1 H), 4.05 (multiplet, 1 H), 6.75 (multiplet).

Anal. Calcd for $C_{24}H_{34}O_3$: C, 77.80; H, 9.25. Found: C, 77.49; H, 9.36.

3β-Acetoxy-12-ethylenedioxy-5α-pregn-16-en-20-one (XIV).—A mixture consisting of 10 g of III, 250 ml of benzene, 0.6 g of *p*-toluenesulfonic acid, and 40 ml of ethylene glycol was heated under reflux with vigorous stirring for 0.5 hr. The water formed was continuously removed with a Dean–Stark water trap. The two-phase mixture was cooled and washed with sodium bicarbonate solution and with water. After drying over magnesium sulfate, removal of the solvent *in vacuo* gave 12.5 g of a glassy residue. This material was dissolved in benzene and chromatographed on 200 g of Florisil. A fraction eluted with 5% ethyl acetate–95% benzene crystallized from isopropyl alcohol to give 8.1 g of crystals which melted at 131–134°. A pure sample was crystallized from the same solvent: mp 140–143°; $[\alpha]D$ +30°; λ_{max} 236 mμ (ε 7500); $\nu_{max}^{CS_2}$ 3050, 1730, 1680, 1365, 1245, 1075, 1032, 975, 822 cm^{-1}; nmr ($CDCl_3$) δ 0.85, 1.15, 2.02, 2.30 (singlets, 3 H each), 3.92 (singlet, 4 H), 4.68 (broad multiplet, 1 H), 6.55 (doublet, 1 H).

Anal. Calcd for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71. Found: C, 71.82; H, 8.75.

3β-Acetoxy-12α-hydroxy-5α-pregn-16-en-20-one (XII) and 3β-Acetoxy-12β-hydroxy-5α-pregn-16-en-20-one (IX).—To a solution of 20 g of dione III in 400 ml of tetrahydrofuran at 6° was added 16.4 g of lithium tri-*t*-butoxyaluminohydride. The resulting solution was maintained at 6–8° for 2 hr and 25 ml of saturated sodium sulfate solution was added slowly with stirring. This mixture was dried over anhydrous sodium sulfate and the solid was removed by filtration. The solvent was removed under reduced pressure to give 19.4 g of a colorless glass. Crystallization from 95% ethanol afforded 10.2 g of crystals, mp 212–217°. The infrared spectrum of this material was identical with that of an authentic sample of 3β-acetoxy-12β-hydroxy-5α-pregn-16-en-20-one. Concentration of the filtrate yielded an additional 2.4 g of crystals. A thin layer chromatogram (silica gel G–15% acetone, 85% benzene) indicated a mixture of two components. This mixture was chromatographed on 60 g of Florisil using a gradient elution system consisting of 500 ml of benzene and 500 ml of a 5% acetone–85% benzene solution. This procedure gave 0.72 g of IX and 1.6 g of a mixture.

Preparative thin layer chromatography of 0.2 g of this mixture on a silica gel plate (40 × 20 × 0.2 cm) eluted with a solution of 15% acetone in benzene afforded 0.081 g of IX. The second component crystallized from ether–petroleum ether (bp 30–60°) to give 0.093 g of pure 3β-acetoxy-12α-hydroxy-5α-pregn-16-en-20-one: mp 191.5–192.5°; $[\alpha]D$ +74°; λ_{max} 237.5 mμ (ε 8850); $\nu_{max}^{CS_2}$ 3610, 3057, 1735, 1663, 1365, 1245, 1030, 822; nmr ($CDCl_3$) δ 0.89 (singlet, 6 H), 2.30, 2.01 (singlets, 3 H each), 4.46 (triplet, 1 H), 4.70 (broad multiplet, 1 H) 6.76 (multiplet, 1 H).

Anal. Calcd for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.90; H, 9.17.

3β-Hydroxy-16α-cyanopregn-5-en-20-one (XX).—To 1 g of I in 50 ml of 95% ethanol was added 0.69 g of sodium cyanide. This mixture was refluxed for 1 hr and cooled to room temperature and the solvent was removed under reduced pressure. Water was added to the residue and the resulting suspension was extracted several times with dichloromethane. After drying over anhydrous sodium sulfate, the combined extracts were evaporated under reduced pressure to give 0.92 g of solid. This material was crystallized from ethyl acetate to give 0.65 g: mp 225–228° [a second crystallization from ethyl acetate raised the melting point to 230–232° (lit.[21b] mp 231–234°)]; $\nu_{max}^{CH_2Cl_2}$ 3600, 2245, 1710, 1362, 1048 cm^{-1}; nmr δ 0.60, 1.02, 2.22 (singlets, 3 H each), 3.53 (broad multiplet, 2 H), 5.36 (multiplet, 1 H).

3β-Acetoxy-16α-cyano-5α-pregnane-12,20-dione (XXI).—A mixture of 1 g of III, 0.72 g of sodium cyanide, and 50 ml of 95% ethanol was refluxed for 1 hr. After cooling, the solvent was removed *in vacuo* and water was added to the residue. This suspension was extracted with methylene chloride and the extracts were dried over anhydrous sodium sulfate. Removal of the solvent gave 0.92 g of a solid. This material was dissolved in a solution consisting of 2 ml of pyridine and 2 ml of acetic anhydride and allowed to stand at room temperature overnight. The liquid was removed *in vacuo* and the residue was dissolved in dichloromethane. This solution was washed with successive portions of dilute hydrochloric acid solution, dilute sodium bicarbonate and water. After drying over sodium sulfate, the solvent was removed and the residue was crystallized from methanol to give 0.72 g of crystals, mp 221–224°. A pure sample crystallized from methanol: mp 225–228°; $[\alpha]D$ +125°; $\nu_{max}^{CH_2Cl_2}$ 2246, 1728, 1710, 1370, 1270, 1030 cm^{-1}; nmr δ 0.90, 0.93, 2.04, 2.35 (singlets, 3 H each), 3.66 (multiplet, 2 H), 4.66 (multiplet, 1 H).

(23) Unless otherwise noted, all melting points were obtained on the Kofler hot stage, optical rotations in chloroform solution and ultraviolet spectra in methanol solution. Nmr spectra were obtained in deuteriochloroform solution using a Varian spectrometer operating at 60 Mc and calibrated against internal tetramethylsilane.

Anal. Calcd for $C_{24}H_{33}O_4N$: C, 72.15; H, 8.33. Found: C, 72.07; H, 8.23.

3β-Acetoxy-16α-(1′-aziridinyl)pregn-5-en-20-one (XXII).—A solution of 12 g of I in 100 ml of ethylenimine containing 2 ml of triethylamine was allowed to stand at room temperature overnight. The liquid was removed under reduced pressure and the residue was crystallized from ether to give 11.7 g of fine needles, mp 156–158°. A pure sample crystallized from ether: mp 158–159° (lit.[21e] mp 152–154°); $[\alpha]D$ −16°; $\nu_{max}^{CS_2}$ 3060, 1735, 1704, 1360, 1240, 1032 cm^{-1}; nmr δ 0.62, 1.02, 2.03, 2.20 (singlets, 3 H each), 4.67 (broad multiplet, 1 H), 5.45 (multiplet, 1 H).

Anal. Calcd for $C_{25}H_{37}NO_3$: C, 75.15; H, 9.33; N, 3.51. Found: C, 74.91; H, 9 34; N, 3.54.

3β-Acetoxy-16α-(1′-aziridinyl)-5α-pregnane-12,20-dione (XXIII).—A solution of 10 g of III in 100 ml of ethylenimine containing 2 ml of triethylamine was allowed to stand at room temperature for 2.5 hr. The liquid was removed *in vacuo* and the residue was crystallized from petroleum ether (bp 30–60°) to give 9.9 g, mp 141–144°. An analytical sample crystallized from ether: mp 146–148°; $[\alpha]D$ +104°; $\nu_{max}^{CS_2}$ 3059, 1735, 1709, 1245, 1035 cm^{-1}; nmr δ 0.92 (singlet, 6 H) 2.02, 2.36 (singlets, 3 H each), 3.47 (doublet, 1 H), 4.70 (broad multiplet, 1 H).

Anal. Calcd for $C_{25}H_{37}NO_4$: C, 72.25; H, 8.98; N, 3.37. Found: C, 72.43; H, 9.03; N, 3.59.

3β-Acetoxy-16α-thiobenzylpregn-5-en-20-one (XXIV).—A mixture of 1.0 g of I in 4 ml of freshly distilled tetrahydrofuran containing 2 ml of benzyl mercaptan and 0.2 ml of a 25% aqueous solution of tetraethylammonium hydroxide was heated under reflux for 1 hr. After cooling, the mixture was diluted with 10 ml of ether, washed with water and dried over anhydrous magnesium sulfate. Evaporation of the solvent afforded 1.3 g of a yellow glass. This residue was dissolved in benzene and percolated through 10 g of Florisil. The fractions eluted with 10% chloroform–90% benzene crystallized from ethanol to give 1.21 g, mp 123–126°. A pure sample had mp 126–127.5° (lit.[20a] mp 124–125°); $[\alpha]D$ −37°; $\nu_{max}^{CS_2}$ 3088, 3068, 3033, 1736, 1708, 1240, 1033, 835 cm^{-1}; nmr δ 0.62, 1.00, 2.01, 2.05 (singlets, 3 H each), 3.72 (singlet, 2 H), 4.63 (broad multiplet), 5.37 (multiplet, 1 H), 7.30 (singlet, 5 H).

Anal. Calcd for $C_{30}H_{40}O_2S$: C, 74.96; H, 8.39. Found: C, 75.12; H, 8.43.

3β-Acetoxy-16α-thiobenzyl-5α-pregnane-12,20-dione (XXV).—To a solution of III in 4 ml of tetrahydrofuran (freshly distilled from lithium aluminum hydride) was added 2 ml of benzyl mercaptan and 0.2 ml of a 25% aqueous solution of tetraethylammonium hydroxide. The resulting mixture was refluxed for 0.5 hr. The reaction mixture was cooled, diluted with 10 ml of ether and washed with dilute sodium hydroxide solution and with water. After the solution was dried over anhydrous magnesium sulfate, evaporation of the solvent yielded 1.6 g of a viscous oil. The residue was dissolved in benzene and chromatographed on 20 g of Florisil. The fractions eluted with 20% chloroform–80% benzene crystallized from 95% ethanol to give 1.12 g, mp 133–135°. An analytical sample had mp 138.5–139.5°; $[\alpha]D$ +64°; $\nu_{max}^{CS_2}$ 3090, 3068, 3033, 1735, 1708, 1230, 1025, 688 cm^{-1}; nmr δ 0.90 (singlet, 6 H), 2.02, 2.26 (singlets, 3 H each), 3.71 (singlet, 2 H), 4.70 (broad multiplet, 1 H), 7.31 (singlet, 5 H).

Anal. Calcd for $C_{30}H_{40}O_4S$: C, 72.54; H, 8.12. Found: C, 72.72; H, 8.12.

3β-Acetoxy-16α-nitromethyl-5α-pregnane-12,20-dione (XXVI).—A mixture of 1 g of III, 2 ml of nitromethane and 0.2 ml of a 1 *M* aqueous solution of tetrabutylammonium hydroxide in 4 ml of tetrahydrofuran was refluxed for 1.5 hr. The reaction was worked up in the usual manner to give 0.928 g of a glassy residue. This material was crystallized from ethanol to give 0.816 g, mp 166–169°. A pure sample had mp 170–171°; $[\alpha]D$ +97°; $\nu_{max}^{CS_2}$ 1722, 1710, 1702, 1550, 1357, 1223, 1028, 1020 cm^{-1}; nmr δ 0.93, 1.00, 2.02, 2.30 (singlets, 3 H each), 3.24 (multiplet, 1 H).

Anal. Calcd for $C_{24}H_{35}NO_6$: C, 66.49; H, 8.14. Found: C, 66.28; H, 8.11.

3β-Acetoxy-16α-(1′-nitroethyl)-5α-pregnane-12,20-dione (XXVII).—To 1 g of III in 4 ml of tetrahydrofuran was added 2 ml of nitroethane and 0.2 ml of a 25% aqueous solution of tetraethylammonium hydroxide. After refluxing for 3 hr, the usual work-up provided 0.96 g of residue. This material was dissolved in benzene and chromatographed on Florisil (20 g). The material eluted with 10% ether–90% benzene crystallized from 95% ethanol to give 0.65 g, mp 126–130°. Concentration of the mother liquor afforded an additional 0.09 g, mp 120–128°. Crystallization from 95% ethanol provided a pure sample: mp 139–141.5°; $[\alpha]D$ +127°; $\nu_{max}^{CS_2}$ 1732, 1705, 1543, 1353, 1224, 1023 cm^{-1}; nmr δ 0.95, 0.97, 2.03, 2.34 (singlets, 3 H each), 1.42 (doublet), 3.30 (multiplet, 2 H), 4.58 (broad multiplet, 1 H).

Anal. Calcd for $C_{26}H_{37}NO_6$: C, 67.09; H, 8.33. Found: C, 67.31; H, 8.19.

3β-Acetoxy-16α-diacetylmethyl-5α-pregnane-12,20-dione (XXVIII).—A mixture of 5 g of III in 20 ml of tetrahydrofuran, 10 ml of acetylacetone and 1 ml of a 1 *M* aqueous solution of tetrabutylammonium hydroxide was refluxed for 3 hr. The usual work-up followed by crystallization from ethanol afforded 4.1 g of crystals mp 161–164°. A pure sample had mp 166–167.5°; $[\alpha]D$ +141°; $\nu_{max}^{CS_2}$ 1737, 1709, 1362, 1242, 1030 cm^{-1}; nmr δ 0.92, 0.95, 2.03, 2.10, 2.15, 2.23 (singlets, 3 H each), 3.37 (multiplet, 3 H), 4.67 (broad multiplet, 1 H).

Anal. Calcd for $C_{28}H_{40}O_6$: C, 71.16; H, 8.53. Found: C, 71.29; H, 8.72.

3β-Acetoxy-16α-(α-carbethoxycyanomethyl)-5α-pregnane-12,20-dione (XXIX).—To 1 g of III in 4 ml of tetrahydrofuran was added 2 ml of ethyl cyanoacetate and 0.2 ml of a 25% aqueous solution of tetraethylammonium hydroxide. After refluxing for 3 hr, the mixture was worked up in the usual manner to give 1.2 g of a syrup. Crystallization from ethanol afforded 0.97 g of crystals, mp 172–176°. An analytical sample had mp 177–179°; $[\alpha]D$ +105°; $\nu_{max}^{CH_2Cl_2}$ 1740, 1712, 1242, 1030 cm^{-1}; nmr δ 0.93, 0.95, 2.02, 2.33 (singlets, 3 H each), 1.30 (triplet, 3 H), 3.50 (doublet + broad multiplet, 2 H), 4.18 (quartet, 2 H), 4.71 (broad multiplet, 1 H).

Anal. Calcd for $C_{28}H_{39}NO_6$: C, 69.25; H, 8.10. Found: C, 69.57; H, 8.35.

3β-Acetoxy-16α-(2′-oxocyclohexyl)-5α-pregnane-12,20-dione (XXX).—A mixture of 15 g of III in 60 ml of tetrahydrofuran, 30 ml of cyclohexanone and 6 ml of a 25% aqueous solution of tetraethylammonium hydroxide was refluxed for 2.5 hr. After the standard work-up procedure, the residue was chromatographed on Florisil (300 g). The material eluted with 20% ethyl acetate–80% benzene crystallized from 95% ethanol to give 12.6 g of crystals, mp 175–179°. Recrystallization from 95% ethanol afforded a pure sample: mp 181–183.5°; $[\alpha]D$ +83°; $\nu_{max}^{CS_2}$ 1735, 1708, 1230, 1023 cm^{-1}.

Anal. Calcd for $C_{29}H_{42}O_5$: C, 74.01; H, 9.00. Found: C, 74.13; H, 8.95.

3β-Acetoxy-16α-(2′-oxocyclopentyl)-5α-pregnane-12,20-dione (XXXI).—A solution of 15 g of III in 60 ml of freshly distilled tetrahydrofuran containing 30 ml of cyclopentanone and 6 ml of an aqueous 25% tetraethylammonium hydroxide solution was heated under reflux for 1.5 hr. After the standard work-up, the syrupy residue was chromatographed on 300 g of Florisil. The fractions eluted with 10% ethyl acetate–90% benzene crystallized from ethanol to give 10.1 g of material which melted at 167–170°. A pure sample was crystallized from ethanol: mp 172–174°; $[\alpha]D$ +115°; $\nu_{max}^{CS_2}$ 1735, 1705, 1238, 1028 cm^{-1}; nmr δ 0.93 (singlet, 6 H), 2.02, 2.35 (singlets, 3 H each), 4.72 (broad multiplet, 1 H).

Anal. Calcd for $C_{28}H_{40}O_5$: C, 73.56; H, 8.83. Found: C, 73.56; H, 8.75.

3β-Hydroxy-16α-nitromethylpregn-5-en-20-one (XXXII).—To 5 g of 3β-hydroxypregn-5,16-dien-20-one dissolved in 100 ml of *t*-butyl alcohol was added 0.9 g of potassium *t*-butoxide and 10 ml of nitromethane. The resulting mixture was maintained at 50° overnight and poured into 500 ml of water with stirring. The precipitated solid was removed by filtration and dried *in vacuo*. A cream colored solid (5 g) was obtained which crystallized from 95% ethanol to give 3.3 g of crystals, mp 219–223°. Concentration of the mother liquor afforded 0.9 g of crystals, mp 217–221°. Several crystallizations from 95% ethanol provided an analytical sample: mp 226–229°; $[\alpha]D$ +21°; $\nu_{max}^{CH_2Cl_2}$ 3600, 1706, 1550, 1370, 1049 cm^{-1}; nmr δ 0.70, 1.03, 2.16 (singlets, 3 H each), 3.44 (broad multiplet, 2 H), 4.31 (doublet, 2 H), 5.39 (multiplet, 1 H).

Anal. Calcd for $C_{22}H_{33}O_4N$: C, 70.37; H, 8.86. Found: C, 70.42; H, 8.79.

3β-Acetoxy-1′,2′-tetramethylene-16β,17α,5α-[16,17-butano-androst-2′-ene]-4′,12-dione (XXXIII).—A mixture of 1 g of XXX in 10 ml of dry benzene and 0.27 g of sodium methoxide was refluxed for 1.5 hr using a water removal trap. After cooling, the solution was washed several times with water, dried over magnesium sulfate and evaporated under reduced pressure. The residue refluxed in 5 ml of acetic anhydride for 0.5 hr and the solution was poured into a large volume of water with stirring. The resulting suspension was extracted several times with ether

and the extracts were evaporated to dryness *in vacuo*. Trituration of the residue with 95% ethanol afforded 0.66 g of crystals, mp 242–244°. A pure sample was crystallized from methanol: mp 242.5–244°; $[\alpha]D$ +140°; λ_{max} 239 mμ (ε 14,000); $\nu_{max}^{CS_2}$ 3025, 1735, 1712, 1685 cm^{-1}; nmr δ 0.92, 1.20, 2.00 (singlets, 3 H each), 4.72 (broad multiplet, 1 H), 5.73 (singlet, 1 H).

Anal. Calcd for $C_{29}H_{40}O_4$: C, 76.95; H, 8.91. Found: C, 77.09; H, 8.95.

3β-Hydroxy-1′,2′-tetramethylene-16β,17α-[16,17-butanoandrosta-2′,5-dien]-4′-one (XXXIV).—To a solution of 1 g of 3β-hydroxypregn-5,16-dien-20-one in 25 ml of dry *t*-butyl alcohol containing 0.896 g of potassium *t*-butoxide was added 2 ml of cyclohexanone. After 15 min crystals began to form. After standing for 1.5 hr, the mixture was poured into a large volume of water with stirring. The resulting precipitate was removed by filtration and dried *in vacuo* giving 1.14 g of powder. This material was percolated through 5 g of Florisil. A fraction eluted with 5% ethyl acetate in chloroform crystallized from methanol to give 0.71 g of tiny plates, mp 230–232°. A pure sample prepared by vacuum sublimation at 210–215° (0.02 mm) had mp 238–240°; $[\alpha]D$ −7°; λ_{max} 239 mμ (14,000); $\nu_{max}^{CH_2Cl_2}$ 3600, 1670, 1605, 1040, 835 cm^{-1}; nmr δ 0.88, 1.05 (singlets, 3 H each), 3.49 (broad multiplet, 1 H), 5.35 (multiplet, 1 H), 5.70 (singlet, 1 H); *m/e* 394.2859 (calcd 394.2872).

Anal. Calcd for $C_{27}H_{38}O_2$: C, 82.18; H, 9.71. Found: C, 81.65; H, 9.74.

1′,2′-Tetramethylene-16β,17α-[16,17-butanoandrosta-2′,4-diene]-3,4′-dione (XXXV).—To a solution of 8 g of XXXIV in 500 ml of acetone at 10° was added with stirring 7.85 ml of a standard chromium trioxide reagent.[22] Nitrogen was bubbled through all solutions before and during the reaction. After 5 min the reaction mixture was diluted with 2500 ml of water and the resulting precipitate was filtered and dried to give 7.6 g of a white powder. The crude product was dissolved in 600 ml of warm methanol and 10 drops of 10% potassium hydroxide solution was added. This solution was heated on a steam bath for 10 min and neutralized with acetic acid. Concentration of this solution gave 6.5 g of crystals: mp 249–253°; $[\alpha]D$ +82°; λ_{max} 240 mμ (ε 28,900); $\nu_{max}^{CS_2}$ 3025, 1675, 1195, 860, 832 cm^{-1}; nmr δ 0.92, 1.22 (singlets, 3 H each), 5.74 (singlet, 2 H).

Anal. Calcd for $C_{27}H_{36}O_2$: C, 82.60; H, 9.24. Found: C, 82.36; H, 9.17.

3β-Acetoxy-1′,2′-trimethylene-5α,16β,17α-[16,17-butanoandrost-2′-ene]-4′,12-dione (XXXVI).—A mixture of 20 g of XXXI and 5.8 g of sodium methoxide in 200 ml of benzene was refluxed with stirring for 2 hr. The water formed was continuously removed using a Dean–Stark water trap. The mixture was cooled and the insoluble material was removed by filtration. The infrared spectrum of this material shows only saturated ketone absorption. The filtrate was evaporated to give 6.5 g of a syrupy residue. This material was refluxed in 30 ml of acetic anhydride for 2 hr and the liquid was removed *in vacuo*. The residue crystallized from methanol to give 5.4 g of crystals, mp 244–248°. A pure sample was prepared by vacuum sublimation at 215–220° (0.02 mm): mp 249–251°; $[\alpha]D$ +128°; λ_{max} 240 mμ (ε 13,800); $\nu_{max}^{CS_2}$ 3035, 1737, 1715, 1674, 1240, 1030 cm^{-1}; nmr δ 0.97, 1.19, 2.02 (singlets, 3 H each), 4.68 (broad multiplet, 1 H), 5.86 (singlet, 1 H); *m/e* 438.2767 (calcd 438.2769).

Anal. Calcd for $C_{28}H_{38}O_4$: C, 76.67; H, 8.73. Found: C, 76.25, H, 8.66.

Registry No.—I, 979-02-2; III, 2611-38-3; VII, 19459-49-5; VIII, 19459-50-8; IX, 6384-56-1; X, 18267-02-2; XI, 2724-68-7; XII, 19459-54-2; XIII, 1169-20-6; XIV, 19459-56-4; XX, 1434-54-4; XXI, 19459-58-6; XXII, 19459-59-7; XXIII, 19459-60-0; XXIV, 19459-61-1; XXV, 19459-62-2; XXVI, 19459-63-3; XXVII, 19459-64-4; XXVIII, 6953-90-8; XXIX, 19459-66-6; XXX, 19459-67-7; XXXI, 19459-68-8; XXXII, 19459-69-6; XXXIII, 19459-70-2; XXXIV, 19459-19-9; XXXV, 19459-20-2; XXXVI, 19459-21-3.

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16-Oxa Steroid. Synthesis and Structural Assignment

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A relatively simple procedure for the opening of ring D followed by the removal of C-16 was utilized for the synthesis of 16-oxa steroids.

The study of the effects of structural modifications of natural steriod hormones upon the biological activities has received considerable attention in the last few years and has led to a number of highly active synthetic modifications. Two recent publications[1,2] on the synthesis of 16-oxa steroid prompts us to report our work on the preparation of some of these compounds. In contrast to previous methods our procedure is stereospecific, consists of fewer steps and gives a higher yield. Moreover, one of the key intermediates (**3b**) in our synthetic project could be utilized in the synthesis of variety of heterocyclic steroids including D-nor oxa[3] and D-nor aza steroids.

The starting material in our synthesis is 3β-hydroxy-16,17-seco-16-norandrostan-15-(2′-indoxyliden)-17-oic acid (**2a**) which was obtained in 80% yield by allowing 3β-acetoxy-5α-androstan-17-one (**1**) to react with *o*-nitrobenzaldehyde, following essentially Hassner's procedure[4] (Scheme I).

Oxidation of methyl 3β-acetoxy-16,17-seco-16-norandrostan-15-(2′-indoxyliden)-17-oate (**2b**) with chromium trioxide in acetic acid at room temperature for 16 hr yielded 3β-hydroxy-15,17-seco-D-norandrostane-15,17-dioic acid 17-methyl ester (**3a**) in 75% yield. The compound on acetylation with acetic anhydride and pyridine gave the corresponding acetate **3b**. 3β-Acetoxy-15,17-seco-D-norandrostane-15,17-dioic acid 17-methyl ester, on treatment with diazomethane, gave the corresponding methyl ester **4**. The α configuration and the axial conformation of the 14 hydrogen in compounds **3a**, **3b**, and **4** is based on the observation of a doublet center around δ 2.5 in the nmr spectrum having a *coupling constant of 10.5 cps* which is characteristic of *trans-diaxial hydrogens*.

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