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Addition of Alkyl Vinyl Ethers to Δ^{16}-20-Keto Steroids. I[1]

J. E. PIKE, M. A. REBENSTORF, G. SLOMP, AND F. A. MACKELLAR

Research Laboratories, The Upjohn Company, Kalamazoo, Michigan

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Reaction of a variety of Δ^{16}-20-keto steroids with methyl vinyl ether has afforded the corresponding pentacyclic dihydropyrans. The addition can be effected selectively on the steroid Δ^{16}-20-keto system leaving other functional groups intact. The stereochemistry at the new asymmetric centers is described.

An important method for the preparation of 16-alkyl steroids has been the addition of methylmagnesium halides to the readily accessible Δ^{16}-20-keto steroids.[2] In many instances these adducts have been converted to 17α-hydroxy-20-keto steroids *via* the intermediate 17(20)-enol acetate.[3] The effect of such changes on biological activity has led us to investigate alternate methods of introducing groups at this position.

A potentially valuable approach seemed to us to lie in a modified Diels–Alder reaction between a Δ^{16}-20-keto steroid and a suitable olefin. Cyclo addition reactions of this type are well documented for simpler molecules[4]; Smith, Norton and Ballard have studied this reaction in detail and have shown that the best results were obtained with alkyl vinyl ethers. This approach seemed particularly attractive since the expected adducts (*e.g.*, 2) would not only possess the desired 16-substituent but would contain as well a 17(20)-double bond for subsequent introduction of the 17α-hydroxyl group.

Reaction of 16-dehydropregnenolone acetate with excess methyl vinyl ether[5] in a sealed vessel at 200° gave a 41% yield of a crystalline product, with the correct analytical and spectral properties for the dihydropyran 2 (R = H). The n.m.r. spectrum[6] (Fig. 1) of the cycloaddition product showed that the addition had occurred in the manner expected from polarity considerations to yield the cyclic 16b-acetal 2. Addition in the opposite sense would have given a 16a,16b-dioxy compound with three similar carbinol hydrogens and an ABC type proton resonance pattern[7] not seen in the spectrum which showed instead a doublet of doublets (299.6, 295.2, 291, 286.6 c.p.s.; J = 8.6, 4.4 c.p.s.) in the region of absorption of hydrogen on carbon bearing two oxygens. The observed multiplet was the X portion of an ABX system[8] corresponding to the 16a and 16b hydrogens.

Two new asymmetric centers were created by the cycloaddition reaction. At C-16, addition from the backside was anticipated by analogy with typical steroid reactions[9] and the new 16-substituent was therefore assigned the α-configuration. In the related Diels–Alder addition of maleic anhydride and a steroid 16,20-diene the α-configuration also was assigned to the new substituent at C-16.[10] Confirmation of this assignment was obtained from further transformations of the adducts,[11] and some additional evidence was derived from substituent additivities[12] in the n.m.r. spectrum (Fig. 1). The 18-H absorption observed at 54 c.p.s. required a net downfield contribution for the

(1) This work was first presented at the 2nd International Symposium on the Chemistry of Natural Products, Prague, Czechoslovakia, August 27 to September 3, 1962.

(2) (a) D. K. Fukushima and T. F. Gallagher, *J. Am. Chem. Soc.*, **72**, 2306 (1950); **73**, 196 (1951); (b) H. Hirschmann, E. B. Hirschmann, and M. A. Daus, *ibid.*, **74**, 539 (1952); (c) J. Romo, M. Romero, C. Djerassi, and G. Rosenkrantz, *ibid.*, **73**, 1528 (1951); (d) D. Gould, E. L. Shapiro, L. E. Finckenor, F. Gruen, and E. B. Hershberg, *ibid.*, **78**, 3158 (1956); (e) J. Romo, *Tetrahedron*, **3**, 37 (1958).

(3) (a) T. H. Kritchevsky and T. F. Gallagher, *J. Am. Chem. Soc.*, **73**, 184 (1951); (b) B. A. Koechlin, T. H. Kritchevsky, and T. F. Gallagher, *ibid.*, **73**, 189 (1951).

(4) R. I. Longley and W. S. Emerson, *ibid.*, **72**, 3079 (1950); C. W. Smith, D. G. Norton, and S. A. Ballard, *ibid.*, **73**, 5267 (1951); **73**, 5273 (1951); W. E. Parham and H. E. Holmquist, *ibid.*, **73**, 913 (1951); W. S. Emerson, G. H. Birum, and R. I. Longley, *ibid.*, **75**, 1312 (1953).

(5) During the course of this work a communication appeared describing the addition of alkyl vinyl ethers to 16-dehydropregnenolone acetate and the conversion of the adduct to the corresponding Δ^4-3-ketone [S. Julia and H. Linares, *Compt. rend.*, **252**, 2560 (1961)].

(6) N.m.r. spectra were observed with a Varian DP-60 or A-60 spectrometer operating at 60 Mc. DP-60 spectra were observed on *ca.* 0.15 *M* solutions (generally unless otherwise indicated in deuteriochloroform) and these spectra were calibrated against internal tetramethylsilane using the audiofrequency side-band technique. Frequencies are reported in cycles per second downfield from tetramethylsilane. The A-60 spectra were run on 0.25 *M* solutions. Any inquiries on the n.m.r. data presented in this paper should be directed to G. Slomp.

(7) S. Castellano and J. S. Waugh, *J. Chem. Phys.*, **34**, 295 (1961).

(8) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p. 132.

(9) L. F. Feiser and M. Feiser, *Experientia*, **4**, 285 (1948).

(10) F. Sondheimer and R. Mechoulam, *J. Org. Chem.*, **24**, 106 (1959); R. H. Mazur and G. P. Mueller, *Chem. Abstr.*, **51**, 2070 (1957); R. H. Mazur, *ibid.*, **51**, 4436 (1957).

(11) J. E. Pike, G. Slomp, and F. A. MacKellar, *J. Org. Chem.*, **28**, 2502 (1963).

(12) A method of calculating absorption frequencies of 18- and 19-hydrogens in steroids uses basic frequencies of 39 and 52 c.p.s., respectively, plus numerical contributions for various substituents. [G. Slomp, private communication in *Mellon NMR Newsletter*, **31**, 8 (1961)]; see also R. Zürcher, *Helv. Chim. Acta*, **44**, 1755 (1961).

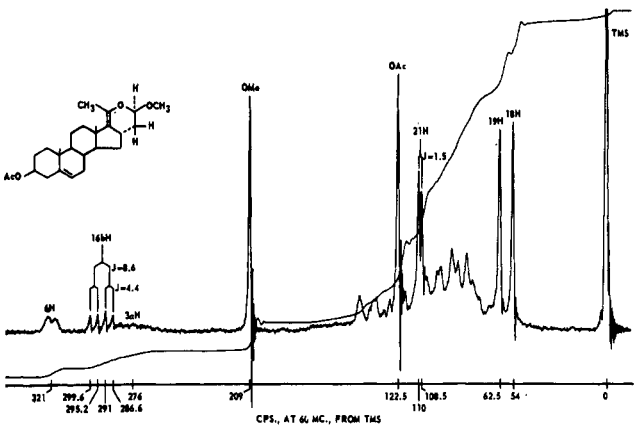
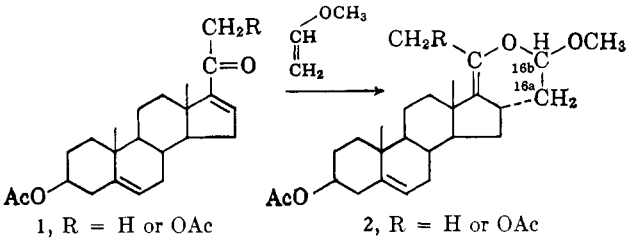
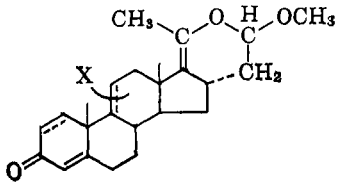


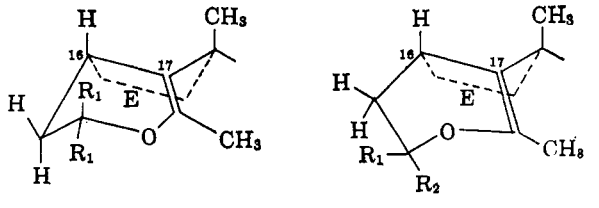
Fig. 1.—N.m.r. spectrum of the cycloaddition product 2.



1, R = H or OAc 2, R = H or OAc

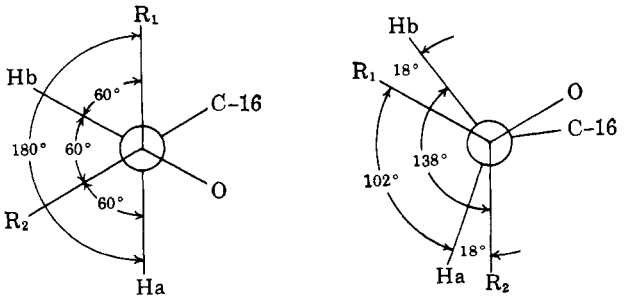


3a, Δ^4, X = H
b, $\Delta^{1,4}$ X = $\Delta^{9(11)}$
c, $\Delta^{1,4}$ X = 9αF, 11βOH



2a, R_1 = OMe, R_2 = H
b, R_1 = H, R_2 = OMe

2c, R_1 = OMe, R_2=H
d, R_1 = H, R_2 = OMe



E-ring of 15 c.p.s. from the basic 18-H absorption at 39 c.p.s. Based on observed contributions of 16 c.p.s. for a model $\Delta^{17(20)}$ steroid (16α-methyl-$\Delta^{17(20)}$-20-acetate), 0 c.p.s for a 16α-methyl group and 5 c.p.s. for a 16β-methyl group, the 16β isomer was expected to have 18-H absorption at 59 c.p.s. and the attachment at C-16 was judged to be α-oriented.

In the second new asymmetric center, the 16b-methoxy group could be assigned the β-configuration on the basis of n.m.r. calculations. The E-ring could exist either in the half-chair (**2a,b**) or half-boat forms (**2c,d**) for which both α- and β-oriented methoxy groups were considered. Only one form (**2c**) possessed dihedral angles of the 16a and 16b hydrogens compatible with the coupling constants observed in the X-multiplet. These coupling constants were converted to angles using the Karplus equations[13] with the modified constants of Lenz and Heeschen[14] (determined on the closely related 2-deoxyglucopyranosides). The two possible angles resulting from each coupling constant (Table I) were compared with the approximate angles observed in Dreiding models for structures **2a–d** (Table II). Good agreement was observed only in the half-boat form with the methoxy group β-oriented **2c** where $J_{4,4} = 132°$ and $J_{8,6} = 11.5°$.[15,16]

TABLE I

ANGLES CALCULATED FROM ABX COUPLING CONSTANTS[13a,14]

	θ, degrees	
J, c.p.s.	Acute	Obtuse
8.6	11.5	158
4.4	45	132

TABLE II

DIHEDRAL ANGLES OBSERVED IN DREIDING MODELS COMPARED WITH ANGLES CALCULATED FROM SPECTRAL DATA

		Degrees		
Structure	<θ	Obsvd.	Calcd.	Δ
2a	R_2Ha	60	11.5	+48.5
	R_2Hb	60	45	+15
2b	R_1Ha	180	158	+22
	R_1Hb	60	45	+15
			132	+48
			11.5	+48.5
2c	R_2Ha	18	45	−27
	R_2Hb	138	158	−20
			11.5	+6.5
			132	+6.0
2d	R_1Ha	102	158	−56
	R_1Hb	18	45	−27
			132	−30
			11.5	+6.5

The vinyl ether addition was readily extended to other Δ^{16}-20-keto steroids where it proceeded selectively and in good yield to give the pentacyclic dihydropyrans. By way of example, the addition was effected on Δ^{16}-20-keto steroids with a Δ^4-3-ketone **3a**, a $\Delta^{1,4,9(11)}$-3-ketone **3b**, an 11β-hydroxy-9α-fluoro system **3c**, and a 21-acetate **2** (R = OAc). The intermediate dihydropyrans, which contain both a 16α-substituent and a

(13) (a) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959); (b) H. Conroy, in "Advances in Organic Chemistry: Methods and Results," Vol. 11, Interscience Publishers, Inc., New York, N. Y., 1960, p. 311; (c) J. I. Musher, *J. Am. Chem. Soc.*, **83**, 1146 (1961); (d) K. L. Williamson and W. S. Johnson, *ibid.*, **83**, 4626 (1961); (e) L. D. Hall, L. Hough, K. A. McLauchlan, and K. Pachler, *Chem. Ind.*, 1465 (1962).

(14) R. W. Lenz and J. P. Heeschen, *J. Polymer Sci.*, **51**, 247 (1961).

(15) Since the sign and magnitude of the difference between the observed and calculated angles were consistent, it may be concluded either that the "Karplus constants" need to be slightly larger or that the carbon atoms in the Dreiding models do not represent precisely the D/E ring system which is more nearly half-boat in form and in which the substituents are more nearly eclipsed. The close agreement made averaging by rapid ring conversion between the two forms seem unlikely.

(16) The α-configuration of the 16b-methoxyl group had been anticipated by the rule of maximum overlap of unsaturation.[10,17,18] It was not certain, however, that isomerization under the conditions of the condensation could be ruled out. The n.m.r. data appears to permit a clear distinction between these possibilities.

(17) K. Alder and G. Stein, *Angew. Chem.*, **50**, 510 (1937).

(18) For a recent review of the stereochemistry of the Diels–Alder reaction, see J. G. Martin and R. K. Hill, *Chem. Rev.*, **61**, 537 (1961); see also J. A. Berson and A. Remanick, *J. Am. Chem. Soc.*, **83**, 4947 (1961).

potential 20-ketone easily functionalized at C-17, have been converted into pentacyclic derivatives of cortical hormones which are described elsewhere.[11,19]

Experimental[20]

16α-Ethyl-16b-methoxy-16b,20-oxidopregna-5,17(20)-dien-3β-ol Acetate (2, R = H).—16-Dehydropregnenolone acetate (150 g.) was heated in an autoclave with methyl vinyl ether (600 ml.) and hydroquinone (0.6 g.) for 24 hr. at 200°; the autoclave was charged with nitrogen at 10 p.s.i. before raising the temperature. After cooling and removing the excess methyl vinyl ether the residual material was dissolved in 500 ml. of methylene chloride and this solution applied to a column of Florisil[21] (1 kg.). The column was eluted with Skellysolve B[22] containing increasing per cents of acetone. Crystalline material was obtained from the Skellysolve B to 5% acetone–Skellysolve B; this was crystallized from acetone–Skellysolve B to give crop 1 and from methanol to give crop 2. (*N.B.* methanol is the solvent of choice.) The two crops were combined to give the adduct 2 (R = H), 72.0 g., 41% yield, m.p. 186–192°. Further crystallization of crop 1 gave material of m.p. 194–195°. An analytical sample was prepared by crystallization from acetone and had m.p. 205–207°.

Anal. Calcd. for $C_{26}H_{38}O_4$: C, 75.32; H, 9.24. Found: C, 75.23; H, 9.11.

The infrared spectrum is in agreement with the dihydropyran structure 2 (R = H); ν_{max}^{Nujol} 1740, 1735, 1695, 1245, 1200, 1155, 1075, 1040, 1020 cm.$^{-1}$.

The ultraviolet spectrum shows end absorption only. The n.m.r. spectrum (see Fig. I) had a singlet at 54 c.p.s.; a doublet at 108.5, 110 c.p.s. (J = 1.5) corresponding to the C-21-methyl split by the 16-hydrogen; a doublet of doublets at 299.6, 295.2, 291, 286.6 c.p.s. (J = 8.6, 4.4) corresponding to the acetal hydrogen at C-16b split by 2 different (geometrical) neighbors at C-16a.

16α-Ethyl-16b-methoxy-6α-methyl-16b,20-oxidopregna-4,17(20)-dien-3-one (3a).—6α-Methyl-16-dehydroprogesterone (20.0 g.)[23] was heated in an autoclave with methyl vinyl ether (100 ml.) and hydroquinone (0.1 g.) for 24 hr. at 200°; the autoclave was charged with nitrogen at 10-p.s.i. gage before raising the temperature. After cooling and removing the excess methyl vinyl ether the residual material was dissolved in methylene chloride (50 ml.) and chromatographed on 800 g. of Florisil made up in Skellysolve B. Elution with increasing percentages of acetone in Skellysolve B gave crystalline material from the 5–10% acetone–Skellysolve B eluates. These fractions were combined and crystallized from methanol to give **3a**, 5.3 g., m.p. 197–201°. Further crystallization from methanol and then from acetone–Skellysolve B gave material with m.p. 203–209°; ν_{max}^{Nujol} 1675, 1695, 1610, 1185, 1160, 1075, 1055, 1020 cm.$^{-1}$; λ_{max}^{EtOH} 241 mμ (ε 16,050).

Anal. Calcd. for $C_{25}H_{36}O_3$: C, 78.08; H, 9.44. Found: C, 77.83; H, 9.66.

16α-Ethyl-9α-fluoro-11β-hydroxy-16b-methoxy-6α-methyl-16b,20-oxidopregna-1,4,17(20)-trien-3-one (3c).—An autoclave was charged with 80 ml. of methyl vinyl ether, 5.0 g. of 9α-fluoro-6α-methyl-11β-hydroxpregna-1,4,16-triene-3,20-dione,[24] and 0.1 g. of hydroquinone (initial pressure, 5–10-p.s.i. gage nitrogen) and heated with agitation for 24 hr. at 200°. The total crude product was evaporated to dryness *in vacuo*, dissolved in methylene chloride (40 ml.), and chromatographed on Florisil (250 g.). Crystalline material was obtained from the 10–15% acetone–Skellysolve B eluates. These were combined and crystallized from methanol to give 1.6 g., m.p. 215–222°, and 0.34 g., m.p. 200–210°.

A portion of the first crop was crystallized twice from methanol to give an analytical sample of **3c**, m.p. 220–225°; ν_{max}^{Nujol} 3305, 1657, 1695, 1614, 1240, 1150, 1125, 1065, 1021 cm.$^{-1}$; λ_{max}^{EtOH} 238 mμ (ε 16,550).

Anal. Calcd. for $C_{25}H_{33}O_4F$: C, 72.11; H, 7.93. Found: C, 72.14; H, 8.11.

16α-Ethyl-16b-methoxy-16b,20-oxidopregn-5,17(20)-diene-3β,21-diol Diacetate (2, R = OAc).—3β,21-Dihydroxypregn-5-en 20-one diacetate[25] (25.0 g.) was heated in an autoclave with methyl vinyl ether (100 ml.) and hydroquinone (0.1 g.) for 24 hr. at 200°; the autoclave was charged with nitrogen at 10-p.s.i. gage before raising the temperature. After cooling and removing the excess methyl vinyl ether the residue was dissolved in 30 ml. of methylene chloride and chromatographed on 1 kg. of Florisil. Elution with increasing per cents of acetone in Skellysolve B gave crystalline material from the 5% acetone–Skellysolve B eluates. These were combined (6.73 g.) and crystallized from methanol to give 5.66 g. of 2 (R = OAc), m.p. 144–148°. Further crystallization from methanol raised the melting point to 150–152°; ν_{max}^{Nujol} 1725, 1245, 1120, 1070, 1005, 1055, 1035, 1020, 1010 cm.$^{-1}$.

Anal. Calcd. for $C_{28}H_{40}O_6$: C, 71.16; H, 8.53. Found: C, 71.23; H, 8.52.

16α-Ethyl-16b-methoxy-6α-methyl-16b,20-oxidopregna-1,4,9(11),17(20)-tetraen-3-one (3b).—6α-Methylpregna-1,4,9(11),16-tetraene-3,20-dione[26] (25.0 g.) was heated in an autoclave with methyl vinyl ether (100 ml.) and hydroquinone (0.1 g.) for 24 hr. at 200°; the autoclave was charged with nitrogen at 10-p.s.i. gage before raising the temperature. After cooling and removing the excess methyl vinyl ether the residual material was dissolved in methylene chloride (50 ml.) and chromatographed on 600 g. of Florisil made up in Skellysolve B. Elution with increasing per cents of acetone in Skellysolve B gave crystalline material from the 5–10% acetone–Skellysolve B eluates. These were combined and crystallized from methanol to give 3.65 g., m.p. 140–168°, and 2.74 g., m.p. 131–134°.

Further crystallization of the first crop from methanol then from acetone–Skellysolve B and finally from methanol gave **3b**, m.p. 171–175°; ν_{max}^{Nujol} 3040, 3020, 1695, 1668, 1663, 1628, 1607, 1080, 1077, 1063, 1050, 1030, 1018 cm.$^{-1}$; λ_{max}^{EtOH} 238 mμ (ε 16,350).

Anal. Calcd. for $C_{25}H_{32}O_3$: C, 78.91; H, 8.48. Found: C, 78.93; H, 8.52.

Acknowledgment.—The authors are indebted to Dr. J. L. Johnson, Mr. W. A. Struck, and associates for the analyses, ultraviolet and infrared spectra, and also to Mr. J. M. Baldwin and Mr. D. T. Kloosterman for technical assistance.

(19) No attempt has been made in this paper to define the minimum conditions necessary to effect the cycloaddition reaction; it is not clear, therefore, whether the product isolated represents a kinetic or thermodynamic product, or indeed, if the reaction is reversible. Attention has been focused in this work on the main, readily isolated, adduct and further work is clearly indicated to establish the nature of any other products.

(20) Melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 221 spectrophotometer from Nujol mulls. Ultraviolet spectra were taken in 95% ethanol solutions using a Cary Model 14 spectrophotometer.

(21) Florisil is a synthetic magnesia–silica gel manufactured by the Floridin Co., Warren, Pa.

(22) A saturated hydrocarbon fraction, b.p. 64–70°.

(23) D. Burn, B. Ellis, V. Petrow, I. A. Stuart-Webb, and D. M. Williamson, *J. Chem. Soc.*, 4092 (1957).

(24) This starting material for **3c** was prepared from 6α-methylpregna-1,4,9(11),16-tetraene-3,20-dione (see ref. 26) by the standard Fried procedure; details of this synthesis will be the subject of a forthcoming publication from these laboratories.

(25) C. Djerassi and C. T. Lenk, *J. Am. Chem. Soc.*, **75**, 3493 (1953).

(26) The starting material for **3b**, 6α-methylpregna-1,4,9(11),16-tetraene-3,20-dione, was first prepared in these laboratories by Dr. B. H. Walker by the dehydration of 11β,17α-dihydroxy-6α-methyl-1,4-pregnadiene-3,20-dione.