ν_{max} 3420, 1769, 1756, 1730, 1670, 1629, 1612, and 1230 cm.$^{-1}$; $[\alpha]^{25}_{D}$ + 87° (methanol).

Anal. Calcd. for $C_{24}H_{31}O_7F$ (450.49): C, 63.98; H, 6.94; F; 4.22; OCH_3, 6.90. Found: C, 64.12; H, 7.26; F, 4.31, OCH_3, 7.58.

9α-Fluoro-11β,17α,21-trihydroxy-6α-methoxy-1,4-pregnadiene-3,20-dione (XIg). A solution of 0.26 g. of the fluorohydrin acetate XIf in 25 ml. of methanol under nitrogen was treated with 0.45 ml. of 10% potassium carbonate. After standing at room temperature under nitrogen for 20 min., the solution was neutralized with acetic acid and the solvent was evaporated. Crystallization from acetone-petroleum ether gave 0.12 g. of XIa, m.p. 263–264°; λ_{max} 238 mμ (ε 14,100); ν_{max} 3430, 1712, 1668, 1630, and 1613 cm.$^{-1}$; $[\alpha]^{25}_{D}$ + 72.5° (methanol).

Anal. Calcd. for $C_{22}H_{29}O_6F$ (408.45): C, 64.69; H, 7.16 F, 4.65; OCH_3, 7.61. Found: C, 64.79; H, 7.41; F, 4.90; OCH_3 8.70.

Acknowledgment. We wish to thank Louis M. Brancone and associates for the analytical data, William Fulmor and asociates for the spectral data and optical rotational data, and Charles Pidacks and associates for the partition chromatographic separations.

PEARL RIVER, N. Y.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, THE UPJOHN CO.]

An Optical Rotatory Dispersion Study of Side Chain Epimers in the Pregnane Series

WILLIAM A. STRUCK AND RONALD L. HOUTMAN

Received March 6, 1961

A number of side chain epimers of pregnan-20-ones have been studied by means of optical rotatory dispersion in order to determine the consistency of the large negative effect encountered with the 17α side chain. This effect has been found to be the same throughout the entire series, and may be used with confidence to determine the configuration of the side chain in pregnan-20-ones complicated by substitution at C-16 in either α or β configuration, and by the presence of additional ketone functions at 3 and 11, even when the 3-ketone is conjugated with a 4 double bond.

The unique contributions of optical rotatory dispersion to the stereochemistry of steroids have been well established by Djerassi and co-workers. One of the more dramatic examples of this use is the differentiation of 5α and 5β isomers of steroids with ketones at C-3 or C-7, a distinction not readily made by other physical methods.[1] Similar striking behavior is noted for 17α- and 17β-acetyl side chains in the pregnane series, as exemplified by 3α-hydroxy-5β-pregnan-20-one acetate and 3α-hydroxy-5β,17α-pregnan-20-one acetate.[2] The 20-ketone in the normal (β) acetyl side chain gives a large positive Cotton effect curve, while the iso (α) side chain gives a Cotton effect which is almost the mirror image.

In the course of a study of 16-substituted pregnenedi- and triones, it became necessary to distinguish between α- and β-acetyl side chains in a group of compounds somewhat more complicated than those cited above. The complicating factors were the existence of a C-4 double bond in conjugation with the 3-ketone, and the presence of certain substituent groups in both the α and β configuration at C-16.

The presence of the conjugated ketone at C-3 would be expected to increase the rotation in a positive direction and introduce the fine structure characteristic of α,β-unsaturated ketones.[3] Substituent groups at C-16 would be expected to contribute effects that would vary depending on the group and its configuration, especially as C-16 would become asymmetric under these conditions.

The perturbing effect of substituents in the vicinity of optically active chromophores, such as the 20-ketone, has been well established. Several examples of α-halo ketones are available which show various vicinal effects.[4] Similarly alkyl substituents, especially in the vicinity of α,β-unsaturated ketones, may exert a profound vicinal action.[5] In general, the axial substituent has the larger effect. Substituents at C-16, therefore, might exert a sufficient vicinal action on the optically active chromophore at C-20 to complicate the behavior of the iso side chain.

In view of these facts it was considered necessary to examine as many pairs of side chain epimers as possible in order to ascertain whether the effect of the acetyl side chain in the α configuration, first noted by Djerassi,[2] was substantially consistent for 3-keto-Δ^4-pregnenes variously substituted at C-16.

The compounds of interest all had the Δ^4,3-ketone as well as the 20-ketone. Some had, in addition, a ketone at C-11, and most were substituted at C-16 with CH_3, CH_2OH, CH_2F, CO_2CH_3, or

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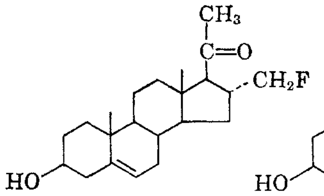
(1) C. Djerassi, *Optical Rotatory Dispersion*, McGraw Hill, New York, 1960, p. 50.

(2) C. Djerassi, *Optical Rotatory Dispersion*, McGraw Hill, New York, 1960, p. 52.

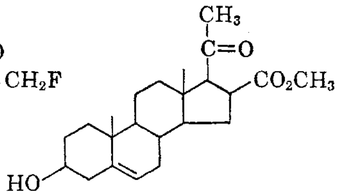
(3) C. Djerassi, R. Riniker, and B. Riniker, *J. Am. Chem. Soc.*, **78**, 6377 (1956).

(4) C. Djerassi, J. Osiecki, R. Riniker, and B. Riniker, *J. Am. Chem. Soc.*, **80**, 1216 (1958).

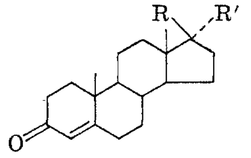
(5) C. Djerassi, O. Halpern, V. Halpern, and B. Riniker, *J. Am. Chem. Soc.*, **80**, 4001 (1958).



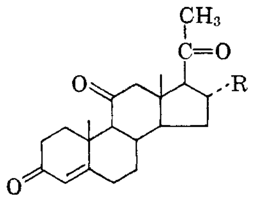
I



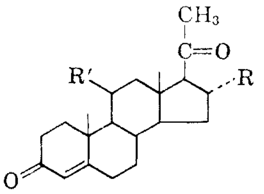
II



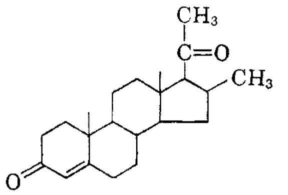
III. R = $COCH_3$; R′ = H
IV. R = H; R′ = $COCH_3$



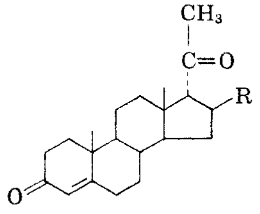
V. R = H
VI. R = CN
VII. R = CH_2F
VIII. R = CO_2CH_3



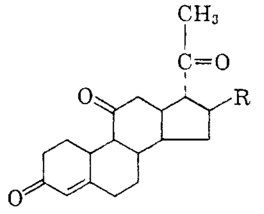
IX. R = H; R′ = OH
X. R = CH_2OH; R′ = OH
XI. R = CH_3; R′ = H



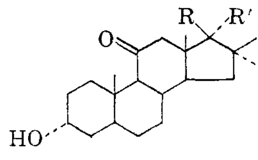
XII



XIII. R = CH_2OH
XIV. R = CH_2F



XV. R = CO_2CH_3
XVI. R = H



XVII. R = $COCH_3$; R′ = R″ = H; R‴ = CN
XVIII. R = R‴ = H; R′ = $COCH_3$; R″ = CO_2CH_3

CN, usually in the opposite configuration of the side chain (III thru XVI).

Fig. 1 shows the rotatory dispersion curves of 16α-fluoromethyl-3β-hydroxy-5-pregnen-20-one (I) and 16β-carbomethoxy-3β-hydroxy-17α-pregn-5-en-20-one (II). These are very much like the curves shown by Djerassi for 3α-hydroxy-5β-pregnan-20-one acetate and 3α-hydroxy-5β,17α-pregnan-20-one acetate,[2] and may be taken as typical of the α *vs.* β side chain behavior in uncomplicated instances. This suggests that the substituents at C-16 have a relatively minor effect, and this will be demonstrated subsequently.

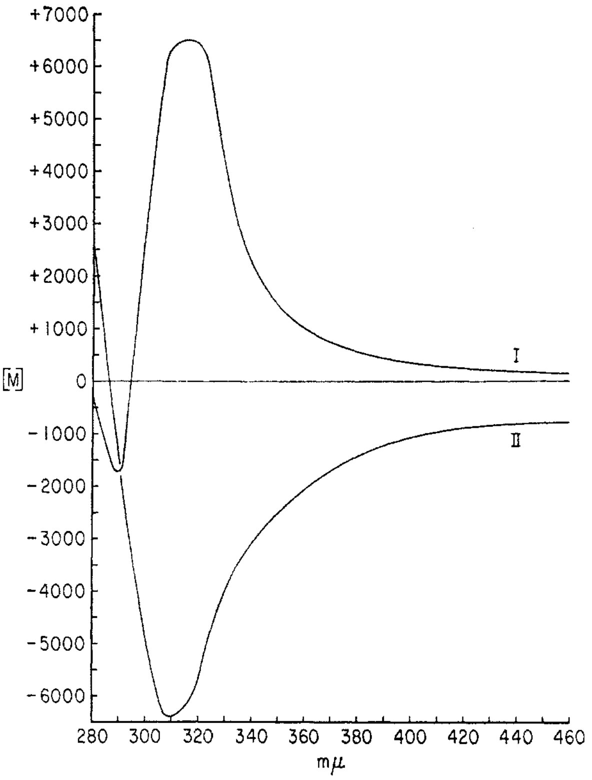


Fig. 1. Rotatory Dispersion Curves of: 16α-Fluoromethyl-3β-hydroxy-5-pregnen-20-one (I); 16β-Carbomethoxy-3β-hydroxy-17α-pregn-5-en-20-one (II)

Fig. 2 shows rotatory dispersion curves for progesterone (III) and 17α-progesterone (IV). These curves are typical of those observed for side chain epimers of 3-keto-Δ^4-pregnenedi- or triones. The large difference between the two is clear, but it is not immediately apparent from simple inspection whether this difference corresponds to the difference seen in Fig. 1. A point of interest is that the fine structure characteristic of the α,β-unsaturated ketones is much more clearly resolved in the 17α compounds than in the 17β compounds.

Fig. 3 shows the near equivalence of a variety of 16α-substituted Δ^4-pregnenetriones. While there are certainly quantitative differences, especially between the extremes of V and VII, these differences are small by comparison with those observed for side chain epimers, as shown in Fig. 2. Fig. 4 shows a similar grouping for some Δ^4-3,20-diones, and again there is a great similarity within the group, indicating that the nature of the substituent at C-16 has a relatively minor effect.

Less evidence is available for evaluating the effect of the configuration of substituents at C-16. Fig. 5 shows rotatory dispersion curves for 16α-(XI) and 16β-methylprogesterone (XII). In both of these compounds the side chain is β, and differences must be attributed to the configuration of the methyl group at C-16. Appreciable differences are noted—sufficiently large to be useful if configuration at C-16 is the issue—but still small by

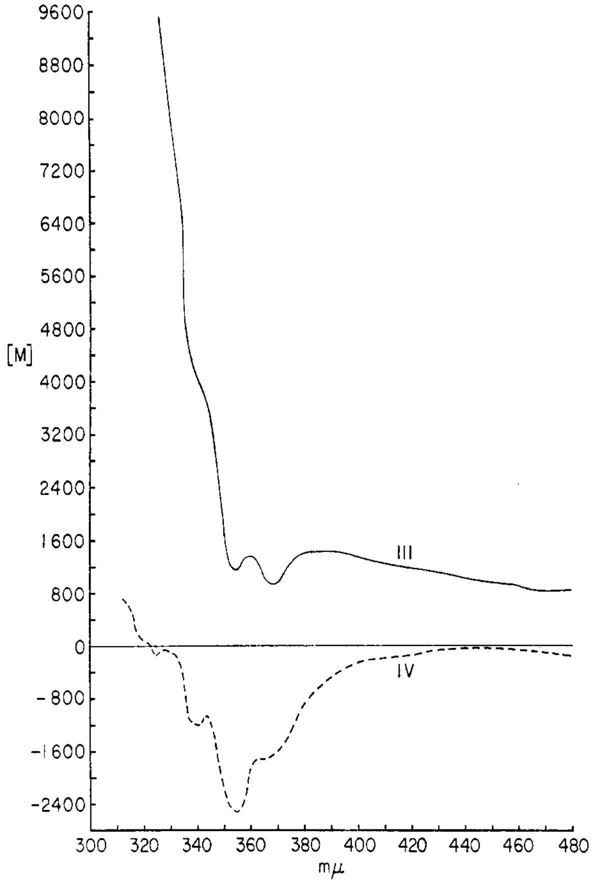


Fig. 2. Rotatory Dispersion Curves of: Progesterone (III); 17α-Progesterone (IV)

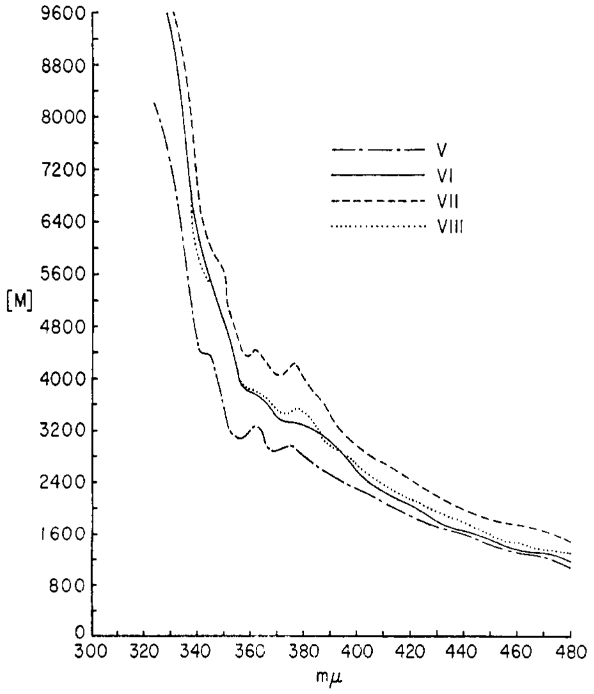


Fig. 3. Rotatory Dispersion Curves of: 11-Ketoprogesterone (V); 16α-Cyano-11-ketoprogesterone (VI); 16α-Fluoromethyl-11-ketoprogesterone (VII); 16α-Carbomethoxy-11-ketoprogesterone (VIII)

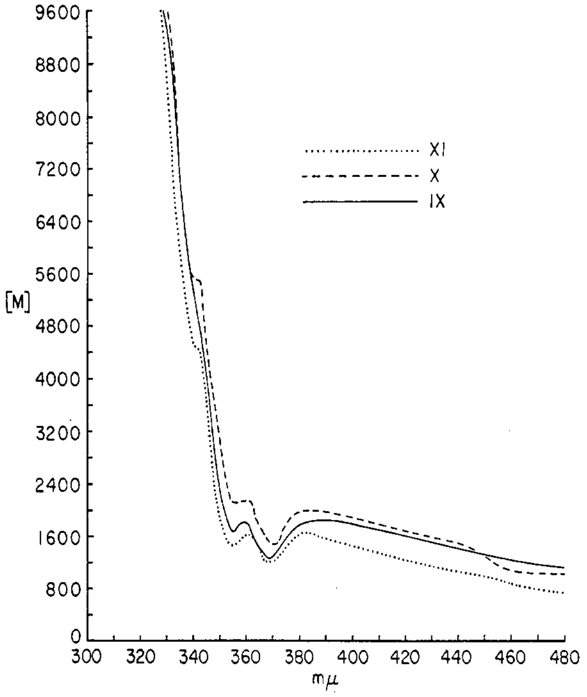


Fig. 4. Rotatory Dispersion Curves of: 11β-Hydroxyprogesterone (IX); 11β-Hydroxy-16α-hydroxymethylprogesterone (X); 16α-Methylprogesterone (XI)

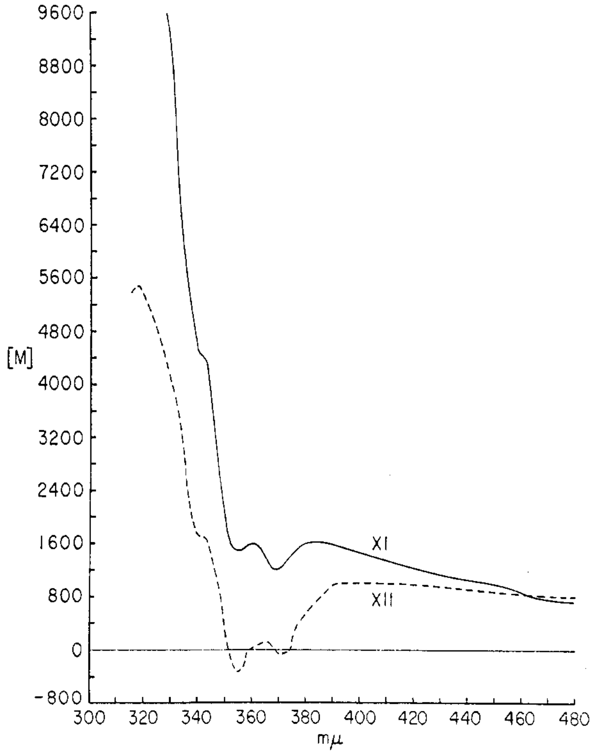


Fig. 5. Rotatory Dispersion Curves of: 16α-Methylprogesterone (XI); 16β-Methylprogesterone (XII)

comparison with the α and β side chain differences shown in Figs. 1 and 2.

To show further that the α *vs.* β side chain effect is consistent throughout this series, a number of α

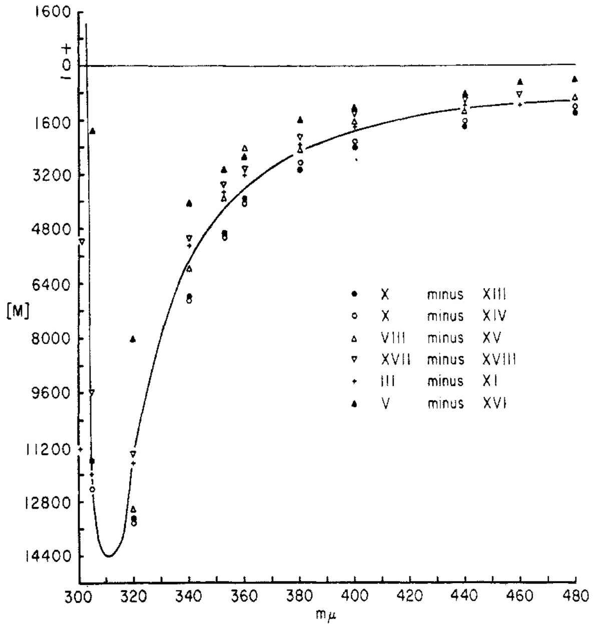


Fig. 6. Average difference curves of: X minus XIII (●); X minus XIV (○); VIII minus XV (△); XVII minus XVIII (▽); III minus XI (+); V minus XVI (▲)

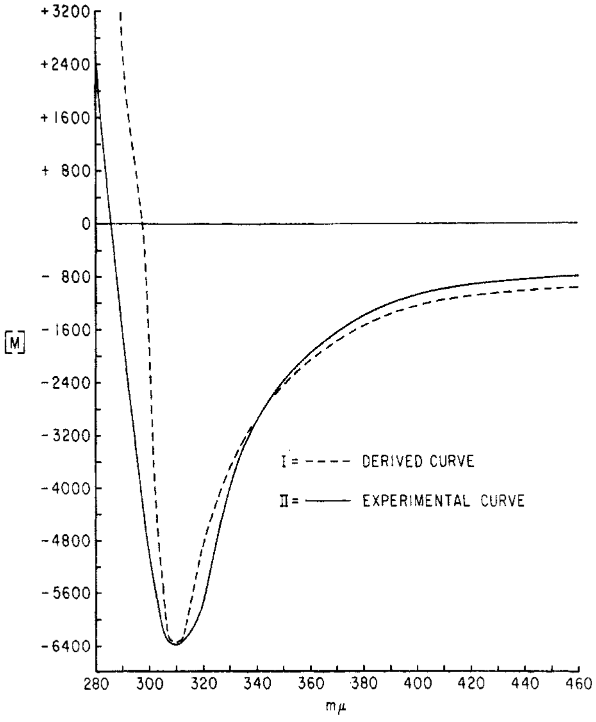


Fig. 7. Derived and experimental curves for 16β-Carbomethoxy-3β-hydroxy-17α-pregn-5-ene-20-one (II)

and β side chain pairs were compared by subtracting algebraically the α from the β at ten wave-length values and assigning a negative sign to the difference. The negative sign was indicated because the effect of the α compared to the β is negative and because it was desired to derive a curve, which, when added algebraically to a β side chain curve, would give a curve typical of the α side chain.

Fig. 6 shows these difference points plotted on one graph. It is apparent that all the points form a pattern and permit the construction of the average curve shown. This average curve represents the "α side chain effect," and when added algebraically to the rotatory dispersion curve of an appropriate ketopregnane or Δ^4- or Δ^5-ketopregnene should give a curve closely approximating what the same or similar compounds with the α side chain would give.

This approach was tried with I. Fig. 7 shows the curve which would be expected if I had an α side chain, obtained by adding algebraically the average curve of Fig. 6 to the actual curve for I (neither I nor II was used in estimating the average curve of Fig. 6). On the same scale is plotted the rotatory dispersion curve of II which is the closest approximation available to a side chain epimer of I. The fact that the two curves are very similar validates the conclusion that the average curve of Fig. 6 is in fact a close approximation to the "α side-chain effect."

It has thus been shown that the "α side-chain effect" in the 20-ketopregnane series typified by Fig. 6 is consistent for the compounds studied, and may be considered diagnostic for the configuration of the side chain in the presence or absence of certain substituents at C-16 and in the presence or absence of a ketone at C-11, and an α,β-unsaturated ketone at C-3.

EXPERIMENTAL

All compounds were from the Upjohn collection and were of analytical purity and well characterized by standard physical and chemical criteria. Some of the materials are described in the companion paper by P. F. Beal and J. E. Pike. All of the compounds were dissolved in dioxane for the rotation measurements.

Optical rotations were measured in a spectropolarimeter assembled from a Rudolph Model 80 photoelectric polarimeter equipped with an oscillating polarizer and a Perkin-Elmer universal monochromator. The source was a high pressure Hanovia Xenon Arc operated from a Rudolph d.c. power supply.

All rotations are reported and plotted as molecular rotations, in order to permit valid comparisons among compounds of different molecular weight.

16α-Fluoromethyl-3β-hydroxy-5-pregnen-20-one (I). (*c*, 0.1009) $[M]_{589}$ +152°; $[M]_{380}$ +565°; $[M]_{317}$ +6792° (peak); $[M]_{300}$ +2827°.

16β-Carbomethoxy-3β-hydroxy-17α-pregn-5-en-20-one (II). (*c*, 0.1031) $[M]_{589}$ −272°; $[M]_{380}$ −1216°; $[M]_{310}$ −6391° (trough); $[M]_{300}$ −4933°; $[M]_{280}$ +2669°.

Progesterone (III). (*c*,0.828) $[M]_{589}$ +459°; $[M]_{378}$ +1311°; $[M]_{368}$ +926°; $[M]_{360}$ +1367°; $[M]_{355}$ +1131°; $[M]_{343}$ +3813°; $[M]_{313}$ +13506°; $[M]_{300}$ +11817°; $[M]_{290}$ +7865°.

17α-Progesterone (IV). (*c*, 0.0995) $[M]_{559}$ −126°; $[M]_{380}$ −844°; $[M]_{365}$ −1754°; $[M]_{363}$ −1754°; $[M]_{355}$ −2525°; $[M]_{343}$ −1097°; $[M]_{340}$ −1213°; $[M]_{330}$ −104°; $[M]_{325}$ −139°; $[M]_{313}$ +752°.

11-Ketoprogesterone (V). (*c*, 0.0996) $[M]_{589}$ +901°; $[M]_{378}$ +3568°; $[M]_{373}$ +3488°; $[M]_{363}$ +3757°; $[M]_{355}$ +3833°; $[M]_{343}$ +5330°; $[M]_{340}$ +5435°; $[M]_{315}$ +9440°; $[M]_{300}$ + 3288°.

16α-Cyano-11-ketoprogesterone (VI). (*c*, 0.1004) $[M]_{589}$ +592°; $[M]_{375}$ +3314°; $[M]_{370}$ +3377°; $[M]_{360}$ +3796°;

$[\mathrm{M}]_{358}$ +3799°; $[\mathrm{M}]_{345}$ +5328°; $[\mathrm{M}]_{318}$ +11969° (peak); $[\mathrm{M}]_{305}$ +10043°.

16α-Fluoromethyl-11-ketoprogesterone (VII). (*c*, 0.1028) $[\mathrm{M}]_{589}$ +910°; $[\mathrm{M}]_{375}$ +4237°; $[\mathrm{M}]_{370}$ +4026°; $[\mathrm{M}]_{360}$ +4412°; $[\mathrm{M}]_{358}$ +4341°; $[\mathrm{M}]_{345}$ +5882°; $[\mathrm{M}]_{318}$ +12569° (max).

16α-Carbomethoxy-11-ketoprogesterone (VIII). (*c*, 0.0993) $[\mathrm{M}]_{589}$ +538°; $[\mathrm{M}]_{375}$ +3485°; $[\mathrm{M}]_{370}$ +3485°; $[\mathrm{M}]_{360}$ +3810°; $[\mathrm{M}]_{355}$ +3849°; $[\mathrm{M}]_{345}$ +5450°; $[\mathrm{M}]_{315}$ +11900° (peak); $[\mathrm{M}]_{300}$ +9140°.

11β-Hydroxyprogesterone (IX). (*c*, 0.098) $[\mathrm{M}]_{589}$ +707°; $[\mathrm{M}]_{385}$ +1860°; $[\mathrm{M}]_{368}$ +1262°; $[\mathrm{M}]_{358}$ +1814°; $[\mathrm{M}]_{355}$ +1678°; $[\mathrm{M}]_{350}$ +2340°; $[\mathrm{M}]_{343}$ +4685°; $[\mathrm{M}]_{330}$ +9105°; $[\mathrm{M}]_{310}$ +13830°; $[\mathrm{M}]_{300}$ +11810°.

11β-Hydroxy-16α-hydroxymethylprogesterone (X). (*c*, 0.097) $[\mathrm{M}]_{589}$ +854°; $[\mathrm{M}]_{380}$ +1965°; $[\mathrm{M}]_{370}$ +1482°; $[\mathrm{M}]_{363}$ +2001°; $[\mathrm{M}]_{355}$ +2113°; $[\mathrm{M}]_{343}$ +5487°; $[\mathrm{M}]_{340}$ +5559°; $[\mathrm{M}]_{330}$ +10070°; $[\mathrm{M}]_{320}$ +13551°; $[\mathrm{M}]_{313}$ +14827°; $[\mathrm{M}]_{300}$ +12084°.

16α-Methylprogesterone (XI). (C 0.0998) $[\mathrm{M}]_{589}$ +402°; $[\mathrm{M}]_{380}$ +1635°; $[\mathrm{M}]_{368}$ +1226°; $[\mathrm{M}]_{360}$ +1602°; $[\mathrm{M}]_{355}$ +1488°; $[\mathrm{M}]_{343}$ +4414°; $[\mathrm{M}]_{340}$ +4512°; $[\mathrm{M}]_{315}$ +13094°; $[\mathrm{M}]_{306}$ +12661°.

16β-Methylprogesterone (XII). (*c*, 1.0) $[\mathrm{M}]_{589}$ +392°; $[\mathrm{M}]_{385}$ +996°; $[\mathrm{M}]_{373}$ −65° $[\mathrm{M}]_{363}$ + 100°; $[\mathrm{M}]_{355}$ −353°; $[\mathrm{M}]_{343}$ + 1698°; $[\mathrm{M}]_{340}$ +1698°; $[\mathrm{M}]_{318}$ +5510° (peak); $[\mathrm{M}]_{315}$ +5390°.

16β-Hydroxymethyl-17α-progesterone (XIII). (*c*, 0.0970) $[\mathrm{M}]_{589}$ −81°; $[\mathrm{M}]_{385}$ −879°; $[\mathrm{M}]_{383}$ −858°; $[\mathrm{M}]_{368}$ −1846°; $[\mathrm{M}]_{360}$ −1719°; $[\mathrm{M}]_{353}$ −2460°; $[\mathrm{M}]_{343}$ −1006°; $[\mathrm{M}]_{340}$ −1130°; $[\mathrm{M}]_{328}$ +480°; $[\mathrm{M}]_{323}$ +145°; $[\mathrm{M}]_{305}$ +2040°.

16β-Fluoromethyl-17α-progesterone (XIV). (*c*, 0.0924) $[\mathrm{M}]_{589}$ −37°; $[\mathrm{M}]_{380}$ −835°; $[\mathrm{M}]_{365}$ −1828°; $[\mathrm{M}]_{363}$ −1760°; $[\mathrm{M}]_{353}$ −2442°; $[\mathrm{M}]_{343}$ −1030°; $[\mathrm{M}]_{340}$ −1180°; $[\mathrm{M}]_{330}$ +442°; $[\mathrm{M}]_{323}$ −22°; $[\mathrm{M}]_{315}$ +356°; $[\mathrm{M}]_{312}$ +356°; $[\mathrm{M}]_{300}$ +2386°.

16β-Carbomethoxy-11-keto-17α-progesterone (XV). (*c*, 0.0991) $[\mathrm{M}]_{589}$ +268°; $[\mathrm{M}]_{375}$ +1754°; $[\mathrm{M}]_{368}$ +1241°; $[\mathrm{M}]_{363}$ +1497°; $[\mathrm{M}]_{353}$ +257°; $[\mathrm{M}]_{345}$ +647°; $[\mathrm{M}]_{338}$ −310°; $[\mathrm{M}]_{330}$ −42°; $[\mathrm{M}]_{310}$ −1448°; $[\mathrm{M}]_{295}$ +1723°.

11-Keto-17α-progesterone (XVI). (*c*, 0.0982) $[\mathrm{M}]_{589}$ +342°; $[\mathrm{M}]_{380}$ +1287°; $[\mathrm{M}]_{368}$ +854°; $[\mathrm{M}]_{363}$ +856°; $[\mathrm{M}]_{355}$ +186°; $[\mathrm{M}]_{345}$ +736°; $[\mathrm{M}]_{340}$ +502°; $[\mathrm{M}]_{333}$ +1126°; $[\mathrm{M}]_{325}$ +427°; $[\mathrm{M}]_{305}$ +3730°.

16α-Cyano-3α-hydroxy-5β-pregnene-11,20-dione (XVII). (*c*, 0.0995) $[\mathrm{M}]_{589}$ +280°; $[\mathrm{M}]_{380}$ +1754°; $[\mathrm{M}]_{318}$ +8803° (peak); $[\mathrm{M}]_{300}$ +4080°.

16β-Carbomethoxy-3α-hydroxy-5β,17α-pregnane-11,20-dione (XVIII). (*c*, 0.1053) $[\mathrm{M}]_{589}$ +19°; $[\mathrm{M}]_{340}$ −683°; $[\mathrm{M}]_{320}$ −2671°; $[\mathrm{M}]_{318}$ −2604°; $[\mathrm{M}]_{306}$ −3450°; $[\mathrm{M}]_{300}$ −1150°.

KALAMAZOO, MICH.

[CONTRIBUTION OF THE RESEARCH LABORATORIES, THE UPJOHN CO.]

The Synthesis of 16α-Fluoromethyl Steroids

P. F. BEAL AND J. E. PIKE

Received March 6, 1961

The preparation of a series of 16α-fluoromethyl steroids is described. Addition of cyanide ion to a Δ^{16}-20-ketone gives a 16α-cyano 20-ketone, which after conversion to a 20-cycloethylene ketal can be converted to a variety of 16α-substituted derivatives. Transformation of one of these products, 16α-fluoromethyl-11-oxoprogesterone, to the corresponding hydrocortisone analogue is reported. Introduction of the Δ^1-double bond and a 9α-fluoro substituent follows established methods to give 9α-fluoro-16α-fluoromethylprednisolone 21-acetate (XIX) for which preliminary biological data are given.

In view of the biological change associated with the introduction of methyl, fluorine, and hydroxyl substituents at C-16 in corticoids,[1] the synthesis of other hydrocortisone derivatives substituted at this position was investigated.

A valuable method for the introduction of substituents at C-16 is the addition of cyanide ion to a Δ^{16}-20-ketone since the resulting 16-nitrile provides a versatile intermediate for futher transformations. Thus Romo[2] converted 16-dehydropregnenolone acetate to a 16α-cyano-20-ketone, which after alkaline hydrolysis, esterification, and Oppenauer oxidation gave a 16-carbomethoxyprogesterone.

Similar work has been reported by Petrow and coworkers.[3] Both groups of workers assigned the 16α,17β configuration to the initial cyanide adduct and also to the subsequent transformation products. More recently Mazur and Cella[4] have recorded work in this series which makes it clear that the further transformations of the correctly assigned 16α-cyano-17β-acetyl adducts under alkaline equilibrating conditions give 17α-acetyl-16β-carboxylic acids. We had also reached the conclusion that a double inversion of configuration had occurred at C-16 and C-17 by an analysis of the optical rotatory dispersion curves of a series of 16β-substituted-17-iso transformation products, and by the conversion of 16β-hydroxymethyl-17-isoprogesterone to the known 16β-methyl-17-isoprogesterone.[5,6]

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[1] (a) L. H. Sarett, *Ann. N. Y. Acad. Sci.*, **82**, 802 (1959); E. Oliveto, *Ann. N. Y. Acad. Sci.*, **82**, 808; and references cited therein; (b) W. M. Moreland, R. G. Berg, and D. P. Cameron, *J. Am. Chem. Soc.*, **82**, 504 (1960); (c) D. E. Ayer and W. P. Schneider, *J. Am. Chem. Soc.*, **82**, 1249 (1960); (d) B. J. Magerlein, R. D. Birkenmeyer, and F. Kagan, *J. Am. Chem. Soc.*, **82**, 1252 (1960).

[2] J. Romo, *Tetrahedron*, Vol. **3**, 37 (1958).

[3] B. Ellis, V. Petrow, and D. Wedlake, *J. Chem. Soc.*, 3748 (1958).

[4] R. H. Mazur and J. A. Cella, *Tetrahedron*, Vol. **7**, 130, 1959.

[5] The transformation in the non-11-oxygenated series will be described in detail in a publication from these Laboratories. For a detailed analysis of the optical rotatory dispersion curves in both series see W. A. Struck and R. Houtman, *J. Org Chem.*, **26**, 3883 (1961).

[6] J. Romo, J. Lepe, and M. Romero, *Bol. Inst. Quim. Univ. N. Auton. Mex.*, 125 (1952).