Reaction of Diazocyclopropane with Steroidal 16-Bromo-17-ketones

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The reaction of diazocyclopropane with both 16α- and 16β-bromo-3β-acetoxy-5β-androstane-11,17-dione has been found to give a mixture of the four possible 16-bromo-17-spiro-oxirans (4a), (4b), (5a), and (5b), of which (17*R*)-3β-acetoxy-16α-bromodispiro[5β-androstane-17,2'-oxiran-3',1''-cyclopropane]-11-one (5a) was found to be the major isomer. Rearrangements of these spiro-oxirans by boron trifluoride to give 17-spirocyclobutanones are described. Mechanisms of both reactions are discussed.

DIAZOCYCLOPROPANE (1) reacts with steroidal ketones to give spiro-oxirans, spirocyclobutanones, or insertion products.[1] 3-Ketones react readily, 20-ketones are less reactive, and 11- and 17-ketones are unreactive. Since α-halogeno-ketones are considerably more reactive towards diazo-compounds than the corresponding unsubstituted ketones,[2] we have studied the reaction between a number of 16-bromo-17-oxo-steroids and diazocyclopropane.

3α-Acetoxy-16α-bromo-5β-androstane-11,17-dione (2a) reacted extremely rapidly giving, in 50% yield, a mixture of spiro-oxirans (4a), (5a), (4b), and (5b), in an approximate ratio of 2 : 8 : 1 : 1, respectively, together with about 25% of an unidentified product. Small amounts of the spiro-oxirans (4a) and (5a) were isolated in a pure state as oils by chromatography, but the two 16β-bromo-isomers (4b) and (5b) could not be separated. Spectral studies were therefore carried out on a 1 : 1 mixture contaminated with small amounts of decomposition products formed from the isomers (4a) and (5a) (see below). The spiro-oxiran structures were deduced from the absence of a 17-ketone peak in the i.r. spectra, which show carbonyl peaks only at 1 730 and 1 710 cm^{-1} for the 3-acetate and 11-ketone groups (no ring insertion or cyclobutanone products [1]). The structures are consistent with the n.m.r. spectra and are confirmed from subsequent rearrangements. The assignment of configuration at C-16 and C-17 is based on the relative positions of the C-13 proton signals in the n.m.r. spectra (Table). The pair of 16β-isomers is readily distinguished from the corresponding pair of 16α-bromo-isomers by the large downfield shift of this signal group due to the

N.m.r. data (τ values) *

Compound	13-CH_3	10-CH_3	Compound	13-CH_3	10-CH_3
(4a)	9.15	8.83	(7a)	9.23	8.97
(5a)	9.24	8.83	(7b)	8.92	8.96
(4b)	8.85	8.83	(8a)	9.10	
(5b)	8.93	8.83	(8b)	9.17	
(6a)	9.16	8.96			

* Solutions in $CDCl_3$ (with a trace of pyridine).

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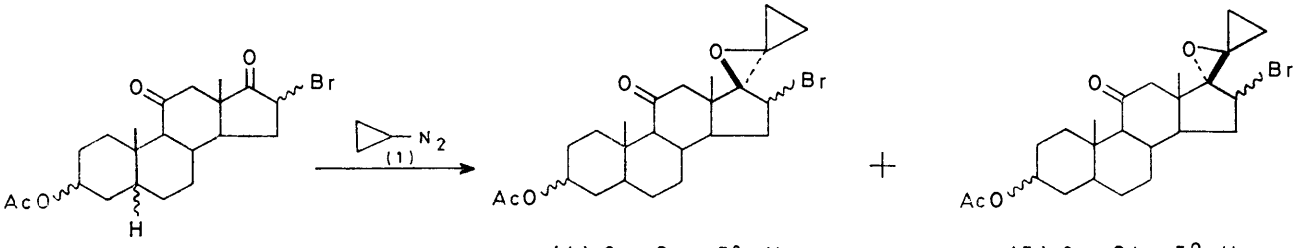
[1] P. Bladen and D. R. Rae, *J. Chem. Soc.*, 1974, 2240.
[2] C. D. Gutche, *Org. Reactions*, 1954, **8**, 364.

influence of the pseudoaxial 16β-bromo-substituents. Bertin and Nedelec [3] have shown that in the isomeric pair of 17-spiro-oxirans (8a) and (9b) the signal for the C-13 protons is more deshielded in the 17β-oxygen isomer (8a) than in the 17α-oxygen isomer (8b) (Table).



(2) 3α-OAc, 5β-H
a; 16α-Br
b; 16β-Br

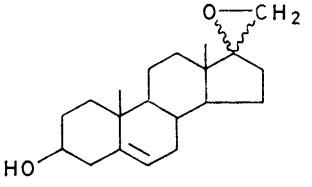
(3) 3β-OAc, 5α-H, 16α-Br

(4) 3α-OAc, 5β-H
a; 16α-Br
b; 16β-Br

(6) 3β-OAc, 5α-H
a; 16α-Br
b; 16β-Br

(5) 3α-OAc, 5β-H
a; 16α-Br
b; 16β-Br

(7) 3β-OAc, 5α-H
a; 16α-Br
b; 16β-Br



(8) a; 17β-O
b; 17α-O

Consequently, in the pair of 16α-bromo-isomers (4a) and (5a) the compound with the lower field signal for the C-13 protons was assigned the 17β-oxygen structure (4a); a similar argument was applied to the 16β-bromo-pair (4b) and (5b).

The reaction of diazocyclopropane with 3α-acetoxy-16β-bromo-5β-androstane-11,17-dione (2b) gave the spiro-oxiran products in the same ratio as was obtained from the 16α-bromo-isomer (2a). Since, however, the reaction is carried out under basic conditions, equilibration of the 16-bromo-substituent can occur before reaction takes place and this could account for the similarity in products.

The reaction of diazocyclopropane with 3β-acetoxy-16α-bromo-5α-androstane-11,17-dione (3) gave a similar mixture of products, in 50% yield, from which three crystalline compounds, in the approximate ratio of 1 : 4 : 1, were obtained and assigned the structures (6a), (7a), and (7b), by analogy with the 5β-series. However since only one isomer with a 16β-bromo-substituent was isolated, no definite inference can be made as to the stereochemistry at C-17, although a direct comparison with a 5β-series indicates the structure (7b) for this compound.

The products obtained from the foregoing reactions indicated that the accepted mechanism [2] for addition of diazo-compounds to ketones, *i.e.* nucleophilic attack of the diazo-carbon atom on the carbon atom of the ketone, is not feasible. The major products of the reactions have 16α-bromo-substituents, and since under basic conditions the 16β-bromo-isomer predominates [4] and both 16α- and 16β-bromo-compounds (2a and b) react to give the products in the same ratio, nucleophilic attack by diazocyclopropane at C-17 from the more sterically favoured α-face cannot be occurring. Other mechanisms for the addition of diazo-compounds to hindered ketones have been proposed,[5] but these do not involve an α-bromo-ketone. Since the 16-bromo-substituent is necessary for reaction to occur it is probable that the enolate ion, formation of which is facilitated by the bromo-substituent, is the reacting species. Reaction of the enolate anion with diazocyclopropane (Scheme 1) would give an intermediate which, by addition of a proton and subsequent ring closure, would give two oxadiazolines (assuming *trans*-addition to the double bond). Collapse of these in a non-stereospecific manner * would give the four spiro-oxirans (4a), (4b), (5a), and (5b).

This mechanism also explains the extreme rapidity of the reaction, which occurs almost instantaneously; such

* In general pyrazolines decompose to the corresponding cyclopropanes with little stereospecificity.[6]

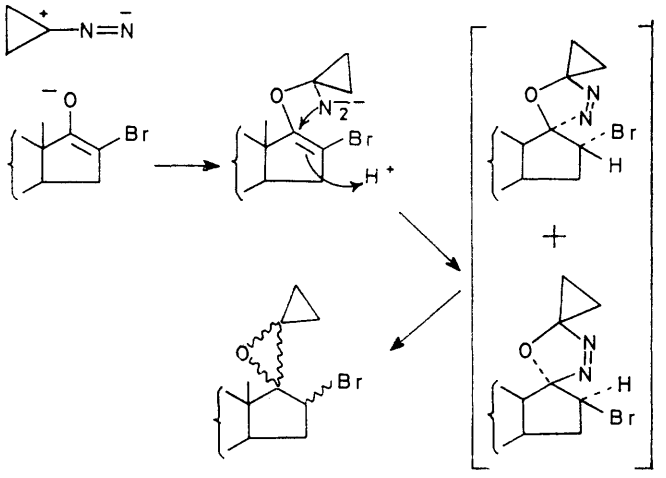
[3] D. Bertin and L. Nedelec, *Bull. Soc. chim. France*, 1964, 2140.

[4] J. Faikos and F. Sorm, *Coll. Czech. Chem. Comm.*, 1959, **24**, 766.

[5] (*a*) C. D. Gutsche and J. E. Bowers, *J. Org. Chem.*, 1967, **32**, 1203; (*b*) J. N. Bradley, G. W. Cowell, and H. Ledwith, *J. Chem. Soc.*, 1964, 4334.

[6] D. E. McGreer, N. W. K. Chiu, M. G. Vinje, and K. C. K. Wong, *Canad. J. Chem.*, 1965, **43**, 1451.

reactions are unusual for 17-oxo-steroids. However, both the 16-bromo- and 11-oxo-functions are necessary for reaction at C-17 to occur; 16α- and 16β-bromo-androst-5-en-17-ones and 3α-acetoxy-3β-androstane-11,17-dione are unreactive towards diazocyclopropane.



SCHEME 1

The nature of the influence of the 11-oxo-group in this reaction is uncertain.

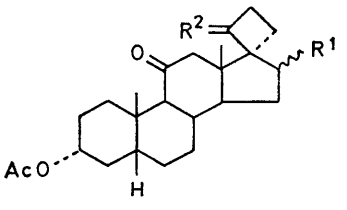
Rearrangement of the Spiro-oxirans.—Owing to the difficulties in chromatographic separation of the spiro-oxirans, only small amounts of pure (4a) and (5a) and a mixture of (4b) and (5b) contaminated with impurities were available for rearrangement studies with boron trifluoride–ether complex.

The epoxide (4a) rearranged in dry benzene to give a single product, shown to be the spirocyclobutanone (9a) by spectroscopic means.

The epoxide (5a) afforded three products, the most abundant of which was isolated by chromatography and identified as the 17-spirocyclobutanone (10a), similar in spectroscopic properties to the isomer (9a). Compound (10a), however, has a negative c.d. curve, whereas the isomer (9a) has a positive c.d. curve. The other two products, obtained in small amounts as a mixture by chromatography, were isolated by fractional crystallisation and shown to be the two Wagner-Meerwein rearrangement products (12a) and (13a) by spectroscopy.

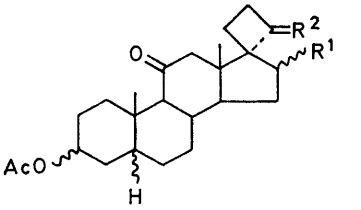
The inseparable mixture of epoxides (4b) and (5b) was contaminated with small amounts of the cyclobutanones (9a) and (10a), arising from spontaneous rearrangement of the epoxides (4a) and (5a). Treatment of this mixture with boron trifluoride–ether gave, besides (9a) and (10a) already present, the cyclobutanone (9b), a small amount of the cyclobutanone (10b), which was not separable from the mixture of (9a) and (10a), and a substantial amount of the two Wagner-Meerwein rearrangement products (12b) and (13b).

The cyclobutanones (9a), (10a), and (9b) each show three carbonyl absorptions at 1 780, 1 730, and 1 710 cm^{-1} for the four-membered ring ketone, the acetoxy-group, and the 11-oxo-group, respectively, and the n.m.r. spectra were consistent with these structures. The cyclobutanone (10b) was not isolated in pure form (see Experimental section) but its presence in the mixture of cyclobutanone isomers (9a), (10b), and (10a) obtained from the rearrangement of the mixture of



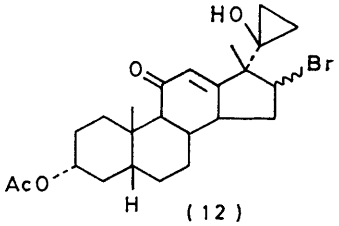
(9)

a; R^1 = 16α-Br, R^2 = O
b; R^1 = 16β-Br, R^2 = O
c; R^1 = H, R^2 = O
d; R^1 = H, R^2 = H,OH



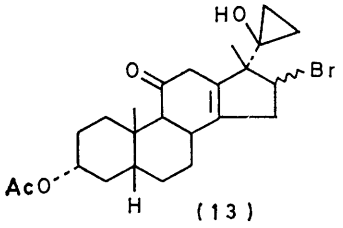
(10) 3α-OAc, 5β-H
a; R^1 = 16α-Br, R^2 = O
b; R^1 = 16β-Br, R^2 = O
c; R^1 = H, R^2 = O
d; R^1 = H, R^2 = H,OH

(11) 3β-OAc, 5α-H
a; R^1 = 16α-Br, R^2 = O



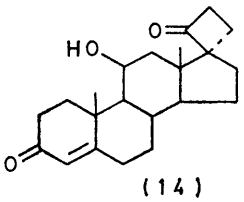
(12)

a; 16α-Br
b; 16β-Br

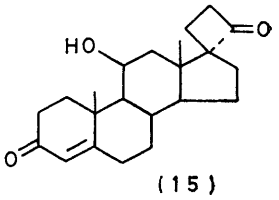


(13)

a; 16α-Br
b; 16β-Br



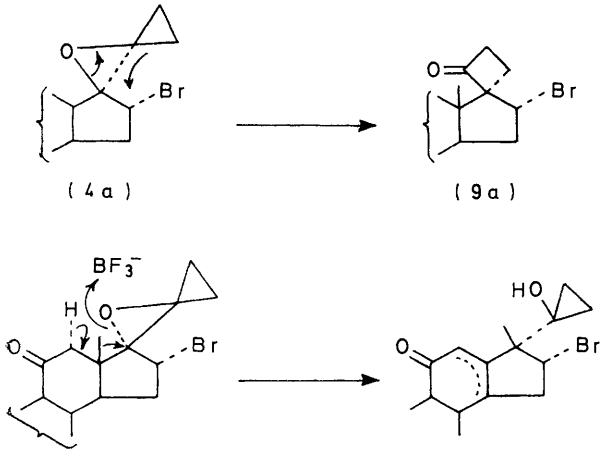
(14)



(15)

spiro-oxirans (4b) and (5b) (see above) was inferred from the n.m.r. spectrum.

The configurations of the cyclobutanones (9a) and (10a) follow directly from the structures of the epoxides (4a) and (5a). Since both these epoxides rearrange to form only one cyclobutanone isomer, the rearrangement is stereospecific and must therefore occur in a concerted manner and not *via* a C-17 cation. Back-side displacement of the 17β-oxygen function by the migrating cyclopropyl bond (Scheme 2) gives the cyclobutanone. For



SCHEME 2

the epoxide (5a) two pathways are possible, displacement of the 17α-oxygen either by the migrating cyclopropyl bond giving the cyclobutanone (10a) or, to a minor extent, by the migrating 10-methyl group to give the two Wagner-Meerwein rearrangement products (12a) and (13a). Similarly the cyclobutanone (9b) is probably formed exclusively from the epoxide (4b), and rearrangement of the epoxide (5b) gives a mixture of the Wagner–Meerwein rearrangement products (12b) and (13b) and the cyclobutanone (10b). In this last instance formation of the cyclobutanone (10b) is less favoured than the formation of (12b) and (13b), which can be attributed to the steric influence of the 16β-bromo-substituent which hinders β-face migration of the cyclopropyl bond to C-17.

Debromination of the cyclobutanone derivatives (9a), (9b), and (10a) with Raney nickel gave, in addition to the corresponding compounds (9c) and (10c), small amounts of the 20-hydroxy-compounds, (9d) and (10d), which were readily reoxidised with chromic acid to the ketones (9c) and (10c).

The n.m.r. spectrum of (10d) showed a large deshielding of the 12α-proton as a consequence of the closeness of the 20β-hydroxy-group which gave rise to a broadened doublet at τ 6.41; the 12β-H signal appeared as a sharp doublet at τ 7.75, and this confirmed the assigned configuration of the cyclobutanone (10c).

The spirobutanone (9c) has a positive c.d. curve and its isomer (10c) a negative c.d. curve. Weichert [7] has recently shown that a compound having a 17-spirocyclobutanone system of stereochemistry similar to that of compound (10c) has a negative o.r.d. curve.

Oxidation with chromic acid of the alcohols obtained by hydrolysis of the spirobutanones (9c) and (10c) gave the corresponding 3-ketones, each of which on bromination gave a mixture of 2β- and 4β-monobromo-derivatives. The 4-bromo-derivative gave the 3,20-bis-semicarbazones of the corresponding Δ^4-3,11,20-triones, which on reduction with sodium borohydride and subsequent hydrolysis gave the 11β-hydroxy-Δ^4-3,20-ketones (14) and (15).

EXPERIMENTAL

N.m.r. spectra were determined at 60 MHz for solutions in $CDCl_3$ with Me_4Si as internal standard. I.r. spectra were recorded for solutions in CH_2Cl_2 and u.v. spectra for ethanolic solutions.

Preparation of an Ethereal Solution of Ethyl N-*Cyclopropyl*-N-*nitrosocarbamate.*—A solution of dinitrogen tetraoxide (20 g) in cold ether (100 ml) was cooled to −40 °C and anhydrous sodium acetate (15 g) was added. The suspension was stirred and allowed to warm to −10 °C, and ethyl *N*-cyclopropylcarbamate (6 g) was slowly added; stirring was continued for a further 0.5 h at −10 °C. The solution was then poured on to ice–water and the ethereal layer was washed with cold aqueous sodium hydrogen carbonate till free of acid, and used immediately.

Addition of Diazocyclopropane to 3α-*Acetoxy*-16α-*bromo*-5β-*androstane*-11,17-*dione* (2a).—An ethereal solution of ethyl *N*-cyclopropyl-*N*-nitrosocarbamate [from ethyl *N*-cyclopropylcarbamate (6 g)] was added to a stirred solution of 3α-acetoxy-16α-bromo-5β-androstane-11,17-dione in ether–methanol; the solution was cooled to −5° and methanolic 2N-potassium hydroxide (25 ml) was added over 10 min with the temperature maintained below 0 °C. After a further 10 min at 0 °C the solution was poured into water and the ethereal layer separated, washed, and distilled to dryness. Reacetylation of the residual oil gave a product which was chromatographed on silica gel. Elution with benzene–ethyl acetate (95 : 5) gave four fractions. The first yielded (17S)-3α-*acetoxy*-16α-*bromo*-*dispiro*-[5β-*androstane*-17,2′-*oxiran*-3′,1″-*cyclopropane*]-11-*one* (4a) as an oil ($[\alpha]_D^{25}$ +3°) which failed to crystallise; the second fraction yielded a mixture of the epoxides (4a) and (5a) and the third fraction yielded the (17R)-*isomer* (5a) ($[\alpha]_D^{25}$ 69°) which failed to crystallise. The fourth fraction gave a non-crystalline mixture of the (17*S*)- and (17*R*)-16β-bromo-isomers (4b) and (5b), which n.m.r. indicated to be a 1 : 1 mixture contaminated with two minor impurities (see text). Elution with 9 : 1 benzene–ethyl acetate gave a yellow oil (250 mg) which appeared homogeneous (t.l.c.) but failed to crystallise and was not identified.

Reaction of Diazocyclopropane with 3α-*Acetoxy*-16β-*bromo*-5β-*androstane*-11,17-*dione* (2b).—This was carried out as described for the 16α-bromo-isomer. Similar work-up and chromatography gave the same products.

Reaction of Diazocyclopropane with 3β-*Acetoxy*-16α-*bromo*-5α-*androstane*-11,17-*dione* (3).—This was carried out as for the 5β-isomer. Elution from silica gel with 95 : 5 benzene–ethyl acetate gave (17S)-3β-*acetoxy*-16α-*bromodispiro*-[5α-*androstane*-17,2′-*oxiran*-3′,1″-*cyclopropane*]-11-*one* (6a) (100 mg), which crystallised from methanol; yield 50 mg; m.p. 156°; $[\alpha]_D^{25}$ −71° (Found: C, 61.8; H, 7.2.

[7] R. Weichert, *Angew. Chem.*, 1970, **82**, 219.

$C_{24}H_{33}BrO_4$ requires C, 61.9; H, 7.2%). Further elution gave the (17R)-*isomer* (7a) (400 mg), which crystallised from methanol; yield 250 mg; m.p. 178—180°; $[\alpha]_D^{25}$ −23° (Found: C, 62.0; H, 7.2%). Further elution gave the (17R)-16β-*bromo-isomer* (7b) (75 mg), which crystallised from methanol; yield 40 mg; m.p. 155—165° (decomp.) (Found: C, 61.7; H, 7.2%).

Treatment of the Spiro-oxiran (4a) *with Boron Trifluoride–Ether Complex*.—The spiro-oxiran (4a) (150 mg) was dissolved in benzene (10 ml) and boron trifluoride–ether (3 drops) was added. The solution was kept at room temperature for 5 min, then poured into aqueous sodium hydrogen carbonate. An ethereal extract gave an oil which on crystallisation from methanol afforded (17S)-3α-*acetoxy*-16α-*bromospiro*-[5β-*androstane*-17,1′-*cyclobutane*]-2′,11-*dione* (9a) (110 mg), m.p. 148—150°, $[\alpha]_D^{25}$ +68.3°, τ 8.85 and 9.14 (10- and 13-CH_3), c.d. (dioxan) $\Delta\varepsilon_{320}$ +2.62sh, $\Delta\varepsilon_{311}$ +3.88, $\Delta\varepsilon_{307}$ +3.76, $\Delta\varepsilon_{305}$ +3.80 (Found: C, 61.9; H, 7.0. $C_{24}H_{33}BrO_4$ requires C, 61.9; H, 7.15%).

Treatment of the Spiro-oxiran (5a) *with Boron Trifluoride–Ether*.—The spiro-oxiran (5a) (200 mg) was dissolved in dry benzene (10 ml) and boron trifluoride–ether (10 drops) was added. The solution was kept at room temperature for 5 min then poured into aqueous sodium hydrogen carbonate. An ethereal extract gave an oil which was chromatographed on silica gel. Elution with 95 : 5 benzene–ethyl acetate gave an oil which crystallised from methanol to yield (17R)-3α-*acetoxy*-16α-*bromospiro*-[5β-*androstane*-17,1′-*cyclobutane*]-2′,11-*dione* (10a) (150 mg), m.p. 184—186°, $[\alpha]_D^{25}$ −4°; c.d. (dioxan) $\Delta\varepsilon_{324}$ −0.70, $\Delta\varepsilon_{315}$ −0.03, $\Delta\varepsilon_{310}$ −0.20, $\Delta\varepsilon_{301}$ +0.44, $\Delta\varepsilon_{292}$ +0.64, τ 8.85 and 9.32 (10- and 13-CH_3) (Found: C, 62.1; H, 7.2%). Elution with 4 : 1 benzene–ethyl acetate gave a fraction which crystallised from methanol to give 3α-*acetoxy*-16α-*bromo*-17α-(1-*hydroxycyclopropyl*)-17β-*methyl*-18-*nor*-5β-*androst*-13-*en*-11-*one* (13a) (20 mg). Recrystallisation gave crystals with m.p. 188—190°, $[\alpha]_D^{25}$ +7.2, $\lambda_{max.}$ (EtOH) 280 nm, $\nu_{max.}$ (KCl) 1 700 (11-oxo), 1 730 (OAc), and 3 552 cm^{-1} (dil. soln.; OH), τ 8.76 (10-CH_3), 9.22 (s, 17-CH_3), 9.25 (m, cyclopropyl protons), and 5.7 (t, 16-H), *m/e* 404 and 406 ($M^+ - CH_3CO_2H$), 385 ($M^+ - Br$), and 347 and 349 ($M^+ - CH_3CO_2H - EtCO$) (Found: C, 62.2; H, 7.1%; M^+, 466.1539 and 464.1565. $C_{24}H_{33}BrO_4$ requires C, 61.9; H, 7.1%; *M*, 466.1543 and 464.1563).

The mother liquors gave a second crop which was crystallised twice from methanol giving 3α-*acetoxy*-16α-*bromo*-17α-(1′-*hydroxycyclopropyl*)-17β-*methyl*-18-*nor*-5β-*androst*-12-*en*-11-*one* (12a) (10 mg), m.p. 152—155°, $[\alpha]_D$ −23.2°, $\lambda_{max.}$ (EtOH) 240 nm (ε 10 000), $\nu_{max.}$ (KCl) 1 669 (11-oxo), 1 730 (OAc), and 3 552 cm^{-1} (dil. soln.; OH), τ 8.75 (s, 10-CH_3), 8.85 (s, 17-CH_3), 9.2 (m, cyclopropyl protons), 4.31 (d, 12-H), and 5.5 (t, 16-H) (Found: C, 61.7; H, 7.0%).

Treatment of the Mixture of Spiro-oxirans (4b) *and* (5b) *with Boron Trifluoride–Ether*.—The mixture (2 g) contaminated with compounds (9a) and (10a) (see text) was dissolved in dry benzene (50 ml) and boron trifluoride–ether (10 drops) was added. The solution was kept at room temperature for 5 min, then washed with aqueous sodium hydrogen carbonate and chromatographed on silica gel. Elution with 95 : 5 benzene–ethyl acetate gave a fraction which n.m.r. showed to be a mixture of the three spirocyclobutanes (9a), (10a), and (10b): τ 9 14, 9.32, and 8.89 (all singlets, 13-CH_3) respectively; these had identical t.l.c. retention times and could not be further purified. Elution with 9 : 1 benzene–ethyl acetate gave crystals (500 mg) which on recrystallisation from methanol afforded pure (17R)-3α-*acetoxy*-16β-*bromospiro*-[5β-*androstane*-17,1′-*cyclobutane*]-2′,11-*dione* (9b), m.p. 235—237°, $[\alpha]_D$ +199°, τ 8.82 and 8.83 (10- and 13-CH_3) (Found: C, 61.8; H, 7.25; Br, 17.2. $C_{24}H_{33}BrO_4$ requires C, 61.9; H, 7.2; Br, 17.2%). Further elution gave a fraction which crystallised from methanol to give 3α-*acetoxy*-16β-*bromo*-17α-(1-*hydroxycyclopropyl*)-17β-*methyl*-18-*nor*-5β-*androst*-13-*en*-11-*one* (13b) (250 mg), m.p. 196—199° (recryst.), $[\alpha]_D^{25}$ +34.2°, $\lambda_{max.}$ (EtOH) 280 nm, $\nu_{max.}$ (KCl) 1 700 (11-oxo), 1 730 (OAc), and 3 605 cm^{-1} (dil. soln.; OH), τ 8.75 (s, 10-CH_3), 9.18 (s, 17-CH_3), 9.15 (m, cyclopropyl protons), and 5.15 (t, 16-H) (Found: C, 61.75; H, 6.7%). The mother liquors gave a further crop which on recrystallisation gave 3α-*acetoxy*-16β-*bromo*-17α-(1-*hydroxycyclopropyl*)-17β-*methyl*-18-*nor*-5β-*androst*-12-*en*-11-*one* (12b) *hemimethanolate* (100 mg) m.p. 146—156°, $[\alpha]_D^{25}$ +14°, $\lambda_{max.}$ (EtOH) 238 nm (ε 10 000), $\nu_{max.}$ (KCl) 1 664 (11-oxo), 1 730 (OAc), 3 578 cm^{-1} (dil. soln.; OH), τ 8.84 (s, 10-CH_3), 9.01 (s, 17-CH_3), 9.2 (m, cyclopropyl protons), 4.1 (d, 12-H), and 5.2 (t, 16-H) (Found: C, 61.1; H, 7.3. $C_{24}H_{33}BrO_4$,0.5CH_3OH requires C, 61.1; H, 7.3%).

Debromination of the Spirocyclobutane (9a).—The 16α-bromo-compound (9a) (100 mg) was dissolved in ethanol, Raney nickel (a few mg) was added, and the suspension was stirred at room temperature for 1 h, filtered, and evaporated to dryness. The crystalline residue (85 mg) crystallised from methanol to give (17R)-3α-*acetoxyspiro*-[5β-*androstane*-17,1′-*cyclobutane*]-2′,11-*dione* (9c) (40 mg), m.p. 141—143°, $[\alpha]_D^{25}$ +114°, c.d. $\Delta\varepsilon_{309}$ +2.44 (Found: C, 74.25; H, 8.8. $C_{24}H_{34}O_4$ requires C, 74.57; H, 8.9%). The mother liquors were evaporated and the residual oil was chromatographed on silica gel. Elution with 9 : 1 benzene–ethyl acetate gave first more cyclobutanone (9c), then a fraction which was crystallised from methanol to give (17R)-3α-*acetoxy*-2′-*hydroxyspiro*-[5β-*androstane*-17,1′-*cyclobutane*]-11-*one* (9d) (10 mg), m.p. 201—203°, $[\alpha]_D^{25}$ +21.4°, $\nu_{max.}$ (CH_2Cl_2) 1 730 (OAc), 1 704 (C=O), and 3 610 cm^{-1} (OH), τ 9.17 (13-CH_3), 8.82 (10-CH_3), 5.74 (1 H, m, 2′-H), and 7.45br (2 H, s, CO·CH_2) (Found: C, 74.2; H, 9.2. $C_{24}H_{36}O_4$ requires C, 74.2; H, 9.3%). The 2′-hydroxy-compound (9d) was oxidised in acetone solution with chromic acid. The product was identical with the cyclobutanone derivative (9c).

Debromination of the Spirocyclobutane (10a).—The 16α-bromo-compound (10a) (1.2 g) was dissolved in ethanol, Raney nickel (500 mg) was added, and the suspension was stirred at room temperature for 15 min. Filtration and evaporation gave a solid which crystallised from methanol to yield (17S)-3α-*acetoxyspiro*-[5β-*androstane*-17,1′-*cyclobutane*]-2′,11-*dione* (10c) (750 mg), m.p. 132—135°, $[\alpha]_D^{25}$ −0.9, c.d. $\Delta\varepsilon_{317}$ −0.44, $\Delta\varepsilon_{314}$ −0.41, $\Delta\varepsilon_{308}$ −0.54, $\Delta\varepsilon_{300}$ −0.42sh (Found: C, 74.3; H, 8.9%). The mother liquors were evaporated and the residue was chromatographed on silica gel. Elution with 9 : 1 benzene–ethyl acetate gave more cyclobutanone (10c). Further elution gave a fraction which crystallised from methanol to give (17S)-3α-*acetoxy*-2′-*hydroxyspiro*-[5β-*androstane*-17,1′-*cyclobutane*]-11-*one* (10d) (100 mg), m.p. 207—210°, $[\alpha]_D^{25}$ +33.2°, $\nu_{max.}$ (CH_2Cl_2) 1 724 (OAc), 1 701 (C=O), and 3 610 cm^{-1} (OH), τ 9.40 (13-CH_3), 8.82 (10-CH_3) (Found: C, 74.3; H, 9.2%). Oxidation of this 2′-hydroxy-compound with chromic acid in acetone gave the cyclobutanone (10c).

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trione.—The spirocyclobutane (9c) (1.1 g) in methanol was hydrolysed with alcoholic potassium hydroxide and the product was oxidised with chromic acid giving the *trione* (720 mg), m.p. 197—201°, $[\alpha]_D^{25}$ +110° (Found: C, 77.25; H, 8.7. $C_{22}H_{30}O_3$ requires C, 77.15; H, 8.8%).

Bromination of (17S)-*Spiro*-[5β-*androstane*-17,1′-*cyclobutane*]-2′,3,11-*trione*. The trione (700 mg) in chloroform (14 ml) and anhydrous acetic acid (1.5 ml) was cooled to −40 °C and treated with 4N-hydrogen bromide in acetic acid (0.3 ml) and a solution (150 g l^{-1}) of bromine in chloroform (2.2 ml). The solution was slowly warmed to room temperature and reaction occurred rapidly at −5 °C. The solution was washed and then evaporated to dryness giving an oil (800 mg) which was chromatographed on silica gel. Elution with 4 : 1 benzene–ethyl acetate gave crystals which were recrystallised from methanol–methylene chloride to yield (17S)-2β-*bromospiro*-[5β-*androstane*-17,1′-*cyclobutane*]-2′,3,11-*trione* (60 mg), m.p. 217—222° (decomp.), $[\alpha]_D^{25}$ +53° ($CHCl_3$) (Found: C, 62.4; H, 6.9. $C_{22}H_{29}BrO_3$ requires C, 62.6; H, 6.9%). Further elution gave crystals, recrystallised from methanol–methylene chloride to yield (17S)-4β-*bromospiro*-[5β-*androstane*-17,1′-*cyclobutane*]-2′,3,11-*trione* (320 mg), m.p. 212—215° (decomp.), $[\alpha]_D^{25}$ +98° ($CHCl_3$) (Found: C, 62.5; H, 7.0%).

(17S)-11β-*Hydroxyspiro*[*androst*-4-*ene*-17,1′-*cyclobutane*]-2′,3-*dione* (14).—The foregoing 4β-bromo-trione (330 mg) was added to a suspension of semicarbazide (1 g) in chloroform (2 ml) and t-butyl alcohol (2 ml) and the mixture was stirred at room temperature for 2 h. The chloroform was evaporated off and methanol (6 ml) and an aqueous solution of semicarbazide hydrochloride (300 mg) and sodium acetate (200 mg) were added. The solution was refluxed for 2 h and cooled, water was added, and the solid formed was collected, dried, and dissolved in tetrahydrofuran (200 ml) containing 5% water. Sodium borohydride (500 mg) was slowly added to the stirred solution (over 8 h) and stirring was continued overnight. Evaporation gave a solid, which was taken up in acetone; concentrated hydrochloric acid (0.5 ml) was added and the suspension was refluxed for 15 min. The solution was poured into water, and an ethereal extract gave an oil which was chromatographed on silica gel. Elution with 3 : 1 benzene–ethyl acetate gave crystals which were recrystallised from acetone to afford the *dione* (14) (190 mg), m.p. 223—227°, $[\alpha]_D$ +186° ($CHCl_3$), $\lambda_{max.}$ (EtOH) 241 nm (ε 14 400) (Found: C, 77.0; H, 8.9. $C_{22}H_{30}O_3$ requires C, 77.15; H, 8.8%).

(17R)-*Spiro*-[5β-*androstane*-17,1′-*cyclobutane*]-2′,3,11-*trione*.— (17*R*)-3α-Acetoxyspiro-[5β-androstane-17,1′-cyclobutane]-2′,11-dione (10c) (2.1 g) in methanol was hydrolysed with alcoholic potassium hydroxide, and the product oxidised with chromic acid giving the *trione* (1.84 g), m.p. 172—175°, $[\alpha]_D$ −21.4° (Found: C, 77.0; H, 8.9. $C_{22}H_{30}O_3$ requires C, 77.15; H, 8.8%).

Bromination of (17R)-*Spiro*-[5β-*androstane*-17,1′-*cyclobutane*]-2′,3,11-*trione*.—The trione (1.34 g) was brominated as described for the (17*S*)-isomer. The product was chromatographed on silica gel. Elution with 4 : 1 benzene–ethyl acetate gave crystals, which crystallised from methanol–methylene chloride to give (17R)-2β-*bromospiro*-[5β-*androstane*-17,1′-*cyclobutane*]-2′,3,11-*trione* (150 mg), m.p. 220—222° (decomp.), $[\alpha]_D^{25}$ −75° ($CHCl_3$) (Found: C, 62.6; H, 7.0. $C_{22}H_{29}BrO_3$ requires C, 62.6; H, 6.9%). Further elution gave crystals which were recrystallised from methanol–methylene chloride to afford (17R)-4β-*bromospiro*-[5β-*androstane*-17,1′-*cyclobutane*]-2′,3,11-*trione* (1.15 g), m.p. 188—190° (decomp.), $[\alpha]_D^{25}$ +27.1° (Found: C, 62.5; H, 7.0%).

(17R)-11β-*Hydroxyspiro*[*androst*-4-*ene*-17,1′-*cyclobutane*]-2′,11-*dione* (15).—(17*R*)-4β-Bromospiro-[5β-androstane-17,1′-cyclobutane]-2′,3,11-trione (1 g) was treated as described for the (17*S*)-4β-bromo-isomer. The product obtained after chromatography was crystallised from acetone giving the *dione* (15) (500 mg), m.p. 166—168°, $[\alpha]_D^{25}$ +38.6° ($CHCl_3$), $\lambda_{max.}$ (EtOH) 241 nm (ε 13 200) (Found: C, 77.1; H, 9.0. $C_{22}H_{30}O_3$ requires C, 77.15; H, 8.8%).

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