3-Methoxy-19-norpregna-1,3,5(10)-trien-21-al (7d).—Unsaturated aldehyde **4d** (2 g) was shaken with 0.2 g of 5% palladium on charcoal in 600 ml of ethanol in an atmosphere of hydrogen at room temperature for 1 hr. Concentration of the filtrates following removal of catalyst and recrystallization from benzene–methylcyclohexane afforded pure **7d** in 75% yield: mp 110–112.5°; $[\alpha]D$ +69°; ir (KBr) 3.65, 5.79 μ; nmr 38 (18 H), and 590 Hz (t, J = 2.5 Hz, CHO).

Anal. Calcd for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.49; H, 9.18.

Catalytic Effect of Cuprous Ion.—When **1a** was refluxed with 10 mol % of cuprous cyanide in dimethylformamide for 2 hr and the reaction mixture concentrated and chromatographed over silica, the only crystalline product isolated was 17-ethynylandrosta-5,16-dien-3β-ol acetate, **8a**: mp 174–176°; $[\alpha]D$ −68° {lit.[19] mp 174°, $[\alpha]D$ −64.2° (di)}.

Registry No.—**2a**, 16934-40-0; **2b**, 16934-41-1; **2d**, 16934-42-2; **2f**, 16934-43-3; **2g**, 16960-05-7; **3a**, 16934-44-4; **3b**, 16934-45-5; **3c**, 16934-46-6; **3d**, 16934-47-7; **4a**, 16934-48-8; **4c**, 16934-49-9; **4d**, 16934-50-2; **4f**, 16934-51-3; **6a**, 16934-52-4; **6c**, 16934-53-5; **7a**, 16934-54-6; **7d**, 16934-55-7.

Carbon 1–Carbon 11 Interactions in Some Oxygenated 5β-Pregnanes and Androstanes[1]

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5β-Androstane-1,3,11,17-tetrone (**3**), 5β-androstane-1,3,17-trione (**6**), 5α-androstane-1,3,17-trione, and 25α_F-5α-spirostane-1,3-dione have been compared with regard to degree of enolization in methanol and dioxane solution and in KBr dispersion. In contrast to the normal behavior of the 11-deoxy-β diketones, the 11-keto-β diketone **3** is but half-enolized even in methanol solution, and is largely or wholly ketonized in less polar solvents. From an examination of the ratio of the enol methyl ethers prepared from each β diketone, it was shown that the tetrone **3** enolizes chiefly to the 1-hydroxy form **7**. Additional examples of 1,11 interaction include the observations that the two 1,11 diketones **26** and **28** are resistant to metal hydride or catalytic reduction, and that the chromic anhydride–pyridine oxidation of 5β-androstane- or 5β-pregnane-1β,3α-diols in the 11-deoxy series furnishes only the 1-keto-3α-ols, whereas similar oxidation of the corresponding 11-keto-1β,3α-diols also affords appreciable amounts of the 3-keto-1β-ols. These results are variously attributed to conformational distortion, hydrogen bonding, or polarization of keto groups.

In an earlier publication[2] we described the isolation from urine of 1β,3α,17α,20β,21-pentahydroxy-5β-pregnan-11-one (**1**, Scheme I) following the administration of 3α,17α,20β,21-tetrahydroxy-5β-pregnan-11-one (β-cortolone, a known metabolite of cortisol in man) to the senior author. The position of the metabolically introduced hydroxyl group in **1** was established by degrading it to the known 5β-androst-1-ene-3,11,17-trione; its configuration was determined primarily from the nuclear magnetic resonance (nmr) spectrum of a second degradation product, namely 1β-hydroxy-3α-acetoxy-5β-androstane-11,17-dione. In this paper the preparation of additional derivatives and degradation products of this metabolite, the partial synthesis of some related steroids, and evidence for the occurrence of various types of 1,11 interaction among certain of these compounds are described.

Oxidative cleavage of the side chain of **1** with sodium periodate[2] followed by further oxidation of the 17-keto steroid **2** thus obtained by Jones' method[3] gave the β diketone, 5β-androstane-1,3,11,17-tetrone (**3**). This product crystallized readily, analyzed correctly, and was chromatographically homogeneous, but its extinction coefficient in methanol (ϵ 6400 at 256 mμ) was only about half the value for the corresponding 11-deoxy-β diketone, namely 5β-androstane-1,3,17-trione [**6**, Scheme I, λ_{max} 258 mμ (ϵ 12,650)].[4] The latter was prepared from **1** *via* **4** and **5** by the sequence outlined in Scheme I.[2]

In view of this observation, we examined in detail the ultraviolet (uv) and infrared (ir) spectra of the tetrone **3** and the trione **6** as well as two β diketones in the 5α series.[5] Table I gives the λ_{max} values and extinction coefficients (ϵ) of these β diketones in neutral and alkaline methanol and in dioxane solution, and their principal bands in the infrared region. The tetrone **3**, which is highly enolized in alkaline methanol, is, like 5α-cholestane-1,3-dione and 25α_F-5α-spirostane-1,3-dione, largely ketonized in dioxane solution and wholly so in KBr dispersion. In contrast, the trione **6** and its 5 epimer are as fully enolized in dioxane solution and in KBr dispersion as they are in methanol.

Tamm and Albrecht[6] attributed the unusual stability of the keto form of 5α-cholestane-1,3-dione in KBr dis-

(1) Supported in part by a research grant, AM 01255, from the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, U. S. Public Health Service.

(2) J. J. Schneider and N. S. Bhacca, *J. Biol. Chem.*, **241**, 5313 (1966).

(3) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

(4) Professor Ch. Tamm and his associates have prepared a number of 11-deoxy-1,3-diketo-5β steroids derived from sapogenins and cardenolides as well as members of the androstane and pregnane series. Their extinction coefficients at 256–257 mμ in ethanol ranged from 15,500 to 15,900 with a mean value of 15,700. We wish to thank Professor Tamm for supplying us with these data prior to publication as well as for samples of 5α-cholestane-1,3-dione and the enol methyl ethers derived from it.

(5) 5α-Androstane-1,3,17-trione was prepared from 5α-androstan-3β-ol-17-one (isoandrosterone) and 25α_F-5α-spirostane-1,3-dione from ruscogenin (see Experimental Section).

(6) Ch. Tamm and R. Albrecht, *Helv. Chim. Acta*, **43**, 768 (1960).

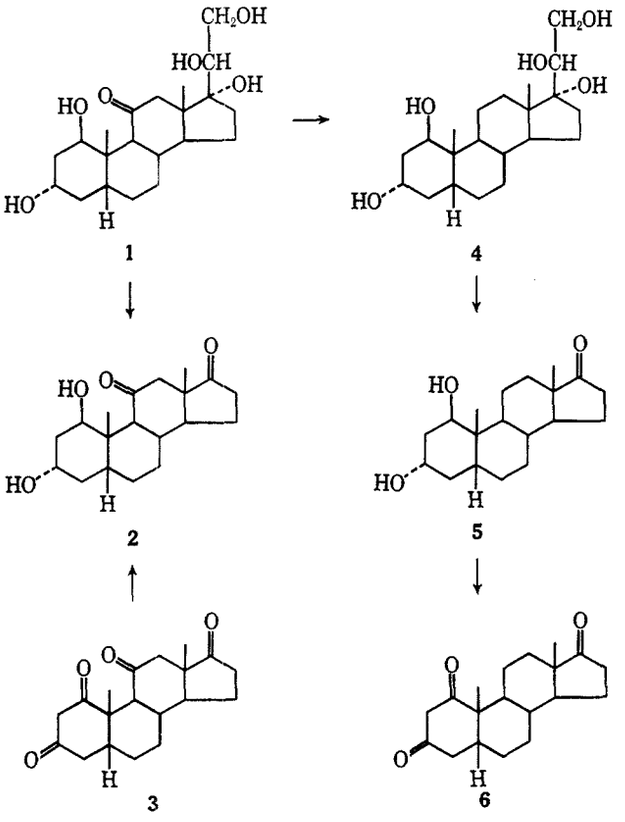
TABLE I

STEROIDAL β DIKETONES. PRINCIPAL BANDS IN ULTRAVIOLET AND INFRARED SPECTRA

Compound	λ_{max} mμ (ε) Methanol	λ_{max} mμ (ε) Alkaline methanol[a]	λ_{max} mμ (ε) Dioxane	Associated OH stretching band[b]	Associated C=O plus C=C stretching bands[c]
5β-Androstane-1,3,11,17-tetrone (3)	256 (6,400)	284 (20,700)	246 (2,050)	Absent	Absent
5β-Androstane-1,3,17-trione (6)	258 (12,650)	282 (25,500)	245 (12,500)	Strong	Strong
5α-Androstane-1,3,17-trione	255 (11,900)	284 (23,400)	245 (11,000)	Strong	Strong
25α_F-5α-Spirostane-1,3-dione	255 (12,000)	284 (24,300)	243 (1,650)	Absent	Absent
25α_F-Spirost-5-ene-1,3-dione[d]	256 (12,900)	283 (23,400)			
5α-Cholestane-1,3-dione[e]	255 (12,600)	285 (27,540)	301 (76)	Absent	Absent

[a] One milliliter of 1 *N* aqueous sodium hydroxide diluted to 100 ml with methanol. [b] 2750–2200 cm^{-1} (KBr dispersion). [c] 1680–1500 cm^{-1} (KBr dispersion). [d] C. W. Shoppee, R. E. Lack, and B. C. Newman, *J. Chem. Soc.*, 339 (1967) (neutral and alkaline ethanol). [e] Tamm and Albrecht[6] (neutral and alkaline ethanol).

SCHEME I



persion chiefly to the formation of an intramolecular hydrogen bridge between the 11α-hydrogen atom and the carbonyl group at C-1 which serves to impede enolization of the latter. It is to be noted, from Table I, that, although 5α-androstane-1,3,17-trione has the same structure as 25α_F-5α-spirostane-1,3-dione and 5α-cholestane-1,3-dione with regard to rings A, B, and C, it differs from them in being highly enolized in dioxane solution and in KBr dispersion. It may be suggested, as an alternative to Professor Tamm's proposal, that the suppression of enolization of 25α_F-5α-spirostane-1,3-dione and of 5α-cholestane-1,3-dione in nonpolar solvents may be due to a long-range effect of the side chain.

The limited enolization of the tetrone **3**, particularly in methanol solution, cannot be ascribed to the *cis* nature of the A/B ring juncture since the 5α- and 5β-11-deoxy-β diketones are equally enolized in various solvents. It seems probable that the aberrant enolization of the tetrone **3** is a consequence of marked conformational distortion of the ring system. The contrasting properties of the tetrone **3** and the trione **6** with respect to degree of enolization also were observed in their circular dichroism (CD) curves and by paper chromatographic means (*vide infra*).

Having established, from its extinction coefficient in methanol, that the tetrone **3** is but half-enolized even in polar solvents, it seemed of interest to determine the relative abundance of its two enolic forms (**7** and **8** in Scheme II). Two considerations make it certain that the 1-hydroxy-1-ene form **7** predominates. First, its formation would be promoted by the stabilizing influence of hydrogen bonding as depicted by **9**. The nmr spectrum of **3** is compatible with this view.[7] Second, the ratio of the enol methyl ethers (**10** and **11**) derived from **3** supports this conclusion. Tamm[8] found that the ratio of the 1-methoxy to the 3-methoxy derivative, obtained on treating 5α-cholestane-1,3-dione with diazomethane, was 0.76. This ratio corresponds reasonably well with the ratios of 0.94 and 0.85 which we noted for the corresponding ethers derived from 11-deoxy-β diketone **6** (**12** and **13**) and from 5α-androstane-1,3,17-trione (**14** and **15**), respectively, but contrasts with the ratio of 1.66 which we obtained in the case of 11-keto-β diketone **3**. Assuming, with Tamm, that the ratio of the enol methyl ethers isolated fairly approximates the ratio of the two enol forms present under the conditions of etherification, it follows that the principal enol in equilibrium with the tetrone **3** must be the 1-hydroxy derivative **7**. It is thus evident that the carbonyl group C-11 controls the *direction* of enolization, presumably through the agency of intramolecular hydrogen bonding, but it is not apparent by what mechanism it contributes to the observed *limit* of enolization.

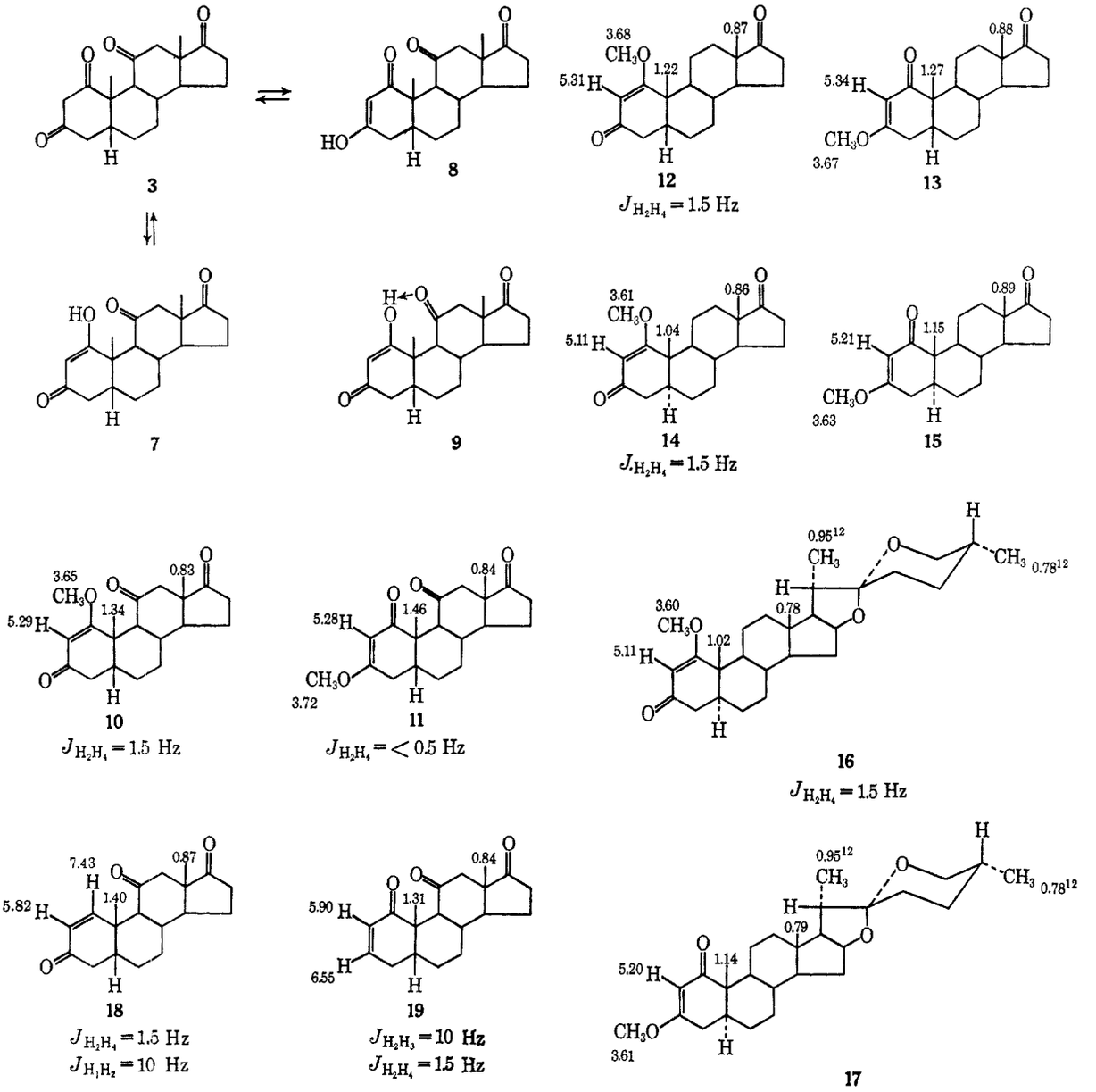
Nmr Spectroscopy Studies.—Proof of structure of the eight enol methyl ethers prepared in this study (Scheme II) required differentiating between individual members of the four pairs. The structures of the 11-keto enol methyl ethers **10** and **11** were distinguished by comparing their spectra with those derived from the unsaturated triketones **18** and **19**.[9] The distinction was made by examination of the nmr patterns caused by the proton α to the carbonyl function in the two ethers. The resonance pattern for H-2 appears as a pair of triplets in the spectrum of **19**. The large splitting of 10 Hz is caused by the interaction of this proton with H-3, whereas the smaller splittings of 1.5 Hz are due to long-range interactions of the C-4 methylene

(7) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry: Illustrations from the Steroid Field," Holden-Day, Inc., San Francisco, Calif., 1964, p 95.

(8) Ch. Tamm, *Helv. Chim. Acta*, **43**, 1700 (1960).

(9) The coupling constants and chemical shifts for **18** and **19** are given in Figure 7 of an earlier paper[2] and are reproduced here in order to facilitate comparisons.

SCHEME II



hydrogens with H-2. Since H-3 (the proton β to the carbonyl function) is replaced by a methoxyl group in **11**, the large splitting of 10 Hz in the resonance of H-2 (the proton α to the carbonyl group) disappears. Furthermore, the smaller couplings of 1.5 Hz due to interaction of H-2 with the methylene hydrogens which was discernible in **19** becomes much smaller in **11** owing to the presence of the methoxyl group at C-3. Thus H-2, which is α to the carbonyl group in **11**, appears as a broad singlet.

The nmr pattern for the proton α to the carbonyl function in **18** (H-2) occurs as a pair of doublets. The large coupling of 10 Hz is attributed to coupling with the β hydrogen (H-1). The smaller splitting of 1.5 Hz is due to long-range coupling[10] of H-2 through the carbonyl group to one of the methylene hydrogens at C-4. This small, very characteristic, coupling is present in the spectrum of **10** and also was observed in the spectra of the 11-deoxy ethers **12**, **14**, and **16**. This makes it possible to distinguish the various ethers in this series.

(10) See ref 7, pp 121–123.

The chemical shifts of C-19 methyl resonances in **18** and **19** are at variance with those of the 11-keto ethers **10** and **11**. This is due to a very unusual dipole–dipole interaction[11] between the C-1 and C-11 carbonyl groups. A detailed analysis of this interaction will be submitted for publication at a later date.

In Table II we have correlated the assigned structures of the eight enol methyl ethers with their absorption characteristics in the ultraviolet and infrared regions and their mobilities in four representative chromatographic systems. The two enol methyl ethers prepared from 5α-cholestane-1,3-dione by Tamm are included for comparison; their structures were determined by chemical means.

These data are in accord with and support the structure assignments. Thus the higher λ_{max} values and larger extinction coefficients for the 1-methoxy member

(11) (a) R. F. Zürcher, *Helv. Chim. Acta*, **46**, 2054 (1963); (b) see ref 7, pp 26, 27.

(12) K. Tori and K. Aono, *Ann. Rept. Shionogi Res. Lab.*, No. 14, 136 (1964).

TABLE II

STEROIDAL ENOL METHYL ETHERS. CORRELATION OF NMR STRUCTURE ASSIGNMENTS WITH OBSERVED CONSTANTS

No.	Nmr designation	Ultraviolet absorption[a] λ_{max}, mμ (ϵ)	Infrared maxima, cm^{-1}, for CH$_3$O—C=C—C=O system[b]		R_f in system[c] 1	2	3	4
10	1-Methoxy-5β-androst-1-ene-3,11,17-trione	258 (14,850)	1582	1638	0.18	0.17	0.08	
11	3-Methoxy-5β-androst-2-ene-1,11,17-trione	250 (12,430)	1619	1655	0.12	0.11	0.18	
12	1-Methoxy-5β-androst-1-ene-3,17-dione	254 (16,300)	1590	1655	0.72	0.56	0.19	
13	3-Methoxy-5β-androst-2-ene-1,17-dione	250 (14,700)	1619	1642	0.84	0.72	0.39	
14	1-Methoxy-5α-androst-1-ene-3,17-dione	255 (15,400)	1570	1648	0.66	0.50	0.19	
15	3-Methoxy-5α-androst-2-ene-1,17-dione	248 (13,030)	1616	1650	0.86	0.76	0.47	
16	1-Methoxy-25α_F-5α-spirost-1-en-3-one	256 (16,770)	1575	1652				0.11
17	3-Methoxy-25α_F-5α-spirost-2-en-1-one	248 (14,670)	1615	1660				0.38
	1-Methoxy-5α-cholest-1-en-3-one	242 (15,850)	1581	1655				0.18
	3-Methoxy-5α-cholest-2-en-1-one	237 (14,500)	1618	1658				0.48

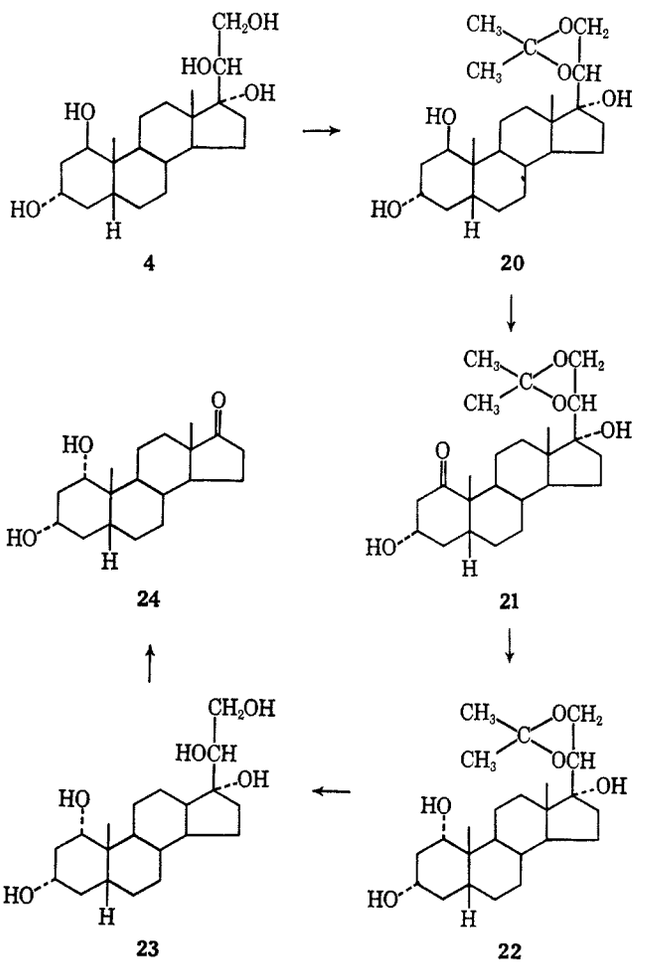
[a] Ultraviolet absorption spectra were obtained in methanol solution. [b] Infrared spectra were obtained in KBr dispersion; C=C stretching bands are in left column and C=O stretching bands in right column. [c] The composition of chromatographic systems referred to by number in this table and in the text appear in Table IV.

of each pair reflect the known differences between the 3-keto-1-ene and 1-keto-2-ene systems.[13] The feature of the infrared spectra useful in this connection is that the C=C stretching bands for the 3-methoxyl derivatives, including that prepared by Tamm, uniformly occur at significantly higher frequencies than is the case for the 1-methoxy forms. This relationship is not evident in the C=O stretching bands.

Partial Synthesis of 5β-Pregnane-1α,3α,17α,20β,21-pentol and of 1α,3α-Dihydroxy-5β-androstan-17-one.—Preparation of the 1 epimers of **1** and of **4** seemed straightforward since oxidation of the 1β,3α-diol (a, e) system under mild conditions would give the 1 ketone predominantly, which on reduction with sodium borohydride would furnish chiefly the more stable α (equatorial) alcohol. The route employed in the 11-deoxy series is outlined in Scheme III. Treatment of **4** with *p*-toluenesulfonic acid in acetone[14] furnished the 20,21-acetonide **20** in good yield, which on oxidation with chromic anhydride in pyridine,[15] reduction with sodium borohydride, and hydrolysis with aqueous acetic acid[16] gave successively the 1-ketoacetonide **21**, the 1α,3α,17α-trihydroxyacetonide **22**, and a product (**23**) which was assigned the structure 5β-pregnane-1α,3α,17α,20β,21-pentol, the 1 epimer of **4**. Sodium periodate oxidation of the pentol **23** provided 1α,3α-dihydroxy-5β-androstan-17-one (**24**), the 1 epimer of **5**.

Similarly, **1** gave a high-melting acetonide (**25**, Scheme IV) in excellent yield. Oxidation of this derivative as above furnished mainly 3α,17α-dihydroxy-20,21-isopropylidenedioxy-5β-pregnane-1,11-dione (**26**), which readily was converted into the unsaturated diketoacetonide **27** by acetylation followed by percolation through neutral alumina.[2] Hydrolysis of the diketoacetonide **26** as above furnished 3α,17α,20β,21-tetrahydroxy-5β-pregnane-1,11-dione (**28**), which on oxidation with sodium periodate provided the known[2] 3α-hydroxy-5β-androstane-1,11,17-trione (**29**). Treatment of the unsaturated diketoacetonide **27** with aqueous acetic acid followed by oxidation of the free compound with sodium periodate gave the known[2] 5β-androst-2-ene-1,11,17-trione (**30**).

SCHEME III



The aim then was to reduce selectively the C-1 carbonyl group of **26** and of **28** with sodium borohydride, using conditions where the C-11 carbonyl group would not be reduced, as in the preparation of 3α,17α,20β,-21-tetrahydroxy-5β-pregnan-11-one from 3α,17α,21-trihydroxy-5β-pregnane-11,20-dione.[2] Reduction did not occur under these conditions as judged by the fact that no substances more polar (less mobile) than **26** or **28** could be detected when the recovered neutral fractions were examined by paper chromatography. Subsequent trials showed that these two ketones were largely unaffected by even vigorous reducing agents such as lithium aluminum hydride (prolonged refluxing

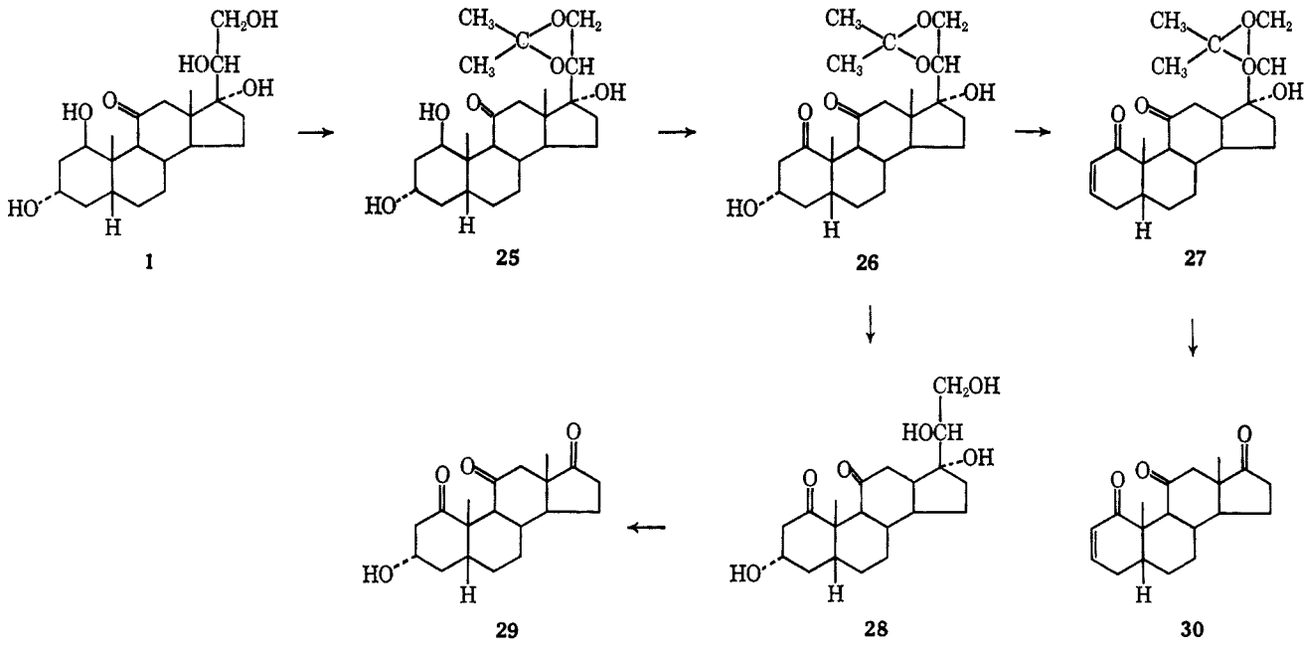
(13) J. P. Dusza, M. Heller, and S. Bernstein, in L. L. Engel, Ed., "Physical Properties of the Steroid Hormones," The Macmillan Co., New York, N. Y., 1963, p 82.

(14) J. H. Fried and A. N. Nutile, *J. Org. Chem.*, **27**, 914 (1962).

(15) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Amer. Chem. Soc.*, **75**, 422 (1953).

(16) M. L. Lewbart, *J. Org. Chem.*, **33**, 1695 (1968).

SCHEME IV



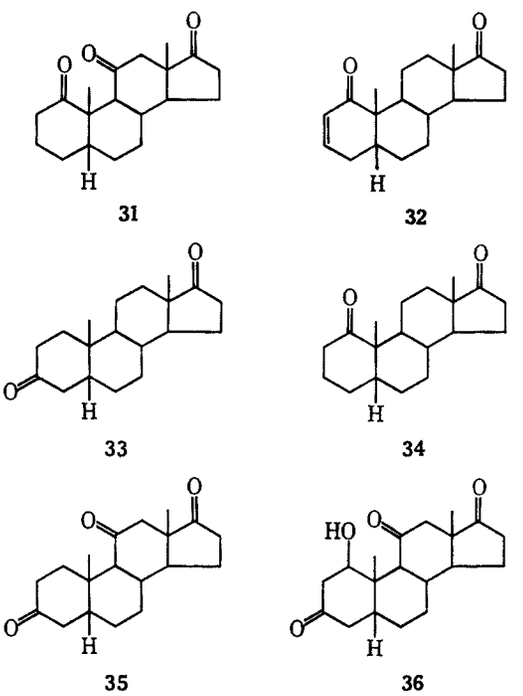
in ether) or hydrogenation at atmospheric pressure, using acetic acid as solvent and freshly prepared platinum catalyst.[17] We attribute this difficulty in reducing either of the two closely approaching carbonyl groups of these cisoid 1,4-diones to a reduction in the degree of polarization of both groups with a consequent reduction in the positive charge on each carbon atom. The adverse effect of this charge distribution on metal hydride reductions is well known.

A similar 1,4 interaction was referred to in our earlier paper.[2] It was noted that the chromic anhydride–pyridine oxidation of **2** gave both 1β-hydroxy-5β-androstane-3,11,17-trione (**36**) and 3α-hydroxy-5α-androstane-1,11,17-trione (**29**), whereas similar oxidation of the 11-deoxydiolone **5** furnished 3α-hydroxy-5β-androstane-1,17-dione as the only recoverable product. The present work provides a second example of this effect. As detailed in the Experimental Section, oxidation of the 11-deoxyacetonide **20** (Scheme III) with this reagent yielded only the 1-ketoacetonide **21**, whereas similar oxidation of the 11-ketoacetonide **25** (Scheme IV) gave the 1,3,11 triketone, the 1-hydroxy-3,11 diketone, and, as the major product, the 3-hydroxy-1,11 diketone **26**. The reduced lability of the C-1 axial hydroxyl group of **2** and of **25** to oxidative attack probably is a manifestation of hydrogen bonding between the oxygen substituents at C-1 and C-11, but it is also possible that the approach of the pyridine–chromic anhydride complex is sterically hindered.

In connection with the evidence indicating interactions in 1,11 diketones, it is of interest to consider the report of Jones and DiGiorgio[18] who examined Dreiding models of the unsaturated triketone **30** (Scheme IV) and the corresponding saturated triketone **31** (Scheme V) and determined their ir spectra in chloroform and carbon disulfide solution. They found that there was no more interaction between the C-1 and C-11 carbonyl groups of these compounds, as judged by displacement of the C-11 band, than in 11,17 diketones generally.

(17) H. C. Brown and C. A. Brown, *J. Amer. Chem. Soc.*, **84**, 1494 (1962).
(18) R. N. Jones and J. B. DiGiorgio, *Can. J. Chem.*, **43**, 182 (1965).

SCHEME V



This is surprising since they noted that the C-1 and C-11 carbonyl groups of **30** are separated by only 3.7 Å (ring-B boat conformation) while those of **31** are separated by 2.8 Å (ring-B chair conformation). As there was no marked absorption above 3000 cm^{-1}, it was concluded that neither steroid was appreciably enolized.

Circular Dichroism Studies.—These results are summarized in Table III. The Cotton effects observed experimentally in the 300-mμ region for the saturated carbonyl chromophores in compounds **1**, **2**, **25**, and **32–34** are in reasonably good agreement with the calculated values (obtained by simple addition of the Cotton effect associated with each carbonyl group). In this respect, the weak Cotton effect of **34** clearly shows that the strong negative effect of the 1 ketone is cancelled by the strong positive optical activity associated with the

TABLE III

CD DATA IN 300-mμ REGION, EXPRESSED AS MOLECULAR ELLIPTICITIES [θ]

Compound	[θ] observed in this work	Calcd Cotton effect[a]
11-Ketocorticoid (**25**)	+600	~+1,200
11-Ketocorticoid (**1**)	+1,250	~+1,200
17-Ketoandrostene derivative (**32**)	+10,500	~+11,400
3,17-Diketo-5β-androstane (**33**)	+9,000	~+10,000
11,17-Diketoandrostene derivative (**10**)	+32,000	~+12,600
11,17-Diketoandrostene derivative (**11**)	+31,300	~+12,600
11,17-Diketoandrostene derivative (**30**)	+18,300	~+12,600
1,17-Diketo-5β-androstane (**34**)	+800	~+300
1β,3α-Dihydroxy-11,17-diketo-5β-androstane (**2**)	+14,000	~+12,600
1,3,17-Triketo-5β-androstane (**6**)	+9,500	~−1,200
1,11,17-Triketo-5β-androstane (**31**)	+15,800	~+1,500
3,11,17-Triketo-5β-androstane (**35**)	+15,200	~+11,000
1β-Hydroxy-3,11,17-triketo-5β-androstane (**36**)	+14,100	~+11,000
1,11-Diketocorticoid (**26**)	+1,900	~−10,000
1,11-Diketocorticoid (**28**)	+1,300	~−10,000
3α-Hydroxy-1,11,17-triketo-5β-androstane (**29**)	+14,000	~+1,500
1,3,11,17-Tetraketo-5β-androstane (**3**)	+23,800	~0

[a] By simple summation of various ketones.

17 chromophore. Conversely, differences are noted between the calculated values and the experimental data observed for steroids **3**, **6**, **10**, **11**, **26**, **28–31**, **35**, and **36**.

It is well known from the work of Djerassi, *et al.*,[19] that the Cotton effect associated with the carbonyl group at C-11 is temperature- and solvent-dependent, probably indicative of the conformational mobility of ring C. Stereochemical and electronic factors could be responsible for conformational changes occurring in ring C of compounds **2**, **3**, **10**, **11**, **26**, **28–31**, **35**, and **36**. However, it is well established that the "additivity rule of chromophores" suffers numerous exceptions in the case of polyketonic compounds presenting the 11-keto chromophore.[20] In particular, it has been shown that the rule is not applicable either to 11,17 diketones[21] or to 3,11,17-triketo steroids.[22] This explains the discrepancies observed between the calculated and observed Cotton effects for numerous compounds in Table III.

The strong positive Cotton effect of the trione **6** around 300 mμ is in agreement with other evidence (Table I) that the β-diketonic system is enolized. This is confirmed by the multiple weak Cotton effects observed at *ca.* 350 mμ which indicates the presence of an α,β-unsaturated ketone. The absence of such effects at *ca.* 350 mμ in the CD curve of the tetrone **3** is in harmony with the view that this compound is largely ketonized under most circumstances. However, it may be argued that in the presence of such an intense Cotton effect the n–π* transition of an α,β-unsaturated ketone may not be detected.

The large positive Cotton effect shown by the saturated triketone **31** suggests that it is conformationally distorted since the molecular ellipticity around 300 mμ is similar to that of the unsaturated triketone **30**. It is to be recalled that there is no evidence from their ir spectra[18] that these ketones are enolized.

Paper Chromatographic Effects.—Interaction in 1,11 diketones also is evident in their partition paper chromatography. For example, we observed (Table II) that the paper chromatographic order of mobility of the six enol methyl ethers **10–15** in systems 1 and 2 (and in a variety of other partitioning systems) was not in harmony with the assigned structures. When it was found that a regular order of mobility was obtained using thin layer (adsorption) chromatography, the R_f values with system 3 constituting an example, it was clear that the noted irregularity consists of a reversal of the relative mobilities of **10** and **11**. When the contribution to polarity of the C-11 carbonyl group in a number of 1,11 diketones was assessed in terms of ΔR_{Mg} values,[23] it was found that this reversal is due to an aberrantly high polarity (low mobility) of **11**, and of all other 1,11 diketones thus far examined, in partitioning systems. A detailed study of this effect and a consideration of possible explanations will be submitted for publication at a later date.

Experimental Section

Melting points were determined with a Fisher-Johns apparatus and are reported uncorrected. Optical rotations were obtained at 26 ± 1°, in methanol solution unless otherwise indicated, at a concentration of around 1% in a Zeiss 0.005° photoelectric polarimeter. Extinction coefficients were determined in a Zeiss PRQ 20A recording spectrophotometer. Infrared spectra were recorded with a Beckman IR-8 instrument. The mass spectrum of 25αF-5α-spirostane-1β,3β-diol was determined by Dr. H. D. Fisher of the West Coast Technical Service using a Hitachi-Perkin-Elmer RMU-6D instrument and an ionization voltage of 70. A description of and references to our paper, thin layer, and column chromatographic techniques appear in a previous publication.[2] For composition of paper, thin layer, and column chromatographic systems, see Table IV. Elementary analyses were carried out by E. Thommen, Basel, Switzerland, Aug. Peisker-Ritter, Brugg, Switzerland, and the Hoffman Laboratories, Wheatridge, Colo. Circular dichroism curves were obtained in dioxane solution with a Jouan dichrograph at the University of Strasbourg, through the kind cooperation of Professor G. Ourisson. Nmr spectra were determined with Varian A-60 or HR-100 spectrometers, using $CDCl_3$ as the solvent and tetramethylsilane as an internal standard of reference.

(19) K. M. Wellman, E. Bunnenberg, and C. Djerassi, *J. Amer. Chem. Soc.*, **85**, 1870 (1963).

(20) P. Crabbé, "Applications de la Dispersion Rotatoire Optique et du Dichroisme Circulaire en Chimie Organique," Gauthier-Villars, Paris, 1968, Chapter VI.

(21) (a) L. Velluz, M. Legrand, and M. Grosjean, "Optical Circular Dichroism. Principles, Measurements and Applications," Verlag-Chemie, Weinheim, 1965; (b) L. Velluz and M. Legrand, *Angew. Chem.*, **73**, 603 (1961).

(22) A. M. Giroud, A. Rassat, and T. Rull, *Bull. Soc. Chim. Fr.*, 2563 (1963).

(23) I. E. Bush, "The Chromatography of Steroids," Pergamon Press Inc., New York, N. Y., 1961, pp 84, 85.

TABLE IV

COMPOSITION OF PAPER, THIN LAYER, AND COLUMN CHROMATOGRAPHIC SYSTEMS

System no.	Composition[a]
1	EA, 40; Iso, 160; AM, 80; HOH, 120 ml
2	Tol, 60; Iso, 140; AM, 150; HOH, 50 ml
3	EA, 20, diluted to 25 ml with Iso
4	EA, 10, diluted to 25 ml with Iso
5	Tol, 120; Iso, 80; AM, 50; HOAc, 20; HOH, 130 ml
6	Iso, 155; III-bu, 45; HOH, 150 ml
7	Tol, 70; Iso, 130; AM, 70; HOAc, 50; HOH, 80 ml
8	Tol, 20; Iso, 180; AM, 160; HOH, 40 ml
9	EA
10	Tol, 45; Iso, 155; AM, 70; HOAc, 50; HOH, 80 ml
11	EA, 5, diluted to 25 ml with Iso
12	Tol, 70; Iso, 130; AM, 160; HOH, 40 ml
13	Tol, 100; Iso, 100; AM, 150; HOH, 50 ml
14	Tol, 150; III-bu, 50; AM, 70; HOH, 80 ml
15	Tol, 140; Iso, 60; AM, 160; HOH, 40 ml

[a] EA = ethyl acetate; Iso = isooctane (2,2,4-trimethylpentane); AM = methanol; Tol = toluene; HOAc = glacial acetic acid; III-bu = *t*-butyl alcohol.

Preparation and Enol Etherification of 5β-Androstane-1,3,11,-17-tetrone (3).—To a solution of 150 mg (0.5 mmol) of 1β,3α-dihydroxy-5β-androstane-11,17-dione (2)[2] in 30 ml of acetone (distilled from $KMnO_4$) at 5° and in a nitrogen atmosphere, 0.45 ml (1.2 mmol) of a solution of 2.67 g of CrO_3 and 2.3 ml of concentrated sulfuric acid diluted to 10 ml with water was added in one portion. After 5 min at 5°, water was added and the solution was extracted with ethyl acetate. The combined extracts were washed with neutral brine, dried with anhydrous sodium sulfate, and evaporated *in vacuo*. Crystallization of most of the product from methanol followed by chromatography of the mother liquor on a 16 × 650 mm Celite column (system 5) gave a total of 95 mg of **5β-androstane-1,3,11,17-tetrone (3)** as needles: mp 182–183°; $[\alpha]_D$ +99°; R_f 0.29 (system 5).

Anal. Calcd for $C_{19}H_{24}O_4$: C, 72.12; H, 7.65. Found: C, 71.80; H, 7.83.

A solution of 60 mg of 5β-androstane-1,3,11,17-tetrone in 3 ml of methanol was allowed to stand at room temperature for 8 hr with an excess of ethereal diazomethane. Examination of the crude product by paper chromatography (system 6), and employing ultraviolet light scanning and the Zimmermann reagent[24] as the detecting methods, showed that the β diketone had reacted completely, giving unequal amounts of two ultraviolet light absorbing, Zimmermann-positive substances with R_f values of 0.16 and 0.30. Chromatography on a 20 × 550 mm Celite column prepared with system 6 easily effected their separation giving, from acetone–ether, 27.8 mg of the mobile ether, **1-methoxy-5β-androst-1-ene-3,11,17-trione (10)**, and, from the same solvent system, 16.7 mg of the polar ether, **3-methoxy-5β-androst-2-ene-1,11,17-trione (11)**. Constants for **10** are mp 181.5–182.5° and $[\alpha]_D$ +163°.

Anal. Calcd for $C_{20}H_{26}O_4 \cdot 0.5C_3H_6O$ (**10**): C, 71.90; H, 8.14; OCH_3, 8.07. Found: C, 72.06; 72.09; H, 8.15, 8.19; OCH_3, 10.72.

Constants for **11** are mp 247–247.5° and $[\alpha]_D$ +28°.

Anal. Calcd for $C_{20}H_{26}O_4$ (**11**): C, 72.70; H, 7.93; OCH_3, 9.39. Found: C, 72.82; H, 8.06; OCH_3, 9.43.

Preparation and Enol Etherification of 5β-Androstane-1,3,17-trione (6).—Oxidation of 60 mg of 1β,3α-dihydroxy-5β-androstan-17-one (**5**)[2] in the manner described above gave, from methanol–ether, 42 mg of **5β-androstane-1,3,17-trione (6)**: mp 239–241°; $[\alpha]_D$ +26°; R_f 0.25 (system 7).[25]

Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.60; H, 8.80.

Treatment of 69 mg of 5β-androstane-1,3,17-trione in methanol solution with an excess of ethereal diazomethane for 12 hr at room temperature, followed by chromatography of the crude extract on a 20 × 650 mm Celite column (system 8), gave two well-separated components. The mobile component furnished, from methanol–ether, 22 mg of **3-methoxy-5β-androst-2-ene-1,17-dione (13)** as needles: mp 191–191.5°; $[\alpha]_D$ −49°; R_f 0.42 (system 8).

Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 76.20; H, 9.07.

Crystallization of the polar component from ethyl acetate–*n*-hexane gave 21 mg of **1-methoxy-5β-androst-1-ene-3,17-dione (12)** as needles: mp 184–184.5°; $[\alpha]_D$ +190°; R_f 0.23 (system 8).

Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 76.11; H, 9.06.

5α-Androstane-1,3,17-trione and Its Enol Methyl Ethers.—Isoandrosterone (3 g) was incubated with shaking for 24 hr at 26° with a flourishing culture of a *Penicillium* species, ATCC 12556.[26] Chromatography of the crude extract on a 50 × 840 mm column of silica gel (system 9) gave, from methanol–ethyl acetate, 685 mg (22%) of needles: mp 202–203°; $[\alpha]_D$ +103°. Its melting point was unaltered on admixture with an authentic sample of **1α,3β-dihydroxy-5α-androstan-17-one**, and their ir spectra in KBr dispersion were identical.

Oxidation of 120 mg of 1α,3β-dihydroxy-5α-androstan-17-one as above, followed by chromatography of the crude product on a 20 × 680 mm Celite column (system 10), gave 65 mg of prisms from methanol (mp 198–199°, $[\alpha]_D$ +274°) assigned the structure **5α-androstane-1,3,17-trione** [lit.[26] mp 157–159°, 199–200°; λ_{max} 254 mμ (ε 12,000)].

Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.19; H, 8.63.

Reaction of 50 mg of 5α-androstane-1,3,17-trione with an excess of ethereal diazomethane as in the previous examples, followed by chromatography of the crude extract on a 16 × 450 mm Celite column (system 8), gave two well-separated components. The mobile fraction, designated **3-methoxy-5α-androst-2-ene-1,17-dione (15)**, gave 19 mg of needles from ethyl acetate: mp 199–200°; $[\alpha]_D$ +278°; R_f 0.51 (system 8).

Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 75.90; H, 8.80.

The polar component, assigned the structure **1-methoxy-5α-androst-1-ene-3,17-dione (14)**, furnished 14 mg of needles from ethyl acetate–*n*-hexane: mp 172.5–173.5°; $[\alpha]_D$ +126°; R_f 0.19 (system 8).

Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 75.88; H, 8.90.

Preparation and Enol Etherification of 25αF-5α-Spirostane-1,3-dione.—A 500-mg sample of 25αF-spirost-5-ene-1β,3β-diol [ruscogenin[27] mp 209–210°; $[\alpha]_D$ −122° ($CHCl_3$)], obtained by saponification of the diacetate, was hydrogenated over a 3-hr period at atmospheric pressure in neutral ethanol–cyclohexane using 5% palladium on carbon (Engelhard Industries) as catalyst. Crystallization of the product from aqueous acetone gave prisms or plates assigned the structure **25αF-5α-spirostane-1β,3β-diol**: mp 211–212°; $[\alpha]_D$ −75° ($CHCl_3$); R_f 0.17 in system 3 (orange fluorescence after spraying with *p*-toluenesulfonic acid and heating at 120°; in this system ruscogenin has an R_f of 0.21 and displays a blue fluorescence). Its mass spectrum showed a single molecular ion (M^+) at *m/e* 432 amu.

Anal. Calcd for $C_{27}H_{44}O_4$: C, 74.95; H, 10.25. Found: C, 74.68; H, 10.20.

Treatment of the free diol with acetic anhydride and pyridine at room temperature followed by crystallization of the product from aqueous acetone and from acetone gave **25αF-5α-spirostane-1β,3β-diol diacetate**[28] as needles: mp 249–250°; $[\alpha]_D$ −72° ($CHCl_3$).

Anal. Calcd for $C_{31}H_{48}O_6$: C, 72.06; H, 9.36; CH_3CO, 16.66. Found: C, 72.32; H, 9.39; CH_3CO, 16.59.

Oxidation of 200 mg of the free diol with Jones' reagent as in the previous examples gave 110 mg of **25αF-5α-spirostane-1,3-**

(24) R. Neher, "Steroid Chromatography," Elsevier, Amsterdam, 1964, p 125.

(25) In addition to its general utility in this study, the paper chromatographic technique made an unique contribution in the case of the β diketones **3** and **6**. Prior to determining their extinction coefficients, the limited enolization of the former readily has demonstrated by comparing the paper chromatographic characteristics of the two ketones. In the absence of acetic acid in the system, both compounds streaked markedly, and it was easily determined how much acid was required in each case to eliminate streaking, presumably by suppressing enolization. Much less acid was required in the system suitable for the tetrone **3** (compare systems 5 and 7, Table IV).

(26) S. Noguchi and D. K. Fukushima, *J. Org. Chem.*, **30**, 3552 (1965).

(27) H. Lapin and C. Sannié, *Bull. Soc. Chim. Fr.*, 1552 (1955).

(28) 25αF-5α-Spirostane-1β,3β-diol has not to our knowledge been prepared previously. Its 5 epimer, isorhodeasapogenin, has these constants: mp 241–243°; $[\alpha]_D$ −71° ($CHCl_3$); diacetate, mp 205° [H. Nawa, *Pharm. Bull.* (Tokyo), **6**, 255 (1958)].

dione as needles from methylene chloride–ethyl acetate: mp 244–245°, $[\alpha]_D$ +9° ($CHCl_3$).

Anal. Calcd for $C_{27}H_{40}O_4$: C, 75.66; H, 9.41. Found: C, 75.80; H, 9.46.

To a solution of 100 mg of 25α_F-5α-spirostane-1,3-dione in 2 ml of methylene chloride, an excess of ethereal diazomethane was added. After 12 hr at room temperature, the solvents were evaporated, and the residue was chromatographed on a 20 × 765 mm silica gel column prepared with system 11 (changed to system 4 after emergence of the mobile component). The mobile fraction gave, from methylene chloride–methanol, 40 mg of **3-methoxy-25α_F-5α-spirost-2-en-1-one** (**17**) as plates: mp 213–214°; $[\alpha]_D$ +53° ($CHCl_3$); R_f 0.38 (system 4).

Anal. Calcd for $C_{28}H_{42}O_4$: C, 75.97; H, 9.57. Found: C, 75.94; H, 9.55.

Crystallization of the polar component from acetone–*n*-hexane gave 32 mg of **1-methoxy-25α_F-5α-spirost-1-en-3-one** (**16**) as needles: mp 203–204°; $[\alpha]_D$ −72° ($CHCl_3$); R_f 0.11 (system 4).

Anal. Calcd for $C_{28}H_{42}O_4$: C, 75.97; H, 9.57. Found: C, 75.94; H, 9.61.

Preparation of 5β-Pregnane-1α,3α,17α,20β,21-pentol (23).—To a solution of 200 mg of 5β-pregnane-1β,3α,17α,20β,21-pentol (**4**, mp 252–253°; $[\alpha]_D$ +6°)[2] in 50 ml of acetone, 50 mg of *p*-toluenesulfonic acid was added. After 30 min at room temperature, 0.3 ml of 1 *N* aqueous sodium hydroxide was added, and the solution was concentrated *in vacuo* to near dryness. The crystalline suspension was dissolved in ethyl acetate, and the solution was washed with dilute sodium hydroxide and neutral brine, dried with anhydrous sodium sulfate, and evaporated. Crystallization of the product from methanol gave 192 mg of stout needles (mp 243–244°; $[\alpha]_D$ +13°) designated as **20,21-isopropylidenedioxy-5β-pregnane-1β,3α,17α-triol** (**20**).[29]

Anal. Calcd for $C_{24}H_{40}O_5$: C, 70.55; H, 9.87. Found: C, 70.73; H, 10.08.

Oxidation of 100 mg of 20,21-isopropylidenedioxy-5β-pregnane-1β,3α,17α-triol with chromic anhydride in pyridine as in our previous publication[2] furnished, from acetone–*n*-hexane and from acetone, 70 mg of **3α,17α-dihydroxy-20,21-isopropylidenedioxy-5β-pregnan-1-one** (**21**): mp 218–219°; $[\alpha]_D$ −73°; R_f 0.36 (system 12).

Anal. Calcd for $C_{24}H_{38}O_5$: C, 70.90; H, 9.42. Found: C, 70.80; H, 9.40.

To a solution of 60 mg of 3α,17α-dihydroxy-20,21-isopropylidenedioxy-5β-pregnan-1-one in 5 ml of methanol, 40 ml of sodium borohydride was added in one portion. After 3 hr at room temperature, acetic acid was added, and the solution was extracted with ethyl acetate after dilution with brine. The organic phase was washed with dilute sodium hydroxide and neutral brine, dried with anhydrous sodium sulfate, and evaporated *in vacuo*. Crystallization from acetone–*n*-hexane gave 40 mg of needles [mp 203–204°; $[\alpha]_D$ +16°; R_f 0.20 (system 13)] assigned the structure **20,21-isopropylidenedioxy-5β-pregnane-1α,3α,17α-triol** (**22**). On admixture with a sample of **20**, its 1 epimer (mp 243–244°), the melting range was 191–195°; their ir spectra were dissimilar.

Anal. Calcd for $C_{24}H_{40}O_5$: C, 70.55; H, 9.87. Found: C, 70.22; H, 9.68.

A solution of 43 mg of 20,21-isopropylidenedioxy-5β-pregnane-1α,3α,17α-triol in 43 ml of 60% (v/v) aqueous acetic acid was allowed to stand at room temperature for 4 hr. The solution was concentrated to dryness *in vacuo*, and the residue was chromatographed on a 16 × 560 mm Celite column prepared with system 14. Crystallization of the recovered product from methanol–ether gave 28 mg of needles [mp 228–229°; $[\alpha]_D$ +10°; R_f 0.21 (system 14)] designated as **5β-pregnane-1α,3α,17α,20β,-21-pentol** (**23**). On admixture with a sample of its 1 epimer (**4**, mp 252–253°), the melting range was 214–218°; their ir spectra were dissimilar.

Anal. Calcd for $C_{21}H_{36}O_5$: C, 68.44; H, 9.85. Found: C, 68.34; H, 9.80.

Oxidation of a 16-mg sample of 5β-pregnane-1α,3α,17α,20β,21-pentol with sodium periodate as previously described[2] gave 9 mg of prisms (mp 230–232°; $[\alpha]_D$ + 101°) assigned the structure **1α,3α-dihydroxy-5β-androstan-17-one** (**24**). Its 1 epimer (**5**) has mp 204–204.5° and $[\alpha]_D$ +95°.[2] A mixture of **5** and **24** melted at 188–192°, and their ir spectra were dissimilar.[30]

Preparation of 3α,17α,20β,21-Tetrahydroxy-5β-pregnane-1,11-dione (28).—Reaction of 400 mg of 1β,3α,17α,20β,21-pentahydroxy-5β-pregnan-11-one (**1**) with *p*-toluenesulfonic acid in acetone as in the preparation of **20** from **4** gave, from methanol–acetone, 405 mg of **1β,3α,17α-trihydroxy-20,21-isopropylidenedioxy-5β-pregnan-11-one** (**25**) as prisms: mp 261–262°; $[\alpha]_D$ +15°.

Anal. Calcd for $C_{24}H_{38}O_6$: C, 68.22; H, 9.06. Found: C, 68.20; H, 9.00.

Oxidation of 300 mg of 1β,3α,17α-trihydroxy-20,21-isopropylidenedioxy-5β-pregnan-11-one with chromic anhydride in pyridine as in the preparation of **21** from **20**, followed by chromatography on a 38 × 755 mm Celite column (system 15) furnished three products. The most mobile fraction gave, from ethyl acetate–*n*-hexane, 40 mg of impure **17α-hydroxy-20,21-isopropylidenedioxy-5β-pregnane-1,3,11-trione**. The fraction of intermediate mobility provided, from ethyl acetate, 85 mg of **1β,17α-dihydroxy-20,21-isopropylidenedioxy-5β-pregnane-3,11-dione**: mp 236–238°; $[\alpha]_D$ +25°. The least mobile (most polar) fraction yielded, from acetone, 145 mg of **3α,17α-dihydroxy-20,21-isopropylidenedioxy-5β-pregnane-1,11-dione** (**26**): mp 278–279°; $[\alpha]_D$ −15°; R_f 0.18 (system 15).

Anal. Calcd for $C_{24}H_{36}O_6$ (**26**): C, 68.54; H, 8.63. Found: 68.53; H, 8.49.

A solution of 30 mg of 3α,17α-dihydroxy-20,21-isopropylidenedioxy-5β-pregnane-1,11-dione in 1 ml each of acetic anhydride and pyridine was allowed to stand at room temperature overnight. The product was recovered in the usual fashion and percolated through a small column of neutral alumina as described in a previous publication.[2] The product was eluted with 0.15% ethanol in benzene and furnished, from methanol, 20 mg of prisms [mp 237–238°; $[\alpha]_D$ +3°; λ_{max} 225 mμ (ϵ 7450)] which were assigned the structure **17α-hydroxy-20,21-isopropylidenedioxy-5β-pregn-2-ene-1,11-dione** (**27**).

Anal. Calcd for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51. Found: C, 71.39; H, 8.54.

Hydrolysis of a sample of 17α-hydroxy-20,21-isopropylidenedioxy-5β-pregn-2-ene-1,11-dione with aqueous acetic acid followed by oxidation of the free compound with sodium periodate gave needles from acetone–*n*-hexane, mp 223–224°. On admixture with an authentic sample of **5β-androst-2-ene-1,11,17-trione** (**30**), mp 223.5–224.5°,[2] its melting point was unaltered. The ir spectra of the two ketones were identical.

Hydrolysis of 3α,17α-dihydroxy-20,21-isopropylidenedioxy-5β-pregnane-1,11-dione (40 mg) with aqueous acetic acid as in the previous examples, followed by crystallization of the product from methanol–ethyl acetate, gave 26 mg of needles (mp 253–254°; $[\alpha]_D$ −1°) designated as **3α,17α,20β,21-tetrahydroxy-5β-pregnane-1,11-dione** (**28**).

Anal. Calcd for $C_{21}H_{32}O_6$: C, 66.29; H, 8.48. Found: C, 66.04; H, 8.50.

Oxidation of a sample of 3α,17α,20β,21-tetrahydroxy-5β-pregnane-1,11-dione with sodium periodate followed by crystallization of the product from methanol gave needles, mp 262–263°. The melting point was unchanged on admixture with an authentic sample of **3a-hydroxy-5β-androstane-1,11,17-trione** (**29**),[2] and their ir spectra were identical.

Registry No.—**1,** 10535-94-1; **2,** 10535-95-2; **3,** 2061-61-2; **6,** 16963-70-5; **10,** 16963-71-6; **11,** 16963-72-7; **12** and **13,** not yet resolved; **14,** 16963-75-0; **15,** 16963-76-1; 5α-androstane-1,3,17-trione, 4171-02-2; 25$_\alpha$F-5α-spirostane-1β,3β-diol, 16963-78-3; 25$_\alpha$F-5α-spirostane-1β,3β-diol diacetate, 16976-44-6; 25$_\alpha$F-5α-spirostane-1,3-dione, 16963-79-4; **16,** 16963-80-7; **17,** 16963-81-8; **20,** 16963-82-9; **21,** 16976-45-7; **22,** 16963-83-0; **23,** 16963-84-1; **25,** 16963-85-2; **26,** 16976-46-8; **27,** 16963-86-3; **28,** 16963-87-4; **29,** 10535-97-4; **30,** 16963-89-6; **31,** 2785-91-3; **32,** 16963-91-0; **33,** 1229-12-5; **34,** 10536-04-6; **35,** 1429-06-7; **36,** 10535-96-3; 1-methoxy-5α-

(29) We are engaged in a study of the preparation, hydrolysis, and properties of steroidal 17,20- and 20,21-acetonides. The principal bands in the ir region of the acetonides prepared in this paper are in close agreement with those found generally for members of the second class.

(30) The forthcoming paper chromatographic study will include an examination of the relative mobilities of the members of five pairs of epimeric 1-ols, including the pairs 4/23 and 5/24.

cholest-1-en-3-one, 16963-96-5; 3-methoxy-5α-cholest-2-en-1-one, 16963-97-6.

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A Synthesis of Estrone *via* Novel Intermediates. Mechanism of the Coupling Reaction of a Vinyl Carbinol with a β Diketone[1]

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An investigation of the coupling reaction of vinylcarbinols with β diketones as exemplified by the condensation of 1-vinyl-1-hydroxy-6-methoxy-1,2,3,4-tetrahydronaphthalene with 2-methylcyclopentane-1,3-dione is presented. Quantitative conversion of 1-vinyl-1-hydroxy-6-methoxy-1,2,3,4-tetrahydronaphthalene into a crystalline isothiuronium salt has provided a versatile intermediate in an improved condensation providing the tricyclic precursor to estrone, **3**. Selective as well as stereospecific reduction of the latter system with lithium tri-*t*-butoxyaluminum hydride afforded the ketol **8**, a key optically resolvable intermediate in the synthesis of estrone.

Ten years have elapsed since Nazarov and collaborators[2] successfully prepared the important vinylcarbinol, 1-vinyl-1-hydroxy-6-methoxy-1,2,3,4-tetrahydronaphthalene (**1**); their attempts, however, to convert **1** into the allylic bromide **4** (X = Br) for purposes of condensation with reactive enolates proved abortive.[3,4] Subsequently, Ananchenko and Torgov discovered that the vinylcarbinol **1** it selfwas capable of direct coupling with 2-methylcyclohexane-1,3-dione in the presence of strong base to give the homolog of the tricyclic diketone **3** in 50% yield.[5] These authors further examined a variety of catalysts to promote this condensation although they later employed Triton B (benzyltrimethylammonium hydroxide) almost exclusively.[6] This procedure has since been generally adopted by contemporaries in the field in its application to the synthesis of estrone employing 2-methylcyclopentane-1,3-dione (**2**) as donor component.[7]

The coupling of a vinylcarbinol with an enolate under presumed conditions of basic catalysis presented a unique reaction type for which a fitting analogy was lacking. By way of rationalization both a simulated Michael process[8] and an SN2′ displacement reaction[9] have been proposed. A close formal analogy of this condensation to the so-called Carroll reaction[10] has already been noted elsewhere.[11] In the latter reaction, for example, acetoacetic ester condenses with phenylvinylcarbinol in the presence of potassium acetate at 200° to give cinnamylacetone. The Carroll reaction has been shown to proceed *via* initial ester exchange to a derived acetoacetate followed by Cope rearrangement.[12] More pertinent to the case at hand are the observations of Marbet and Saucy[10b] that tertiary vinylcarbinols rearrange *via* their isopropenyl ethers to γ,δ-unsaturated carbonyl systems. The possibility of a formal Carroll reaction in the case of the condensation of **1** and **2** *via* an intermediate enol ether was ruled out by our own observations through the employment of vinylcarbinol possessing ^{18}O in the carbinol grouping. In the event of a formal Carroll reaction the carbinol ^{18}O would have been transferred to the pertinent carbonyl function of the cyclopentandione moiety, a consequence not observed.

It appeared to us on the basis of the prior art to be patently unsound that alkali should catalyze the condensation of **1** with **2**. To gain substantiation for this point of view the two components were allowed to react in the presence of 1 equiv of alkali instead of the fractional equivalent which had always been employed previously.[6,7] Under the conditions that employed 1 mol equiv of alkali *no condensation* whatsoever was observed between **1** and **2**. It was thereby evident that the condensation of Torgov and Ananchenko is not base catalyzed, but is in fact an acid-catalyzed reaction with the β diketone functioning autocatalytically. It was likewise evident that the previous success of this condensation was due to the extent that the β diketone had not been converted into its salt by added alkali, mistakenly believed to catalyze the reaction. In substantiation thereof we observed that, when **1** and **2** were warmed together in *t*-butyl alcohol in the absence of any external catalyst, coupling proceeded smoothly to give **3** directly

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