Acknowledgment. The authors would like to thank Dr. T. F. Gallagher for his interest and encouragement. They would like to thank Mrs. Beatrice S. Gallagher and staff for the infrared spectra.

NEW YORK 21, N. Y.

[CONTRIBUTION FROM THE DEPARTMENT OF NATURAL PRODUCTS RESEARCH, MEAD JOHNSON AND CO.]

The Synthesis of 16α-Methoxyhydrocortisone Acetate and Congeners

GEORGE R. ALLEN, JR.,[1] AND NANCY A. AUSTIN

Received April 3, 1961

Alkylation of 3,20-bisethylenedioxy-16α,17α-dihydroxy-5-pregnene (V), and 3,20-bisethylenedioxy-16α,17α-dihydroxy-5-pregnene-11-one (VII) with methyl iodide gave the corresponding 16α-methoxy derivatives. Use of this reaction in conjunction with known procedures furnished the 16α-methoxy analogs of 17α-hydroxyprogesterone, Reichstein's Substance S, 4-androstene-3,17-dione, 21-deoxycortisone, 21-deoxyhydrocortisone, cortisone acetate, hydrocortisone acetate, prednisone acetate, prednisolone acetate, 21-deoxy-9α-fluorohydrocortisone, 9α-fluorohydrocortisone acetate, and 9α-fluoroprednisolone acetate.

Since 1956 several laboratories have studied the effects on corticoid activity brought about by the substitution of certain groups in the C-16 position of hydrocortisone and its congeners. Initially, Bernstein and his co-workers[2] found that 9α-fluoro-16α-hydroxyprednisolone is a potent glucocorticoid lacking the salt-retaining properties of the 9α-fluorocorticoids. Subsequently, Fried and his collaborators[3] reported on the marked potentiation of the glucocorticoid activity of this compound by 16,17-acetal and -ketal formation. The introduction of a methyl group in either the α- or β-orientation at C-16,[4] as well as the 16α-fluoro atom,[5] also has a favorable effect on the corticoid activity of the parent hormones. In contrast to the above results, substitution of 16β-hydroxy,[6] 16β-fluoro,[7] 16β-methoxy,[8] and 16,16-*gem*-dimethyl[9] groupings in hydrocortisone and related hormones has a detrimental effect on the activity of these compounds. It may be noted that modified hormones bearing the 16α-hydroxy, 16α,17α-isopropylidenedioxy, 16α-methyl and 16β-methyl groups are of proved value as anti-inflammatory agents in human therapy.[10]

Because the masking of the glycol grouping in 9α-fluoro-16α-hydroxyprednisolone by ketal or acetal formation has an advantageous effect on its activity, it appeared desirable to prepare an analog of this compound in which one of the glycol hydroxyl groups was masked. Etherification was chosen as the method for effecting this modification, and in view of the frequency of success with various substituents at C-16 the preparation of 16α-methoxy analogs of hydrocortisone and its congeners was undertaken.[11]

16α-Methoxypregnane derivatives (*B*) may be conveniently prepared by the 1,4-addition of methanol to a 16-dehydro-20-ketone (*A*).[12] However, this procedure was considered unsatisfactory for our purposes, since the subsequent introduction of the 17α-hydroxy group would require treatment

---

(1) Present address: Lederle Laboratories Division, American Cyanamid Co., Pearl River, N. Y.

(2) S. Bernstein, R. H. Lenhard, W. S. Allen, M. Heller, R. Littell, S. M. Stolar, L. I. Feldman, and R. H. Blank, *J. Am. Chem. Soc.*, **78**, 5693 (1956); **81**, 1689 (1959).

(3) J. Fried, A. Borman, W. B. Kessler, P. Grabowich, and E. F. Sabo, *J. Am. Chem. Soc.*, **80**, 2338 (1958).

(4) (a) G. E. Arth, D. B. R. Johnston, J. Fried, W. W. Spooncer, D. R. Hoff and L. H. Sarett, *J. Am. Chem. Soc.*, **80**, 3160 (1958); (b) G. E. Arth, J. Fried, D. B. R. Johnston, D. R. Hoff, L. H. Sarett, R. H. Silber, H. Stoerk, and C. A. Winter, *J. Am. Chem. Soc.*, **80**, 3161 (1958); (c) E. P. Oliveto, R. Rausser, A. L. Nussbaum, W. Gebert, E. B. Hershberg, S. Tolksdorf, M. Eisler, P. L. Perlman, and M. M. Pechet, *J. Am. Chem. Soc.*, **80**, 4428 (1958); (d) E. P. Oliveto, R. Rausser, L. Weber, A. L. Nussbaum, W. Gebert, C. T. Coniglio, E. B. Hershberg, S. Tolksdorf, M. Eisler, P. L. Perlman, and M. M. Pechet, *J. Am. Chem. Soc.*, **80**, 4431 (1958); (e) D. Taub, R. D. Hoffsommer, H. L. Slates, and N. L. Wendler, *J. Am. Chem. Soc.*, **80**, 4435 (1958); (f) D. Taub, R. D. Hoffsommer, H. L. Slates, C. H. Kuo, and N. L. Wendler, *J. Am. Chem. Soc.*, **82**, 4012 (1960); (g) E. P. Oliveto, R. Rausser, H. L. Herzog, E. B. Hershberg, S. Tolksdorf, M. Eisler, P. L. Perlman, and M. M. Pechet, *J. Am. Chem. Soc.*, **80**, 6687 (1958).

(5) B. J. Magerlein, R. D. Birkenmeyer, and F. Kagan, *J. Am. Chem. Soc.*, **82**, 1252 (1960).

(6) S. Bernstein, M. Heller, and S. M. Stolar, *J. Am. Chem. Soc.*, **81**, 1256 (1959).

(7) D. E. Ayer and W. P. Schneider, *J. Am. Chem. Soc.*, **82**, 1251 (1960).

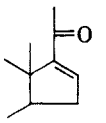
(8) W. T. Moreland, R. G. Berg, D. P. Cameron, C. E. Maxwell III, J. S. Buckley and G. D. Laubach, *Chem. & Ind. (London)*, 1084 (1960).

(9) R. D. Hoffsommer, H. L. Slates, D. Taub, and N. L. Wendler, *J. Org. Chem.*, **24**, 1617 (1959).

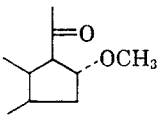
(10) *Cf. J. Am. Med. Assoc.*, **170**, 194 (1959); J. L. Hollander, *J. Am. Med. Assoc.*, **172**, 306 (1960); J. H. Glyn and D. B. Fox, *Brit. Med. J.*, 876 (1960).

(11) During the course of this work V. Petrow and D. M. Williamson [*J. Chem. Soc.*, 3595 (1959)] reported that 16α-methoxydeoxycorticosterone [G. Cooley, B. Ellis, and V. Petrow, *J. Chem. Soc.*, 1813 (1954)] lacks the salt-retaining properties of deoxycorticosterone.

(12) D. K. Fukushima and T. F. Gallagher, *J. Am. Chem. Soc.*, **73**, 196 (1951).



A



B

with strong acid[13] or strong base.[14] In either case the 16α-methoxy-20-ketone system would be expected to undergo elimination.[12,15] Therefore, we investigated the preferential alkylation of a 16α,17α-dihydroxypregnane as a procedure for the preparation of the desired 17α-hydroxy-16α-methoxy-20-ketones. Such an approach appeared feasible in view of the known relative unreactivity of the tertiary 17α-hydroxy group. Conformational considerations lead to the same expectation. Thus, the 17α-hydroxy group is quasi-axial and the 16α-hydroxy group is bisectional, regardless of whether ring D exists in the half-chair (C_2) or envelope (C_s) conformation.[16] Since axial substituents react more sluggishly than equatorial ones, we were hopeful that the quasi-axial 17α-hydroxy group would react less readily than the bisectional 16α-hydroxy group.[17,18]

3,20-Bisethylenedioxy-16α,17α-dihydroxy-5-pregnene (V)[19] was chosen for alkylation studies; in this model, ring A is protected against alkylation at C-4[20] and the side-chain against D-homoannulation.[21] Treatment of V with 1.5 molar equivalents of potassium *t*-butoxide and one molar equivalent of methyl iodide in refluxing *t*-butyl alcohol gave, in 40% yield, a product which was shown by subsequent experiments to be the desired 3,20-bisethylenedioxy-17α-hydroxy-16α-methoxy-5-pregnene (VI). When two molar equivalents of methyl iodide were used no dialkylated material could be isolated, even on careful chromatography of the reaction products. The latter conditions gave VI in 51–58% yield, along with a 39–29% recovery of the diol V.

Hydrolysis of the methoxybisketal VI with 60% formic acid furnished *17α-hydroxy-16α-methoxyprogesterone* (XIII) in 90% yield. Rearrangement of the sidechain during or subsequent to ketal removal was precluded by the reconversion of XIII into bisketal VI.

The structure of the methoxybisketal VI was established unequivocally by the following transformations with hydrolysis product XIII, analysis of which showed the presence of one methoxy group. This diketone was preferentially reduced at C-20 with sodium borohydride[22] to give 17α,20β-dihydroxy-16α-methoxy-4-pregnene-3-one (III). The latter substance formed an acetonide (IV) and was cleaved by periodic acid to give *16α-methoxy-4-androstene-3,17-dione* (XV), the infrared spectrum of which clearly indicated the presence of a five-membered ring carbonyl group. Thus, it is evident that alkylation of the bisketal V had occurred preferentially at the 16α-hydroxy group, since formation of an androstenedione would not have been possible with a 17α-methoxy derivative.

The results of acetylation experiments are also consistent with the assigned 16α-methoxy structures. When the methoxybisketal VI and 17α-hydroxy-16α-methoxyprogesterone (XIII) were treated with acetic anhydride and pyridine at room temperature, each was recovered unchanged. Under the same conditions the 16α,17α-dihydroxybisketal V and 16α,17α-dihydroxyprogesterone form monoacetates.[19] It is interesting to note that attempted acetylation of 17α-hydroxy 16α-methoxyprogesterone (XIII) with acetic anhydride-acetic acid-*p*-toluenesulfonic acid according to the general procedure of Turner[23] afforded a 78% recovery of XIII accompanied by 13% of the 3-enol acetate XXIII.

The final point to be resolved was whether the presence of a 16α-methoxy group is compatible with the preferred procedures for the introduction of the required 21-oxygen function. These procedures involve displacement of a 21-halogen.[24] Inasmuch as a 16α,17α-isopropylidenedioxy grouping impedes displacement reactions at this position,[25] it was of interest to determine whether a 16α-methoxy group exerts a similar effect. Ap-

(13) T. H. Kritchevsky and T. F. Gallagher, *J. Biol. Chem.*, **179**, 507 (1949).

(14) *Inter alia* see J. A. Hogg, P. F. Beal, A. H. Nathan, F. H. Lincoln, W. P. Schneider, B. J. Magerlein, A. R. Hanze, and R. W. Jackson, *J. Am. Chem. Soc.*, **77**, 4436 (1955).

(15) G. Cooley, B. Ellis, and V. Petrow, *J. Chem. Soc.*, 1813 (1954).

(16) The present status of the problem concerning the conformation of the cyclopentane ring is well summarized by Brutcher and his associates [*J. Am. Chem. Soc.*, **81**, 4915 (1959)]. Also *cf.* J. Fishman and C. Djerassi, *Experientia*, **16**, 138 (1960).

(17) Indeed, this behavior is noted on mild acetylation of 16α,17α-glycols.[19] After this work was completed it was reported that diazomethane and fluoboric acid treatment of this system also affords preferential reaction at the 16α-hydroxy group [S. Bernstein, M. Heller, and S. M. Stolar, *Chem. & Ind. (London)*, 516 (1961)].

(18) However, it may be noted that the quasi-equatorial hydroxyl group of testosterone is reported not to undergo alkylation using conditions essentially identical with those of this work [N. W. Atwater, *J. Am. Chem. Soc.*, **79**, 5315 (1957); **82**, 2847 (1960)].

(19) W. S. Allen and S. Bernstein, *J. Am. Chem. Soc.*, **78**, 1909 (1956).

(20) R. B. Woodward, A. A. Patchett, D. H. R. Barton, D. A. J. Ives, and B. R. Kelly, *J. Am. Chem. Soc.*, **76**, 2852 (1954).

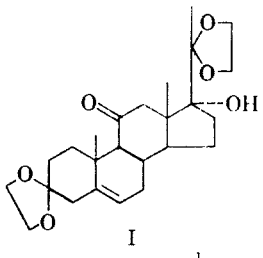
(21) (a) H. E. Stavely, *J. Am. Chem. Soc.*, **61**, 79 (1939); **62**, 489 (1940); **63**, 3127 (1941); (b) L. Ruzicka and H. F. Meldahl, *Helv. Chim. Acta*, **21**, 1760 (1938); **22**, 421 (1939); **23**, 364 (1940).

(22) J. K. Norymberski and G. F. Woods, *J. Chem. Soc.*, 3426 (1955).

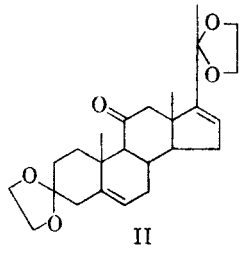
(23) R. B. Turner, *J. Am. Chem. Soc.*, **75**, 3489 (1953).

(24) G. Rosenkranz, J. Pataki, St. Kaufmann, J. Berlin, and C. Djerassi, *J. Am. Chem. Soc.*, **72**, 4081 (1950).

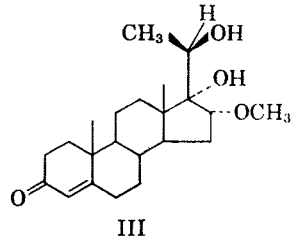
(25) G. R. Allen, Jr. and M. J. Weiss, *J. Am. Chem. Soc.*, **81**, 4968 (1959).



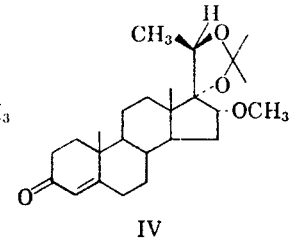
I



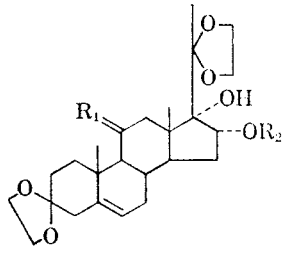
II



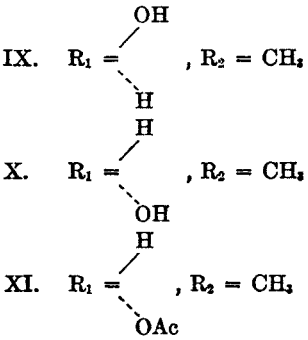
III



IV



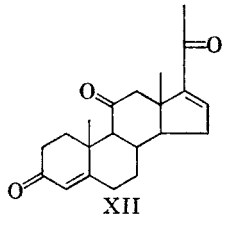
V. $R_1 = H_2$, $R_2 = H$
VI. $R_1 = H_2$, $R_2 = CH_3$
VII. $R_1 = O$, $R_2 = H$
VIII. $R_1 = O$, $R_2 = CH_3$



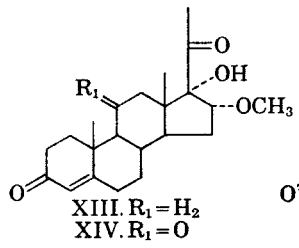
IX. R_1 = , $R_2 = CH_3$

X. R_1 = , $R_2 = CH_3$

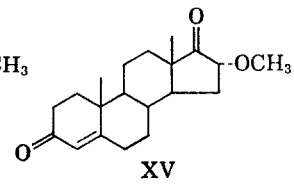
XI. R_1 = , $R_2 = CH_3$



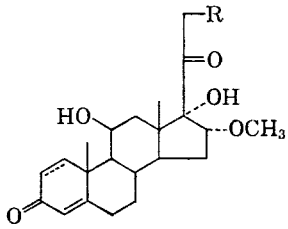
XII



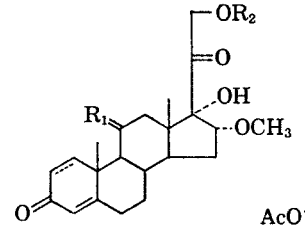
XIII. $R_1 = H_2$
XIV. $R_1 = O$



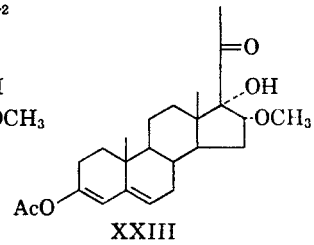
XV



XVI. R = H
XVII. R = OAc
XVIII. R = OAc, $\Delta^{1,4}$



XIX. $R_1 = H_2$, $R_2 = H$
XX. $R_1 = H_2$, $R_2 = Ac$
XXI. $R = O$, $R_2 = Ac$
XXII. $R_1 = O$, $R_2 = Ac$, $\Delta^{1,4}$



XXIII

parently it does not, for the 21-acetoxylation of XIII could be effected with facility by the procedure of Ringold and Stork.[26] Subsequent deacetylation afforded *16α-methoxy Substance S* (XIX). This product gave monoacetate XX on reacetylation and on reaction with sodium bismuthate[27] suffered side-chain cleavage yielding the 16α-methoxy-17-ketone XV.

Having resolved the anticipated potential synthetic difficulties, a procedure now was available for the preparation of 16α-methoxyhydrocortisone and congeners. The key intermediate for the 11-oxygenated series, 3,20-bisethylenedioxy-16α,17α-dihydroxy-5-pregnene-11-one (VII), was prepared from 3,20-bisethylenedioxy-17α-hydroxy-5-pregnene-11-one (I)[28,29] by elimination of the 17α-hydroxy group with thionyl chloride in pyridine[30] and *cis*-hydroxylation with osmium tetroxide[31] of the 16,17-double bond in the derived olefin II.[29,32]

Alkylation of the dihydroxybisketal VII with methyl iodide gave the desired 16α-methoxybisketal VIII in 74% yield. The 16α-methoxy structure was assigned to this product by analogy to the results recorded above for the 11-deoxy series, and further unequivocal evidence for this assignment is given below. Hydrolysis of the 16α-methoxybisketal VIII with 60% formic acid gave *16α-methoxy-21-deoxycortisone* (XIV). The possibility of side-chain rearrangement during the hydrolysis procedure was precluded by reconversion of XIV into VIII.

Reduction of VIII with sodium borohydride in the presence of alkali[29] gave two products. In view of the known steric course of this reaction the major product, isolated in 90% yield, must be the 11β-hydroxy epimer IX, and the minor product, isolated in 3% yield, the 11α-hydroxy epimer X. With pyridine-acetic anhydride the major product was recovered unchanged, and the minor product afforded the monoacetate XI. These results confirm the epimeric assignment at C-11

(26) H. J. Ringold and G. Stork, *J. Am. Chem. Soc.*, 80, 250 (1958).

(27) C. J. W. Brooks and J. K. Norymberski, *Biochem. J.*, 55, 371 (1953).

(28) A. Bowers and H. J. Ringold, *J. Am. Chem. Soc.*, 80, 3091 (1958).

(29) S. Bernstein, J. J. Brown, L. I. Feldman, and N. E. Rigler, *J. Am. Chem. Soc.*, 81, 4956 (1959).

(30) W. S. Allen and S. Bernstein, *J. Am. Chem. Soc.*, 77, 1028 (1955).

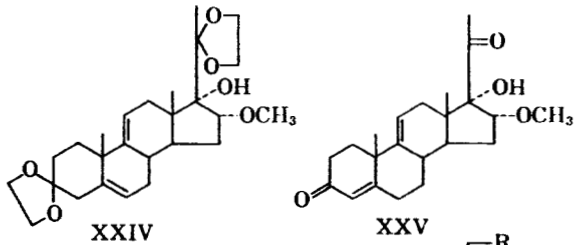
(31) W. S. Allen and S. Bernstein, *J. Am. Chem. Soc.*, 78, 1909 (1956).

(32) It may be noted that formic acid hydrolysis of the 16-dehydrobisketal II gave the known 4,16-pregnadiene-3,11,20-trione (XII) [B. J. Magerlein, D. A. Lyttle, and R. H. Levin, *J. Org. Chem.*, 20, 1709 (1955)].

and the presence of the 16α-methoxy group. Hydrolysis of the 11β-epimeride with 60% formic acid gave *16α-methoxy-21-deoxyhydrocortisone* (XVI). That no rearrangement had occurred during hydrolysis was demonstrated by oxidation of XVI with the pyridine–chromium trioxide complex[33] to the above described XIV. Analytical data for 16α-methoxy-21-deoxyhydrocortisone showed the presence of one methoxyl group and three C-methyl groups. These data clearly indicate that only one methyl group[34] was introduced during alkylation of VII, and that carbon alkylation at C-9 (or C-12) had not taken place.[35]

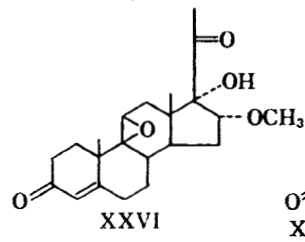
The 21-deoxy compounds XIV and XVI were converted into *16α-methoxycortisone acetate* (XXI) and *16α-methoxyhydrocortisone acetate* (XVII), respectively, by the modified haloform reaction and subsequent acetolysis.[26] Selenium dioxide dehydrogenation[36] of XXI and XVII afforded *16α-methoxyprednisone acetate* (XXII) and *16α-methoxyprednisolone acetate* (XVIII), respectively.

For the preparation of the 16-methoxy analogs of 9α-fluorohydrocortisone[37] and 9α-fluoroprednisolone,[38] the 11β-hydroxybisketal IX was treated with phosphorus oxychloride in pyridine.[39] Formic acid hydrolysis of the resulting 3,20-bisethylenedioxy-17α-hydroxy-16α-methoxy-5,9(11)-pregnadiene (XXIV), which was also obtained from the 11α-hydroxybisketal X, afforded 17α-hydroxy-16α-methoxy-4,9(11)-pregnadiene-3,20-dione (XXV). This product could be reketalized to give XXIV. By established procedures[37] compound XXV was converted into *9α-fluoro-16α-methoxy-21-deoxyhydrocortisone* (XXVIII) *via* bromohydrin XXVII and epoxide XXVI. It is interesting to note that epoxide formation from bromohydrin XXVII on treatment with potassium acetate in boiling ethanol proceeded normally and without destruction of the D-ring side-chain. This fact was readily demonstrated by opening of the epoxide XXVI with hydrogen bromide to give the starting bromohydrin in good yield. The stability of the D-ring side-chain toward potassium acetate in the 16α-methoxy series stands in contrast to its sensitivity toward this reagent in the 16α-hydroxy series.[29] This difference in behavior is indirect evidence supporting the retro-aldolization mechanism advanced by Kuo, Taub, and Wendler[40] to explain the ease with which 16ζ, 17α-dihydroxy-20-ketopregnanes undergo D-homoannulation.

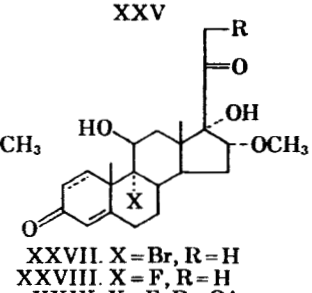


XXIV

XXV



XXVI



XXVII. X = Br, R = H
XXVIII. X = F, R = H
XXIX. X = F, R = OAc
XXX. X = F, R = OAc, $\Delta^{1,4}$

Application of the 21-acetoxylation procedure of Ringold and Stork[26] to 21-deoxyfluorohydrin XXVIII gave *9α-fluoro-16α-methoxyhydrocortisone acetate* (XXIX), which on dehydrogenation afforded *9α-fluoro-16α-methoxyprednisolone acetate* (XXX).

Some comment concerning the effect of the 16α-methoxy group on infrared spectra and optical rotations seems worthwhile. The infrared spectra of the 16α-methoxy ketones showed a moderately strong C—O stretching band at 1105–1095 cm.$^{-1}$ in chloroform solution; whereas the spectra of the corresponding unsubstituted steroids, when the comparison could be made, did not exhibit this band. Jones and Herling[41] have previously recorded frequencies of 1102–1098 cm.$^{-1}$ for the C—O stretching band of certain 3-, 6-, and 16-methoxy steroids. In the spectrum of the 16α-methoxybisketals this band is obscured by one of the principal C—O stretching bands of the ketal functions. It can be seen from pairs 1–3 in Table

(33) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc.*, 75, 4830 (1953).

(34) Elemental analysis of VIII did not distinguish between $C_{26}H_{38}O_7$ (C, 67.51; H, 8.28) and $C_{27}H_{40}O_7$ (C, 68.04; H, 8.46) formulations.

(35) The 96% recovery of 3,20-bisethylenedioxy-17α-hydroxy-5-pregnene-11-one (I) from a similar alkylation experiment was indicative that carbon alkylation would not occur. Fried and his co-workers [*J. Am. Chem. Soc.*, 82, 1684 (1960)] have also reported the relative inability of C-9 in an 11-keto system to undergo base-catalyzed alkylation. In this connection Jones and his associates [*J. Chem. Soc.*, 2156 (1958)] have reported that the activation of C-9 in an 11-ketone by a 7(8)-double bond permits facile alkylation at this site.

(36) (a) C. Meystre, H. Frey, W. Voser, and A. Wettstein, *Helv. Chim. Acta*, 39, 734 (1956); (b) S. Szpilfogel, T. Posthumus, M. DeWinter, and D. Van Dorp, *Rec. trav. chim.*, 75, 475 (1956).

(37) J. Fried and E. F. Sabo, *J. Am. Chem. Soc.*, 79, 1130 (1957).

(38) (a) R. F. Hirschmann, R. Miller, R. E. Beyler, L. H. Sarrett, and M. Tishler, *J. Am. Chem. Soc.*, 77, 3166 (1955); (b) J. Fried, K. Florey, E. F. Sabo, J. E. Herz, A. R. Restivo, A. Borman, and F. M. Singer, *J. Am. Chem. Soc.*, 77, 4181 (1955); (c) J. A. Hoff, F. H. Lincoln, A. H. Nathan, A. R. Hanze, W. P. Schneider, P. F. Beal, and J. Korman, *J. Am. Chem. Soc.*, 77, 4438 (1955).

(39) S. Bernstein, R. Littell, and J. H. Williams, *J. Am. Chem Soc.*, 75, 4830 (1953).

(40) H. Kuo, D. Taub, and N. L. Wendler, *Chem. & Ind. (London)*, 1128 (1959).

(41) R. N. Jones and F. Herling, *J. Org. Chem.*, 19, 1252 (1954).

I that the average rotatory contribution (−168) of the 16α-methoxy group in 17α-hydroxy-4-pregnene-3,20-dione derivatives is in the expected negative direction. Moreover, the order of magnitude is about the same as that recorded for certain 16α-methoxy-20-ketopregnanes (−200).[12] Introduction of the 16α-methoxy group into 17α,20β-dihydroxy-4-pregnene-3-one also causes a negative shift (pair 4), the order of magnitude being greater (−282). In contrast, the contribution of the 16α-methoxy group is negligible when there is a carbonyl group at C-17 (pair 5). The average contribution of the 16α-methoxy group in 11β,17α-dihydroxypregnenes (pairs 6–8) is about the same order of magnitude (−162) as the contribution in the corresponding 11-deoxy derivatives. However, the average contribution (−95) of this group in the 11-keto series (pairs 9–11) is significantly lower. This also appears to be true of the 9,11-fluorohydrins (pairs 12–14) where the average contribution is −126.

During the course of this investigation a series of 16β-methoxy derivatives was described by other workers,[8,42] and a direct comparison of the α and β-epimerides was possible in two cases. The contribution of the 16β-methoxy group in 16β-methoxy Substance S is also negative (−39). However, the α-epimer is the more levorotatory, the ΔM_D (16α–16β) being −175°. Quite surprisingly, the contribution (−91) of the *16β-oriented* group in 9α-fluoro-16-methoxyhydrocortisone acetate is in the same direction and of similar magnitude as that of the *16α-oriented group*. Although the 16α-epimer is the more levorotatory, these observations indicate that assignment of configuration by molecular rotational differences can not always be made with safety when only one 16-methoxy epimer is available.

Finally, in contrast to other 16α-substituted steroid hormones of the hydrocortisone-cortisone class, the 16α-methoxy derivatives have little, if any, anti-inflammatory action as measured by the cotton-pellet granuloma inhibition assay.[43]

TABLE I

MOLECULAR ROTATIONS AND MOLECULAR ROTATION DIFFERENCES[a]

Pair No.	Compound	M_D	ΔM_D (16α-CH_3O)
1	17α-Hydroxyprogesterone[b]	+366	
	17α-Hydroxy-16α-methoxyprogesterone	+262	−104
2	17α,21-Dihydroxyprogesterone (Substance S)[c]	+457	
	17α,21-Dihydroxy-16α-methoxyprogesterone	+243	−214
3	21-Acetoxy-17α-hydroxyprogesterone (Substance S acetate)[d,e]	+572	
	21-Acetoxy-17α-hydroxy-16α-methoxyprogesterone[e]	+385	−187
4	17α,20β-Dihydroxy-4-pregnene-3-one[e,f]	+214	
	17α,20β-Dihydroxy-16α-methoxy-4-pregnene-3-one[e]	− 68	−282
5	4-Androstene-3,17-dione[e,g]	+566	
	16α-Methoxy-4-androstene-3,17-dione[e]	+564	− 2
6	21-Deoxyhydrocortisone[b]	+535	
	16α-Methoxy-21-deoxyhydrocortisone	+400	−135
7	Hydrocortisone acetate[h]	+660	
	16α-Methoxyhydrocortisone acetate	+475	−185
8	Prednisolone acetate[i]	+466	
	16α-Methoxyprednisolone acetate	+300	−166
9	21-Deoxycortisone[b]	+688	
	16α-Methoxy-21-deoxycortisone	+600	− 88
10	Cortisone acetate[b]	+870	
	16α-Methoxycortisone acetate	+769	−101
11	Prednisone acetate[i]	+745	
	16α-Methoxyprednisone acetate	+650	− 95
12	9α-Fluoro-21-deoxyhydrocortisone[j]	+496	
	9α-Fluoro-16α-methoxy-21-deoxyhydrocortisone	+370	−126
13	9α-Fluorohydrocortisone acetate[e,k]	+588	
	9α-Fluoro-16α-methoxyhydrocortisone acetate[e]	+443	−145
14	9α-Fluoroprednisolone acetate[l,m]	+424	
	9α-Fluoro-16α-methoxyprednisolone acetate[m]	+315	−109

[a] Dioxane solvent except where otherwise noted. [b] This work. [c] C. Meystre and K. Miescher, *Helv. Chim. Acta*, **34**, 2286 (1951). [d] B. A. Koechlin, T. H. Kritchevsky, and T. F. Gallagher, *J. Am. Chem. Soc.*, **73**, 189 (1951). [e] Chloroform solvent. [f] J. Romo, M. Romero, C. Djerassi, and G. Rosenkranz, *J. Am. Chem. Soc.*, **73**, 1528 (1951). [g] G. Rosenkranz, O. Mancera, and F. Sondheimer, *J. Am. Chem. Soc.*, **77**, 145 (1955). [h] *Merck Index*, Merck and Co., Inc., Rahway, N. J., 7th ed., 1960, p. 532. [i] H. L. Herzog, C. C. Payne, M. A. Jevnik, D. Gould, E. L. Shapiro, E. P. Oliveto, and E. B. Hershberg, *J. Am. Chem. Soc.*, **77**, 4781 (1955). [j] J. Fried, J. E. Herz, E. F. Sabo, A. Borman, F. M. Singer, and P. Numerof, *J. Am. Chem. Soc.*, **77**, 1068 (1955). [k] Ref. 25. [l] Ref. 26. [m] Acetone solvent.

EXPERIMENTAL[44]

3,20-Bisethylenedioxy-17α-hydroxy-16α-methoxy-5-pregnene (VI). *A*. Into 880 ml. of *t*-butyl alcohol was placed 3.77 g. (0.0965 g.-atom) of potassium; after reaction had ceased, 28.10 g. (0.0645 mole) of 3,20-bisethylenedioxy-16α,17α-dihydroxy-5-pregnene (V)[19] was added. The mixture was heated at reflux temperature with mechanical stirring.

(42) W. T. Moreland, R. G. Berg, and D. P. Cameron, *J. Am. Chem. Soc.*, **82**, 504 (1960).

(43) The biological assays were performed by Dr. G. R. McKinney and his associates of the Pharmacology Department of these laboratories.

(44) All melting points were determined on a Fisher-Johns block and are uncorrected. Ultraviolet spectra were measured in methanol solution on a Cary recording spectrophotometer. Unless otherwise specified the infrared spectra were determined in chloroform solution on a Baird spectrophotometer (Model AB-2). We wish to thank Dr. L. Throop and his associates for these measurements. Optical rotations were determined at 24° in a 2-dm. semimicro tube; concentrations were approximately 2% for ketal derivatives and 1% for ketones; except where otherwise noted dioxane was used as the solvent. Microanalyses were furnished by The Sprang Microanalytical Laboratory, Ann Arbor, Mich., and The Schwarzkopf Microanalytical Laboratory, Woodside, L. I.

A solution of 18.28 g. (0.129 mole, 8.00 ml.) of methyl iodide in 240 ml. of *t*-butyl alcohol was added dropwise over a period of 5 hr., whereafter heating and stirring was continued for 45 min. The cooled mixture was poured into 1500 ml. of water and extracted with chloroform. The combined chloroform extracts were washed with saline, dried over magnesium sulfate and taken to dryness. The crude material was chromatographed on silica gel[45]; the solids eluted by a 15% ether-in-benzene solution were recrystallized from acetone to give 16.70 g. (58% yield) of crystals, m.p. 238–240°. The analytical specimen, prepared in a similar experiment, had a m.p. of 233–234°; $[\alpha]_D$ −85.7°; only end absorption in the ultraviolet; ν_{max} 3450, 1100 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{40}O_6$: C, 69.61; H, 8.99. Found: C, 69.83; H, 8.79.

The column was then washed with acetone, and the eluted solid was recrystallized from acetone to give 8.20 g. (29% recovery) of V as crystals, m.p. 258–262°.

When the ratio of methyl iodide to glycol was one, the yield of the methoxy compound VI dropped to 40%.

B. A mixture of 0.136 g. (0.38 mmole) of 17α-hydroxy-16α-methoxyprogesterone (XIII), 10 mg. of *p*-toluenesulfonic acid hydrate, 25 ml. of benzene, and 10 ml. of ethylene glycol was heated at reflux temperature for 24 hr.; the water was collected in a modified Dean-Stark apparatus. The cooled mixture was made alkaline by the addition of solid sodium bicarbonate and diluted with water. The organic layer was washed further with water, dried over magnesium sulfate, and taken to dryness. The residue was recrystallized from acetone to give 89 mg. (52% yield) of crystals, m.p. 230–234°. An additional recrystallization gave 63 mg. of crystals, m.p. 236–238.5°. Identity of this material with that prepared in Method A was shown by mixture melting point and infrared spectral comparisons.

17α-Hydroxy-16α-methoxyprogesterone (XIII). A solution of 0.356 g. of 3,20-bisethylenedioxy-17α-hydroxy-16α-methoxy-5-pregnene (VI) in 5 ml. of 60% formic acid was heated on the steam bath for 15 min. The hot solution was diluted with water, cooled, and filtered to give 0.258 g. (90% yield) of shiny white plates, m.p. 165–167°. Three recrystallizations of this material from acetone-hexane gave 0.200 g. of plates, m.p. 165–167°; $[\alpha]_D$ +73°; λ_{max} 243 mμ (ε 16,750); ν_{max} 3400, 1710, 1675, 1645, 1105 cm.$^{-1}$

Anal. Calcd. for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95; OCH_3, 8.62. Found: C, 73.66; H, 9.06; OCH_3, 8.75.

17α,20β-Dihydroxy-16α-methoxy-4-pregnene-3-one (III). A solution of 0.721 g. (2.0 mmoles) of 17α-hydroxy-16α-methoxyprogesterone (XIII) in 100 ml. of methanol was cooled to 0° with magnetic stirring and treated with 0.113 g. (3.0 mmoles) of sodium borohydride. After stirring the solution at 0° for 1 hr., it was acidified with 0.5 ml. of glacial acetic acid and taken to dryness. The residue was distributed between ethyl acetate and water, and the organic layer was washed successively with sodium bicarbonate solution and saline, dried over magnesium sulfate and taken to dryness. The residue was chromatographed on silica gel using a 10% ether-in-benzene solution to elute the material, 125 ml. fractions being collected. The solids in fractions 3–8 were combined and recrystallized from acetone-hexane to give 0.201 g. (28% recovery) of XIII as white crystals, m.p. 165–167°. Its identity was established by mixed melting point and infrared spectral comparisons.

Fractions 9–15 contained oils that were not investigated. The solids in fractions 16–25 were combined and crystallized from acetone-hexane to give 0.220 g. (30% yield) of solid, m.p. 149–153°. Three additional recrystallizations from this solvent pair gave white crystals, m.p. 188–191°; $[\alpha]_D$ −18.4° (chloroform); λ_{max} 242 mμ (ε 15,000); ν_{max} 3550, 1653, 1615, 1100 cm.$^{-1}$

Anal. Calcd. for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45. Found: C, 73.18; H, 9.45.

On treatment with acetone and perchloric acid[46] this material gave the acetonide IV; recrystallization from acetone-hexane furnished white prisms, m.p. 202–205°; $[\alpha]_D$ −36.3°; λ_{max} 240 mμ (ε 16,700); ν_{max} 1650, 1615, 1210, 1100, 1090 cm.$^{-1}$

Anal. Calcd. for $C_{25}H_{38}O_4$: C, 74.59; H, 9.52. Found: C, 74.92; H, 9.55.

16α-Methoxy-4-androstene-3,17-dione (XV). *A.* A solution of 0.724 g. (2.0 mmoles) of 17α,20β-dihydroxy-16α-methoxy-4-pregnene-3-one (III) in 20 ml. of methanol was treated with a solution of 0.570 g. (2.5 mmoles) of paraperiodic acid in 2 ml. of water and kept at room temperature for 21 hr., whereafter it was diluted with water and extracted with methylene chloride. The extracts were washed successively with sodium bicarbonate solution and saline, dried with magnesium sulfate, and taken to dryness. The residual oil was chromatographed on silica gel. The column was washed with a 10% ether-in-benzene solution, 125-ml. fractions being collected. The material in fractions 3 and 4 crystallized on removal of the solvent to give 85 mg. of solid which had ν_{max}^{Nujol} 1745, 1640 (very weak), 1100 cm.$^{-1}$

The materials in fractions 11 and 12 as well as 13–20, the latter group being eluted by a 20% ether-in-benzene solution, were combined and recrystallized from acetone-hexane to give 0.286 g. (45% yield) of XV as white crystals, m.p. 132–134°; $[\alpha]_D$ +178° (chloroform); λ_{max} 240 mμ (ε 16,200); ν_{max} 1745, 1640 (very weak), 1100 cm.$^{-1}$

Anal. Calcd. for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 75.75; H, 8.81.

B. To a solution of 17α,21-dihydroxy-16α-methoxyprogesterone (XIX) (150 mg.) in 30 ml. of 50% acetic acid was added sodium bismuthate (1.2 g.). The resulting mixture was magnetically stirred at room temperature for 2 hr. The suspension was filtered, and the residue was washed with hot chloroform. The chloroform layer from the combined filtrate and washings was then washed successively with water, sodium bicarbonate solution, and water, dried over magnesium sulfate and taken to dryness. Chromatography of the residue as described above gave 62 mg. (49% yield) of white crystals, m.p. 132–134°. Mixture melting point and infrared spectral comparisons showed this material to be identical with that of Method A.

Acid-catalyzed acetylation of 17α-hydroxy-16α-methoxyprogesterone (XIII). A solution of 0.116 g. (0.32 mmole) of 17α-hydroxy-16α-methoxyprogesterone and 0.116 g. of *p*-toluenesulfonic acid hydrate in 5 ml. of glacial acetic acid and 1 ml. of acetic anhydride was magnetically stirred at room temperature for 1 hr. The solution was diluted with water and extracted with methylene chloride. The organic extract was washed with water, dried over magnesium sulfate, and taken to dryness. The oily residue was adsorbed from benzene onto a column prepared from 2 g. of silica gel and benzene (column size: 1.0 × 17 cm.). The material eluted by benzene-ether (94:6) was recrystallized from dilute methanol to give 13 mg. (13% yield) of crystals, m.p. 112–115°; ν_{max}^{Nujol} 3450, 1750, 1704, 1665, 1640, 1245–1205, 1105 cm.$^{-1}$ This material was regarded as *3-acetoxy-17α-hydroxy-16α-methoxy-3,5-pregnadiene-20-one* (XXIII).

The material eluted by benzene-ether (4:1) was recrystallized from acetone-hexane to give 91 mg. (78% recovery) of IV as plates, m.p. 163–165°. Its identity was shown by mixture melting point and infrared spectral comparisons.

17α,21-Dihydroxy-16α-methoxyprogesterone (*16α-methoxy Reichstein's Substance S*) (XIX). A mixture of 2.890 g. (7.91 mmoles) of 17α-hydroxy-16α-methoxyprogesterone (XIII), 4.08 g. (16.1 mmoles) of iodine, 4.08 g. (72.8 mmoles) of calcium oxide, 22 ml. of tetrahydrofuran (containing peroxides equivalent to 10 mg. of iodine per ml.) and 13.5 ml. of methanol was magnetically stirred at room temperature for 4 hr. The then essentially colorless mixture was poured into 750 ml. of ice water containing 1.5 g. of sodium

(45) A product of Davison Chemical Co., Baltimore, Md.

(46) J. Fried, A. Borman, W. B. Kessler, P. Grabowich, and E. F. Sabo, *J. Am. Chem. Soc.*, **80**, 2339 (1958).

thiosulfate. Glacial acetic acid (15 ml.) was added and the mixture was stirred for a few minutes and then extracted with methylene chloride. The combined extracts were washed with saline, dried over magnesium sulfate and taken to dryness. The residue was magnetically stirred with 7.5 g. of potassium acetate in 75 ml. of boiling acetone for 16 hr. The mixture was diluted with water; and the crude product, isolated with methylene chloride, was dissolved in 38 ml. of methanol and treated with a solution of 1.5 g. of sodium bisulfite in 22 ml. of water. This solution was heated at reflux temperature with magnetic stirring for 1 hr. The product, isolated with methylene chloride, was dissolved in 100 ml. of methanol, and the solution was swept thoroughly with nitrogen. A 10% potassium carbonate solution (1.5 ml.) was added, and the solution was magnetically stirred under an atmosphere of nitrogen for 1 hr. After acidification of the solution with glacial acetic acid, the product was isolated with methylene chloride in the usual manner. The material was adsorbed from benzene onto a column prepared from benzene and silica gel, and the column was washed with a 10% ether-in-benzene solution, 125-ml. fractions being collected. The material eluted in fractions 5–14 did not give a positive test for an α-ketol with alkaline tetrazolium reagent. Fractions 15 and 16 gave oils on removal of the solvents. These fractions were not investigated further. The material eluted in fractions 17–31 were combined and recrystallized from acetone-hexane to give 1.094 g. (38% g. yield) of crystals, m.p. 163–167°. This material gave a positive test for an α-ketol with alkaline tetrazolium reagent, and a mixture with starting material melted at 151–161°. A sample was recrystallized three times from acetone-hexane to give the analytical specimen as white crystals, m.p. 169–171°; $[\alpha]_D$ + 64.5°; λ_{max} 241 mμ (ϵ 17,700); ν_{max} 3500, 1700, 1655, 1620, 1225,1100 cm.$^{-1}$

Anal. Calcd. for $C_{22}H_{32}O_4$: C, 70.18; H, 8.57. Found: C, 70.30; H, 8.53.

Acetylation with pyridine and acetic anhydride at room temperature gave the *21-monoacetate* (XX) as white needles, m.p. 143–144.5°, after recrystallization from acetone-hexane. The material had $[\alpha]_D$ + 92.2° (chloroform), + 98° (ethanol); λ_{max} 241 mμ (ϵ 20,200); ν_{max} 3500, 1740, 1715, 1650, 1615, 1230, 1098 cm.$^{-1}$

Anal. Calcd. for $C_{24}H_{34}O_5$: C, 68.87; H, 8.19. Found: C, 68.87; H, 8.17.

3,20-Bisethylenedioxy-5,16-pregnadiene-11-one (II). A solution of 20.40 g. (47.4 mmoles) of 3,20-bisethylenedioxy-17α-hydroxy-5-pregnene-11-one (I)[13,14] in 400 ml. of pyridine was cooled to 0°. Thionyl chloride (80 ml.) was slowly added and the solution was kept at 0° for 16 hr. The resulting mixture was poured, with caution, onto about 1000 ml. of cracked ice water. The product was isolated with chloroform, and the residue remaining after removal of the solvent was dissolved in toluene. Removal of this solvent removed traces of pyridine from the product. The residue was recrystallized from acetone to give 11.54 g. of white needles, m.p. 176–178°. A second crop, weighing 1.08 g. (65% yield), was isolated from the mother liquor. A specimen from a similar experiment was recrystallized twice from acetone–hexane to give white needles, m.p. 178–180°; $[\alpha]_D$ −11° (chloroform), +5.4°; ν_{max}^{KBr} 1702, 1670, 1625, 1100, 1048, 1031 cm.$^{-1}$ Reported[29] values are m.p. 186–188°; $[\alpha]_D$ −14° (chloroform); ν_{max}^{KBr} 1704, 1672, 1623, 1095, 1042, 1031 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{34}O_5$: C, 72.43; H, 8.27. Found: C, 72.21; H, 8.04.

4,16-Pregnadiene-3,11,20-trione (XII). 3,20-Bisethylenedioxy-5,16-pregnadiene-11-one (II) (0.213 g.) was hydrolyzed with 4 ml. of 60% formic acid. The crude product was chromatographed on silica gel. The material which was eluted by a 20% ether-in-benzene solution was recrystallized from ethyl acetate-petroleum ether (b.p. 60–68°) to give 0.111 g. (67% yield) of white needles, m.p. 202–204°; $[\alpha]_D$ +228°; λ_{max} 237 mμ (ϵ 25,700); ν_{max} 1700, 1665, 1630, 1608 cm.$^{-1}$ Reported[32] values are m.p. 202–204° and λ_{max} 236 mμ (ϵ 24,875).

Anal. Calcd. for $C_{21}H_{28}O_3$: C, 77.27; H, 8.03. Found: C, 77.63; H, 8.20.

3,20-Bisethylenedioxy-16α,17α-dihydroxy-5-pregnene-11-one (VII). A mechanically stirred solution of 15.90 g. (39.4 mmoles) of 3,20-bisethylenedioxy-5,16-pregnadiene-11-one (II) in 200 ml. of benzene and 10 ml. of pyridine was treated with a solution of 10.00 g. (39.4 mmoles) of osmium tetroxide in 150 ml. of benzene. The resulting black solution was stirred at room temperature for 17.5 hr., whereafter it was stirred with an additional 250 ml. of benzene, 200 ml. of methanol, and a solution of 71 g. of sodium sulfite and 71 g. of potassium bicarbonate in 800 ml. of water for 4 hr. The mixture was filtered, and the residue was washed thoroughly with several portions of hot chloroform. The aqueous layer was separated from the combined filtrate and washings, and the organic layer was washed with saline, dried over magnesium sulfate, and taken to dryness. The residue was triturated with acetone and filtered to give 15.23 g. (86% yield) of white crystals, m.p. 243–246°. Material from a similar experiment was recrystallized twice from chloroform-hexane to give clusters of white crystals, m.p. 248–250°; $[\alpha]_D$ −1.94°; ν_{max} 3510, 1704, 1680, 1114, 1042 cm.$^{-1}$

Anal. Calcd. for $C_{25}H_{38}O_7$: C, 66.94; H, 8.09. Found: C, 66.69: H, 8.21.

3,20-Bisethylenedioxy-17α-hydroxy-16α-methoxy-5-pregnene-11-one (VIII). *Method A.* 3,20-Bisethylenedioxy-16α,17α-dihydroxy-5-pregnene-11-one (VII) (22.23 g.) was methylated by the procedure used for diol V. The product was chromatographed on silica gel. The solids eluted with a 20% ether-in-benzene solution were combined and recrystallized from acetone to give 16.78 g. (74% yield) of white prismatic needles, m.p. 250.5–252.5°. Material from a similar experiment was recrystallized from acetone-hexane to give prismatic needles, m.p. 250–251.5°; $[\alpha]_D$ −41.5°; ν_{max} 3450, 1700, 1670, 1110 (broad), 1060, 1004 cm.$^{-1}$

Anal. Calcd. for $C_{26}H_{38}O_7$: C, 67.51; H, 8.28. Found: C, 67.87; H, 8.32.

The column was then washed with acetone, and the solid eluted was crystallized from chloroform-hexane to give 4.08 g. (18% recovery) of diol III as white crystals, m.p. 250–252°. The infrared spectrum of this material was identical with that of the analytical sample.

Method B. 17α-Hydroxy-16α-methoxy-4-pregnene-3,11,-20-trione (XIV) (0.137 g.) (see below) was ketalized by the benzene-ethylene glycol procedure. The crude product, isolated in the usual manner, was chromatographed on silica gel. The solid eluted by a 20% ether-in-benzene solution was recrystallized from acetone-hexane to give 0.108 g. (64% yield) of white prismatic needles, m.p. 244–246°. The identity of this material with that prepared in Method A was shown by mixture melting point and infrared spectral comparisons.

17α-Hydroxy-16α-methoxy-4-pregnene-3,11,20-trione (16α-methoxy-21-deoxycortisone) (XIV). *Method A.* Hydrolysis of 1.809 g. (3.92 mmoles) of 3,20-bisethylenedioxy-17α-hydroxy-16α-methoxy-5-pregnene-11-one (XIV) with 30 ml. of 60% formic acid gave 1.437 g. of white crystals, m.p. 205–214°. A sample of this material was chromatographed on Florisil[47]; the solid eluted by a 5% acetone in petroleum ether (b.p. 60–68°) solution was recrystallized from acetone-hexane to give white crystals, m.p. 212.5–214.5°; $[\alpha]_D$ +160°; λ_{max} 238 mμ (ϵ 13,620); ν_{max} 3510, 1710, 1670, 1630, 1100 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{30}O_5$: C, 70.56; H, 8.08. Found: C, 70.81; H, 8.03.

Method B. A solution of 50 mg. of 11β,17α-dihydroxy-16α-methoxyprogesterone (XVI) (see below) in 1.5 ml. of pyridine was treated with a slurry of 62 mg. of chromium trioxide in 2.5 ml. of pyridine at 5°. The resulting solution was

(47) A product of the Floridin Co., Warren, Pa.

kept at room temperature for 16 hr. The product, isolated with chloroform in the usual manner, was recrystallized from acetone-hexane to give 27 mg. (55% yield) of white crystals, m.p. 206–210°. The infrared spectra of this material and that prepared by Method A were identical.

Reduction of 3,20-bisethylenedioxy-17α-hydroxy-16α-methoxy-5-pregnene-11-one with sodium borohydride. A mixture of 16.78 g. (36.4 mmoles) of 3,20-bisethylenedioxy-17α-hydroxy-16α-methoxy-5-pregnene-11-one (VIII), 30.2 g. (0.080 mole) of sodium borohydride, 3.30 g. (0.0825 mole) of sodium hydroxide and 500 ml. of ethanol was heated at reflux temperature for 19 hr. with mechanical stirring. The mixture was diluted with water, and the products were isolated with chloroform. The residue remaining on removal of the solvent was crystallized from acetone-hexane to give 11.82 g. of *3,20-bisethylenedioxy-11β,17α-dihydroxy-16α-methoxy-5-pregnene* (IX) as white prisms, m.p. 181–183°. The mother liquor was taken to dryness, and the residue was chromatographed on silica gel. The solid eluted with a 20% ether-in-benzene solution was recrystallized from acetone-hexane to give 3.34 g. (90% total yield) of white prisms, m.p. 181–183°. Material from a similar experiment was obtained as white crystals, m.p. 182–184°; $[\alpha]_D$ −77.5°; ν_{max} 3450, 1100 (broad), 1060, 1004 cm.$^{-1}$

Anal. Calcd. for $C_{26}H_{40}O_7$: C, 67.21; H, 8.68. Found: C, 67.08; H, 8.53.

This material was recovered after treatment with acetic anhydride in pyridine at room temperature for 18 hr.

The above column was then washed with acetone, and the eluted solid was recrystallized from chloroform-hexane to give 500 mg. (3% yield) of *3,20-bisethylenedioxy-11α,17α-dihydroxy-16α-methoxy-5-pregnene* (X) as white needles, m.p. 235–240°. Two additional recrystallizations from the same solvent pair gave white needles, m.p. 244–246°; $[\alpha]_D$ −67°; ν_{max} 3500, 1100 (broad), 1058, 1002 cm.$^{-1}$

Anal. Calcd. for $C_{26}H_{40}O_7$: C, 67.21; H, 8.68. Found: C, 66.92; H, 8.70.

Upon acetylation with acetic anhydride and pyridine this material gave the monoacetate XI which was obtained by recrystallization from acetone-hexane as white needles, m.p. 244–245°; $[\alpha]_D$ −89.5°; λ_{max}^{KBr} 3420, 1740, 1640, 1255, 1100 cm.$^{-1}$

Anal. Calcd. for $C_{28}H_{42}O_8$: C, 66.38; H, 8.36. Found: C, 66.27; H, 8.30.

11β,17α-Dihydroxy-16α-methoxyprogesterone (16α-methoxy-21-deoxyhydrocortisone) (XVI). Hydrolysis of 4.88 g. (10.5 mmoles) of 3,20-bisethylenedioxy-11β,17α-dihydroxy-16α-methoxy-5-pregnene (IX) with 50 ml. of 60% formic acid gave 3.474 g. (88% yield) of white crystals, m.p. 217–222°. A sample of this material was eluted from Florisil with a 10% acetone in petroleum ether (b.p. 60–68°) solution and recrystallized from acetone-hexane to give white needles, m.p. 220–223°; $[\alpha]_D$ +106°; λ_{max} 242 mμ (ε 16,610); ν_{max} 3450, 1702, 1670, 1635, 1102 cm.$^{-1}$

Anal. Calcd. for $C_{22}H_{32}O_5$: C, 70.18; H, 8.57; OCH_3, 8.24; C-CH_3, 3.0. Found: C, 70.32; H, 8.45; O-CH_3, 8.46; C-CH_3, 2.1.

16α-Methoxycortisone acetate (XXI). *Method A.* A mixture of 2.000 g. (5.34 mmoles) of 17α-hydroxy-16α-methoxy-4-pregnene-3,11,20-trione (XIV), 2.80 g. (10.84 mmoles) of iodine, 2.76 g. (49.2 mmoles) of calcium oxide, 9 ml. of methanol, and 15 ml. of tetrahydrofuran (peroxide content equivalent to 10 mg. of iodine per ml.) was magnetically stirred at room temperature for 4 hr. Although the iodine color was not discharged at this time, it had faded perceptibly. The mixture was poured into 500 ml. of ice water containing 1.0 g. of sodium thiosulfate, stirred a few minutes, and then treated with 10 ml. of glacial acetic acid and extracted with methylene chloride (150 ml., 2 × 100 ml.). The combined methylene chloride extracts were washed with saline until the washes were neutral, dried over magnesium sulfate, and taken to dryness below room temperature. The residue was dissolved in 50 ml. of acetone containing 5.00 g. of potassium acetate, and this mixture was heated at reflux temperature for 16 hr. The cooled mixture was diluted with water and extracted with methylene chloride. The crude product was heated at reflux temperature with 1.0 g. of sodium bisulfite in 15 ml. of water and 25 ml. of methanol for 1 hr. The mixture was diluted with water and the product was isolated with methylene chloride. The crude material was adsorbed from methylene chloride onto a column prepared from Florisil and petroleum ether (b.p. 60–68°) (column size: 1.8 × 40 cm.). The column was washed with 500 ml. of a 5% acetone in petroleum ether solution and these washes were discarded. The column was then washed with a 10% acetone in petroleum ether solution, 125-ml. fractions being collected. The solids eluted in fractions 1 and 2 did not give a positive terazolium test for an α-ketol, whereas fractions 3 and 4 did. The last two fractions were combined with the subsequent 30% acetone in petroleum ether eluates, and the solid contained therein was recrystallized from acetone-hexane to give 1.017 g. (43% yield) of white crystals, m.p. 207–210°. Material from a similar experiment was recrystallized three times from acetone-hexane to give white glistening blades, m.p. 208.5–211.0°; $[\alpha]_D$ + 178°; λ_{max} 238 mμ (ε 17,600); ν_{max} 3480, 1750, 1734, 1708, 1675, 1630, 1275, 1240, 1100 cm.$^{-1}$

Anal. Calcd. for $C_{24}H_{32}O_7$: C, 66.65; H, 7.46; O—CH_3, 7.16. Found: C, 66.65; H, 7.53; O—CH_3, 7.29.

Method B. A solution of 0.100 g. (0.23 mmole) of 16α-methoxyhydrocortisone acetate (XVII) in 3 ml. of pyridine was treated with a slurry of 0.124 g. of chromium trioxide in 5 ml. of pyridine as described in the conversion of XVI into XIV. The product was recrystallized from acetone-hexane to give 72 mg. of blades, m.p. 208.5–210.5°. The identity of this material with that of Method A was established by mixture melting point and infrared spectral comparisons.

16α-Methoxyhydrocortisone acetate (XVII). A mixture of 2.974 g. (7.91 mmoles) of 16α-methoxy-21-deoxyhydrocortisone (XVI), 4.08 g. (16.1 mmoles) of iodine, 4.08 g. (72.8 mmoles) of calcium oxide, 13.5 ml. of methanol, and 22 ml. of aged tetrahydrofuran was treated as described in Method A for the preparation of XXI. The crude iodo derivative was treated with 7.5 g. of potassium acetate in 75 ml. of boiling acetone to effect acetolysis. The crude product was reduced with 1.5 g. of sodium bisulfite in 22 ml. of water and 38 ml. of methanol. The resulting material (2.563 g.) was adsorbed from methylene chloride onto a Florisil column. The column was washed with a 10% acetone in petroleum ether solution, 125-ml. fractions being collected. The solids eluted in fractions 2–12 (1.323 g.) were mixtures of XVI and XVII. The material eluted in fractions 13–18, the last three fractions being 30% acetone in petroleum ether, was recrystallized from acetone-hexane to give 0.608 g. (17% yield) of white needles, m.p. 234–236°. This material gave a positive test for an α-ketol with alkaline tetrazolium reagent, and it had $[\alpha]_D$ +109°; λ_{max} 242 mμ (ε 17,300). ν_{max} 390, 1750, 1730, 1665, 1630, 1278, 1240, 1100 cm.$^{-1}$

Anal. Calcd. for $C_{24}H_{34}O_7$: C, 66.34; H, 7.89. Found: C, 66.02; H, 7.66.

16α-Methoxyprednisone acetate (XXII). A solution of 0.600 g. (1.38 mmoles) of 16α-methoxycortisone acetate (XXI), 0.320 g. (2.88 mmoles) of selenium dioxide, 0.1 ml. of pyridine, and 35 ml. of *t*-butyl alcohol was heated at reflux temperature under a nitrogen atmosphere with magnetic stirring for 28 hr. The mixture was filtered with the aid of Celite, and the residue was washed with several portions of hot ethyl acetate. The combined filtrate and washings were taken to dryness. The residue was dissolved in chloroform, and this solution was washed with saline, dried over magnesium sulfate, and taken to dryness. The residue was chromatographed on Florisil; the solid eluted by a 10% acetone in petroleum ether solution was recrystallized from acetone-hexane to give 0.378 g. (64% yield) of white needles, m.p. 204–206°. Material from a similar experiment was recrystallized three times from acetone-hexane to give white needles, m.p. 204–206°; $[\alpha]_D$ +151°; λ_{max} 239 mμ

(ϵ 17,950); ν_{max} 3480, 1750, 1730, 1708, 1665, 1620, 1278, 1240, 1100 (broad) cm.$^{-1}$

Anal. Calcd. for $C_{24}H_{30}O_7$: C, 66.96; H, 7.02; O—CH_3, 7.21. Found: C, 66.80; H, 7.11; O—CH_3, 7.27.

16α-Methoxyprednisolone acetate (XVIII). A mixture of 0.212 g. (0.487 mmole) of 16α-methoxyhydrocortisone acetate (XVII), 0.112 g. (1.01 mmoles) of selenium dioxide, 0.035 ml. of pyridine, and 12 ml. of *t*-butyl alcohol was treated as described in the preparation of XXII. The crude product was chromatographed on Florisil, and the material eluted by acetone in petroleum ether (1:9 and 2:8) was recrystallized from acetone-hexane to give 0.115 g. (55% yield) of white needles, m.p. 242–242.5°. The analytical sample had a m.p. of 244.0–245.5° (sl. dec.); $[\alpha]_D$ +69.5°; λ_{max} 243 mμ (ϵ 15,700); ν_{max} 3450, 1750, 1735, 1665, 1635, 1615, 1240, 1100 cm.$^{-1}$

Anal. Calcd. for $C_{24}H_{32}O_7$: C, 66.65; H, 7.46. Found: C, 66.26; H, 7.41.

3,20-Bisethylenedioxy-17α-hydroxy-16α-methoxy-5,9(11)-pregnadiene (XXIV). *Method A.* A solution of 3.223 g. (6.93 mmoles) of 3,20-bisethylenedioxy-11β,17α-dihydroxy-16α-methoxy-5-pregnene (IX) in 32 ml. of pyridine was chilled in an ice bath and treated with 2.6 ml. of phosphorus oxychloride. The solution was allowed to stand at room temperature for 45 hr. and then cautiously poured into cracked ice-water. The solid was collected by filtration and recrystallized from chloroform-hexane to give 2.903 g. (94% yield) of white crystals, m.p. 219–221°. Material from a similar experiment was recrystallized three times from chloroform-hexane to give white crystals, m.p. 216–218°; $[\alpha]_D$ −47°; ν_{max} 3520, 1704, 1118, 1100, 1060, 998 cm.$^{-1}$

Anal. Calcd. for $C_{26}H_{38}O_6$: C, 69.93; H, 8.58. Found: C, 69.95; H, 8.79.

Method B. A solution of 0.100 g. (0.215 mmole) of 3,20-bisethylenedioxy-11α,17α-dihydroxy-16α-methoxy-5-pregnene (X) in 1 ml. of pyridine was treated with 0.08 ml. of phosphorus oxychloride as described in Method A. The crude solid was chromatographed on silica gel; the solid eluted by benzene-ether (8:2) was recrystallized from chloroform-hexane to give 62 mg. (64% yield) of white crystals, m.p. 219–221°. The infrared spectra of this material and that of Method A were identical.

Method C. A mixture of 0.192 g. (0.54 mmole) of 17α-hydroxy-16α-methoxy-4,9(11)-pregnadiene-3,20-dione (XXV), 50 mg. of *p*-toluenesulfonic acid hydrate, 20 ml. of benzene, and 10 ml. of ethylene glycol was treated in the usual manner. The crude product, isolated from the benzene layer, was recrystallized from chloroform-hexane to give 0.110 g. (46% yield) of white crystals, m.p. 210–213°. Mixture melting point and infrared spectral comparisons showed this material to be identical with the analytical sample.

17α-Hydroxy-16α-methoxy-4,9-(11)-pregnadiene-3,20-dione (XXV). Hydrolysis of 3.500 g. (7.85 mmoles) of 3,20-bisethylenedioxy-17α-hydroxy-16α-methoxy-5,9(11)-pregnadiene (XXIV) with 35 ml. of 60% formic acid gave 2.689 g. (89% yield) of white crystals, m.p. 198–200°. A sample was recrystallized three times from methanol to give white plates, m.p. 196–198°; $[\alpha]_D$ +71.5° (chloroform); λ_{max} 240 mμ (ϵ 17,200); ν_{max} 3550, 1700, 1660, 1615, 1100 (broad) cm.$^{-1}$

Anal. Calcd. for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44. Found: C, 73.79; H, 8.71.

9α-Bromo-11β,17α-dihydroxy-16α-methoxyprogesterone (XXVII). *Method A.* A mixture of 4.557 g. (12.7 mmoles) of 17α-hydroxy-16α-methoxy-4,9(11)-pregnadiene-3,20-dione (XXV), 45 ml. of peroxide-free dioxane, and 7 ml. of 0.5*N* perchloric acid was cooled with magnetic stirring to about 15°. *N*-Bromoacetamide (2.000 g., 14.5 mmoles) was added over 30 min. in six approximately equal portions. All solid dissolved within this period, and the solution was stirred for an additional 30 min. The excess *N*-bromoacetamide was destroyed by addition of a saturated sodium sulfite solution, and the solution was diluted with water. Filtration gave 4.447 g. of crystals, m.p. 164–167° dec. The mother liquor gave an additional 0.358 g. of material (83% yield). A sample was recrystallized five times from acetone-hexane to give white crystals, m.p. 165–167° dec. after darkening from 150°; $[\alpha]_D$ +118° (chloroform); λ_{max} 245 mμ (ϵ 15,500); ν_{max} 3500, 1700, 1660, 1635, 1100 cm.$^{-1}$

Anal. Calcd. for $C_{22}H_{31}BrO_5 \cdot {}^1/_2C_3H_6O$: C, 58.25; H, 7.07; Br, 16.49. Found: C, 58.24; H, 7.54; Br. 16.41.

Method B. A solution of 0.200 g. (0.54 mmole) of 9β,11β-epoxy-17α-hydroxy-16α-methoxyprogesterone (XXVI) in 14 ml. of carbon tetrachloride–glacial acetic acid (1:1) was treated with 0.8 ml. of 30% hydrogen bromide in glacial acetic acid and kept at room temperature for 10 min. The product was isolated with methylene chloride and crystallized from acetone-hexane to give 0.232 g. (79% yield) of crystals, m.p. 162–166° dec. after prior darkening. The infrared spectra of this material and that obtained in Method A were identical.

9β,11β-Epoxy-17α-hydroxy-16α-methoxyprogesterone (XXVI). A solution of 4.296 g. (9.45 mmoles) of 9α-bromo-11β,17α-dihydroxy-16α-methoxyprogesterone (XXVII) and 4.30 g. of potassium acetate in 200 ml. of ethanol was heated at reflux temperature for 16 hr. The resulting mixture was concentrated to a volume of about 50 ml. and diluted with water to furnish 3.234 g. (91% yield) of crystals, m.p. 157–162°. For analysis a sample was recrystallized five times from acetone-hexane to give white crystals, m.p. 176–178°; $[\alpha]_D$ −30.3° (chloroform); λ_{max} 243 mμ (ϵ 14,800); ν_{max} 3440, 1700, 1655, 1620, 1100 cm.$^{-1}$

Anal. Calcd. for $C_{22}H_{30}O_5$: C, 70.56; H, 8.08. Found: C, 70.61; H, 8.13.

9α-Fluoro-11β,17α-dihydroxy-16α-methoxyprogesterone (XXVIII). To 5 ml. of methylene chloride previously chilled to −50° was added 3 ml. of anhydrous hydrogen fluoride. This solution was added to a solution of 0.374 g. (1.0 mmole) of 9β,11β-epoxy-17α-hydroxy-16α-methoxyprogesterone (XXVI) in 5 ml. of methylene chloride and 5 ml. of tetrahydrofuran which was previously chilled to −50°. The resulting cherry red solution was placed in an ice bath and magnetically stirred for 4 hr., after which it was poured into sodium bicarbonate solution and diluted with methylene chloride. The organic layer was separated, dried over magnesium sulfate, and taken to dryness. The residue was recrystallized from acetone-hexane to give 0.183 g. (47% yield) of white needles, m.p. 247–251° dec. An additional recrystallization gave the analytical specimen, m.p. 250–252° dec.; $[\alpha]_D$ +93.6°; λ_{max} 240 mμ (ϵ 17,200); ν_{max} 3475, 1708, 1663, 1630, 1100 cm.$^{-1}$

Anal. Calcd. for $C_{22}H_{31}FO_5$: C, 66.98; H, 7.92; F, 4.82. Found: C, 66.93; H, 8.42; F, 4.82.

9α-Fluoro-16α-methoxyhydrocortisone acetate (XXIX). A mixture of 1.165 g. (2.95 mmoles) of 9α-fluoro-11β,17α-dihydroxy-16α-methoxyprogesterone (XXVIII), 1.55 g. (6.00 mmoles) of iodine, and 1.52 g. (27.1 mmoles) of calcium oxide in 5 ml. of methanol and 8.3 ml. of tetrahydrofuran (aged) was treated as described in the preparation of XXI. The product from the sodium bisulfite treatment was chromatographed on silica gel. The column was washed with benzene-ether (85:15), 125-ml. fractions being collected. The materials in fractions 4–6 crystallized on scratching but gave negative tests for an α-ketol. Fractions 7–15 contained materials that gave a positive test for an α-ketol, but which failed to crystallize. From fractions 16–29, eluted by benzene-ether (3:1), there was obtained crystalline material which on recrystallization from acetone-hexane gave 0.548 g. (43% yield) of white crystals, m.p. 196–199°. Two additional recrystallizations sharpened the range to 196–198°. This material had $[\alpha]_D$ +98° (chloroform); λ_{max} 239 mμ (ϵ 16,100); ν_{max} 3440, 1735, 1720, 1650, 1617, 1230, 1095, 1027 cm.$^{-1}$

Anal. Calcd. for $C_{24}H_{33}FO_7 \cdot C_3H_6O$: C, 63.51; H, 7.70; F, 3.72. Found: C, 63.93; H, 7.85; F, 3.64.

9α-Fluoro-16α-methoxyprednisolone acetate (XXX). A

solution of 0.330 g. (0.73 mmole) of 9α-fluoro-16α-methoxyhydrocortisone acetate (XXIX) and 0.175 g. (1.57 mmoles) of selenium dioxide in 18 ml. of *t*-butyl alcohol containing 0.055 ml. of pyridine was treated as described in the preparation of XXII. The crude material was chromatographed on silica gel. The solids eluted by benzene-ether (3:1) were combined and recrystallized from acetone-hexane to give 0.103 g. (32% yield) of crystals, m.p. 226–229° dec. An additional recrystallization gave the analytical specimen (40 mg.) as white crystals, m.p. 238–240° dec.; $[\alpha]_D$ + 70.5° (acetone); λ_{max} 240 mμ (ε 17,100); ν_{max} 3400, 1730, 1712, 1650, 1612, 1600, 1230, 1098 cm.$^{-1}$

Anal. Calcd. for $C_{24}H_{31}FO_7$: C, 63.98; H, 6.94; F, 4.22. Found: C, 64.50; H, 7.77; F, 4.63.

EVANSVILLE 21, IND.

[CONTRIBUTION FROM THE DIVISION OF CHEMICAL RESEARCH, G. D. SEARLE & CO.]

Retropinacol Rearrangement of Estradiol 3-Methyl Ether

WILLIAM F. JOHNS

Received April 20, 1961

Distillation of estradiol 3-methyl ether from boric acid gives preponderantly the olefin *2*. The by-products of this reaction have been isolated and characterized. Other methods of effecting the rearrangement are described.

Among the possible synthetic routes to 18-nor steroids is that utilizing retropinacolic elimination of the C-17 substituent of a suitable androstane or estrane. In this reaction migration of the angular methyl group to C-17 occurs, leaving, ideally, a double bond located between carbons 13 and 17 (such as olefin *2*). Such compounds are excellent starting materials for the preparation of hormonal analogs lacking a C-13 substituent.[1,2]

Among the first of a large number of such rearrangements in steroid literature is that contained in the structure elucidation of estradiol by Cohen, Cook, and Hewett[3]; methyl migration was observed both with estradiol 3-methyl ether and with 17α-methylestradiol 3-methyl ether upon treatment with Lewis acid catalysts. Later Miescher and Kagi[4] proved that treatment of 17α-hydroxyandrostanes with formic acid gave as a major product a $\Delta^{13(17)}$, 17-methyl steroid ("pseudoandrostene"), the rearrangement in this case being facilitated by the coplanarity of the four centers involved.[5] "Retro"-steroids, postulated to be Δ^{13},-17-methylandrostenes and -estratetraenes, were prepared in the same period by treatment of 17-chloroandrostanes (or -estratrienes) with base.[6] More recently the reaction of 17β-tosylates with various nucleophilic agents has been investigated; the products are in part the 13(17)-olefins.[2,7] Finally, both androstanes[8] and pregnanes[9] possessing a C-17–tertiary hydroxyl have been shown to undergo this rearrangement readily under acidic conditions.

The use of this reaction in the synthesis of 18-nor hormones was unattractive due to the difficulties in obtaining starting materials of the proper configuration and/or in the subsequent low yields of the desired isomer. These objections were removed by the discovery that estradiol 3-methyl ether on distillation from boric acid yields 65–70% of olefin *2*.[10] Ozonolysis of *2* to a diketone (*6*) (λ_{max} 5.83 μ) established the ditertiary nature of the double bond. Base treatment of this diketone led to a hydroxy ketone (*9*) (NMR showed only *O*-methyl, no C-methyl) which formed in turn an unsaturated ketone (*8*) whose ultraviolet absorption (λ_{max} 239 mμ) eliminates two (*3*, *10*) of the three possible ditertiary olefins not conjugated with the A-ring. Thus only structure *2* is consistent with the data.[11] Conclusive proof of the structure of this olefin was obtained by its conversion to 18-norestrone methyl ether.[1]

Accompanying olefin *2* were several products isolated by osmium tetroxide hydroxylation of the entire olefin mixture and subsequent chromatographic analysis. The glycols obtained were oxidized with periodate and the cleavage products were treated with base to complete the identifications. Additional quantities of these cleavage

(1) W. F. Johns, *J. Am. Chem. Soc.*, **80**, 6456 (1958).
(2) G. Stork, H. N. Khastgir, and A. J. Solo, *J. Am. Chem. Soc.*, **80**, 6457 (1958).
(3) A. Cohen, J. W. Cook, and C. L. Hewett, *J. Chem. Soc.*, 445 (1935).
(4) K. Miescher and H. Kagi, *Helv. Chim. Acta*, **32**, 761 (1949); **22**, 683 (1939).
(5) D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953).
(6) U. Westphal, Y.-L. Wang, and H. Hellmann, *Ber.*, **72**, 1233 (1939).
(7) O. S. Madaeva, *J. Gen. Chem. U.S.S.R.*, **25**, 1373 (1958), *Zhur. Obshchei Khim.*, **27**, 2573 (1957); F. Sondheimer, O. Mancera, M. Urquiza, and G. Rosenkranz, *J. Am. Chem. Soc.*, **77**, 4145 (1955); J. Elks and C. W. Shoppee, *J. Chem. Soc.*, 241 (1953).
(8) O. S. Madaeva, *J. Gen. Chem. U.S.S.R.*, **26**, 3267 (1956); N. L. Wendler, R. P. Graber, and G. G. Hazen, *Tetra.*, **3**, 144 (1958); V. Tortorella, G. Lucente, and A. Romeo, *Annal. Chim. (Rome)*, **50**, 1198 (1960).
(9) See, for example, H. L. Herzog *et al.*, *J. Am. Chem. Soc.*, **81**, 6478, 6483 (1960); J. E. Herz *et al.*, *J. Am. Chem. Soc.*, **78**, 4813 (1956); R. Hirschmann *et al.*, *J. Am. Chem. Soc.*, **78**, 4814 (1956).
(10) Dr. D. A. Tyner of these laboratories was the first to utilize these conditions and we wish to thank him for allowing us to identify and exploit the products.
(11) *Cf.* ref. 4 for a similar proof of structure.