Notes

Ring-D-Bridged Steroid Analogs. X.[1] Synthesis and Nuclear Magnetic Resonance Spectral Properties of 3β-Acetoxy-14α,17α-ethano-5,15-pregnadien-20-one, 3β-Acetoxy-14α,17α-ethano-5-pregnen-20-one, and 3β-Acetoxy-16,16′-cyclo-14α,17α-ethano-5-pregnen-20-one

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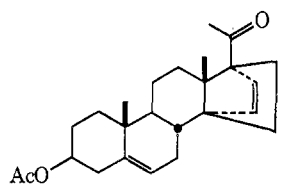
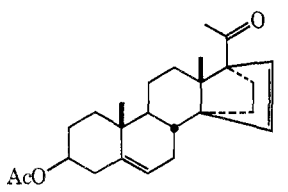
In a study of the nmr spectra of ring-D-bridged steroid analogs, we noted that the 13β-methyl hydrogens of various substituted 14α,17α,etheno-15-pregnen-20-ones are deshielded by approximately 0.3 ppm relative to those of the corresponding compounds in which the 15,16 double bond or both double bonds are saturated. It seemed of interest to determine empirically whether this deshielding could be caused by the 15,16 double bond of such a bridged steroid or whether it was caused by other factors present in the doubly unsaturated steroids.

In the course of other studies, we had synthesized 3β-acetoxy-14α,17α-etheno-5-pregnen-20-one (**1**).[2] Selective catalytic hydrogenation of **1** afforded 3β-acetoxy-14α,17α-ethano-5-pregnen-20-one.



1



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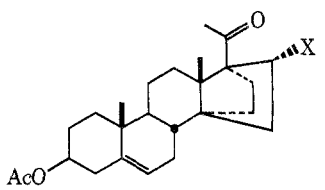
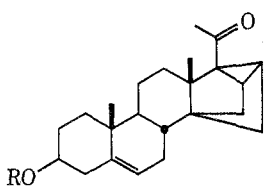


3, X = I
4, X = CO_2H
5, X = NHC(=O)OMe
6, X = N(N=O)C(=O)OMe



7, R = Ac
8, R = H

As previously reported,[3] treatment of the iodide **3** with potassium hydroxide in refluxing ethanol led only to the hydrolysis of the acetate moiety. In a further attempt to obtain 3β-acetoxy-14α,17α-ethano-5,15-pregnadien-20-one (**2**), we also treated **3** with KO-*t*-Bu in *tert*-butyl alcohol, but we again failed to effect dehydrohalogenation.

3β-Acetoxy-14α,17α-ethano-20-oxo-5-pregnene-16α-carboxylic acid (**4**) was transformed, by a modification of the Curtius rearrangement,[3,4] into the urethane **5**. Dinitrogen tetroxide was used to convert the urethane into the *N*-nitroso derivative **6**.[5] The latter compound was not isolated because it decomposed during work-up to give a difficultly separable mixture of the desired olefin **2** and of an isomeric substance. The latter compound had ir and nmr spectra and melting point virtually identical with those previously observed for a by-product isolated on Hunsdiecker degradation of **4**. A satisfactory analysis had not been obtained for the by-product of the Hunsdiecker reaction, but it had been hydrolyzed to afford a substance analyzing as $C_{23}H_{36}O_3$. In view of its origin[6] and of its properties,[7] we assigned the nortricyclene structure **7** to the by-product isolated from the *N*-nitrosourethane decomposition. A reinvestigation of the $C_{23}H_{36}O_3$ substance showed that it was a monohydrate, since, on reacetylation, it gave **7**, identical in all respects with that formed in the *N*-nitrosourethane formation.

Tables published by Jackman[9] for estimating the long-range shielding effect of a double bond allow one to estimate that a double bond in the α bridge of our system should result in deshielding of the C-18 protons by 0.02–0.13 ppm while a double bond in the β bridge should result in their being shielded by approximately 0.05 ppm. In contrast, calculations by ApSimon's method[10] indicate that a double bond in either bridge should result in deshielding, but that a double bond in the α bridge causes the greater effect (shifts of approximately 0.05 and 0.01 ppm for the α and β bridges, respectively).

The nmr spectra of 3β-acetoxy-14α,17α-ethano-5-pregnen-20-one, 3β-acetoxy-14α,17α-etheno-5-pregnen-20-one (**1**), and 3β-acetoxy-14α,17α-ethano-5,15-pregnadien-20-one (**2**) in $CDCl_3$ had peaks corresponding to the C-18 hydrogens at δ 0.90, 0.90, and 0.89, respectively. While these results are in slightly better accord with the predictions based on Jackman's models than with those based on ApSimon's, the differences

(1) For part IX see A. J. Solo, J. N. Kapoor, S. Eng, and J. O. Gardner, *Steroids*, **18**, 251 (1971).
(2) A. J. Solo and B. Singh, *J. Med. Chem.*, **9**, 957 (1966).
(3) A. J. Solo, B. Singh, E. Shefter, and A. Cooper, *Steroids*, **11**, 637 (1968).
(4) J. Weinstock, *J. Org. Chem.*, **26**, 3511 (1961).
(5) (a) W. M. Jones and D. L. Muck, *J. Amer. Chem. Soc.*, **88**, 3798 (1966); (b) E. H. White, *ibid.*, **77**, 6008 (1955).
(6) (a) E. H. White, *ibid.*, **77**, 6011, 6014 (1955); (b) R. Huisgen and H. Reimlenger, *Justus Liebigs Ann. Chem.*, **599**, 183 (1956); (c) R. H. Shapiro, J. H. Duncan, and J. C. Clopton, *J. Amer. Chem. Soc.*, **89**, 1442 (1967), and references cited therein; (d) C. J. Collins and B. M. Benjamin, *ibid.*, **92**, 3182 (1970).
(7) Note especially the abnormal chemical shift of the C-21 hydrogens of **7** and **8**. We attribute this shift to long-range shielding by the cyclopropyl group.[8]
(8) L. M. Jackman and S. Sternhill, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, Elmsford, N. Y., 1969, pp 98–101, and references cited therein.
(9) Reference 8, pp 83–88, and references cited therein.
(10) J. W. ApSimon, W. G. Craig, P. V. Demarco, D. W. Mathieson, L. Saunders, and W. B. Whalley, *Tetrahedron*, **23**, 2357 (1967).

are too small to permit a clear decision between the methods, especially in view of the unknown effect of such substituents as the acetyl group in the steroids.[11] However, these findings do clearly indicate that the anomalous deshielding of the C-18 hydrogens of substituted 14α,17α-etheno-15-pregnen-20-ones cannot be attributed solely to the presence of the 15,16 double bond.[12]

Experimental Section

Melting points were determined in open capillary tubes on a Mel-Temp apparatus and are uncorrected. Elemental analyses were performed by Galbraith Microanalytical Laboratories, Knoxville, Tenn. The ir spectra were determined on a Beckman IR-8 spectrophotometer. Nmr spectra were run in $CDCl_3$ on a Varian A-60 spectrometer and are reported in parts per million downfield from a TMS standard.

3β-Acetoxy-14α,17α-ethano-5-pregnen-20-one.—A solution of 120 mg of **1** in 110 ml of ethanol and 5 ml of H_2O was hydrogenated over 30 mg of 10% Pd/C at an initial pressure of 3.16 kg/cm² for 16 hr. Standard work-up afforded 3β-acetoxy-14α,17α-ethano-5-pregnen-20-one in a yield of 68 mg as colorless needles (from ethanol): mp 140–141°; ν^{Nujol} 1739, 1701, 1239 cm⁻¹. The nmr spectrum had peaks at δ 0.90 (s, C-18 H's), 1.04 (s, C-19 H's), 2.02 [s, OC(=O)CH_3], 2.10 (s, C-21 H's), and 5.40 (m, C-6 vinyl H).

Anal. Calcd for $C_{25}H_{36}O_3$: C, 78.08; H, 9.44. Found: C, 78.12; H, 9.50.

3β-Acetoxy-16α-carbomethoxyamido-14α,17α-ethano-5-pregnen-20-one (5).—A solution of 1.00 g of **4** in 75 ml of acetone was cooled in an ice bath, and a solution of 0.41 g of triethylamine in 25 ml of acetone was added to it dropwise, with stirring. The resulting solution was stirred for 0.5 hr, and then 0.43 g of ethyl chloroformate in 25 ml of acetone was added dropwise. Stirring was then continued for 1.5 hr. A solution of 0.34 g of NaN_3 in 1 ml of water was then poured into the cold solution. The resulting mixture was stirred for 3 hr and was then concentrated under vacuum. The residue was partitioned between ether and water. The organic layer was dried, filtered, and concentrated. The residue was dissolved in 65 ml of benzene and heated under reflux for 1 hr. After 15 ml of absolute methanol had been added to the hot solution, reflux was continued overnight. The resulting solution was concentrated. The residue crystallized from ethanol to afford **5** in a yield of 0.89 g (66%), as colorless prisms: mp 225–226°; ν^{CHCl_3} 3468, 1720, 1512, 1250–1210, and 1030 cm⁻¹. The nmr spectrum had singlets at δ 1.05 (C-18 and 19 H's), 2.04 [OC(=O)CH_3], 2.18 (C-21 H's), 3.67 (OCH_3), and a multiplet at 5.38 (C-6 H).

Anal. Calcd for $C_{27}H_{29}NO_5$: C, 70.87; H, 8.59; N, 3.06. Found: C, 70.98; H, 8.48; N, 2.97.

3β-Acetoxy-14α,17α-ethano-5,15-pregnadien-20-one (2).—A mixture of 475 mg of **5** and 107 mg of NaOAc in 10 ml of ether was stirred and cooled in a Dry Ice–acetone bath while approximately 0.2 ml of N_2O_4 (purified by passage through P_2O_5) was added. Stirring was continued for 1 hr in the cold and then for 10 min at 0°. The inorganic salt was removed by filtration. The filtrate was extracted with 5% aqueous $NaHCO_3$ and then was washed with water. The neutral solution was dried ($MgSO_4$), filtered, and concentrated. The residue, on tlc, appeared to consist of starting material and of two faster moving spots of very similar R_f. The mixture was purified by thick layer chromatography on silica gel. The plates were developed three times with 15% ethyl acetate–85% hexane, and the fast-moving zone was rechromatographed under similar conditions. The fastest moving band gave **2** in a yield of 23 mg, as fine colorless needles from MeOH: mp 120–121°; ν^{CHCl_3} 1725, 1691, 1252, and 1025 cm⁻¹. The nmr spectrum had singlets at δ 0.89 (C-18 H's), 1.04 (C-19 H's), 2.03 [OC(=O)CH_3], and 2.17 (C-21 H's) and peaks corresponding to vinyl hydrogens at δ 5.45 (C-6 H, m), 6.02 (C-15 H, d, J = 6 Hz), and 6.18 (C-16 H, d, J = 6 Hz).

Anal. Calcd for $C_{25}H_{34}O_3$: C, 78.49; H, 8.96. Found: C, 78.68; H, 9.06.

3β-Acetoxy-14α,17α-ethano-16,16′-cyclo-5-pregnen-20-one (7).

A.—Extraction of the second fastest moving band on the tlc of the reaction mixture, which gave **2**, afforded **7**, in a yield of 50 mg, as colorless prisms from MeOH: mp 190–190.5°; ν^{CHCl_3} 1723, 1666, 1253, and 1025 cm⁻¹. The nmr spectrum had singlets at δ 1.01 (C-18 H's), 1.04 (C-19 H's), 1.90 (C-21 H's shielded by cyclopropane), and 2.03 [OC(=O)CH_3)], and a multiplet corresponding to the C-6 vinyl hydrogen at δ 5.38.

Anal. Calcd for $C_{25}H_{34}O_3$: C, 78.49; H, 8.96. Found: C, 78.51; H, 9.12.

B.—During the work-up of the mixture resulting from Hunsdiecker reaction of **4**, the crude product was chromatographed over alumina and benzene eluted **3**. Further development of the column with 1:1 benzene–ethyl acetate resulted in the elution of a fraction which crystallized from ethanol to give 143 mg (31%) of impure **7** as white crystals, mp 189.5–190.5°.

Anal. Calcd for $C_{25}H_{34}O_3$: C, 78.49; H, 8.96; mol wt, 382.5. Found: C, 76.45, 76.64, 77.38; H, 8.92, 8.80, 8.74; mol wt, 390.

C.—Acetylation of **8**, by the usual method, afforded **7** which crystallized from ethanol as colorless needles identical in melting points, mixture melting point, ir, and nmr with **7** prepared as in A.

3β-Hydroxy-14α,17α-ethano-16,16′-cyclo-5-pregnen-20-one (8).—A mixture of 158 mg of **7** (prepared as in B), 300 mg of KOH, 25 ml of MeOH, and 3 ml of H_2O was stirred at room temperature for 48 hr and then under reflux for 6 hr. The mixture was cooled to room temperature and then concentrated under reduced pressure. The residue was partitioned between ether and H_2O. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue crystallized from MeOH to afford **8** as tiny colorless rods, in a yield of 125 mg: mp 183–185°; ν^{Nujol} 3600, 1662 cm⁻¹. The nmr spectrum had singlets at δ 0.98 (C-18 H's), 1.03 (C-19 H's), and 1.87 (C-21 H's shielded by cyclopropane) and a multiplet at δ 5.39 (C-6 H).

Anal. Calcd for $C_{23}H_{32}O_2 \cdot H_2O$: C, 77.05; H, 9.56. Found: C, 77.20; H, 9.61.

Later, 44 mg of **8** was purified by tlc on silica gel. The plate was developed with 20% EtOAc in benzene. The sample isolated (34 mg) was dissolved in ethanol containing 5% benzene and evaporated to dryness under vacuum. This process was then repeated six times. The residue was dried for 3 days at 100° over P_2O_5.

Anal. Calcd for $C_{23}H_{32}O_2$: C, 81.13; H, 9.47. Found: C, 79.35; H, 9.53.

Registry No.—**1**, 19605-66-4; **2**, 35639-00-0; **5**, 35639-01-1; **7**, 35639-02-2; **8**, 35639-03-3.

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(11) N. Bhacca and D. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, p 29.

(12) The methyl hydrogens of 7-methylbicyclo[2.2.1]heptene have been reported to appear in the nmr spectrum (CCl_4) at δ 0.70 for the cis compound and at δ 0.79 (CCl_4) for the trans.[13]

(13) Reference 8, p 84.

A Facile Synthesis of (±)-*ar*-Artemisene *via* Olefin Metalation

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The monocyclic diterpene hydrocarbon *ar*-artemisene (**8**) was isolated from wormwood oil by Šorm and coworkers in 1951.[1] Its racemate was later synthesized

(1) F. Šorm, M. Suchý, F. Vonášek, J. Plíva, and V. Herout, *Collect. Czech. Chem. Commun.*, **16**, 268 (1951); *Chem. Listy*, **45**, 135 (1951).