J = 6.5 cps); $[\phi]^{25}_{589}$ +141, $[\phi]^{25}_{365}$ 0, $[\phi]^{25}_{310}$ −3800, $[\phi]^{25}_{296}$ 0, $[\phi]^{25}_{270}$ +8460, $[\phi]^{25}_{240}$ +10,600 (*c* 0.16, 95% ethanol).

Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 80.01; H, 8.29.

A second crop (45 mg, mp 257–259°) was obtained from methanol–benzene. Final elution of column with methanol–chloroform (1:10) yielded polar impurity (85 mg).

Δ^5-Etiojerven-3β-ol-17-one 17-Ethylene Ketal 3-Acetate (X).—A solution of Δ^5-etiojerven-3β-ol-17-one 17-ethylene ketal (IX, 3.52 g) in pyridine (47.0 ml) and acetic anhydride (47.0 ml) was left to stand at room temperature for 19.5 hr. The reaction mixture was added slowly to a mixture of ice, 2 *N* sodium carbonate solution, and chloroform. The aqueous layer was extracted twice with chloroform and the organic layer was then washed with 2 *N* sodium carbonate solution and water (three times). After drying over sodium sulfate, the chloroform was evaporated under reduced pressure to give a glassy residue. The residue was repeatedly treated with benzene and the benzene solutions evaporated. The resulting crystalline material was recrystallized from isopropyl ether to give prisms of X (3.89 g, mp 146–147°, 98% yield). A sample was recrystallized from ether: mp 147–148°; $[\alpha]^{27}D$ −32° (*c* 1.00); λ_{max} 5.80, 8.00 μ; nmr τ 4.62 (C-6, multiplet, 1 H), 5.40 (C-3, multiplet, 1 H), 6.03 (ketal, singlet, 4 H), 7.97 (AcO, singlet, 3 H), 9.02 (C-19, singlet, 3 H), 9.15 (C-18, doublet, 3 H, J = 5.5 cps); benzene solution, 4.67 (J = 5 cps), 5.22, 6.37, 8.23, 9.17, 8.97 (J = 5 cps), respectively.

Anal. Calcd for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.65; H, 9.11.

Etiojervane-5α-bromo-3β,6β-diol-17-one 17-Ethylene Ketal 3-Acetate (XII).—A mixture of Δ^5-etiojerven-3β-ol-17-one 17-ethylene ketal 3-acetate (X, 500 mg) and N-bromoacetamide (250 mg) in ether (12 ml), water (0.55 ml), and 60% perchloric acid (0.1 ml) was stirred in the dark at 22° for 15 min and then at room temperature for 40 min. The mixture was then diluted with ether and 1% sodium thiosulfate (50 ml). The aqueous layer was extracted once more with ether and the combined organic layers were washed with saturated sodium bicarbonate and water (twice). The ether layer was dried over sodium sulfate and evaporated to give a crystalline residue, which was recrystallized from ether to give the bromohydrin XII (206 mg, mp 154–155°). A sample was recrystallized from ether three times to give pure XII: mp 159–160°; $[\alpha]^{25}D$ −24° (*c* 1.10); λ_{max} 2.80, 2.90, 5.80, 8.00 μ; nmr τ 4.48 (C-3, multiplet, 1 H), 5.70 (C-6, multiplet, 1 H), 6.08 (ketal, singlet, 4 H), 7.70 (HO, singlet, 1 H), 7.98 (AcO, singlet, 3 H), 8.70 (C-19, singlet, 3 H), 9.16 (C-18, doublet, 3 H, J = 6 cps).

Anal. Calcd for $C_{23}H_{35}O_5Br$: C, 58.59; H, 7.48; Br, 16.96. Found: C, 58.60; H, 7.49; Br, 16.79.

Registry No.—III, 15314-12-2; V, 15296-93-2; VI, 15352-73-5; VII, 15296-94-3; VIII, 15314-13-3; IX, 15314-14-4; X, 15296-95-4; XI, 15314-15-5; XII, 15296-96-5; XIII, 15296-97-6; XIV, 15296-98-7.

A Study of the Ozonolysis of the Cross-Conjugated Steroidal $\Delta^{1,4}$-3-Ketone System[1]

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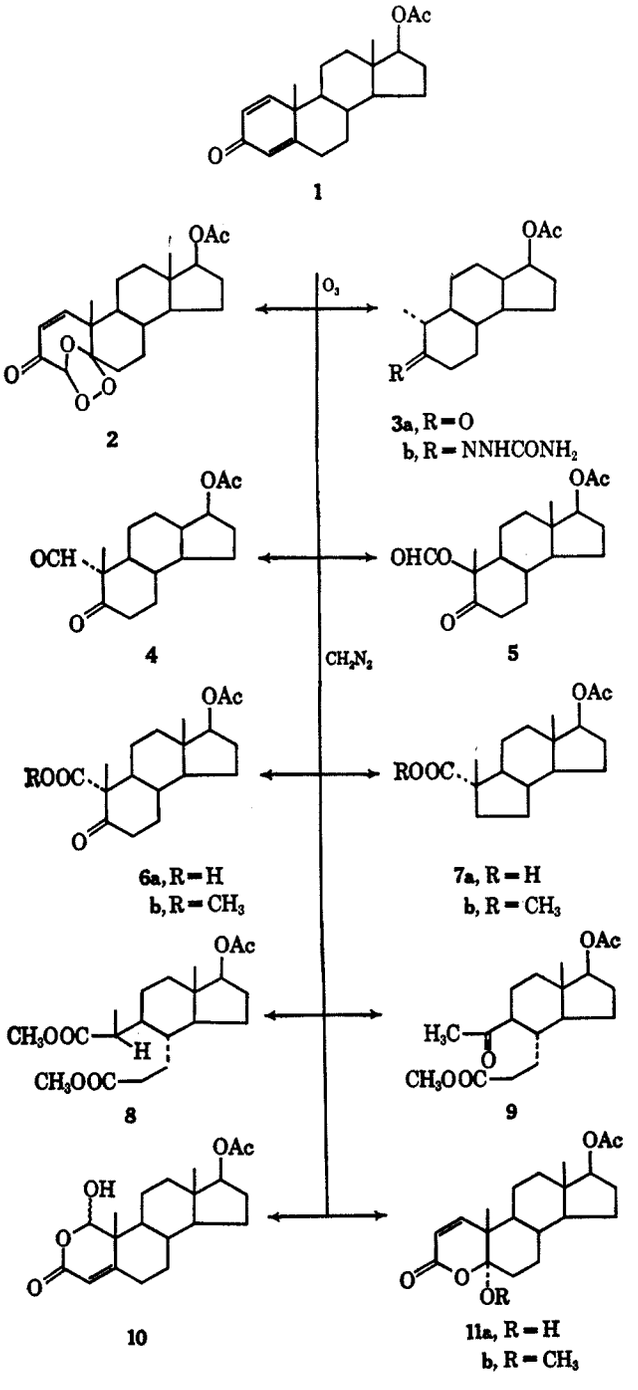
Several years ago, Caspi and co-workers[3] reported the results of their studies concerned with the ozonolysis of several steroidal $\Delta^{1,4}$-3-ketones. In essence these workers found that the nature and amounts of products formed are highly dependent on the structure of the starting material and also on the reaction conditions employed. As part of a program designed to yield steroids containing heteroatoms in their skeletal ring systems, we investigated the ozonolytic cleavage of 1-dehydrotestosterone acetate (1) to determine the feasibility of using such a method to effect a synthetically useful degradation of ring A. Unfortunately, our ozonation efforts consistently led to complex mixtures of products under the conditions tried, the results largely running parallel with those reported earlier.[3] For example, when an ethyl acetate solution of 1-dehydrotestosterone acetate (1) was treated with ozone for 6 hr and worked up in the normal fashion, compounds **2**, **3a**, **4**, and **5** were isolated from the neutral fraction, while the acidic portion (after esterification) yielded the esters **6b**, **7b**, **8**, and **9**. Compounds



(1) This work was supported by Grant AM09003, National Institute of Arthritis and Metabolic Diseases, U. S. Public Health Service.

(2) Postdoctoral Research Associate, 1965–1967.

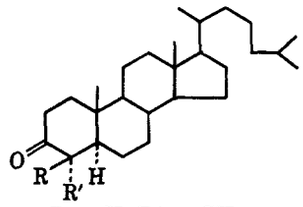
(3) (a) E. Caspi, W. Schmid, and B. T. Khan, *Tetrahedron*, **18**, 767 (1962); (b) E. Caspi, B. T. Khan, and S. N. Balasubrahmanyam, *ibid.*, 1013 (1962); (c) S. N. Balasubrahmanyam, E. Caspi, and B. T. Khan, *J. Chem. Soc.*, 761 (1963).

having structures analogous to **3**, **4**, and the esters **6b–9** have been obtained in previous ozonation reactions involving the Δ^4-3-keto system; however, the isolation of the ozonide **2** and of the formate **5** is unique.

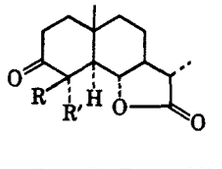
The structure assigned to the ozonide is based on the following information. The compound analyzes for the formula $C_{21}H_{28}O_6$, its mass spectrum shows a parent ion peak at the required *m/e* 376, and it gives a positive peroxide test.[4] The infrared spectrum exhibits two bands at 1685 and 1610 cm^{-1} which are indicative of an α,β-unsaturated ketone, while the nuclear magnetic resonance (nmr) spectrum shows the AB pattern typical of the Δ^1-3-keto system. Further, the proton at C-4 couples with the C-2 proton (J = 1.5 cps). To gain additional support for the structure, **2** was treated with aqueous hydrogen peroxide at reflux temperature, whereby it was converted to the lactol **11a**. The latter compound was also isolated from the neutral fraction of an ozonation mixture and will be described more fully later.

The one piece of evidence which appeared not to fit structure **2** is the ultraviolet absorption spectrum. On the basis of the Woodward rules,[5a] one calculates an ultraviolet absorption maximum at 227 mμ for the Δ^1-3-keto system. Dreiding models of the two stereoisomers possible for the ozonide **2** show that in either case it is difficult for the α,β-unsaturated keto system to be coplanar, and hence one might expect an absorption maximum at a wavelength lower than the one calculated. In fact, however, the absorption maximum for this compound appears at 237.5 mμ. It seems then that in this case the Δ^1-3-keto system exhibits a bathochromic shift due to a "second-order effect"[5b] arising from an interaction of the enone chromophore with the π electrons of the ozonide ring oxygen atoms. To ascertain that the substance was not altered during the spectral determination, a thin layer chromatogram was carried out on the sample before and after exposure. The R_f values of the spots observed were identical.

The ketone **3a**, which presumably arises *via* the decarboxylation of the β-keto acid **6a**, was obtained as an oil which could not be crystallized, even though Hartshorn and Jones[6] have reported this compound as a low melting solid. The substance was identified from its infrared and nmr spectra and by its conversion into the crystalline semicarbazone **3b**. We assigned the C-19 methyl group[7] the more stable equatorial position on the basis of the circular dichroism (CD) curve for this substance. The curve exhibits a negative Cotton effect the magnitude of which ([θ] −5015) compares much more favorably with those reported for 4α-methyl-5α-cholestanone[8] (**12a**, [θ] ~4440)[9,10] and α-tetrahydrosantonin[11] (**13a**, [θ] 3260)[9] which have α-methyl groups in an equatorial conformation,



12a, R = H; R′ = CH_3
b, R = CH_3; R′ = H



13a, R = H; R′ = CH_3
b, R = CH_3; R′ = H

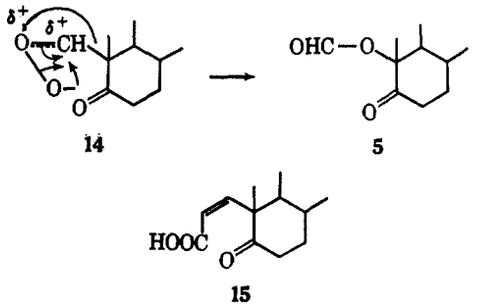
rather than their axial methyl counterparts, **12b** ([θ] 1100) and **13b** ([θ] 795). From the octant rule a strong positive contribution to the CD curve would be predicted for an axial β-methyl group in ketone **3a**.

The known keto aldehyde **4**[12] was readily identified from the ultraviolet absorption spectrum, which indicated the lack of conjugation, and the infrared spectrum which exhibits a band at 2715 cm^{-1} suggestive of aldehydes.[13] The presence of an aldehyde group was confirmed by a peak at 9.49 ppm in the nmr spectrum.

The oxidation of the aldehyde **4** to the acid **6a** was found to be difficult. When such oxidation attempts were made with chromium trioxide in acetic acid,[14a] alkaline potassium permanganate,[14b] or alkaline silver oxide,[15] either complex mixtures or only poor yields of the desired acid were obtained.[16]

Support for the structure shown for **5** was forthcoming from the nmr spectrum which shows a band at 8.00 ppm indicative of a formyl type proton. The mass spectrum of **5** shows a parent peak at 322 mass units required for the structure indicated. It also contains a peak at M - 28 indicative of the loss of CO, a process known to be quite favorable in the case of formates.[17] Further, a metastable peak associated with this fragmentation occurs at 268.4 mass units (calcd: *m/e* 268.4).

It is known that esters can be produced in ozonation reactions,[18] and the formation of the formate **5** can be readily explained by the rearrangement of the ozonolysis zwitterion intermediate **14**. It could also be formed by the direct attack of ozone on the keto aldehyde **4** by a mechanism proposed by Leffler,[18] should the keto



14 **5**

15

(4) P. S. Bailey, *Chem. Rev.*, **58**, 987 (1958).

(5) A. I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products," The Macmillan Co., New York, N. Y., 1964, (a) p 56 ff, (b) p 71 ff.

(6) M. P. Hartshorn and E. R. H. Jones, *J. Chem. Soc.*, 1312 (1962).

(7) For simplicity, steroid numbering of the carbon atoms of all products has been retained.

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

(9) The [θ] values were calculated from the rotatory dispersion curves using a corollary of the Kronig–Kramers theorem, as expressed by A. Moscowitz [*Tetrahedron*, **13**, 48 (1961)]. See also P. Crabbe, "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1965, p 19.

(10) The trough of this curve was not recorded because it fell outside the range of the instrument. For this calculation, the lowest recorded value was used; the true [θ] value is perhaps slightly higher than the value indicated.

(11) C. Djerassi, R. Riniker, and B. Riniker, *J. Am. Chem. Soc.*, **78**, 6362 (1956).

(12) J. A. Vida and M. Gut, *J. Med. Chem.*, **6**, 792 (1963).

(13) N. B. Colthup, L. H. Daly, and S. E. Wiberley, "Introduction to Infrared and Raman Spectroscopy," Academic Press Inc., New York, N. Y., 1964, p 199.

(14) (a) H. Koechlin and T. Reichstein, *Helv. Chim. Acta*, **30**, 1673 (1947); (b) G. W. Barber and M. Ehrenstein, *Ann.*, **603**, 89 (1957).

(15) F. Asinger, *Ber.*, **75**, 656 (1942), and references therein cited.

(16) *Cf.* ref 3a.

(17) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, Inc., San Francisco, Calif., 1967, p 175.

(18) J. E. Leffler, *Chem. Rev.*, **45**, 403 (1949).

aldehyde be present during the ozone addition. Essentially nothing is known about the stereochemistry of this ester-forming reaction so it is not possible to define this aspect at the C-10 position in **5** with certainty. Conceivably, the mechanism is similar to that of the Baeyer–Villiger reaction, in which case the natural configuration of the C-19 methyl group would be retained.[19]

The esters **6b**, **7b**, **8**, and **9** were obtained as crystalline solids, and their structures were assigned on the basis of elemental analyses, the ultraviolet, infrared, and nmr spectra, and the rotatory dispersion (RD) curves for **7b**, **8**, and **9**. The ester **7b**, along with the corresponding acid **7a**, had been reported previously by Jeger and co-workers, who also unequivocally established their structures.[20] Compounds having structures **7**, **8**, and **9** are somewhat unusual as products of an ozonation reaction. However, similar substances have been isolated from ozonations of $\Delta^{1,4}$-3-keto steroids. Reasonable mechanistic interpretations as to how these products might arise, based on what was previously known about peroxide induced cleavage reactions, have been advanced.[3b,c]

In some of their studies Caspi and co-workers isolated products having lactol structures.[3a-c] Whereas we found no trace of such compounds in our runs carried out over a 6-hr period, we were able to isolate two lactols, as well as the ozonide **2** and the keto aldehyde **4**, when the ozonation was conducted for only 45 min. The nmr, ultraviolet, and infrared spectra for these substances are in agreement with the structures **10** and **11a**, and the stereochemical assignments have been made by analogy with similar substances reported by the earlier workers.[3a-c] The lactol structures **10** and **11a** are preferred over the open keto acid forms (*e.g.*, **15**) because the infrared spectrum in each case shows a sharp band in the hydroxyl region, distinctly different from the broad associated hydroxyl bands encountered in acids.[21] When lactol **11a** was treated with diazomethane, it was readily converted to the methoxy derivative **11b**.

Experimental Section[22]

Ozonation Experiments.—Some preliminary experiments were run in order to determine the length of time necessary to yield practical quantities of products. In each experiment, 100 mg of the starting ketone **1** in 35 ml of ethyl acetate cooled to −70° (Dry Ice–methanol) was used. In one series, ozonized air was passed through the solution for 15 min, 30 min, 1 hr, and 6 hr; while in another series ozonized oxygen was used for time intervals of 15 min, 30 min, 1 hr, 2 hr, 3 hr, and 6 hr. After ozonation, the reaction mixture was usually decomposed with water for 12 hr at room temperature and separated into a neutral fraction and an acidic fraction. After esterification with diazomethane, the acidic fraction was easily separated by tlc. Aqueous hydrogen peroxide was also used to decompose the reaction mixture, by allowing the latter to react with this reagent for 2.5 hr at reflux. In all cases the reaction products in the neutral and ester fractions were examined by tlc. Although these studies showed that after 15 min a complex mixture of products was already present, it was found that practical yields of products were formed only after a considerably longer period of time. Two typical runs are described below. In each case the weights of products given are those of the purified material.

Ozonation for 6 hr.—A solution of 2.30 g of 1-dehydrotestosterone acetate (**1**) in 250 ml of ethyl acetate was treated with ozonized oxygen at −70°. The course of the reaction was followed by ultraviolet absorption spectroscopy, the peak at 244 mμ usually disappearing in about 30 min. After 6 hr the ozonation was discontinued and the mixture was stirred with 30 ml of water for 12 hr at room temperature. The phases were separated and the ethyl acetate portion was partitioned into a neutral fraction (0.59 g) and an acidic fraction (1.1 g) by the usual sodium bicarbonate extraction procedure. A solid crystallized from the ethyl acetate (neutral) fraction which was separated by filtration. Upon recrystallization from ether and then ethyl acetate, this product yielded 42 mg (1.6%) of the ozonide **2**, mp 138–140°.

The mother liquor remaining after the isolation of **2** was chromatographed on a silica gel column. Elution of the column with a mixture of acetone–*n*-hexane (1:99) caused the separation of 70 mg of an oil which was not further investigated since spectral data indicated that it was probably a nonsteroid. When elution was continued with a mixture of acetone–hexane (3:97), 80 mg (4.1%) of the ketone **3** was obtained as an oil. This was followed with acetone–hexane (5:95) which yielded a solid substance. When this material was recrystallized from an acetone–*n*-pentane mixture, 250 mg (12%) of pure keto aldehyde **4** was obtained. An elution mixture of acetone–hexane (10:90) gave a solid which yielded 38 mg (1.7%) of the formate **5** after recrystallization from acetone–*n*-hexane.

The acidic fraction resisted attempts at crystallization, so it was esterified with ethereal diazomethane. The mixture of esters was then readily resolved by chromatography on a silica gel column. Elution of the column with an acetone–*n*-hexane mixture (1:99) yielded a solid which was recrystallized from acetone–*n*-pentane to give 180 mg (8.3%) of the ester **7b**. Upon increasing the acetone concentration in the eluent to 3:97, a small amount of solid was obtained which was recrystallized from acetone–*n*-pentane to give 8.0 mg (0.34%) of keto ester **6b**. Elution with a 5:95 acetone–hexane mixture led to the separation of a third substance which was recrystallized from *n*-hexane to yield 70 mg (2.7%) of **8**, and with a 10:90 acetone–hexane mixture yet another solid was obtained. When the latter was recrystallized from hexane, 50 mg (2.2%) of the keto diester **9** was recovered.

In another run, the ozonation was repeated with 1.0 g of starting ketone **1** in the manner described above. The mixture was then reduced to about one-third in volume under reduced pressure and heated at reflux for 2.5 hr with 1.5 ml of 30% hydrogen peroxide in 10 ml of water. The mixture was cooled by the addition of ice and extracted with ether. The ethereal phase was extracted with aqueous sodium bicarbonate which was then acidified with dilute hydrochloric acid. A solid separated which was filtered to give 500 mg of crude product. Three recrystallizations from acetone–*n*-hexane yielded 200 mg (22%) of pure acid **7a**, mp 187–189°. When treated with ethereal diazomethane this substance gave the ester **7b**, mp 82–83°. The mother liquor of the acidic fraction, as well as the neutral fraction, were not further investigated.

Ozonation for 45 Min.—A solution of 2.00 g of 1-dehydrotestosterone acetate (**1**) in 230 ml of ethyl acetate was treated with ozonized oxygen for 45 min at −70°. The resulting mixture was stirred with 20 ml of water at room temperature for 12 hr and then evaporated to dryness under vacuum at room temperature. The remaining solid was treated with ether whereby all

(19) R. B. Turner, *J. Am. Chem. Soc.*, **72**, 878 (1950); K. Mislow and J. Brenner, *ibid.*, **75**, 2318 (1953).

(20) B. Nann, D. Gravel, R. Schorta, H. Wehrli, K. Schaffner, and O. Jeger, *Helv. Chim. Acta*, **46**, 2473 (1963); B. Nann, H. Wehrli, K. Schaffner, and O. Jeger, *ibid.*, **48**, 1680 (1965); J. Frei, C. Ganter, D. Kägi, K. Kocsis, M. Miljkovic, A. Siewinski, R. Wenger, K. Schaffner, and O. Jeger, *ibid.*, **49**, 1049 (1960).

(21) R. N. Jones and C. Sandorfy, "Technique of Organic Chemistry," W. West, Ed., Vol. IX, Interscience Publishers, Inc., New York, N. Y., 1956, p 425; *cf.* ref 3a-c.

(22) All melting points were determined in a heated oil bath and are corrected. The nmr spectra were determined in deuteriochloroform solution (unless specified otherwise) on a Varian A-60 spectrometer and chemical shift values are given in parts per million (ppm) measured downfield from tetramethylsilane used as an internal standard. The infrared spectra were determined in the solid state in a potassium bromide matrix on a Perkin-Elmer Infracord Model 337. The ultraviolet absorption spectra were obtained with a Cary Model 14 or a Coleman-Hitachi Model EPS-3T spectrophotometer. The circular dichroism and rotatory dispersion curves were determined on a Durrum-Jasco ORD/UV-5 instrument with CD attachment, and the mass spectra were obtained with an Atlas Model CH-4 spectrometer. Both thin layer and column chromatography were carried out on silica gel G (E. Merck AG, Darmstadt, Germany; U. S. distributor is Brinkmann Instruments, Inc., Cantiague Road, Westbury, N. Y.) and the microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. The ozonation reactions were carried out using a Welsbach Model T-23 ozonator.

products dissolved except the ozonide **2**. On filtering the solution, 350 mg (15%) of the ozonide was obtained, mp 133–135°. After recrystallization from ether–ethyl acetate the melting point was raised to 138–140°.

The remaining mother liquor was separated into neutral and acidic fractions, and the neutral fraction was chromatographed on a silica gel column. Elution with 300 ml of *n*-hexane yielded 50 mg of an impure oil which was not further investigated. Continued elution with an acetone–hexane mixture (1:100) gave 85 mg (4.6%) of the keto aldehyde **4**, while acetone–hexane in the ratio 2:100 caused separation of 25 mg of the lactol **10** which was recrystallized from acetone–*n*-hexane to give 15 mg (0.7%) of the product as needle-like crystals, mp 220–221°. Further elution with acetone–hexane (3:100) gave first 100 mg (4.7%) of a mixture of **10** and **11a**, followed by 60 mg (2.8%) of lactol **11a**. Part of this was recrystallized from ethyl acetate–methanol yielding pure material, mp 185–186°.

17β-Acetoxyandrost-1-en-3-one Ozonide (2).—For analysis, a sample was recrystallized twice from ether–ethyl acetate: mp 138–140°; the mass spectrum showed major peaks at *m/e* 43, 55, 278, and M⁺ at 376; CD (27°, *C* 0.00016, chloroform) $[\theta]_{265}$ −496, $[\theta]_{293}$ −1903, $[\theta]_{322}$ −1034, $[\theta]_{345}$ −1613, $[\theta]_{352}$ −1530, $[\theta]_{358}$ −1655, $[\theta]_{369}$ −899, $[\theta]_{380}$ −496 (shoulder), $[\theta]_{390}$ 0; λ_{max}^{EtOH} 237 mμ (log ε 4.013); nmr,[7] 0.82 (3 H, singlet, C-18 CH_3), 1.20 (3 H, singlet, C-19 CH_3), 2.02 (3 H, singlet, C-17 acetate), 4.57 (1 H, triplet, *J* = 8 cps, C-17 H), 5.43 (1 H, perturbed doublet,[23] *J* = 1.5 cps, C-4 H), AB quartet with doublets[23] centered at 5.78 (1 H, *J* = 13 cps, each peak further split into a doublet,[23,24] *J* = 1.5 cps, C-2 H), and 6.19 ppm (1 H, *J* = 13 cps, C-1 H).

Anal. Calcd for $C_{21}H_{28}O_6$: C, 67.00; H, 7.50. Found: C, 66.90; H, 7.56.

17β-Acetoxy-5,10-seco-A-tetranorandrostan-5-one (3a).—This substance was obtained as an oil (lit.[11] mp 53–56°), CD (27°, *C* 0.0027, methanol) $[\theta]_{254}$ 0, $[\theta]_{291}$ −5015, $[\theta]_{320}$ 0; major infrared bands (chloroform) at 1735, 1702, 1248, and 1045 cm⁻¹; nmr,[7,25] 0.85 (3 H, singlet, C-18 H), 0.95 (3 H, doublet,[23] *J* = 6.5, C-19 CH_3), 1.97 (3 H, singlet, C-17 acetate), 2.25, partially obstructed quartet, C-19 H), and 4.57 ppm (1 H, triplet, C-17 H).

17β-Acetoxy-5,10-seco-A-tetranorandrostane-5-semicarbazone (3b).—A mixture of 25 mg (0.90 mmole) of the ketone **3a**, 50 mg (0.45 mmole) of semicarbazide hydrochloride, and 50 mg (0.61 mmole) of sodium acetate in methanol–water (2:1) was stirred at room temperature for 15 min. The mixture was allowed to stand at room temperature for 4 hr and the solid which had formed was separated by filtration. When this product was recrystallized from methanol, 15 mg (50%) of the desired semicarbazone **3b** were obtained, mp 235–237°. The infrared spectrum showed the following bands among others: 3400, 3210, 1745, 1690, 1660, 1575, 1450, 1265, 1050, and 775 cm⁻¹.

Anal. Calcd for $C_{18}H_{29}N_3O_3$: C, 64.45; H, 8.71; N, 12.53. Found: C, 64.48; H, 8.47; N, 12.39.

17β-Acetoxy-5-oxo-1,5-seco-A-trinorandrostan-1-al (4).—An analytical sample was recrystallized twice from acetone–pentane, mp 133–135° (lit.[12] mp 129–130°); CD (27°, *C* 0.0033, chloroform) $[\theta]_{252}$ 0, $[\theta]_{302}$ −7570, $[\theta]_{344}$ 0. The infrared spectrum showed bands at 2715, 1735, 1690, 1240, 1040, 1020, and 750 cm⁻¹; and the nmr spectrum[7] exhibited bands at 0.85 (3 H, singlet, C-18 CH_3), 1.25 (3 H, singlet, C-19 CH_3), 2.02 (3 H, singlet, C-17 acetate), 4.55 (1 H, triplet, C-17 H), and 9.49 ppm (1 H, singlet, aldehydic C-H).

Anal. Calcd for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.68; H, 8.60.

When this substance was recrystallized from methanol, a broad melting point (138–152°) was observed.

17β-Acetoxy-10-formoxy-1,5-seco-A-trinorandrostan-5-one (5).—An analytical sample was recrystallized from acetone–*n*-hexane, mp 115–117°. The infrared spectrum exhibited the following bands among others: 2873, 2852, 1732, 1715 (slight shoulder), 1232 and 1152 cm⁻¹; while the nmr spectrum[7] showed bands at 0.80 (3 H, singlet, C-18 CH_3), 1.28 (3 H, singlet, C-19 CH_3), 2.02 (3 H, singlet, C-17 acetate), 4.62 (1 H, triplet, *J* = 7.5 cps, C-17 H), and 8.00 ppm (1 H, singlet, formate H).

Anal. Calcd for $C_{18}H_{26}O_5$: C, 67.06; H, 8.13. Found: C, 66.50; H, 8.63.

(23) The chemical shift values for all doublets and quartets were measured at the geometrical midpoint between the peaks.

(24) This additional splitting is due to a coupling of the protons at C-4 and C-2.

(25) Determined in carbon tetrachloride solution.

The mass spectrum for this compound showed the following major peaks: *m/e* 41, 43, 55, 149, 177, and 322 (M⁺).

Dodecahydro-6β-acetoxy-3β,5aβ-dimethyl-*as*-indacene-3α-carboxylic Acid (7a).—A sample for analysis was recrystallized twice from acetone–hexane, mp 187–189° (lit.[20] mp 188–189°). The infrared spectrum showed bands at 3570–2790 (broad), 1725, 1690, 1296, 1278, 1210, 1050, and 1035 cm⁻¹.

Anal. Calcd for $C_{17}H_{26}O_4$: C, 69.36; H, 8.90. Found: C, 69.23; H, 8.89.

Methyl Dodecahydro-6β-acetoxy-3β-5aβ-dimethyl-*as*-indacene-3α-carboxylate (7b).—An analytical sample was recrystallized from acetone–pentane, mp 82–83° (lit.[20] 83°). The compound gave a plain positive ORD curve, $[\alpha]^{27}D$ +9.5° (*c* 0.4, methanol) [lit.[20] $[\alpha]D$ +10°, +13° ($CHCl_3$)]; the mass spectrum showed major peaks at *m/e* 43, 161, 163, 189, 248, 249, and 308 (*M*⁺); the infrared spectrum exhibited bands at 1740, 1725, 1450, 1375, 1246, 1210, 1120, 1048, and 1035; and the nmr spectrum[7] showed bands at 0.77 (3 H, singlet, C-18 CH_3), 1.08 (3 H, singlet, C-19 CH_3), 1.95 (3 H, singlet, C-17 acetate), and 3.62 ppm (3 H, singlet, methyl ester).

Anal. Calcd for $C_{18}H_{28}O_4$: C, 70.10; H, 9.15. Found: C, 69.90; H, 9.15.

17β-Acetoxy-1,5-seco-A-trinorandrostan-3-one-1-carboxylic Acid (6a).—The keto aldehyde **4** (85 mg, 0.28 mmole) was oxidized using 150 mg (1.50 mmoles) of chromium trioxide in 4 ml of 90% aqueous acetic acid at room temperature for 8 hr. The excess chromium trioxide was destroyed with methanol and the mixture was diluted with water. The mixture was extracted with ether and the ether layers were washed with aqueous sodium bicarbonate solution. The neutral fraction gave a tlc showing five spots; this fraction was not further investigated. The bicarbonate fraction was acidified with dilute HCl and extracted with ether. Removal of the ether under reduced pressure yielded a crude solid which was recrystallized several times from acetone–pentane to yield 8.0 mg (8.9%) of the keto acid **6a**, mp 177–179°. Significant bands appeared in the infrared spectrum[24] at 3300 (broad), 1740, 1708, 1700, and 1245 cm⁻¹; the ultraviolet spectrum showed a band at $\lambda_{max}^{CH_3OH}$ 292 mμ (log ε 2.391).

Anal. Calcd for $C_{18}H_{26}O_5$: C, 67.06; H, 8.13. Found: C, 67.38; H, 8.28.

Methyl 17β-Acetoxy-1,5-seco-A-trinorandrostan-3-one-1-carboxylate (6b).—For analysis, this compound was recrystallized from methanol, mp 122–124°. The infrared spectrum[25] showed bands at 1745, 1710, and 1243 cm⁻¹.

Anal. Calcd for $C_{19}H_{28}O_5$: C, 67.83; H, 8.39. Found: C, 68.09; H, 8.52.

Methyl 5β-(1-Carboxyethyl)-3aα,4β-5,6,7,7a-hexahydro-1β-acetoxy-7aβ-methyl-4-indanpropionate (8).—An analytical sample was obtained by recrystallization from *n*-hexane, mp 57–58°; plain positive ORD curve, $[\alpha]^{27}D$ +37° (*c* 0.6, methanol); significant infrared spectrum bands were at 1725 (multiple shouldered), 1254, 1195, 1152, and 1030 cm⁻¹; nmr peaks were at [7,25] 0.74 (3 H, singlet, C-18 CH_3), 1.04 (3 H, doublet,[23] *J* = 7 cps, C-19 CH_3), 1.95 (3 H, singlet, C-17 acetate), 2.65 (1 H, quartet,[23] *J* = 7 cps, C-10 H), 3.60 and 3.62 (6 H, overlapping singlets, two methyl esters), and 4.54 ppm (1 H, triplet, *J* = 7 cps, C-17 H).

Anal. Calcd for $C_{20}H_{32}O_6$: C, 65.19; H, 8.75. Found: C, 65.34; H, 8.91.

Methyl 5β-Acetyl-3α,4β,5,6,7,7a-hexahydro-1β-acetoxy-7aβ-methyl-4-indanpropionate (9).—This compound was recrystallized from *n*-hexane for analysis, mp 45–46°; the mass spectrum showed major peaks at *m/e* 43, 147, 179, 206, 264 and M⁺ at 324. ORD (27°, *c* 0.003 methanol) values were $[\phi]_{265}$ +4471°, $[\phi]_{282}$ 0°, $[\phi]_{309}$ −2430°, $[\phi]_{325}$ −1264°. The infrared spectrum[25] showed bands at 1745, 1710, and 1242 cm⁻¹, while the nmr spectrum[7] exhibited peaks at 0.82 (3 H, singlet, C-18 H), 1.95 (3 H, singlet, C-17 acetate), 2.10 (3 H, singlet, methyl ketone), 3.58 (3 H, singlet, methyl ester), and 4.57 ppm (1 H, triplet, C-17 H).

Anal. Calcd for $C_{18}H_{28}O_5$: C, 66.64; H, 8.70. Found: C, 66.42; H, 8.57.

Reaction of the Ozonide 2 with Hydrogen Peroxide.—A mixture consisting of 2.0 ml of 30% hydrogen peroxide in 3.0 ml of water was added to a solution of 50 mg of the ozonide **2** in 25 ml of ethyl acetate. After refluxing the mixture for 0.5 hr, tlc showed the presence of the starting material as well as two new products. Heating was continued for an additional 2 hr after which time tlc showed the absence of starting material (highest R_f), a decrease in the intensity of one spot (intermediate R_f), and an increase in intensity of the other (lowest R_f). The phases were separated and the ethyl acetate portion was washed with aqueous

sodium bicarbonate, dilute hydrochloric acid, and water. The organic solvent was removed under reduced pressure and the remaining solid was recrystallized from ethyl acetate–methanol to yield **17β-acetoxy-5-hydroxy-4-oxa-5α-androst-1-en-3-one (11a)**, mp 185–186°. The infrared spectrum of this compound showed bands at 3600–3100 (broad), 1730, 1710, 1690, 1620, 1251, 1040, and 958 cm^{-1}; ultraviolet absorption, λ_{max}^{MeOH} 217.5 mμ (log ε 3.905); nmr,[7] 0.81 (3 H, singlet, C-18 CH_3), 1.25 (3 H, singlet, C-19 CH_3), 2.03 (3 H, singlet, C-17 acetate), 4.27 (1 H, broad singlet which disappears upon the addition of D_2O, C-5 OH), 4.59 (1 H, triplet, J = 8 cps, C-17 H), AB quartet with doublets[28] centered at 5.93 (1 H, J = 10 cps, C-2 H), and at 6.66 ppm (1 H, J = 10 cps, C-1 H).

Anal. Calcd for $C_{20}H_{28}O_5$: C, 68.94; H, 8.10. Found: C, 68.82; H, 8.20.

The methyl derivative **11b** was prepared by treating the lactol **11a** with ethereal diazomethane. The product was recrystallized from methanol: mp 115–117°; λ_{max}^{EtOH} 215 mμ (log ε 3.887); infrared spectrum bands at 1730 (shoulder), 1720, 1635, 1255, 1213, 1183, 1049, and 830 cm^{-1}.

Anal. Calcd for $C_{21}H_{30}O_5$: C, 69.59; H, 8.34. Found: C, 69.74; H, 8.47.

17β-Acetoxy-1-hydroxy-2-oxa-4-androsten-3-one (10).—For analysis, a sample was recrystallized twice from acetone–*n*-hexane, mp 220–221°. The infrared spectrum showed bands at 3600–3100 (broad), 1740, 1715, 1705 (shoulder), 1630, 1250, 1230, 1041, and 962 cm^{-1}; ultraviolet absorption was at λ_{max}^{EtOH} 227 mμ (log ε 4.130); nmr[7] peaks were at 0.79 (3 H, singlet, C-18 CH_3), 1.17 (3 H, singlet, C-19 CH_3), 1.97 (3 H, singlet, C-17 acetate), 4.55 (1 H, unresolved triplet, C-17 H), 5.49 (1 H, singlet, C-1 H), and 5.71 ppm (1 H, singlet, C-4 H).

Anal. Calcd for $C_{20}H_{28}O_5$: C, 68.94; H, 8.10. Found: C, 68.99; H, 8.10.

Registry No.—2, 15266-94-1; **3a**, 15266-95-2; **3b**, 15266-96-3; **4**, 15266-97-4; **5**, 15266-98-5; **6a**, 15266-99-6; **6b**, 15267-00-2; **7a**, 15267-01-3; **7b**, 6224-23-3; **8**, 15292-86-1; **9**, 15292-87-2; **10**, 15292-88-3; **11a**, 15285-89-9; **11b**, 15267-34-2.

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The Addition of Formaldehyde to Levopimaric Acid and Methyl Levopimarate

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Formaldehyde readily combines with levopimaric acid at low temperatures to give a Diels–Alder adduct in good yield.[2] This is somewhat surprising since formaldehyde is generally considered a poor dienophile.[3-7]

If levopimaric acid and methyl levopimarate are allowed to combine with paraformaldehyde under identical conditions, both give a Diels–Alder adduct. The yields of each adduct, however, differ significantly, the levopimaric acid adduct being formed in almost quantitative yield while the ester adduct is formed in at best 10% yield. From data such as this, it seems reasonable to assume that the free carboxyl group of levopimaric acid in some way enhances the reaction rate.

Because paraformaldehyde added to levopimaric acid only at temperatures above which paraformaldehyde rapidly decomposed to monomeric formaldehyde gas, we surmised that monomeric formaldehyde was the reacting species. This was tested by allowing ethereal and chloroform solutions of monomeric formaldehyde to react with levopimaric acid at low temperature. In both instances levopimaric acid–formaldehyde adduct was formed in yields of 30 and 50%, respectively. Thus, monomeric formaldehyde adds to levopimaric acid under conditions under which paraformaldehyde does not add and paraformaldehyde adds at a significant rate only at temperatures above which it rapidly decomposes; therefore, monomeric formaldehyde is the reacting species.

A carboxyl group could assist in enhancing the reaction rate by polarization of the entering formaldehyde molecule either (1) intramolecularly or (2) intermolecularly. If intermolecular hydrogen bonding causes the increased reaction rate, then one might expect equimolar mixtures of levopimaric acid and methyl levopimarate to give equimolar mixtures of ester and acid adducts. If, on the other hand, an intramolecular process causes the increased rate of reaction, the acid and ester adducts should be formed in the same ratio as if formed from pure acid and ester, respectively.

To test this hypothesis, mixtures of methyl levopimarate, paraformaldehyde, and levopimaric acid were combined and the reaction products were examined by nmr spectroscopy (see Experimental Section). From the nmr spectrum of such a mixture, the amount of methyl levopimarate that has reacted to form adduct can be calculated. Similar experiments were performed with mixtures of methyl levopimarate, paraformaldehyde, and levopimaric acid–formaldehyde adduct. The results of these experiments are reported in Table I.

TABLE I

PER CENT METHYL LEVOPIMARATE THAT REACTED WITH FORMALDEHYDE TO FORM ADDUCT

Composition	Intensity of A	Intensity of B	Me-LPA reacted, %
100% Me-LPA	11	70	15.7
100% Me-LPA	15	240	6.3
64% Me-LPA 36% LPA	36	45	29
68% Me-LPA 32% LPA	100	130	33
49% Me-LPA 51% adduct	48	34	37

From the data in Table I, it is obvious that the percentage of methyl levopimarate which has been consumed is greater when the experiments are run in the presence of levopimaric acid or levopimaric acid–formaldehyde adduct than when only methyl levopimarate is present. This evidence implicates the

(1) (a) To whom communication regarding this work should be sent. (b) Taken in part from the Ph.D. thesis of J. L. McClanahan, The University of Mississippi, 1967.

(2) B. A. Parkin, Jr., and G. W. Hedrick, *J. Org. Chem.*, **30**, 2356 (1965).

(3) T. L. Gresham and T. R. Steadman, *J. Am. Chem. Soc.*, **71**, 737 (1949).

(4) W. F. Gresham and W. E. Grigsby, U. S. Patent 2,493,964 (1960).

(5) O. C. Dermer, L. Kohn, and W. J. Nelson, *J. Am. Chem. Soc.*, **73**, 5869 (1951).

(6) D. G. Kubler, U. S. Patent 2,905,699 (1959).

(7) D. G. Kubler, *J. Org. Chem.*, **27**, 1435 (1962).