The infrared absorption spectra were identical with those of authentic N,N'-dimethylformamidine.[14] This amidine was isolated in 34% yield based on hydrogen cyanide used. Then the distillation residue was extracted several times with hot water. The two-dimensional paper chromatogram[15] of the aqueous extract showed four spots under ultraviolet radiation. The supernatant solution of this extract was passed through a column of Dowex 50W (X4, 100–200 mesh, H^+ form). Then the column was washed with water and eluted with 0.1 *N* hydrochloric acid. Four peaks were obtained from the column. 1-Methyl-4-methylamino-5-cyanoimidazole of mp 178–178.4° was obtained from peak I.

Anal. Calcd for $C_6H_8N_4$: C, 52.92; H, 5.92; N, 41.15. Found: C, 53.25; H, 5.81; N, 41.38.

The isolated substance showed ultraviolet absorption maxima at 241 and 270 mμ in 0.1 *N* sodium hydroxide solution, which closely resemble those of 4-amino-5-cyanoimidazole. Its infrared absorption spectrum exhibited a characteristic band due to the cyano group at 2220 cm^{-1}, and was identical with that of an authentic sample. Authentic 1-methyl-4-methylamino-5-cyanoimidazole was prepared from 1-methyl-4-amino-5-imidazolecarboxamide[16] by N-methylation with methyl iodide in dilute sodium hydroxide solution, followed by dehydration of the carbamoyl group with phosphoryl chloride. On evaporation of peaks II and III separately, two derivatives of N-methyl-substituted adenine were obtained. The former showed ultraviolet absorption maxima at 265 mμ in 0.1 *N* hydrochloric acid and 270 mμ in 0.1 *N* sodium hydroxide solution and the latter at 280 mμ in 0.1 *N* hydrochloric acid and 277 mμ in 0.1 *N* sodium hydroxide solution. The infrared absorption spectra of these compounds were identical with those of the authentic samples of 6-methylamino-9-methylpurine[17] and 6-methylamino-7-methylpurine,[18] respectively. Attempts to isolate the substance from peak IV were unsuccessful. It was presumed from ultraviolet absorption spectra, however, that the substance was a methylamidino derivative of 1-methyl-4-methylamino-5-cyanoimidazole.

(14) A. Pinner, *Ber.*, **16**, 358 (1883).

(15) First solvent, *n*-C_3H_7OH–NH_3–H_2O (20:12:3, v/v); second solvent, *n*-C_4H_9OH–CH_3CO_2H–H_2O (4:1:1, v/v).

(16) R. K. Robins and R. N. Prasad, *J. Am. Chem. Soc.*, **79**, 6401 (1957).

(17) R. K. Robins and H. H. Lin, *ibid.*, **79**, 490 (1957).

(18) E. C. Taylor and P. K. Loeffler, *ibid.*, **82**, 3147 (1960).

Registry No.—I, 74-90-8; ammonia, 7664-41-7; VII, 73-24-5; VIII, 1122-28-7; N,N-dimethylformamidine, 2304-00-9; 1-methyl-4-methylamino-5-cyanoimidazole, 15353-10-3.

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Steroid Hormone Analogs. III.[1] The Synthesis and Stereochemistry of C-Nor-D-homoprogesterone Analogs[2]

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The synthesis is described of the C-nor-D-homo-11-keto-17-hydroxyprogesterone derivatives XX and XXII, which possess the progesterone configuration at each of the ring junctions. Jervine was degraded to the diketone IV by standard procedures. Treatment of IV with ethylidenetriphosphorane under Wittig reaction conditions yielded the geometric isomers, V and VI, and alkaline hydrolysis afforded VII and VIII, respectively. Spectral studies showed (1) that V and VII possess C/D-*trans*, C-18β-(equatorial)-methyl, and C-21-*cis*-methyl configurations and (2) that VI possesses the less stable C/D-*cis* junction and is epimerized at C-12 during alkaline hydrolysis to VIII, with C/D-*trans*, C-18β-(equatorial)-methyl, and C-21-*trans*-methyl configurations. Oppenauer oxidation of VII and VIII gave XI and XII, respectively. Epoxidation of XI gave the isomeric oxides XIII and XIV and chemical and spectral arguments are advanced for assignment of β-epoxide and α-epoxide configurations, respectively. Attempted oxidation of XIII with dimethyl sulfoxide–boron trifluoride etherate gave XVII, which was oxidized with chromic acid–pyridine to XVIII. Oxidation of XI or XII with osmium tetroxide and hydrogen peroxide under neutral conditions yielded the epimeric ketones XX and XXII. Spectral and chemical evidence are adduced for assignment of the C-nor-D-homo-11-keto-17α-hydroxyprogesterone structure for XX and the C-nor-D-homo-11-keto-17β-hydroxyprogesterone structure for XXII.

Recent years have witnessed continuing interest in the modification of the basic steroid skeleton of hormones to seek analogs with enhanced or more specific pharmacological properties. In view of the natural occurrence of the C-nor-D-homo steroid ring system (*e.g.*, in jervine (I)[3,4]), the synthesis of related hormone analogs has been a particularly attractive target.[1,5–9] We described herewith the synthesis of the first C-nor-D-homoprogesterone derivatives which possess the progesterone configuration at each of the ring junctions.

An earlier approach[1] to C-nor-D-homoprogesterone derivatives started from $\Delta^{5,12,17(20)}$-17-ethyletiojervatrien-3β-ol-11-one 3-acetate (II)[3,5,10] and proceeded *via* hydroxylation of the 17,20 double bond. However, the latter approach proved to be impractical, owing largely to the sensitivity of the 17,20 bond to oxidative cleavage in the 12,13-unsaturated derivatives. The approach described in the present work proceeds *via*

(1) Part II: S. M. Kupchan, T. Masamune, and G. W. A. Milne, *J. Org. Chem.*, **29**, 755 (1964).

(2) This investigation was supported in part by Public Health Service Research Grant HE-02275 from the National Heart Institute.

(3) J. Fried and A. Klingsberg, *J. Am. Chem. Soc.*, **75**, 4929 (1953).

(4) For a recent review of the chemistry and stereochemistry of jervine, see S. M. Kupchan and A. W. By in "The Alkaloids," Vol. X, R. H. Manske, Ed., Academic Press Inc., New York, N. Y., 1967.

(5) S. M. Kupchan and S. D. Levine, *J. Am. Chem. Soc.*, **86**, 701 (1964).

(6) S. M. Kupchan, A. W. By, and M. S. Flom, *J. Org. Chem.*, in press.

(7) T. Masamune, K. Orito, and A. Murai, *Bull. Chem. Soc. Japan*, **39**, 2503 (1966).

(8) (a) W. F. Johns, *J. Org. Chem.*, **29**, 2545 (1964); (b) W. F. Johns and I. Laos, *ibid.*, **30**, 123, 4220 (1965).

(9) H. Mitsuhashi and K. Kawahara, *Tetrahedron*, **21**, 1215 (1965), and the references cited there.

(10) The designation etiojervane is used, as in our earlier reports,[1,5] to describe 17aβ-methyl-C-nor-D-homo-18-nor-5α,13β-androstane. It should be noted that the same term has *subsequently* been used to designate two different stereoisomers.[7,8a]

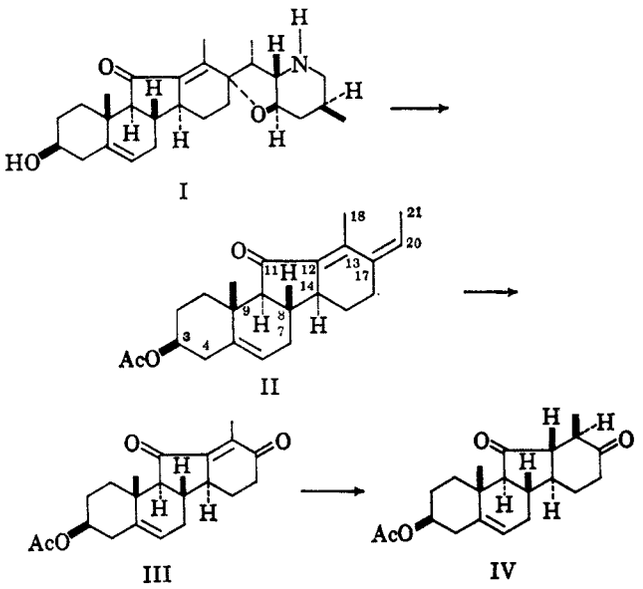
TABLE I
NMR DATA

Compd	C-19 CH_3	C-18 CH_3	C-21 CH_3	CH_3COO–	C-3 H	C-6 H	C-20 H
IV	8.91 (3 H) s	8.66 (3 H) d J = 7 cps	...	7.97 (3 H) s	5.38 (1 H) m	4.56 (1 H) m	...
IV[a]	9.01 (3 H) s	8.47 (3 H) d J = 7 cps	...	8.22 (3 H) s	5.28 (1 H) m	4.76 (1 H) m	...
V	8.98 (3 H) s	8.78 (3 H) d J = 6.5 cps	8.40 (3 H) d J = 6.5 cps	8.00 (3 H) s	5.43 (1 H) m	4.58 (1 H) m	4.75 (1 H) q J = 6.5 cps
V[a]	9.02 (3 H) s	8.46 (3 H) d J = 6 cps	8.39 (3 H) d J = 6.5 cps	8.25 (3 H) s	5.20 (1 H) m	4.70 (1 H) m	4.70 (1 H) q J = undefined
VI	8.88 (3 H) s	9.05 (3 H) d J = 6.5 cps	8.41 (3 H) d J = 6.5 cps	7.98 (3 H) s	5.43 (1 H) m	4.58 (1 H) m	4.75 (1 H) q J = 6.5 cps
VI[a]	8.89 (3 H) s	9.03 (3 H) d J = 6.5 cps	8.50 (3 H) d J = 7 cps	8.22 (3 H) s	5.32 (1 H) m	4.78 (1 H) m	4.78 (1 H) q J = undefined

[a] Spectra were determined in benzene.

cleavage of the side chain to the 17-ketone III,[3] reduction of the 12,13 double bond to yield IV,[3] and reintroduction of the side chain at C-17 by a suitable alkylation (Scheme I).

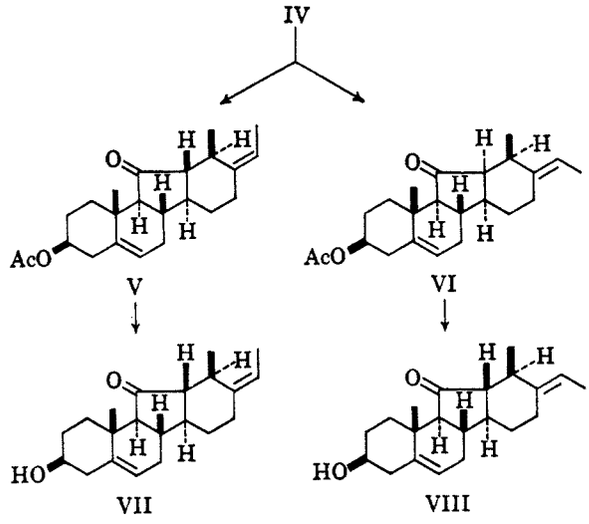
SCHEME I



As expected, the Wittig reagent[11] reacted with IV only at position 17 to give two isomeric compounds which were isolated after reacetylation of the crude reaction product and separation by column chromatography on acid-washed alumina. The major isomer (30–35% yield), Δ^5-17-*cis*-ethylideneetiojerven-3β-ol-11-one 3-acetate (V), was slightly less polar than the minor isomer (10–15% yield), Δ^5-17-*trans*-ethylideneetiojerven-3β-ol-11-one 3-acetate (VI). The reacetylation was necessary in order to overcome difficulties encountered during attempted isolation of the corresponding alcohols. The infrared spectra of both isomers were very similar.

Of particular interest were the nmr spectra of V and VI, from which much information was gained about the structure and stereochemistry of the compounds (see Table I). The presence of a doublet assignable to the C-21 methyl group and a quartet assignable to the C-20 vinyl proton in the spectrum of each isomer confirmed the addition of an ethylidene group to the 17-ketone in IV. The C-18 methyl signal in IV had the lowest chemical shift (τ 8.66), due to double deshielding by both the C-11 and C-17 carbonyl groups. In V the C-18 methyl group is deshielded only by the C-11 carbonyl group and its signal is slightly shifted upfield (τ 8.78), while in the isomeric compound VI there is a marked shielding of the C-18 methyl group and a shift of its signal to an upfield position (τ 9.05). The latter observation accords best with the view that the C/D ring junction in VI is *cis* and the C-18 methyl group is axial; this places the methyl group above the plane of the carbonyl group and results in shielding. The formation of the minor isomer VI can be rationalized by assuming that IV, with the C/D rings *trans* fused, underwent equilibration at C-12 under the basic Wittig reaction conditions to a C/D-*cis*-fused product (Scheme II).

SCHEME II



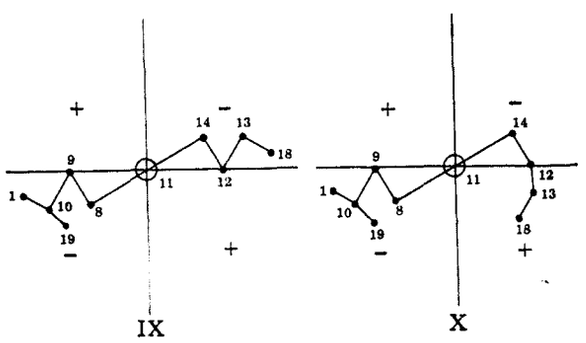
Aromatic solvents, such as benzene, can exert appreciable influence on the chemical shifts of protons on methyl groups near a carbonyl function and this effect has been well documented for the angular methyl groups in steroids.[12] The nmr spectra of IV, V, and VI were determined in benzene and compared with those in deuteriochloroform (see Table I). Small solvent shifts were observed for the C-19 methyl protons, *viz.*, $\Delta\tau$ 0.10, 0.04, and 0.01 for IV, V, and VI, respectively. Examination of Dreiding models revealed that, in each

(11) F. Sondheimer and R. Mechoulam, *J. Am. Chem. Soc.*, **80**, 3087 (1958).

(12) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, Chapter 7.

case, the C-19 methyl protons lie approximately on, or slightly below, a reference plane drawn through the carbonyl carbon and perpendicular to the direction of the C–O bond and the observed effects are therefore in good accord with earlier empirical generalizations.[13] Downfield shifts of $\Delta\tau$ −0.19 and −0.32, respectively, were observed for the C-18 methyl protons of IV and V. The molecular models of the latter C/D-*trans* compounds clearly showed that the C-18 methyl protons lie above the reference plane and the observed shifts are in accord with prediction. The small solvent-induced shift ($\Delta\tau$ −0.02) for the C-18 methyl protons of VI supports the assignment of the C/D-*cis* ring junction and the axial position for the C-18 methyl group in VI.

Confirmatory evidence for the stereochemistry of V and VI came from ORD studies (see Figure 1). Both compounds showed ORD curves with negative Cotton effects. However, the amplitudes for V and VI differed markedly. The difference was readily explicable in terms of octant rule considerations for hexahydroindanones, advanced earlier by Klyne.[14] Examination of molecular models revealed (as represented in the octant projections IX for V and X for VI) that the cyclopentanone ring is severely skewed in both V and VI and both C-8 and C-14 appear in negative quadrants. The strong negative amplitude for V is attributable to the fact that additional carbons fall in negative quadrants, while the diminished amplitude in VI is attributable to the fact that C-13 and C-18 fall in a positive quadrant in the C/D-*cis*-fused compound. These considerations support assignment of C/D-*trans* configuration to V and C/D-*cis* configuration to VI.



Hydrolysis of the C-3 acetate esters in V and VI with 5% potassium hydroxide in methanol at room temperature for 24 hr gave, after crystallization from ether, high yields of the corresponding alcohols, Δ^5-17-*cis*-ethylideneetiojerven-3β-ol-11-one (VII), and Δ^5-17-*trans*-ethylideneetiojerven-3β-ol-11-one (VIII). The hydrolysis of the esters was confirmed by the appearance of absorption peaks at 2.80 μ (OH) and the absence of the band at 8.00 μ (C–O stretching of the ester), in the respective infrared spectra. The nmr spectrum of VII, when compared with that of V, indicated the absence of the methyl signal for the C-3 acetate and an appropriate shift to higher field of the C-3 proton (τ 6.59, 1 H, m). The hydroxyl signal at τ 8.12 disappeared upon deuteration. The C-18 methyl proton signal appeared at τ 8.68 (3 H, d, J = 6 cps), indicating no change in configuration at C-12. The nmr spectrum of VIII was different in several respects from that of its precursor VI. The C-18 methyl signal of VIII appeared at τ 8.81 (3 H, d, J = 6.5 cps), suggesting that isomerization in base of VI at C-12 had occurred during ester hydrolysis. This isomerization placed the C-18 methyl group back into the C-18 β (equatorial) position, subject to the deshielding influence of the C-11 ketone. The C-19 methyl proton signal appeared in a normal position at τ 8.95, whereas in VI the C-19 methyl protons were slightly deshielded owing to the close proximity of the C-18β (axial) methyl group. The peak for the C-3 acetate was absent and the C-3 proton signal was shifted to a higher field (τ 6.52, 1 H, m). As in VII, the hydroxyl signal at τ 8.13 disappeared upon deuteration.

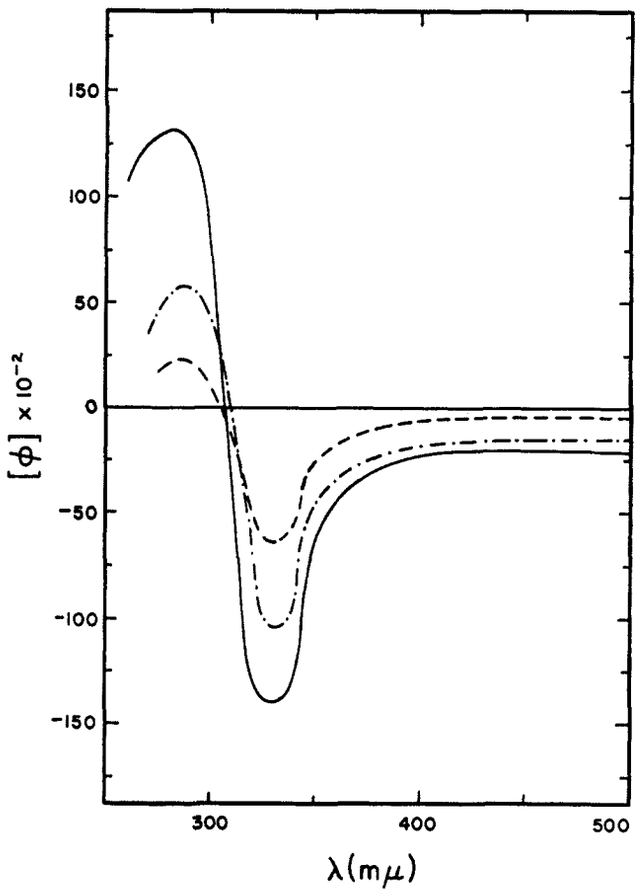


Figure 1.—ORD curves for IV (———), V (-·-·-), and VI (- - -).

Further comparison of the nmr spectra of VII and VIII indicated differences in the chemical shifts for the C-18 as well as the C-21 methyl groups. The C-18 methyl doublet in VII appeared at τ 8.68, while in VIII the doublet appeared at τ 8.81. This downfield shift of the C-18 methyl signal in VII (−0.13 ppm) is attributable to the proximity of the C-21 methyl group, this, owing to electronic repulsion of the hydrogens, deshields the C-18 methyl group.[15,16] The signal for the C-21 methyl group in VII appeared at τ 8.40 and in VIII at τ 8.45; the deshielding effect of the C-18 methyl on

(13) (a) D. H. Williams and N. S. Bhacca, *Tetrahedron*, **21**, 2021 (1965); (b) D. H. Williams and D. A. Wilson, *J. Chem. Soc., Sect. B*, 144 (1966); (c) J. Ronayne and D. H. Williams, *ibid.*, 540 (1967).

(14) (a) W. Klyne, *Tetrahedron*, **13**, 29 (1961); (b) W. Klyne, *Bull. Soc. Chim. France*, 1396 (1960); (c) P. M. Bourn and W. Klyne, *J. Chem. Soc.*, 2044 (1960).

(15) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, pp 189–190.

(16) M. Tomoeda, M. Inuzuka, and T. Furuta, *Tetrahedron Letters*, 1233 (1964).

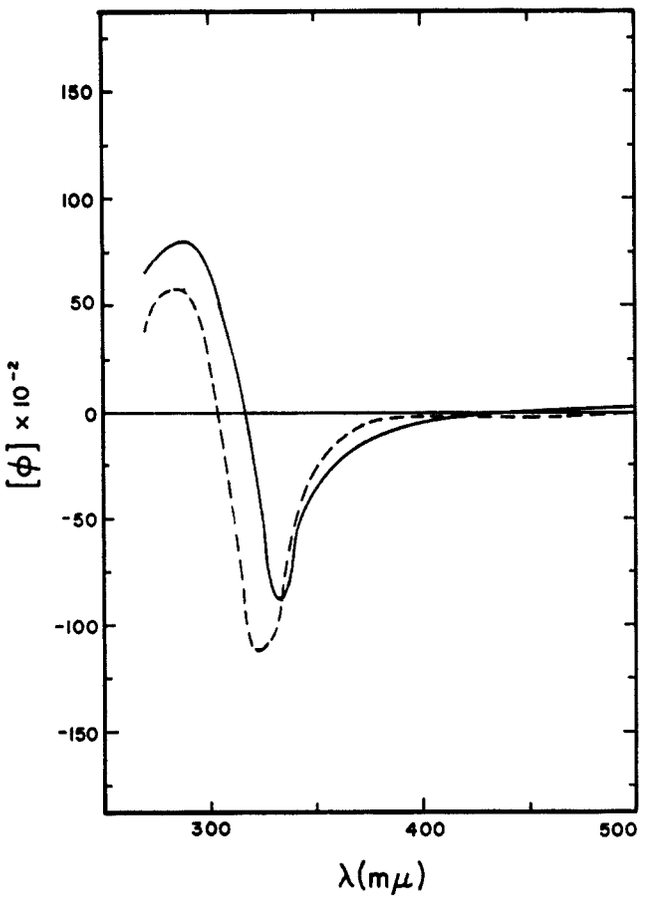


Figure 2.—ORD curves for VII (———) and VIII (- - -).

the C-21 methyl is more pronounced in VII. Consequently, the C-21 methyl was assigned the *cis* configuration in VII and the *trans* configuration in VIII and the *cis* and *trans* configurations for the C-21 methyl were likewise assigned to the parent compounds V and VI, respectively.

Further support for the retention of configuration at C-12 in VII and inversion of configuration at C-12 in VIII was obtained by ORD studies. The ORD curves (see Figure 2) of VII and VIII were in good agreement with that of V, indicating a C/D-*trans* junction in both VII and VIII.

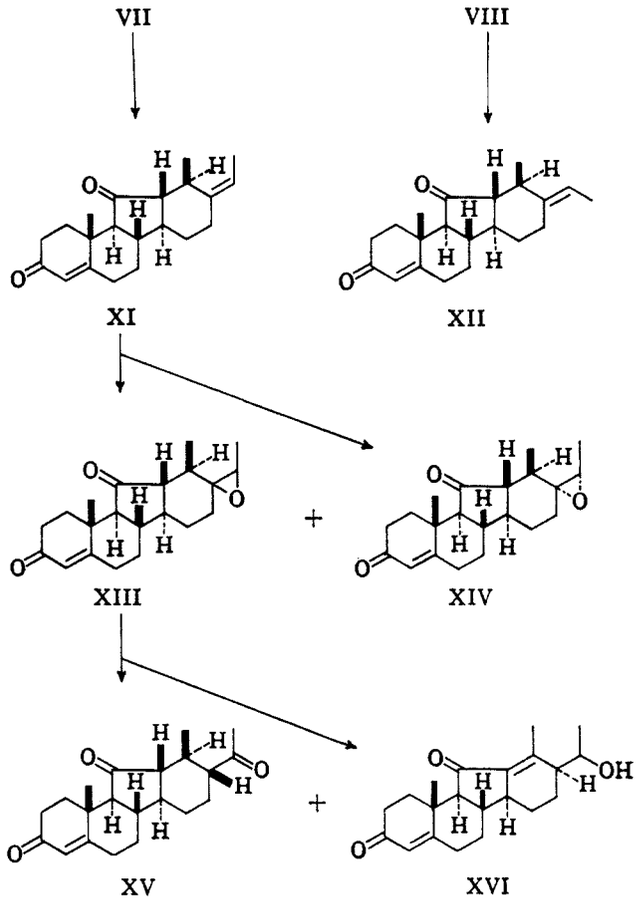
The stability of the C/D-*trans* system, with the C-18β (equatorial) methyl group, in V, VII, and VIII, and the instability of the C/D-*cis* system, with the C-18β (axial) methyl group, in VI finds precedent in the earlier observations on C/D-*cis*–*trans* equilibria in tetrahydrojervine derivatives with open ring E[17] and in perhydroindanone derivatives.[18]

Attempted Wittig alkylation of IV under the modified conditions of Corey, *et al.*,[19] gave an intractable mixture of products. Crystalline isolates from column chromatography, each initially thought to be homogeneous on the basis of melting point and tlc behavior, proved to be mixtures of isomeric products. In retrospect, the greater complexity of the reaction product mixture may have been attributable to an enhancement of rate of isomerization in dimethyl sulfoxide and base.

(17) O. Wintersteiner and M. Moore, *Tetetrahedron*, **20**, 1947 (1964).
(18) (a) H. O. House and G. H. Rasmussen, *J. Org. Chem.*, **28**, 31 (1963); (b) W. Hückel, M. Sachs, J. Yantschulewitch, and F. Nerdel, *Ann.*, **618**, 155 (1953).
(19) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **84**, 866 (1962).

The next step in the synthesis was the addition of oxygen functions to the $\Delta^{17(20)}$ double bond. Exocyclic double bonds are generally more vulnerable than endocyclic double bonds to addition reactions. However, the selective oxidation of the $\Delta^{17(20)}$ double bond in VII (Scheme III), either by epoxidation with *m*-perphthalic

SCHEME III



acid or by osmylation, could not be achieved without simultaneous oxidation of the Δ^5 double bond, as evidenced by tlc analysis of the products.

In order to reduce the nucleophilicity of the second double bond, compound VII was oxidized by the Oppenauer method, using the procedure of Kupchan, Masamune, and Milne,[5] to afford the oxidation product, Δ^4-17-*cis*-ethylideneetiojervene-3,11-dione (XI), in 65–70% yield. The infrared spectrum indicated the absence of hydroxyl absorption at 2.80 μ and the appearance of new bands at 6.02 μ (Δ^4-3-one) and 6.20 μ (conjugated double bond) in addition to the band at 5.80 μ (five-membered ring carbonyl). The ultraviolet spectrum showed λ_{max} 236 mμ (ϵ 17,000), in good agreement with the presence of a Δ^4-3-one system. The nmr spectrum indicated a downfield shift of the vinyl proton to τ 4.24 (C-4 vinyl proton) and, for the first time in the series, a clear quartet for the C-20 vinyl proton at τ 4.74 (J = 7 cps). The signal for the C-19 protons appeared at τ 8.77 and those of C-18 at τ 8.80 (doublet, J = 7 cps).

Likewise, compound VIII was oxidized by the Oppenauer method to give Δ^4-17-*trans*-ethylideneetiojervene-3,11-dione (XII), also in 65–70% yield. The infrared and ultraviolet spectra of XII were similar to those of XI. In order to prove that oxidation of VII

TABLE II
NMR DATA

Compd	C-19 CH_3	C-18 CH_3	C-21 CH_3	C-6 H	C-3 H	OH	C-20 H	C-4 H	C-16 H
VII	9.00 (3 H) s	8.68 (3 H) d J = 6 cps	8.40 (3 H) d J = 6 cps	4.60 (1 H) m	6.59 (1 H) m	8.12 (1 H) m	4.75 (1 H) q J = 6 cps	...	...
VIII	8.95 (3 H) s	8.81 (3 H) d J = 6.5 cps	8.45 (3 H) d J = 6.5 cps	4.62 (1 H) m	6.52 (1 H) m	8.13 (1 H) s	4.77 (1 H) q J = 6.5 cps	...	...
XI	8.77 (3 H) s	8.80 (3 H) d J = 7 cps	8.42 (3 H) d J = 7 cps	...	...	...	4.74 (1 H) q J = 7 cps	4.24 (1 H) s	...
XIII	8.85 (3 H) s	8.85 (3 H) d J = 6 cps	8.75 (3 H) d J = 6 cps	...	...	...	7.18 (1 H) q J = 6 cps	4.22 (1 H) s	...
XVIII	8.80 (3 H) s	8.80 (3 H) d J = 7 cps	7.71 (3 H) s	...	...	...	...	4.23 (1 H) s	3.25 (1 H) m
XX	8.79 (3 H) s	8.69 (3 H) d J = 6.5 cps	7.62 (3 H) s	...	...	6–6.5 (1 H) broad m	...	4.23 (1 H) s	...
XXII	8.79 (3 H) s	8.74 (3 H) d J = 6 cps	7.76 (3 H) s	...	...	7.20 (1 H) s	...	4.22 (1 H) s	...

and VIII to XI and XII, respectively, under Oppenauer conditions did not involve isomerization at any center, the ORD curves of XI and XII were determined and compared with those of their precursors (see Figure 3). Both compounds showed equal negative Cotton effects, in excellent agreement with those for VII and VIII, and indicative that no isomerization had occurred at any of the asymmetric centers.

Treatment of XI with about 10 equiv of monoperphthalic acid in ether solution at room temperature for 24 hr led to exclusive attack on the $\Delta^{17(20)}$ double bond to produce high yields of two isomeric epoxides, which were separated by fractional crystallization from ether. The major isomer, Δ^4-17-ethyletiojervene-3,11-dione 17β,20β-oxide (XIII), was obtained in 65% yield, while the minor isomer, Δ^4-17-ethyletiojervene-3,11-dione 17α,20α-oxide (XIV), was obtained in 20% yield and showed a lower R_f value than XIII. The infrared spectra of both isomers were very similar and showed absorption bands at 5.79 μ (five-membered ring carbonyl), 6.00 μ (Δ^4-3-one), 6.20 μ (conjugated double bond), and 9.70, 9.50, and 11.02 μ (epoxide). Their ultraviolet spectra were analogous to those of the parent compounds and possessed maxima at 236 mμ. The nmr spectrum of XIII (see Table II) showed the C-20 proton signal as a well-resolved quartet centered at τ 7.18 (J = 6 cps) and the C-21 methyl signal as a doublet at τ 8.75 (J = 6 cps). A doublet assigned for the C-18 methyl appeared at τ 8.85 (J = 6 cps), overlapping the singlet due to the C-19 methyl group.

In order to prepare a C-nor-D-homoprogesterone analog, it was necessary to transform the epoxide XIII into a C-20 ketone. Treatment of XIII with boron trifluoride etherate in dry benzene at room temperature for 5 min gave two main products, which were separated by preparative tlc. The compound of higher R_f was Δ^4-17α-ethyletiojervene-3,11,20-trione (XV). The structure was supported by its infrared spectrum, which showed a new carbonyl absorption at 5.84 μ (C-20 carbonyl), in addition to the bands at 5.78 μ (five-membered ring carbonyl), 6.00 μ (Δ^4-3-one), and 6.20 μ (conjugated double bond) and its ultraviolet spectrum with λ_{max} 237 mμ (ϵ 18,000). Compound XV did not isomerize in base, an indication that the compound is in its most stable (C/D-*trans*) form, and that the acetyl side chain is α (equatorial). $\Delta^{4,12(13)}$-17β-Ethyletiojerven-20β-ol-3,11-dione (XVI) was isolated from the second band. The infrared spectrum showed absorption bands at 2.80 μ (C-20 hydroxyl), a new carbonyl band at 5.85 μ, and the absence of the original band at 5.78 μ, indicative of conjugation of the five-membered ring carbonyl. The peaks at 6.00 and 6.12 μ were unchanged. The ultraviolet spectrum showed no absorption at 236 mμ for the chromophore in ring A; instead, there appeared a more intense absorption at higher wavelength, λ_{max} 247 mμ (ϵ 24,480). The formation of XV and XVI from XIII can be rationalized on the basis of mechanisms proposed earlier for the opening of steroidal epoxides in Lewis acids.[20] The formation of the elimination product XVI is explicable on the basis that the 17,20-epoxide in XIII occupies the antiparallel configuration to the C-13α (axial) H, which in turn is antiparallel to the C-12β (axial) H. On this account, the epoxide in XIII was assigned the β configuration and the epoxide in isomer XIV the α configuration.

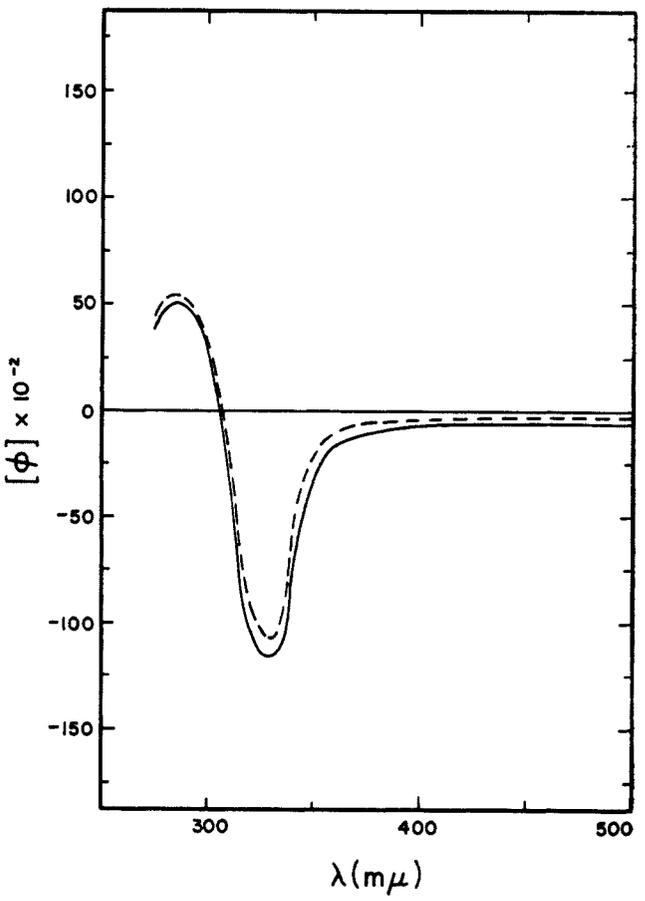
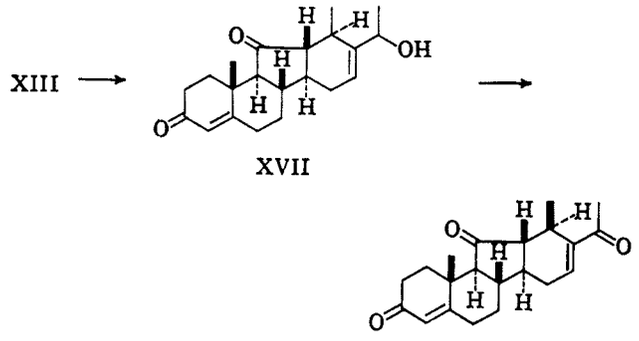


Figure 3.—ORD curves of XI (- - -) and XII (———).

Several attempts were made to convert the epoxy compound XIII into 17,20-oxygenated C-nor-D-homo-

(20) H. B. Henbest and T. I. Wrigley, *J. Chem. Soc.*, 4596 (1957).

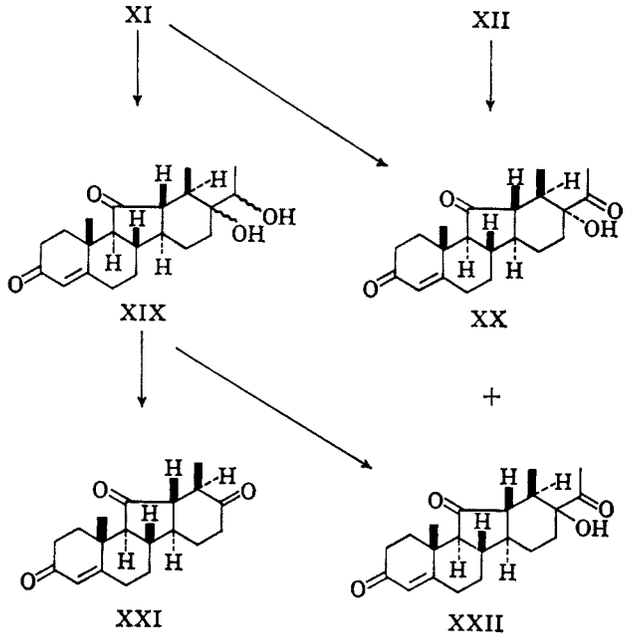
progesterone derivatives. Treatment of XIII with potassium dichromate in acetic acid[21] or with perchloric acid in acetone[22] gave intractable mixtures of products. Treatment of XIII on a steam bath in dimethyl sulfoxide with boron trifluoride etherate[23] gave almost a quantitative yield of $\Delta^{4,16}$-17-ethyletiojervadien-20β-ol-3,11-dione (XVII). Oxidation of XVII with chromic acid in pyridine gave a high yield of $\Delta^{4,16}$-17-ethyletiojervadiene-3,11,20-trione (XVIII). The ultraviolet spectrum of XVIII, λ_{max} 232.5 mμ (ϵ 24,500),



indicated the presence of two overlapping chromophores. Strong absorption bands at 6.00 μ (Δ^4-3-one and Δ^{16}-20-one) and 6.20 μ (Δ^4 and Δ^{16} conjugated) appeared in its infrared spectrum. The direction of elimination of water to produce the trisubstituted double bond (Δ^{16}), instead of the more stable tetrasubstituted double bond (Δ^{13}), was evident from its nmr spectrum, which showed two vinyl proton signals, a singlet at τ 4.22 (C-4 proton), and a multiplet at τ 3.25 (C-16 proton), in good agreement for the position of a proton on the β carbon of an α,β-unsaturated ketone. Furthermore, a singlet at τ 7.70 (C-21 methyl group) corresponded to that expected for a methyl ketone. The signal for the C-18 methyl doublet overlapped with that for the C-19 singlet and both appeared at τ 8.80. The position of the C-18 methyl group signal indicated that no isomerization at C-12 had occurred. The elimination of water to produce the trisubstituted double bond (Δ^{16}), instead of the tetrasubstituted (Δ^{13}), could be rationalized upon examination of molecular models. The 16,17 double bond appears to introduce much less strain in ring D than the 13,17-double bond.

The unpromising experiences with the epoxide XIII led to consideration of alternative methods of selective oxidation of the 17,20 double bond in XI. Treatment of XI with 1 equiv of osmium tetroxide in ether at room temperature for 58 hr gave a gray precipitate of the osmate esters which was collected and decomposed into the diols, either with sodium bisulfite in pyridine[24] or with 7% mannitol in 1% potassium hydroxide solution.[25] The mixture of α- and β-*cis*-glycols (XIX), obtained in over 80% yield, showed spectral properties which confirmed the exclusive oxidation of the 17,20 double bond (Scheme IV). Thus the infrared spectrum showed absorption bands at 2.80 and 2.90 μ (broad and

SCHEME IV



intense owing to H bonding) and an unchanged carbonyl region with bands at 5.78 μ (five-membered ring carbonyl), 6.00 μ (Δ^4-3-one), and 6.20 μ (conjugated double bond). Moreover, there was an absorption band at 236 mμ in the ultraviolet spectrum. The glycols could not be separated by column chromatography and an attempt was made to oxidize to a mixture of 20-ketones. However, oxidation of the glycol mixture under a variety of conditions gave, in high yield, the known cleavage product, Δ^4-etiojervene-3,11,17-trione (XXI) (*cf.* ref 1).

Another procedure involved oxidation of the 17,20 double bond with a catalytic amount of osmium tetroxide in the presence of potassium chlorate in tetrahydrofuran and water at 48° for a period of 24 hr. Thin layer chromatography of the crude product indicated a high yield of the glycols (XIX) and minute amounts of the hydroxy ketones. The crude reaction mixture was oxidized with chromic acid in pyridine and the reaction product was chromatographed on acid-washed alumina. A fraction eluted with 30% ether in benzene failed to crystallize, but tlc, infrared, and ultraviolet analyses indicated it to be the dehydrated product XVII. Elution with 40% ether in benzene gave low yields of the desired product, Δ^4-17-ethyletiojerven-17α-ol-3,11,20-trione (XX). Further elution with ether also gave low yields of the isomeric product, Δ^4-17-ethyletiojerven-17β-ol-3,11,20-trione (XXII).

Ultimately, the synthesis of the hydroxy ketones XX and XXII was achieved by a one-step oxidation of the 17,20 double bond in XI under neutral conditions according to the procedure of Miescher and Schmidlin.[26] Treatment of XI with a catalytic amount of osmium tetroxide and hydrogen peroxide in *t*-butyl alcohol and water under a nitrogen atmosphere gave good yields of XX and XXII after chromatography on silica gel. In an analogous manner compound XII was also converted into XX and XXII, in confirmation of the argument presented earlier that compounds VII and VIII differed only in the orientation of the C-21 methyl

(21) L. F. Fieser, *J. Am. Chem. Soc.*, **75**, 4386 (1953).
(22) R. Takasaki, *Chem. Pharm. Bull.* (Tokyo), **10**, 445 (1962).
(23) T. Cohen and T. Tsuji, *J. Org. Chem.*, **26**, 1681 (1961).
(24) J. S. Baran, *ibid.*, **25**, 287 (1960).
(25) N. L. Wendler, R. B. Graber, R. E. Jones, and M. Tishler, *J. Am. Chem. Soc.*, **74**, 3630 (1952).
(26) K. Miescher and J. Schmidlin, *Helv. Chim. Acta*, **33**, 1840 (1950).

group about the $\Delta^{17(20)}$ double bond. Consequently, the derivatives obtained from VII and VIII (*i.e.*, XI and XII) bear the same relationship.

The characteristics of the infrared spectrum of XX differed from those of XXII. The spectrum of XX showed a weak absorption band for the hydroxyl group at 2.90 μ and three distinct carbonyl bands at 5.78 μ (five-membered ring carbonyl), 5.86 μ (C-20 carbonyl), and 6.00 μ (Δ^4-3-one), while the spectrum of XXII showed two absorption bands for the hydroxyl group at 2.80 μ (sharp but weak) and 2.90 μ (broad and intense, indicating strong H bonding). Examination of the carbonyl region suggested that the C-17 hydroxyl is chelated with the C-20 ketone since the band at 5.86 μ was less intense than the other two bands at 5.78 μ (five-membered ring carbonyl) and 6.00 μ (Δ^4-3-one). Hydrogen bonding between the C-17 hydroxyl and the C-20 ketone is most effective when both groups are in the same plane. Examination of molecular models showed that in the case of the equatorial alcohol, when the C-20 ketone is in the same plane as the alcohol, there is a steric interaction between the C-21 methyl group and the C 12β (axial) hydrogen. For this reason the β-acetyl side chain is forced out of the plane of the hydroxyl group and chelation is not favored. In the axial alcohol, the α-acetyl side chain has no steric interactions when the C-20 ketone is in the same plane with the 17 hydroxyl and chelation is favored. A preliminary assignment was made based on the infrared spectral observations and XX was assigned the 17α-hydroxy configuration (no H bonding) and XXII the 17β-hydroxy configuration (strongly H bonded). The ultraviolet spectra of XX and XXII were very similar, with λ_{max} 236 mμ (ϵ 17,000) and λ_{max} 236 mμ (ϵ 18,000), respectively.

Examination of Table II shows that the nmr spectra of XX and XXII are similar and no stereochemical conclusions can be deduced from them. The signal for the C-21 methyl group protons in XX appeared at τ 7.62 while the signal of those of XXII was shifted upfield by 0.14 ppm (τ 7.76). In compound XX the hydroxyl signal appears as a complex multiplet between τ 6.0 and 6.5 (1 H) while in XXII it appears as a single peak at τ 7.20. Both signals disappeared upon exchange with deuterium when the compounds were shaken with D_2O. The positions of the C-18 methyl group doublet in the spectra of both compounds XX and XXII (τ 8.69 and 8.74, respectively) were in good agreement with those of other C/D-*trans* compounds containing the C-18β (equatorial) methyl group, an indication that no isomerization had taken place at C-12.

The fact that compound XVIII showed one intense absorption maximum in the ultraviolet region(λ_{max}^{EtOH} 232.5 mμ (ϵ 24,500)) for both chromophores in the ring A and ring D made it possible to determine the rate of elimination of water in compounds XX and XXII by ultraviolet analysis. Indeed, when alcohols XX and XXII were dissolved in methylene dichloride containing 0.3% phosphorous oxychloride and the increase in absorptions were observed at appropriate time intervals (equal concentrations of XX and XXII were used), the rate of incremental increase in absorption observed for XXII was much faster than for XX, indicating a more facile dehydration of XXII. Axial alcohols eliminate water many times faster than the equatorial alcohols and the observed rates of elimination were therefore in good agreement with the preliminary configurational assignments based on the infrared spectral observations.

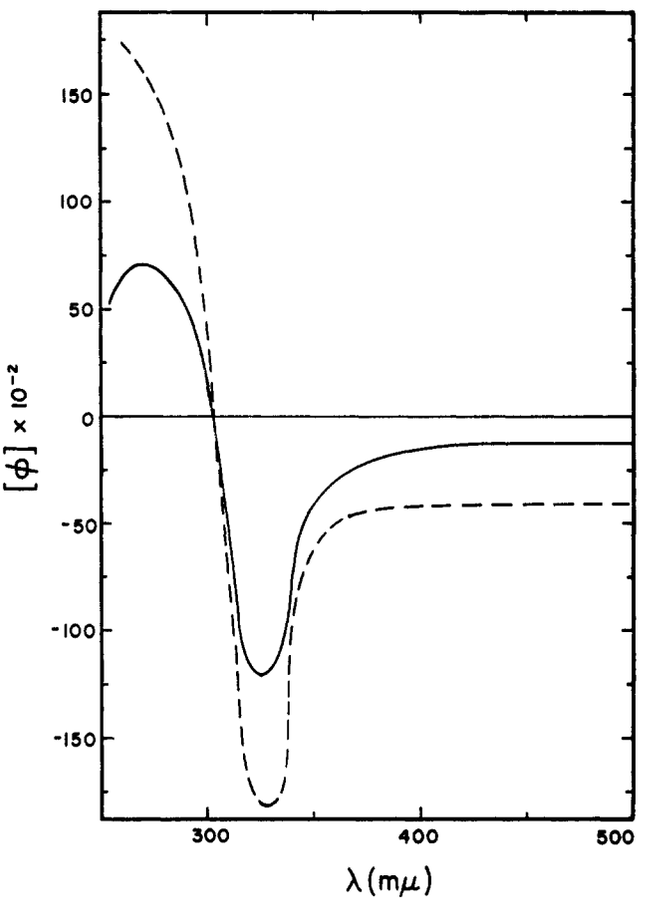
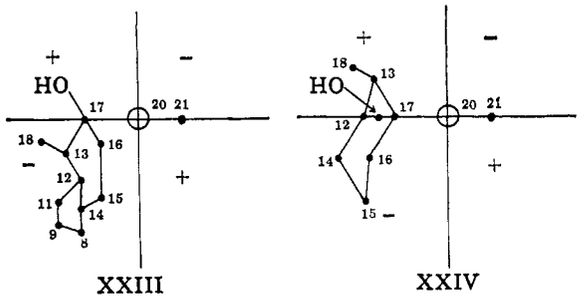


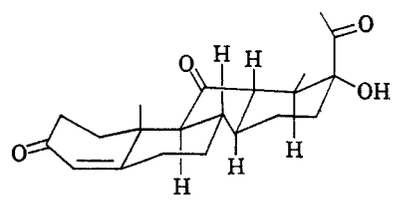
Figure 4.—ORD curves for XX (- - -) and XXII (———).

Confirmatory evidence for the assignment of stereochemistry came from ORD studies (see Figure 4) on XX and XXII. The contributions due to the C-3 and C-11 ketones were expected to be the same as in the parent compound XI (a = −164°). It has been suggested earlier that the β-acetyl side chain in XX is out of the plane of the 17α-hydroxyl group, owing to steric interaction with the C-12β (axial) hydrogen. Examination of molecular models indicated that a strong negative Cotton effect is predicted for the 17β-acetyl group, since, when the β-acetyl group is fitted into the octant projection, the rest of the molecule falls in a negative quadrant (see XXIII). This is in good agreement with the experimental amplitude found for XX (a = −374°). In the other isomer, XXII, it has been shown that there is chelation between the 17β hydroxyl and the C-20 ketone and that the α-acetyl side chain is fixed in the

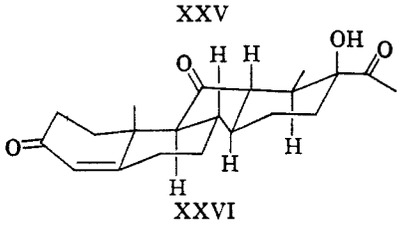


plane of the 17β hydroxyl. Examination of molecular models indicated a slight contribution to the Cotton effect for the 17-ketone according to the octant projection, since part of the molecule falls in a positive quadrant and the other part of it falls in a negative quadrant and these appear to counterbalance each other (see XXIV). This is also in good agreement with the experimental value found for XXII ($a = -193°$).

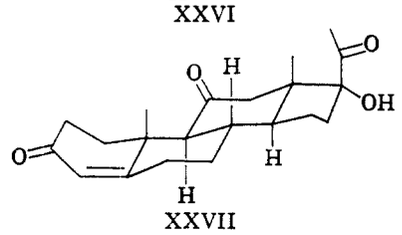
The spectral data of all the intermediates discussed have supported assignment of configuration at C-12, C-13, and C-17. The configurations at the other four asymmetric centers, C-8, C-9, C-10, and C-14, in jervine have earlier been established to be the same as in normal steroids, *i.e.*, C-8β, C-9α, C-10β, and C-14α.[3] Isomerization at C-9 during the transformations from jervine is regarded as exceedingly unlikely, because the C-9α configuration has been shown to be favored in C-nor steroids.[27] Furthermore, the data in Table I and II show that the chemical shifts for the C-19 methyl group in all intermediates are in good agreement with those expected for compounds with a B/C-*trans* ring juncture.[28] The equatorial alcohol XX may be regarded as C-nor-D-homo-11-keto-17α-hydroxyprogesterone, since it possesses the progesterone configuration at each of the ring junctions and the planarity of this molecule (*cf.* XXV) resembles the planarity of naturally occurring 11-keto-17α-hydroxyprogesterone (XXVII). The axial alcohol XXII, C-nor-D-homo-11-keto-17β-hydroxyprogesterone, may be represented as in XXVI.



XXV



XXVI



XXVII

Experimental Section[29]

Δ⁵-Etiojerven-3β-ol-11,17-dione acetate (IV) was prepared *via* II[3,5] and III.[3] The product showed λ_{max} 5.78, 5.80, 5.82, 8.00 μ; ORD $[\phi]_{280}^{peak}$ +13261°; $[\phi]_{330}^{trough}$ −14294°; $a = -275°$.

Δ⁵-17-*cis*-Ethylideneetiojerven-3β-ol-11-one Acetate (V) and Δ⁵-17-*trans*-Ethylideneetiojerven-3β-ol-11-one Acetate (VI).—To a stirred suspension of ethyltriphenylphosphonium bromide (6.5 g, mp 206–208°) in anhydrous ether (50 ml) was added a solution of 15% *n*-butyllithium in *n*-hexane (7.7 ml) at room temperature under a nitrogen atmosphere. The mixture was stirred for 2 hr. A solution of IV (3.0 g, mp 171–172°) in dried tetrahydrofuran (10 ml) was then added dropwise during a period of 15 min. The reaction mixture was stirred for an additional 4 hr and allowed to stand at room temperature overnight. Tetrahydrofuran (50 ml) was added and at the same time the ether was distilled off until most of the latter was displaced. The stirred mixture was refluxed for 6 hr, cooled, and treated with ether (100 ml) and water (100 ml). The organic layer was washed successively with 5% hydrochloric acid solution, a saturated sodium bicarbonate solution, and water. The ether was dried over anhydrous magnesium sulfate and evaporated to dryness to provide a residue (4.25 g) which was reacetylated by treating at room temperature for 15 hr with acetic anhydride (20 ml) and pyridine (20 ml). The reaction mixture was poured over cracked ice and more water was added. The yellow gum which separated was extracted with ether (three 50-ml portions) and the combined ether extracts were washed with a saturated sodium bicarbonate solution, 5% hydrochloric acid, and finally with water. The ether solution was dried over anhydrous sodium sulfate and evaporated to dryness to give a brownish semisolid (3.5 g) which was chromatographed on acid-washed alumina (100 g) packed in petroleum ether. Elution with petroleum ether in benzene (1:1, 1.5 l., and 1:4, 1 l.) gave, upon evaporation, a white solid (V, 1.1 g) which crystallized from methanol (1.0 g, mp 144–146°). A sample was recrystallized from methanol for analysis: mp 146–147°; $[\alpha]^{28}D$ − 181° (*c* 0.16); λ_{max} 5.80, 8.00 μ; ORD $[\phi]_{280}^{peak}$ +5729°; $[\phi]_{331}^{trough}$ −10442°; $a = -161°$.

Anal. Calcd for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 77.41; H, 8.97.

Continued elution with benzene (1 l.) yielded a mixture of V and VI (0.2 g). Further elution with benzene (1 l.) yielded a solid which crystallized from methanol to afford VI (0.15 g, mp 152–154°). A sample was recrystallized from methanol to yield the analytical sample: mp 153–154°; $[\alpha]^{29}D$ −79° (*c* 0.57); λ_{max} 5.80, 8.00 μ; ORD $[\phi]_{287}^{peak}$ +2194°; $[\phi]_{330}^{trough}$ −6546°; $a = -87°$.

Anal. Calcd for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 77.44; H, 9.14.

Δ⁵-17-*cis*-Ethylideneetiojerven-3β-ol-11-one (VII).—A solution of V (360 mg, mp 146–147°) in 5% potassium hydroxide in methanol (20 ml) was allowed to stand at room temperature for 24 hr. Water was added and part of the methanol was evaporated under vacuum. A fine white solid separated and this was extracted with ether (150 ml). The ether extract was washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness. Crystallization of the residue (310 mg) from a mixture of ether and petroleum ether gave prisms of VII (290 mg, mp 172–174°). Two further recrystallizations from ether gave the analytical sample as fine needles: mp 174.5–175.5°; $[\alpha]^{30}D$ +27° (*c* 0.15, dioxane, from ORD); λ_{max} 2.80, 5.78, 6.10 μ (weak); ORD $[\phi]_{290}^{peak}$ +8252°; $[\phi]_{332.5}^{trough}$ −8886°; $a = -171°$.

Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.43; H, 9.55.

Δ⁵-17-*trans*-Ethylideneetiojerven-3β-ol-11-one (VIII).—A solution of VI (460 mg, mp 153–154°) in 5% potassium hydroxide in methanol (20 ml) was allowed to stand at room temperature for 24 hr. Water was added and a fraction of the methanol was distilled off under reduced pressure, whereby a fine solid pre-

(27) (a) G. Ourisson, P. Witz, and H. Hermann, *Bull. Soc. Chim. France*, 1090 (1963); (b) G. Ourisson, J. Winter, and M. Rajic, *ibid.*, 1363 (1964).

(28) (a) P. W. Schiess, D. M. Bailey, and W. S. Johnson, *Tetrahedron Letters*, 549 (1963); (b) D. M. Bailey, D. P. G. Hamon, and W. S. Johnson, *ibid.*, 555 (1963).

(29) Melting points were determined on a Fisher-Johns melting point apparatus. Values of $[\alpha]D$, in chloroform unless otherwise specified, have been approximated to the nearest degree. Ultraviolet absorption spectra were determined in 95% ethanol on a Beckman Model DK2A recording spectrophotometer. Infrared absorption spectra were recorded in chloroform (unless otherwise specified) on a Beckman Model 5A double-beam infrared recording spectrophotometer. Optical rotatory dispersions were determined in dioxane on a Cary Model 60 spectropolarimeter. Nuclear magnetic resonance spectra were recorded on a Varian Associates recording spectrometer (A-60A) at 60 Mc/sec in deuterated chloroform (unless otherwise specified) using tetramethylsilane as an internal standard. Chemical shifts were recorded in τ values (parts per million); multiplicity of signals is designated as follows: s, singlet; d, doublet; q, quartet; and m, multiplet center. Microanalyses were carried out by J. F. Alicino, Metuchen, N. J., and Spang Microanalytical Laboratory, Ann Arbor, Mich. Thin layer chromatography (tlc) was carried out with silica gel G and silica gel $F_{254+366}$ (Brinkmann Instruments). Alumina refers to Merck acid-washed alumina. Pyridine was dried over potassium hydroxide. Boron trifluoride etherate was freshly distilled before use. Benzene was distilled and dried over sodium. Dioxane was purified as described by A. Vogel, "Practical Organic Chemistry," 3rd ed, Longsmans, Green and Co., London, 1961, p 177. Aluminum isopropoxide refers to Eastman practical grade. Petroleum ether refers to the fraction of bp 60–68°.

cipitated which was extracted with ether (200 ml). The ethereal extract was washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness to leave a white residue (420 mg). The solid was crystallized from a mixture of ether and petroleum ether to afford white needles of VIII (380 mg, mp 204–205°). The analytical sample was prepared by recrystallization from ether to yield needles: mp 205–206°; $[\alpha]^{20}D$ +21° (c 0.117, dioxane, from ORD); λ_{max} 2.80, 5.78, 6.10 μ (weak); ORD $[\phi]^{peak}_{285}$ +5924°; $[\phi]^{trough}_{322}$ −11336°; a = −172°.

Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.11; H, 9.65.

Δ⁴-17-*cis*-Ethylideneetiojervene-3,11-dione (XI).—To a mixture of dry toluene (250 ml) and cyclohexanone (20 ml) was added VII (1.23 g) and some toluene (80 ml) was distilled off. Aluminum isoproproxide (1.5 g) in toluene (15–20 ml) was added to the hot reaction mixture and refluxing was continued for 2.5 hr. To the cooled reaction mixture was added a saturated solution of Rochelle's salt (50 ml) and the mixture was steam distilled until the distillate became clear. The aqueous layer was extracted with chloroform (300 ml) and the chloroform solution was washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness. The residue was crystallized from ether to provide prisms of XI (0.5 g, mp 163–165.5°). The mother liquor was chromatographed on 20 g of acid-washed alumina packed in benzene. The fraction eluted with benzene (1.5 l.) was evaporated to dryness and the residue was crystallized from ether to yield more of the product (0.4 g, mp 163–165°). Recrystallization from ether gave the analytical sample: mp 164.5–165.5°; $[\alpha]^{27}D$ −185° (c 0.54); λ_{max} 5.80, 6.02, 6.20 μ; λ_{max} 236 mμ (ε 17,000); ORD $[\phi]^{peak}_{286}$ +5467°; $[\phi]^{trough}_{329}$ −10935°; a = −164°.

Anal. Calcd for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.79; H, 9.05.

Δ⁴-17-*trans*-Ethylideneetiojervene-3,11-dione (XII).—To a mixture of dry toluene (50 ml) and cyclohexanone (8 ml) was added VIII (0.35 g, mp 204–206°) and toluene (20 ml) was distilled off. A solution of aluminum isopropoxide (0.3 g) in toluene (10 ml) was added and the refluxing was continued for 2.5 hr. A saturated solution of Rochelle's salt (15 ml) was added after cooling and the mixture was steam distilled until the distillate became clear. The aqueous layer was extracted with chloroform (75 ml) and the chloroform was evaporated to dryness after being washed with water and dried over sodium sulfate. The residue (0.41 g) was chromatographed on acid-washed alumina (10 g) packed in petroleum ether. The fractions eluted with mixtures of benzene–petroleum ether (1:3, 250 ml), (1:1, 500 ml), (3:1, 500 ml), and benzene (500 ml) were combined and evaporated to dryness to yield a residue which was crystallized from ether to afford needles of XII (0.22 g, mp 173–175°). Recrystallization from ether yielded the analytical sample: mp 175–176°; $[\alpha]^{27}D$ −132° (c 0.85); λ_{max} 5.78, 6.00, 6.20 μ; λ_{max} 236 mμ (ε 16,900); ORD $[\phi]^{peak}_{286}$ +4999°; $[\phi]^{trough}_{329}$ −11663°; a = −166°.

Anal. Calcd for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.63; H, 8.89.

Δ⁴-17-Ethyletiojervene-3,11-dione 17ζ,20ζ-Oxides (XIII and XIV).—To a solution of XI (0.41 g, mp 164–165°) in dry ether (125 ml) was added a solution of monoperphthalic acid in ether (15 ml, 75 mg/ml) and the mixture was allowed to stand in the dark at room temperature for 24 hr. After washing the reaction mixture first with a saturated solution of sodium bicarbonate and then with water, it was dried over anhydrous sodium sulfate and concentrated to about 20 ml. Upon standing, the major product, Δ⁴-17-ethylethiojervene-3,11-dione 17β,20β-oxide (XIII, 0.17 g, mp 193–194°) crystallized in the form of needles. Further concentration of the mother liquor and cooling provided more of XIII (0.07 g, mp 192–194°). One more recrystallization from ether gave the analytical sample: mp 193–194°; $[\alpha]^{26}D$ −76° (c 0.51); λ_{max} 5.79, 6.00, 6.20, 9.70, 10.50, 11.02 μ; λ_{max} 236 mμ (ε 18,000).

Anal. Calcd for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 77.03; H, 8.83.

The mother liquor was further concentrated and a few drops of petroleum ether were added. Upon standing for a long time the minor isomer, Δ⁴-17-ethyletiojervene-3,11-dione 17α,20α-oxide (XIV, 0.06 g, mp 185–186°), crystallized as large prisms: $[\alpha]^{26}D$ +84° (c 0.39); λ_{max} 5.79, 6.00, 6.20, 9.70, 10.50, 11.02 μ; λ_{max} 236 mμ (ε 18,000).

Anal. Calcd for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.88; H, 8.69.

Δ⁴-17-Ethyletiojervene-3,11,20-trione (XV).—A solution of the β-epoxide XIII (0.1 g, mp 194–195°) in dry benzene (5 ml, distilled over sodium metal) was treated with 3–4 drops of freshly distilled boron trifluoride etherate (bp 126°) for 7 min at room temperature. The reaction was stopped by shaking the benzene solution with sodium bicarbonate solution (10 ml) and ether (30 ml). The organic layer was washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness to give a yellowish gum (0.103 g), which failed to crystallize from a variety of solvents.

Preparative tlc on silica gel F (1 mm thick), separation of the fluorescing bands, and elution of the bands with chloroform gave three compounds. From the band of highest R_f was isolated starting material (XII, 30 mg, mp 192–195°). The residue from the second band was crystallized from ether to give pure needles of Δ⁴-17-ethyletiojervene-3,11,20-trione (XV, 20 mg, mp 188–190°). The analytical sample was prepared by recrystallization from ether to yield needles: mp 189–190°; $[\alpha]^{20}D$ +115° (c 0.17, dioxane, from ORD); λ_{max} 5.78, 5.84, 6.00, 6.20 μ; λ_{max} 237 mμ (ε 18,000); ORD $[\phi]^{peak}_{305}$ +7593°; $[\phi]^{trough}_{332.5}$ −1708°; a = −93°.

Anal. Calcd for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.85; H, 8.64.

The material obtained from the third band also crystallized from ether to yield a pure sample of Δ⁴,¹²⁽¹³⁾-17β-ethylethiojervadien-20β-ol-3,11-dione (XVI, 20 mg, mp 205–206°): λ_{max} 2.80, 5.85, 6.00, 6.10 μ; λ_{max} 247 mμ (ε 24,400).

Anal. Calcd for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.59; H, 8.50.

Δ⁴,¹⁶-17-Ethyletiojervadiene-3,11,20-trione (XVIII).—A solution of XIII (65 mg, mp 194–195°) in purified tetrahydrofuran (5 ml) and dimethyl sulfoxide (5 ml) was refluxed for 5 hr in the presence of a catalytic amount of boron trifluoride ethereate (bp 126°, 1 drop). White fine needles precipitated upon addition of water (30 ml). The solid was filtered, washed with water, taken up in chloroform (20 ml), and the chloroform solution was dried over anhydrous sodium sulfate. Evaporation of the chloroform gave a white solid which crystallized from a mixture of chloroform and ether to provide Δ⁴,¹⁶-17-ethyletiojervadien-20β-ol-3,11-dione (XVII, 60 mg, mp 197–198°): λ^{Nujol}_{max} 2.80, 3.00 (broad), 5.78, 6.00, 6.20 μ; λ_{max} 236 mμ (ε 15,500).

A solution of compound XVII (50 mg) in pyridine (5 ml) was treated slowly with a solution of chromic acid (20 mg) in pyridine (15 ml) and the mixture was allowed to stand at room temperature for 15 hr. The reaction mixture was poured over cracked ice and was extracted with ether (150 ml). The ethereal layer was washed with 5% hydrochloric acid, sodium bicarbonate solution, and then water. The ether solution was dried over anhydrous sodium sulfate and was then evaporated to dryness to yield a white solid (XVIII, 42 mg, mp 196–200°). Two recrystallizations from ether–petroleum ether gave pure needles of Δ⁴,¹⁶-17-ethyletiojervadiene-3,11,20-trione: mp 198.5–200°; $[\alpha]^{28}D$ −70° (c 0.49); λ_{max} 5.75, 6.00 (very intense), 6.20 μ (intense); λ_{max} 232.5 mμ (ε 24,500).

Anal. Calcd for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03. Found: C, 77.44; H, 8.18.

Δ⁴-17-Ethyletiojervene-17ζ,20ζ-diol-3,11-dione (XIX).—A solution of compound XI (40 mg, mp 175.5–176.5°) in anhydrous ether (5 ml) was treated dropwise with a solution of osmium tetroxide (31 mg) in anhydrous ether (2 ml) over a period of 15 min at room temperature. The reaction mixture was allowed to stand in the dark for 58 hr. The precipitated osmate esters were collected and decomposed to the diols by either of two methods.

Method 1.—A solution of the osmate esters in chloroform was shaken with 7% mannitol in 1% potassium hydroxide solution (15 ml) for a period of 12 hr. The organic layer was washed with water, dried over anhydrous sodium sulfate, and was evaporated to dryness to provide a purplish gum (44 mg).

Method 2.—The osmate esters (600 mg) were dissolved in pyridine (7 ml) and the solution was treated while stirring for 30 min with sodium bisulfite (0.9 g) in water (15 ml) and pyridine (10 ml). The reaction mixture was then extracted with chloroform (150 ml) and the chloroform layer was washed three times with 5% hydrochloric acid solution, twice with water, and dried over anhydrous sodium sulfate. The chloroform solution was filtered through Celite and evaporated to dryness to yield a crude gummy mixture of the diols (485 mg).

The crude reaction product was chromatographed on acid-washed alumina (15 g) packed in benzene. Elution with 1%

methanol in ether (2 l.) and 5% methanol in ether (0.5 l.) provided, after evaporation to dryness, a grayish gum which solidified upon trituration with ether (XIX, 387 mg). The solid product showed λ_{max} 2.80, 2.90 (broad and intense), 5.78, 6.00, 6.20 μ; λ_{max} 236 mμ.

The mixture of diols was then utilized as such.

Δ^4-Etiojervene-3,11,17-trione (XXI).—A mixture of the epimeric diols (XIX, 25 mg) was oxidized with chromic acid (20 mg) in glacial acetic acid (10 ml) and water (1 ml) at room temperature for a period of 4 hr. The reaction mixture was poured over cracked ice and was extracted with chloroform (30 ml). The chloroform layer was washed with a saturated sodium bicarbonate solution, water, and was then dried over anhydrous sodium sulfate. Evaporation of the chloroform gave a brownish solid which was crystallized from acetone–petroleum ether to provide needles of XXI: mp 214–216°; λ_{max} 5.78, 5.85, 6.00, 6.20 μ (superimposable upon that of the authentic sample); λ_{max} 236 mμ (ϵ 15,500); mixture melting point with the authentic sample was undepressed.

Δ^4-17-Ethyletiojerven-17α-ol-3,11,20-trione (C-Nor-D-homo-11-keto-17α-hydroxyprogesterone) (XX) and Δ^4-17-Ethyletiojerven-17β-ol-3,11,20-trione (C-Nor-D-homo-11-keto-17β-hydroxyprogesterone) (XXII). Method A.—To a stirred solution of XI (700 mg, mp 164–165°) in *t*-butyl alcohol under a nitrogen atmosphere was added a solution of 1.5 *M* H_2O_2 (4 ml) in *t*-butyl alcohol (5 ml), followed by a solution of osmium tetroxide (25 mg) in *t*-butyl alcohol (10 ml) which was added slowly over a period of 1 hr. Stirring was continued for 48 hr, after which was added a solution of sodium sulfite (0.7 g) in water (5 ml) and the stirring was continued for an additional 15 min. Water was added and the reaction mixture was extracted with ether (0.5 l.). The ethereal extract was washed with water and dried over anhydrous sodium sulfate. Evaporation of the ether to dryness gave a solid (0.95 g).

Column chromatography of the residue on silica gel (30 g) packed in benzene and elution with chloroform–benzene mixtures (up to 50% $CHCl_3$, 2 l.) gave starting material (300 mg). Further elution with chloroform–benzene (1:1, 1 l.) provided, after evaporation to dryness, a white solid (280 mg, mp 208–212°) composed mainly of XX. Crystallization from chloroform–petroleum ether gave white needles: mp 215–216°; $[\alpha]^{26}D$ +54° (*c* 0.52); λ_{max} 2.85 (weak), 5.78, 5.84, 6.00, 6.20 μ; λ_{max} 236 mμ (ϵ 17,100); ORD $[\phi]_{270}^{peak}$ +17411°; $[\phi]_{332}^{trough}$ −17360°; a = −347°.

Anal. Calcd for $C_{21}H_{28}O_4$: C, 73.22; H, 8.19. Found: C, 73.28; H, 8.45.

Continued elution with chloroform (1 l.) yielded a white solid (250 mg, mp 225–232°) composed mainly of XXII. Crystallization from chloroform–petroleum ether afforded colorless plates: mp 230–235° dec; $[\alpha]^{27}D$ +56° (*c* 0.43); λ_{max} 2.80, 2.90 (broad and intense), 5.78, 5.84 (moderate), 6.00, 6.20 μ; λ_{max} 236 mμ (ϵ 18,000); ORD $[\phi]_{280}^{peak}$ +7021°; $[\phi]_{328}^{trough}$ −12287°; a = −193°.

Anal. Calcd for $C_{21}H_{28}O_4$: C, 73.22; H, 8.19. Found: C, 73.48; H, 8.39.

Oxidation of XII (60 mg) according to the procedure above yielded three major bands when chromatographed on preparative tlc on silica gel F. The bands were extracted with 1% methanol in chloroform. Band I yielded starting material (20 mg). Band II yielded pure XX (18 mg, mp 215–216°) after crystallization from chloroform–petroleum ether. Band III yielded pure XXII (25 mg) after crystallization from chloroform–petroleum ether.

Method B.—To a solution of potassium chlorate (100 mg) and a catalytic amount of osmium tetroxide (5–10 mg) in tetrahydrofuran (10 ml) and water (5 ml) was added a solution of XI (150 mg, mp 164–165°) in tetrahydrofuran (5 ml). The solution was maintained at 48–50° for a period of 24 hr (or until the disappearance of XI, followed by tlc). Water was added and the resulting precipitate was extracted with ether (200 ml) and the ethereal extract was washed with water and dried over anhydrous sodium sulfate. Evaporation of the ether gave a grayish gum composed mainly of XIX (155 mg), which was dissolved in pyridine (10 ml) and treated with a solution of chromic acid (80 mg) in pyridine (10 ml). The reaction mixture was allowed to stand at room temperature for 30 min and refrigerated for an additional 18 hr. This was poured over cracked ice and water was added before extraction with chloroform (100 ml). The chloroform layer was washed successively with 5% hydrochloric acid solution, 5% sodium bicarbonate solution, and water, and was then dried over anhydrous sodium sulfate. The chloroform was evaporated to dryness to leave a brown residue (120 mg), which was chromatographed on acid-washed alumina (4 g) packed in benzene. Elution with 30% ether in benzene (200 ml) gave an oil (40 mg, λ_{max} 5.78, 6.00, 6.20 μ; λ_{max} 249 mμ) which failed to crystallize. This was believed to be the dehydrated product, $\Delta^{4,16}$-17-ethyletiojervadiene-3,11,20-trione (XVIII). Further elution with 40% ether in benzene gave a solid (25 mg) which crystallized from chloroform–petroleum ether as white needles (XX, mp 215–216°). Continued elution with ether (400 ml) gave a solid (27 mg) which also crystallized from chloroform–petroleum ether to provide colorless plates of XXII, mp 230–234° dec.

Registry No.—IV, 15285-77-5; V, 15285-78-6; VI, 15285-79-7; VII, 15285-80-0; VIII, 15285-81-1; XI, 15285-66-2; XII, 15285-67-3; XIII, 15285-68-4; XIV, 15285-69-5; XV, 15285-70-8; XVI, 15285-71-9; XVII, 15285-72-0; XVIII, 15285-73-1; XIX, 15285-74-2; XX, 15314-05-3; XXI, 15285-75-3; XXII, 15285-76-4.

Sesquiterpene Lactones of *Encelia farinosa* Gray[1]

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Two sesquiterpene lactones isolated from *Encelia farinosa* Gray (Compositae, tribe Heliantheae), farinosin and encelin, have been found to have the structures **2** and **5**, respectively. Encelin, dehydrofarinosin, is also obtained by dehydration of farinosin. Farinosin is the principal lactonic constituent of the leaves while encelin is found in the green stems. As the plant becomes senescent and scarious the compounds disappear.

Encelia farinosa Gray (tribe Heliantheae) is a composite abundant on the southwestern deserts. The plant is a perennial, flowering in March and April. The leaves and stems of early spring growth contain components that are characterizable as sesquiterpene lactones and which disappear as the temperatures rise in early summer and the plant becomes scarious. An examination of *E. farinosa* was undertaken because relatively little study has been devoted to members of the Heliantheae, of which members of the widely studied genus *Ambrosia* have been designated as a subtribe.[2]

Two sesquiterpene lactones, farinosin and encelin, have been isolated from *E. farinosa*. The former is the principal component of the leaves, which contain but traces of encelin; the latter is present in the green stems. Farinosin, mp 200–201°, has the composition

(1) Contribution No. 2151 from the Department of Chemistry, U.C.L.A.

(2) P. A. Munz and D. D. Keck, "A California Floria," University of California Press, Berkeley, 1959, p 1100. However, W. L. Jepson ("A Manual of the Flowering Plants of California," Associated Students Store, University of California, Berkeley, 1923) confers tribal status (Ambrosieae) upon the ragweeds.