Photochemical Cycloadducts.[1] V.[2] Photochemical Addition of Olefins to the Steroidal 1-En-3-one System

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Steroidal 1-en-3-ones are surprisingly unreactive toward photocycloaddition with olefins. Ethylene, acetylene, 1,1-difluoroethylene, and maleic anhydride fail to add to a variety of 1-en-3-ones both under unsensitized and sensitized conditions at room temperature. 1,1-Dichloroethylene adds to 17β-acetoxy-5α-androst-1-en-3-one (**1**) to give the *trans* fused head-to-tail adduct (**2**). Vinyl acetate also adds to **1** to give both *trans* and *cis* fused head-to-tail adducts (**12**) and (**13a**). The structure and stereochemistry of these adducts are proved by chemical, spectroscopic, and X-ray crystallographic methods.

The steroidal 16-en-20-one system appears to undergo photochemical cycloaddition to the conjugated double bond very readily. Under mild conditions 3β-acetoxypregna-5,16-dien-20-one reacts with a variety of olefins, acetylene, and hexafluoroacetone to give 16,17-cyclobutanes, 16,17-cyclobutenes, and 16,17-oxetanes.[2,4] Likewise, the steroidal 4,6-dien-3-one system reacts readily, and photochemical cycloaddition products of 17β-acetoxyandrosta-4,6-dien-3-one with ethylene and with maleic anhydride have been isolated and characterized.[5]

Surprisingly, the steroidal 1-en-3-one system has proved to be much less reactive under the same conditions. Thus all attempts to add ethylene to the Δ^1 double bond of 17α,20:20,21-bismethylenedioxy-5α-pregn-1-en-3-one, 5α-androst-1-en-3-one, 17β-acetoxy-5α-androst-1-en-3-one, and 17β-acetoxy-2-methyl-5α-androst-1-en-3-one were unsuccessful. In each case ethylene was bubbled through a benzene or dioxane solution of the steroid, and the mixture was irradiated with a medium-pressure mercury lamp in water-cooled Pyrex apparatus for 2–18 hr. In all experiments, starting material was recovered in high yield and tlc examination of the reaction mixture showed no evidence of any addition product being formed. Negative results were also obtained when 17α,20:20,21-bismethylenedioxy-5α-pregn-1-en-3-one and 17β-acetoxy-2-methyl-5α-androst-1-en-3-one were irradiated with ethylene in dioxane solution in the presence of benzophenone. Attempts to add maleic anhydride to 17α,20:20,21-bismethylenedioxy-5α-pregn-1-en-3-one and to 17β-acetoxy-2-methyl-5α-androst-1-en-3-one by irradiation in dioxane solution, both in the presence and absence of benzophenone, also failed, as did attempted addition of acetylene to 17β-acetoxy-2-methyl-5α-androst-1-en-3-one in dioxane solution. Successful photocycloaddition to a 1-en-3-one steroid was finally achieved using unsymmetrical alkenes as addenda, and this paper described the addition of 1,1-dichloroethylene and of vinyl acetate to 17β-acetoxy-5α-androst-1-en-3-one (**1**).

Irradiation of benzene solution of **1** containing 1,1-dichloroethylene[6] afforded large amounts of a polymeric material derived from the olefin together with a mixture of steroidal products. Chromatographic separation of the latter gave 17β-acetoxy-1β,2α-(1′,1′-dichloroethylene)-5α-androstan-3-one (**2**) in 16% yield. The *trans* fusion of the cyclobutane ring in **2** was shown by equilibration with neutral alumina which gave the *cis* fused isomer **3a**. The same isomerization was effected by treating **2** with *p*-toluenesulfonic acid in benzene.

The nmr spectrum of **2** suggests that the two chlorine atoms are situated at position 1′. The 1 proton appears as a doublet at 2.58 ppm, J = 14 Hz, the 2′ protons as two overlapping quartets centered at 2.69 and 2.93 ppm, respectively, $J_{2',2'}$ = 12 Hz, $J_{2',2}$ = 7 and 9 Hz, and the 2 proton as a multiplet centered at 3.25 ppm. If the chlorine atoms were at position 2′, the same spin–spin coupling pattern would be expected, but the doublet would then be ascribable to the 2 H and this signal would be expected to appear downfield from the 1-H multiplet.

The 19-H resonance of **2** at 1.30 ppm is strongly deshielded relative to the 19-H signal of dihydrotestosterone acetate which occurs at 1.03 ppm. This suggests the 1β,2α stereochemistry for the cyclobutane ring in which the chlorine atoms are in the close proximity to the C-19 angular methyl group, rather than the alternative 1α,2β structure. On epimerization of **2** to the *cis* fused isomer **3a**, the 19-H resonance moves upfield to 1.10 ppm. This upfield shift is attributed to ring A of **3a** assuming a boat conformation, in which the C-19 angular methyl group lies partly within the shielding cone of the C-3 carbonyl group.

The argument for 1β,2α stereochemistry of **2** based on the downfield position of its 19-H resonance is not unequivocal. The nmr data are also compatible with 1α,2β stereochemistry for adduct **2**, if one assumes that the low-field position of the 19-H resonance is due to a transmitted electronegative effect of the two chlorine atoms. Although this effect would have to be transmitted through five σ bonds, it is known that a 9α-fluorine atom deshields the 19-H resonance by 0.133 ppm.[7] This ambiguity has been resolved by an X-ray

(1) Publication No. 368 from the Syntex Institute of Organic Chemistry.

(2) For part IV, see P. Sunder-Plassmann, P. H. Nelson, P. H. Boyle, A. Cruz, J. Iriarte, P. Crabbé, J. A. Zderic, J. A. Edwards, and J. H. Fried. *J. Org. Chem.*, **34**, 3779 (1969).

(3) Syntex Postdoctoral Fellow, 1966–1967, on leave of absence from Trinity College, Dublin.

(4) P. Sunder-Plassmann, P. H. Nelson, L. Durham, J. A. Edwards, and J. H. Fried, *Tetrahedron Lett.* 653 (1967); P. Sunder-Plassmann, J. Zderic, and J. H. Fried, *ibid.*, 3451 (1966).

(5) P. H. Nelson, J. W. Murphy, J. A. Edwards, and J. H. Fried, *J. Amer. Chem. Soc.*, **90**, 1307 (1968).

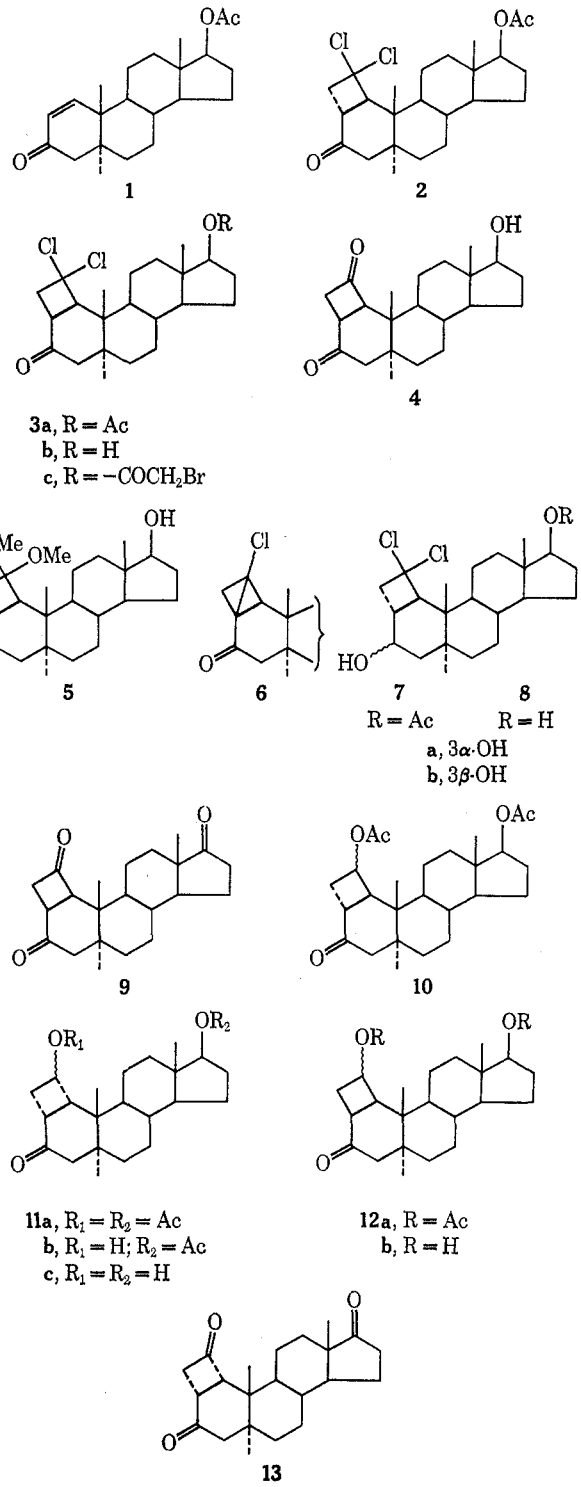
(6) While this work was in progress, O. L. Chapman described the photochemical addition of 1,1-dichloroethylene to isophorone to give the *cis*-fused 3′,3′-dichloroethylene adduct. See Abstracts of the 12th National Organic Symposium of the American Chemical Society Burlington, Vt., June 18–22, 1967, p, 118.

crystallographic analysis of the bromoacetate derivative **3c** kindly performed by Dr. Christensen of these laboratories. Dr. Christensen's results show that the cyclobutane ring of **3c** has the $1\beta,2\beta$ stereochemistry and the A ring exists in the boat conformation.[8] It follows that the initial adduct **2** must have $1\beta,2\alpha$ stereochemistry.

Treatment of adduct **2** with potassium hydroxide in aqueous dioxane afforded a mixture of products which on chromatography gave low yields of the *cis* fused 17β-alcohol **3b** and the cyclobutanone **4**. The latter showed a strong absorption in its infrared spectrum at 1775 cm^{-1}. A much more convenient route to the cyclobutanone **4** was achieved by refluxing either **3a** or **3b** in 1% methanolic potassium hydroxide when the dimethyl ketal **5** was obtained. This on hydrolysis with sulfuric acid in aqueous dioxane gave **4** in good yield. The ketal **5** could also be obtained directly from the *trans* fused adduct **2** by treatment with methanolic potassium hydroxide, when concomitant epimerization of C-2 and hydrolysis of the *gem*-dichloro group occurred. Compound **4** was oxidized with chromium trioxide in acetone to give the triketone **9**, showing three carbonyl bands at 1775, 1730, and 1705 cm^{-1} in its infrared spectrum. The hydrolysis of the *gem*-dichloro group in **3a** and **3b** by methanolic potassium hydroxide is of interest since this reaction is considered to proceed through the bicyclobutane intermediate **6**.[9] Indeed, the importance of the anionic center at C-2 for promoting hydrolysis of the *gem*-dichloro group is evident from methanolysis experiments conducted on the 3-hydroxy compounds **7a** and **7b**. Thus, boiling 1% methanolic potassium hydroxide smoothly transformed the latter substances into their respective diols, **8a** and **8b**, without affecting the *gem*-dichloro groupings.

The 3-hydroxy compounds, **7a** and **7b**, were obtained from **2** by hydrogenation over a platinum catalyst, the stereochemistry at C-3 being assigned on the basis of the chemical shift and the half band width of the 3-H signal[10] as well as the chemical shift of the 19-H signal.

When **1** was irradiated with vinyl acetate[11] in benzene solution, a complex mixture of products was obtained. Column and preparative thin layer chromatography over silica gel effected a partial separation of the mixture and gave two pure products, **10** and **11a**, in low yields. The *trans*-cyclobutane ring fusion in **10** was demonstrated by equilibration on neutral alumina, when *cis* fused **12a** was obtained. The 19-H resonance of **10** shows an upfield shift of 0.23 ppm on this epimerization, suggesting that ring A in **12a** exists in the boat form. The $1\beta,2\alpha$ stereochemistry of **10** and also the position of the cyclobutane acetoxy group at C-1′ were established by hydrolysis of **10** to the corresponding diol **12b** (also obtained by hydrolysis of **12a**), followed by oxidation to a triketone which was identical in all respects with the triketone **9** obtained previously from



1 **2** **4**

3a, R = Ac
b, R = H
c, R = $-COCH_2Br$

5 **6** **7** **8**

R = Ac R = H
a, 3α-OH
b, 3β-OH

9 **10**

11a, $R_1 = R_2 = Ac$
b, $R_1 = H$; $R_2 = Ac$
c, $R_1 = R_2 = H$

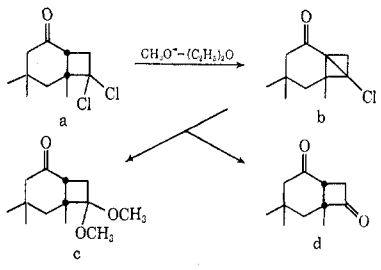
12a, R = Ac
b, R = H

13

(7) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, p 21.

(8) Full details of the X-ray analysis will be reported elsewhere by Dr. A. Christensen.

(9) Chapman has shown that treatment of the bicyclic adduct (a) with sodium methoxide in ether yields the bicyclobutane (b) which is transformed by exposure to methanolic sodium methoxide and aqueous base into the dimethyl ketal (c) and the cyclobutanone (d), respectively. See ref 6.



(10) For examples illustrating the use of band width at half-height in determining the axial or equatorial orientation of an alicyclic methine proton, see A. Hassner and C. Heathcock, *J. Org. Chem.*, **29**, 1350 (1964), and references cited therein.

(11) After the completion of this work the photochemical addition of vinyl acetate to the Δ^4-3 ketone system was reported: S. Terao, S. Tsushina, I. Agata, and T. Miki, *Kogyo Kagahu Zasshi*, **72**, 203 (1969).

the 1,1-dichloroethylene adduct **2**. The stereochemistry at C-1′ is unknown.

On treatment of the second photoadduct **11a** with neutral alumina, no trace of isomerized product could be detected, indicating the cyclobutane ring fusion to be *cis*. Hydrolysis of the adduct **11a** gave the diol **11c** which on oxidation gave a triketone **13**, showing three carbonyl bands at 1775, 1740, and 1700 cm^{-1} in its infrared spectrum, and a three-proton multiplet centered at 3.05 ppm together with a one-proton multiplet centered at 3.60 ppm in its nmr spectrum. Absence of a downfield doublet assignable to the 2-H proton precludes the alternative 2′-oxo structure. Since this triketone was different from the one previously obtained (**9**), it must have the 1α,2α stereochemistry as also must the initial adduct **11a**.

Although a complete product analysis was not undertaken, the present results are consistent with those of previous workers who have studied the photochemical addition of alkenes to α,β-unsaturated ketones. Thus, *trans* fusion of the cyclobutane ring in the photoadduct seems to be predominant.[11] Secondly, all of the 1,2 adducts are derived by addition of the carbon of the alkene bearing the electronegative substituent(s) to the β-carbon atom of the enone.[9,12,13] In the work of Miki and coworkers, however, describing some photoadducts of alkenes with testosterone acetate, both head-to-tail and head-to-head adducts are reported, and in some reactions the 4α,5α *cis* fused adducts were predominant.[11]

Despite the ready addition of both vinyl acetate and 1,1-dichloroethylene to 17β-acetoxy-5α-androst-1-en-3-one (**1**), neither of these alkenes reacts with 17β-acetoxy-2-methyl-5α-androst-1-en-3-one. This result agrees with Corey's observation that alkylation of C-2 of an enone is deleterious to the photochemical addition of an alkene.[12] 1,1-Difluorethylene, on the other hand, does not react even with **1**, another demonstration of the unreactivity of the steroidal 1-en-3-one system.

Experimental Section[14]

Irradiation Experiments.—All photolyses were conducted at 15–20° in Pyrex apparatus, using a 200-W Hanovia 654-A-36 medium-pressure mercury lamp as the source of ultraviolet light.

Photochemical Addition of 1,1-Dichloroethylene to 17β-Acetoxy-5α-androst-1-en-3-one (1).—A solution of **1** (6.0 g) and 1,1-dichloroethylene (40 ml) in benzene (75 ml) was irradiated for 4 hr. The reaction mixture was filtered to remove polymeric material and the vessel was cleaned. More 1,1-dichloroethylene (10 ml) was added and irradiation was continued. After a total irradiation period of 12.5 hr, the reaction mixture was filtered, the combined residues of polymeric material were washed with methylene dichloride, and the washings were added to the filtrate. Evaporation of solvent gave a viscous gum which partially dissolved on trituration with ether leaving a white solid residue (2.2 g). Chromatography on a column of silica gel (250 g), eluting with hexane–ethyl acetate (85:1), gave 17β-acetoxy-1β,2α-(1′,1′-dichloroethylene)-5α-androstan-3-one (**2**, 1.21 g, 16% yield): mp 253°; $[\alpha]_D$ +54°; ν_{max} 1725, 1720, 1240 cm^{-1}; nmr (100 Mc) 0.83 (s, 18-H), 1.30 (s, 19-H), 2.02 (s, 17β-acetoxy H), 2.58 (d, $J_{1,2}$ = 14 Hz, 1-H), 2.69 (q, $J_{2',2'}$ = 12, $J_{2,2'}$ = 7 Hz, 2′ H), 2.93 (q, $J_{2',2'}$ = 12, $J_{2,2'}$ = 9 Hz, 2′-H), 3.25 (m, 2-H), 4.60 ppm (m, 17α-H). *Anal.* Calcd for $C_{23}H_{32}O_3Cl_2$: C, 64.63; H, 7.54; Cl, 16.59. Found: C, 64.72; H, 7.70; Cl, 16.47.

Conversion of 1β,2α Adduct (2) into the 1β,2β Adduct (3a). (a) With *p*-Toluenesulfonic Acid.—A solution of **2** (0.89 g) and *p*-toluenesulfonic acid monohydrate (0.15 g) in benzene (110 ml) was refluxed for 16 hr. The solution was cooled, washed with aqueous sodium carbonate and water, dried ($MgSO_4$), and evaporated, yielding a clear oil (0.89 g) which solidified on standing. Chromatography on a column of silica gel (60 g), eluting with hexane–ethyl acetate (17:3) afforded 17β-acetoxy-1β,2β-(1′,1′-dichloroethylene)-5α-androstan-3-one (**3a**): mp 220°; $[\alpha]_D$ +93°; ν_{max} 1730, 1715, 1245 cm^{-1}; nmr (100 Mc) 0.80 (s, 18-H), 1.10 (s, 19-H), 2.03 (s, 17β-acetoxy H), 3.1–3.7 (complex spin pattern, four protons, 1-H, 2-H, 2′-H), 4.60 ppm (m, 17α-H). *Anal.* Calcd for $C_{23}H_{32}O_3Cl_2$: C, 64.63; H, 7.54; Cl, 16.59. Found: C, 64.64; H, 7.48; Cl, 16.76.

(b) **With Alumina.**—A solution of **2** (0.27 g) in ethyl acetate (40 ml) and chloroform (10 ml) was stirred with neutral alumina (27 g, Woelm activity grade I) for 5.75 hr. The residue obtained after removal of alumina and evaporation of solvent was chromatographed on preparative tlc plates (hexane–ethyl acetate, 3:1) to give starting material **2** and **3a** identical with the product obtained above.

17β-Hydroxy-1β,2β-(1′,1′-dichloroethylene)-5α-androstan-3-one (3b).—A solution of 17β-acetoxy-1β,2β-(1′,1′-dichloroethylene)-5α-androstan-3-one (**3a**, 0.76 g) and *p*-toluenesulfonic acid monohydrate (0.76 g) in methanol (100 ml) was refluxed for 6 hr. The reaction mixture was diluted with benzene (200 ml) and the resulting solution was washed with water, aqueous sodium carbonate solution, and water, dried ($MgSO_4$), and evaporated. The residual yellow oil was dissolved in benzene–methylene dichloride. Addition of hexane precipitated a solid which on crystallization from ethyl acetate gave white crystals of the 17-alcohol (**3b**): mp 204–205°; ν_{max} 3550, 1700 cm^{-1}; nmr (100 Mc) 0.76 (s, 18-H), 1.11 (s, 19-H), 1.55 (broad s, disappeared on addition of D_2O, –OH), 3.20–3.75 ppm (complex spin pattern, five protons, 17α-H, 1-H, 2-H, 2′-H); mass spectrum *m/e* 384 (M^+ for ^{35}Cl), 386 (M^+ for ^{37}Cl).

17β-Bromoacetoxy-1β,2β-(1′,1′-dichloroethylene)-5α-androstan-3-one (3c).—A methylene dichloride solution of 17β-hydroxy-1β,2β-(1′,1′-dichloroethylene)-5α-androstan-3-one (**3b**, 0.210 g) was treated with 1.5 mol α-bromoacetyl bromide and then with 1.5 mol of pyridine, both in methylene dichloride at room temperature for 72 hr. The reaction mixture was washed with water, dried ($MgSO_4$), and evaporated. Chromatography of the residue on a column of silica gel (30 g), eluting with hexane–ethyl acetate (9:1), gave crystals of the 17β-bromoacetate (**3c**, 0.19 g): mp 181–182°; ν_{max} 1725, 1705 cm^{-1}; nmr (60 Mc) 0.83 (s, 18-H), 1.09 (s, 19-H), 3.78 (s, $-COCH_2Br$), 4.65 ppm (m, 17α-H). *Anal.* Calcd for $C_{23}H_{31}O_3BrCl_2$: C, 54.54; H, 6.17. Found: C, 54.45; H, 6.13.

Treatment of 17β-Acetoxy-1β,2α-(1′,1′-dichloroethylene)-5α-androstan-3-one (2) with Potassium Hydroxide in Dioxane.—Potassium hydroxide (2.0 g) in water (10 ml) was added to a solution of **2** (0.76 g) in dioxane (150 ml). A clear oil separated and the mixture was stirred at 90° for 3 hr, when it was poured into water and neutralized with sulfuric acid. The clear yellow solution was extracted with ethyl acetate and the extract was washed with water, dried ($MgSO_4$), and evaporated, giving a yellow solid (0.64 g). This was chromatographed on a column of silica gel (60 g), eluting first with hexane and finally with hexane–ethyl acetate (2:1) using a continuous solvent gradient technique. Two main products were isolated: 17β-hydroxy-1β,2β-(1′,1′-dichloroethylene)-5α-androstan-3-one (**3b**, 85 mg, least polar), identical with **3b** described above, and 17β-hydroxy-1β,2β-ethyl-

(12) E. J. Corey, J. D. Bass, R. LeMahieu, and R. B. Mitra, *J. Amer. Chem. Soc.*, **86**, 5570 (1964).

(13) J. W. Hanifin and E. Cohen, *Tetrahedron Lett.*, 5421 (1966); N. C. Yang, *Pure Appl. Chem.*, **9**, 591 (1964).

(14) Melting points are corrected and were taken on a Fisher-Johns apparatus or a Thomas–Hoover capillary apparatus. Optical rotations were measured in dioxane solution at 27° and infrared spectra were determined in KBr disks unless otherwise specified. Ultraviolet spectra were measured on a Cary Model 14 spectrometer. We wish to thank Dr. L. Throop and his staff for these measurements. Nmr spectra were recorded for 5–10% solutions (w/v) in deuteriochloroform containing tetramethylsilane as internal reference on Varian A-60 and HA-100 spectrometers. Chemical shifts are reported as parts per million on the δ scale to the nearest 0.01 ppm. Coupling constants are in cycles per second to the nearest 0.5 Hz. We thank Mr. J. W. Murphy and Miss J. Tremble for assistance with these measurements. In the presentation of data, s = singlet, d = doublet, t = triplet, and m = multiplet. Mass spectra were obtained with an Atlaswerke CH-4 spectrometer equipped with a direct inlet system. Spectra were measured at an ionizing potential of 70 eV and an acceleration voltage of 3 kV. We wish to thank Dr. L. Tökes and Mr. J. Smith for assistance with these measurements. Microanalyses were performed by Dr. A. Bernhardt, Mülheim (Ruhr), West Germany. Tlc plates with a thickness of 0.25-mm silica gel GF_{254} (E. Merck AG Darmstadt) were used.

ene-5α-androstane-1′,3-dione (**4**, 25 mg, most polar), which had mp 194–195°; ν_{max} 3300, 1775, 1705 cm^{-1}; nmr (100 Mc) 0.75 (s, six protons, 18-H, 19-H), 1.55 (broad s, disappeared on addition of D_2O, –OH), 3.0–3.3, 3.5–3.8 ppm (complex pattern, five protons, 1-H, 2-H, 2′-H, 17α-H). *Anal.* Calcd for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 75.91; H, 9.20.

17β-Hydroxy-1β,2β-(1′,1′-dimethoxyethylene)-5α-androstan-3-one (5).—A solution of 17β-acetoxy-1β,2α-(1′,1′-dichloroethylene)-5α-androstan-3-one (**2**, 0.37 g) in 1% methanolic potassium hydroxide was refluxed for 1.5 hr. The solution was concentrated to half its volume and poured into ice water (300 ml). Crystallization of the precipitated solid from methanol gave **5** (0.20 g): mp 156–157° (the compound melted and resolidified at 95–100°); $[\alpha]_D$ +95°; ν_{max} 1705, 1695 cm^{-1} (KBr), 3620, 1700 cm^{-1} ($CHCl_3$); nmr (60 Mc) 0.77 (s, 18-H), 0.90 (s, 19-H), 1.77 (s, disappeared on addition of D_2O, –OH), 3.12, 3.20 (two s, –OMe), 3.6 ppm (m, 17α-H), mass spectrum *m/e* 376 (M^+). This product partially decomposed on repeated crystallization and an analytically pure sample could not be obtained.

Treatment of **3a** or **3b** with 1% methanolic potassium hydroxide as described above also yielded the dimethyl ketal **5**.

17β-Hydroxy-1β,2β-ethylene-5α-androstane-1′,3-dione (4).—A solution of 17β-hydroxy-1β,2β-(1′,1′-dimethoxyethylene)-5α-androstan-3-one (**5**, 90 mg) in dioxane (2.2 ml) and water (2 ml) containing 1 drop of 50% sulfuric acid was heated at 100° for 0.75 hr. After cooling, the reaction mixture was diluted with ethyl acetate and the solution was washed with water, dried ($MgSO_4$), and evaporated, giving dione **4** (44 mg), identical with the product already described.

1β,2β-Ethylene-5α-androstane-1′,3,17-trione (9).—An excess of Jones reagent (2 ml) was added to a solution of 17β-hydroxy-1β,2β-ethylene-5α-androstane-1′,3-dione (**4**, 30 mg) in acetone (5 ml). After allowing the mixture to stand at room temperature for 15 min, it was diluted with water and extracted with ethyl acetate. The extract was washed with water, dried ($MgSO_4$), and evaporated, yielding a solid (25 mg) which on crystallization from hexane–ethyl acetate gave white crystals of the triketone **9**: mp 246–248°; $[\alpha]_D$ +156°; ν_{max} 1775, 1730, 1705 cm^{-1}; nmr (100 Mc) 0.77 (s, 19-H), 0.88 (s, 18-H), 3.0–3.8 ppm (complex spin pattern, four protons, 1-H, 2-H, 2′-H). *Anal.* Calcd for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.72; H, 8.41.

Hydrogenation of 17β-Acetoxy-1β,2α-(1′,1′-dichloroethylene)-5α-androstan-3-one (2).—A suspension of anhydrous sodium acetate (0.38 g) and 5% platinum-on-carbon catalyst (0.57 g) in a solution of **2** (1.13 g) in ethyl acetate (200 ml) was hydrogenated at atmospheric temperature and pressure until uptake of hydrogen ceased. Filtration and evaporation of the reaction mixture gave a white solid (1.08 g) which was chromatographed on a column of silica gel (100 g), eluting with hexane–ethyl acetate (4:1). 17β-Acetoxy-1β,2α-(1′,1′-dichloroethylene)-5α-androstan-3α-ol (**7a**, 0.50 g) was eluted first: mp 208°; $[\alpha]_D$ +42°; ν_{max} 3450, 1715, 1275 cm^{-1}; nmr (60 Mc) 0.81 (s, 18-H), 1.09 (s, 19-H), 1.77 (s, disappeared on addition of D_2O, –OH), 2.01 (s, 17β-acetoxy-H), 4.02 (broad s, $W_{1/2}$ = 6 Hz, 3β-H), 4.60 ppm (m, 17α-H). *Anal.* Calcd for $C_{23}H_{34}O_3Cl_2$: C, 64.33; H, 7.98; Cl, 16.51. Found: C, 74.06; H, 8.16; Cl, 16.70. 17β-Acetoxy-1β,2α-(1′,1′-dichloroethylene)-5α-androstan-3β-ol (**7b**, 0.50 g) was eluted next: mp 231°; $[\alpha]_D$ +8°; ν_{max} 3620, 1720 cm^{-1} ($CHCl_3$); nmr (60 Mc) 0.82 (18-H), 1.13 (19-H), 1.80 (s, disappeared on addition of D_2O, –OH), 2.03 (s, 17β-acetoxy H), 3.60 (m, $W_{1/2}$ = *ca.* 17 Hz, 3α-H), 4.60 ppm (m, 17α-H). *Anal.* Calcd for $C_{23}H_{34}O_3Cl_2$: C, 64.33; H, 7.98; Cl, 16.51. Found: C, 64.20; H, 8.08; Cl, 16.63.

Hydrolysis of 17β-Acetoxy-1β,2α-(1′,1′-dichloroethylene)-5α-androstan-3α-ol (7a).—A solution of **7a** (0.15 g) in 1% methanolic potassium hydroxide (25 ml) was refluxed for 1.5 hr. The solution was poured into water (75 ml) and the mixture was extracted with ethyl acetate. The extract was washed with water, dried ($MgSO_4$), and evaporated, giving a white solid (0.15 g). Crystallization from hexane–ethyl acetate afforded pure 3α,17β-diol **8a**: mp 203°; $[\alpha]_D$ +46°; ν_{max} 3625, 3460 cm^{-1} ($CHCl_3$). *Anal.* Calcd for $C_{21}H_{32}O_2Cl_2$: C, 65.11; H, 8.33; Cl, 18.31. Found: C, 64.84; H, 8.46; Cl, 18.13; mass spectrum, *m/e* 386, 388 (m^+). Similar hydrolysis of **7b** gave 3β,17β-diol **8b**: mp 217–220°; $[\alpha]_D$ +22°; ν_{max} 3350 cm^{-1} (Nujol). *Anal.* Calcd for $C_{21}H_{32}O_2Cl_2$: Cl, 18.31. Found: Cl, 17.83; mass spectrum, *m/e* 386, 388 (M^+).

Photochemical Addition of Vinyl Acetate to 17β-Acetoxy-5α-androst-1-en-3-one (1).—A solution of **1** (1.56 g) in vinyl acetate (47 ml) and benzene (20 ml) was irradiated for 13 hr. Evaporation of the solvent gave a clear viscous oil which was chromatographed on a column of silica gel (285 g), eluting with hexane–ethyl acetate (solvent composition changed gradually from 83:17 to 50:50, using a continuous solvent gradient technique) and collecting 20-ml fractions. Fractions 86–99 contained two main components (tlc) and these were separated by preparative tlc (hexane–ethyl acetate 85:15, each plate run nine successive times). The product of greatest R_f proved to be starting material **1** (7 mg). The other product was 17β-acetoxy-1α,2α-(1′ξ-acetoxyethylene)-5α-androstan-3-one (**11a**, 32 mg, 2% yield): mp 168°; $[\alpha]_D$ +12°; ν_{max} 1730, 1700 cm^{-1}; nmr (100 Mc) 0.80 (s, 18-H), 0.96 (s, 19-H), 1.98, 2.02 (two s, acetoxy H), 2.4–3.0 (complex pattern), 4.58 (m, 17α-H), 5.10 ppm (m, 1′-H). *Anal.* Calcd for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71. Found: C, 72.22; H, 8.79. Fractions 106–152 were combined and evaporated, affording a gum which contained three principal components (tlc). The gum was triturated with hexane–ethyl acetate, giving a white solid which on crystallization from hexane–ethyl acetate gave pure 17β-acetoxy-1β,2α-(1′ξ-acetoxyethylene)-5α-androstan-3-one (**10**, 0.17 g, 9% yield): mp 202–205°; $[\alpha]_D$ +65°; ν_{max} 1735, 1725, 1715, 1255 cm^{-1}; nmr (100 Mc) 0.79 (s, 18-H), 1.03 (s, 19-H), 1.97 (s, 1′-acetoxy H), 2.01 (s, 17β-acetoxy H), 4.5–4.9 ppm (m, two protons, 17α-H, 1′-H). *Anal.* Calcd for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71. Found: C, 72.10; H, 8.79.

17β-Acetoxy-1β,2β-(1′ξ-acetoxyethylene)-5α-androstan-3-one (12a).—A solution of **10** (0.24 g) in ether (95 ml) and ethyl acetate (5 ml) at 20° was stirred with neutral alumina (24 g, Woelm activity grade I) for 0.75 hr. Filtration followed by evaporation of solvent gave a white solid (0.24 g). Crystallization from hexane–ethyl acetate gave **12a**: mp 165°; $[\alpha]_D$ +45°; ν_{max} 1730, 1720 cm^{-1}; nmr (100 Mc) 0.76 (s, 18-H), 0.80 (s, 19-H), 2.00, 2.03 (two s, acetoxy H), 2.6–3.1 (complex pattern, three protons), 4.65 (m, 17α-H), 5.02 ppm (m, 1′-H). *Anal.* Calcd for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71. Found: C, 71.61; H, 8.68.

17β-Hydroxy-1β,2β-(1′ξ-hydroxyethylene)-5α-androstan-3-one (12b).—A solution of 17β-acetoxy-1β,2α-(1′ξ-acetoxyethylene)-5α-androst-3-one (**10**, 0.126 g) and potassium hydroxide (2.0 g) in methanol (100 ml) and water (2 ml) was allowed to stand at 20° for 5 hr. The mixture was poured into water (250 ml) and extracted with ether. The extract was washed with water, dried ($MgSO_4$), and evaporated. The white solid residue (0.08 g) was crystallized from hexane–ethyl acetate giving the 1′ξ,17β-diol (**12b**): mp 198°; $[\alpha]_D$ +107°; ν_{max} 3300, 1700 cm^{-1} (Nujol); nmr 0.72 (s, 18-H), 0.77 (s, 19-H), 3.62 (m, 17α-H), 4.05 ppm (m, 1′-H). *Anal.* Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.67; H, 9.85. **12b** was also obtained by similar hydrolysis of 1′ξ,17β-diacetate (**12a**).

Oxidation of 17β-Hydroxy-1β,2β-(1′ξ-hydroxyethylene)-5α-androstan-3-one (12b).—Oxidation of **12b** with chromium trioxide in acetone yielded a triketone identical in spectra, tlc, and mixture melting point with triketone **9** already described.

Treatment of 17β-Acetoxy-1α,2α-(1′ξ-hydroxyethylene)-5α-androstan-3-one (11a) with Alumina.—A solution of **11a** (99 mg) in dry ether (55 ml) was stirred with neutral alumina (8.1 g, Woelm activity grade I) at 20° for 5 hr. The alumina was filtered off and washed with ethyl acetate and then with methylene dichloride. Evaporation of the combined solutions gave a white solid (63 mg). This was separated into two components by preparative tlc (hexane–ethyl acetate, 40:60). The less polar product (23 mg) was identical (melting point, mixture melting point, ir, nmr, tlc) with the starting material. The more polar product (15 mg) was probably 17β-acetoxy-1α,2α-(1′ξ-hydroxyethylene)-5α-androstan-3-one (**11b**): nmr (60 Mc) 0.78 (s, 18-H), 0.93 (s, 19-H), 1.98 (s, 17β-acetoxy H), 4.08 (m, 1′-H), 4.53 ppm (m, 17α-H).

17β-Hydroxy-1α,2α-(1′ξ-hydroxyethylene)-5α-androstan-3-one (11c).—A solution of 17β-acetoxy-1α,2α-(1′ξ-hydroxyethylene)-5α-androstan-3-one (**11a**, 0.21 g) and potassium hydroxide (2.3 g) in methanol (115 ml) and water (2.3 ml) was allowed to stand at room temperature for 6 hr. The solution was then poured into water and extracted with ethyl acetate. The extract was washed with water, dried ($MgSO_4$), and evaporated. Crystallization of the residue (0.17 g) from aqueous ethanol gave white needles of 1′ξ,17β-diol (**11c**): mp 115–116°; $[\alpha]_D$ –3°; ν_{max} 3450, 1700 cm^{-1} ($CHCl_3$); nmr (60 Mc) 0.75 (s, 18-H), 0.97 (s, 19-H), 3.5–4.2 ppm (m, 1′-H and 17α-H). *Anal.* Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 76.08; H, 9.98.

1α,2α-Ethylene-5α-androstane-1′,3,17-trione (13).—17β-Hydroxy-1α,2α-(1′ξ-hydroxyethylene)-5α-androstan-3-one (**11c**, 45 mg) was dissolved in acetone (5 ml) and excess Jones reagent was added. After allowing the mixture to stand at 20° for 15 min, it was poured into water and extracted with ethyl acetate. The extract was washed with water, dried ($MgSO_4$), and evaporated, yielding a white solid (34 mg) which on crystallization from hexane–ethyl acetate gave 1′,3,17-trione (**13**): mp 207°; $[\alpha]_D$ +86° ($CHCl_3$); ν_{max} 1775, 1735, 1700 cm^{-1} ($CHCl_3$); nmr (100 Mc) 0.86 (s, 18-H), 0.89 (s, 19-H), 2.7–3.4 (m, three protons), 3.45–3.75 ppm (m, one proton). *Anal.* Calcd for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.21; H, 8.41.

Registry No.—**2**, 24467-63-8; **3a**, 24515-46-6; **3b**, 24467-64-9; **3c**, 24467-65-0; **4**, 24467-66-1; **5**, 24467-67-2; **7a**, 24467-68-3; **7b**, 24467-69-4; **8a**, 24467-70-7; **8b**, 24467-71-8; **9**, 24515-47-7; **10**, 24523-22-6; **11a**, 24467-72-9; **11b**, 24467-73-0; **11c**, 24515-48-8; **12a**, 24467-74-1; **12b**, 24471-11-2; **13**, 24471-12-3.

Synthetic Approaches to Some of the *Lythraceae* Alkaloids[1]

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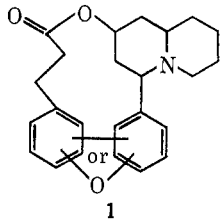
The uncoupled precursor (**20**) to dihydrolyfoline (**22**), a *Lythraceae* alkaloid was prepared by a biogenetic-type synthesis, based upon the assumption that the alkaloids arise from phenylpropane, acetate, and/or lysine sources. Condensation of the acryloylacetic ester (**12**) with Δ^1-piperideine (**7**) gave 1-carbethoxy-2-keto-4-(3-benzyloxy-4-methoxyphenyl)-*trans*-quinolizidine (**13**). Decarboxylation of **13** and reduction of the tetraphenylborate salt of the resulting ketone (**14**) with $NaBH_4$ gave a mixture of alcohols from which the axial isomer (**16**) was separated. Esterification of the alcohol (**16**) with *p*-benzyloxyhydrocinnamic acid and debenzylation yielded the desired compound (**20**). Preliminary attempts to couple **20** oxidatively to provide dihydrolyfoline (**22**) or another of the *Lythraceae* alkaloids have failed.

The alkaloids of the genera *Heimia* and *Decodon*, family *Lythraceae*, are a series of about 17 compounds corresponding to **1**. These alkaloids[2] contain a quinolizidine ring bearing phenyl and phenylpropionyloxy substituents. The two benzene rings are joined either by a biphenyl or a biphenyl–ether bridge. The structures of the alkaloids are based upon chemical correlations[3] with lythrine (**2**) and vertaline (**3**), whose structures were solved by X-ray analysis.[4]

Experimental data about the biosynthesis of these compounds was not available when this investigation was initiated.[5] Therefore, it was necessary for us to suggest a plausible route by which they might be formed *in vivo*. For the purpose of discussion, the molecules may be divided into cinnamate and 4-phenylquinolizidine portions. Considering the type and the oxygenation patterns of the phenyl–phenyl system, it seems logical to believe that these alkaloids are formed by an oxidative phenol coupling of the two portions.[6] Whether the phenyl–phenyl connection is made before or after the ester formation is debatable.



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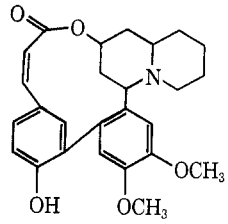

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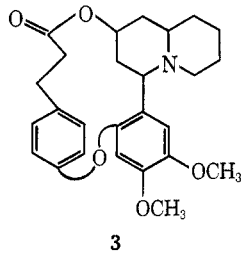

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It has been suggested[7] without experimental data that the quinolizidine ring system (**5**) could arise from isopelletierine (**4**) and a suitably substituted benzaldehyde as shown in Scheme I. This approach was used[8] for the preparation of a mixture of *cis*- and *trans*-4-phenyl-2-ketoquinolizidines (**5** with no substituents) which was reduced to give a mixture of the epimeric alcohols. No reactions have been reported with oxygenated quinolizidines.

It would seem equally logical that the quinolizidine system might arise from a suitable phenyl–polyketide precursor such as **6** and Δ^1-piperideine (**7**). We would like to report the application of this approach in the synthesis of these alkaloids. The original plan was to prepare the uncoupled precursor (**20**) to the alkaloids and oxidize it to form the phenyl–phenyl connection to yield dihydrolyfoline (**22**). Compound **20** was prepared as

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