Reactions of Steroidal Ketones with Diazocyclopropane

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Diazocyclopropane reacts with pregn-4-ene-3,20-dione (7) to give a ring expansion product, spiro[cyclopropane-1,4'-A-homopregn-4a'-ene]-3',20'-dione, and further reaction of this compound occurs with an excess of diazocyclopropane to give several cyclobutanone derivatives. Diazocyclopropane reacts with cholestan-3-one to give mainly cyclobutane derivatives, and with two pregnan-20-ones to give only cyclobutanone products. 20-Oxo-groups with electronegative substituents at C-17 react with diazocyclopropane to give only 20-spirocyclopropane derivatives.

We have reported [1] that reaction of diazocyclopropane with pregna-4,16-diene-3,20-dione (1) and 3β-acetoxypregna-5,16-dien-20-one (2) gives 4'β,5'-dihydro-[17α,16-*c*]pyrazoles ([17α,16α-*c*]pyrazolines) (3) and (4). Other products formed in these reactions have now been isolated and these and the products formed on treating diazocyclopropane with a variety of steroidal ketones are now described.

Three by-products in the reaction of (1) with diazocyclopropane were isolated by chromatography and assigned structures (5), (6a), and (6b), mainly on the basis of spectroscopic evidence. All three compounds show i.r. absorptions at 1700 and 1530 cm^{-1} for the 20-oxo and $-N{=}N-$ groups and the 21-methyl groups appear in the n.m.r. spectra as singlets at δ 2·25 typical for [17α,16α-*c*]pyrazoline compounds.[1] Compound (5) (M^+ $C_{27}H_{36}N_2O_2$) shows an additional i.r. absorption at 1690 cm^{-1} and no u.v. absorption at 240 nm. Compounds (6a) and (6b) (M^+ $C_{30}H_{40}N_2O_2$) were isolated as a 1 : 1 mixture (g.l.c.) and were not separated; they are apparently formed by attack of two molecules of diazocyclopropane on the initially formed pyrazolino-compound (3), in the sequence (3) ⟶ (5) ⟶ (6). The i.r. spectrum of the mixture shows an absorption at 1770 cm^{-1} corresponding to the four-membered ring ketone and there is no strong u.v. absorption. The n.m.r. spectrum of the mixture shows only three methyl singlets but since the signal for the olefinic 4a-H appears as two merged, broad singlets, the compounds are probably isomeric at C(3).

In order to clarify the reaction between diazocyclopropane and a Δ^4-3-oxo-steroid, the reaction between diazocyclopropane and pregn-4-ene-3,20 dione (7) was investigated. This reaction, however, was unexpectedly complicated by reaction of the diazo-compound with the 20-oxo-group, and rapidly gave a complex mixture from which five compounds were isolated by chromatography and assigned structures (8)—(11a and b), on the basis of

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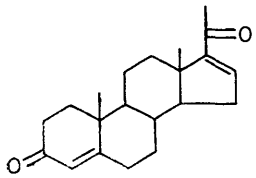
[1] P. Bladon, D. R. Rae, and A. D. Tait, *J.C.S. Perkin I*, 1974, 1468.

spectroscopic evidence. Other more minor components of the mixture were not isolated. The major compound isolated (8) (M^+ $C_{24}H_{34}O_2$) shows i.r. carbonyl absorptions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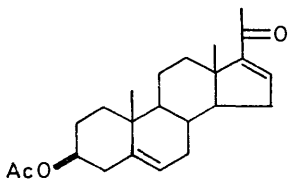
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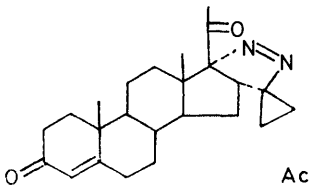
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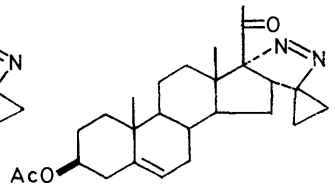
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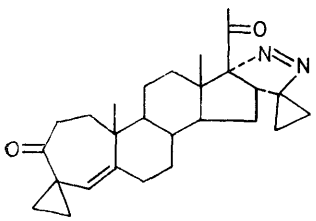
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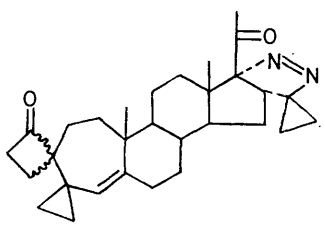
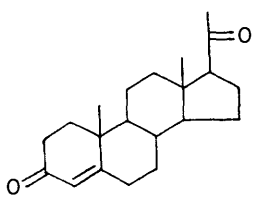

(6a and b)

at 1690 and 1710 cm^{-1} for the 3- and 20-oxo-groups respectively, and no u.v. absorption at 240 nm. The n.m.r. spectrum shows three singlets for the 18-, 19-, and 21-methyl groups and a broadened singlet for the olefinic 4a-H.

giving the A-homo-steroids (5) and (8). Since further reaction of the A-homo-compound (8) with diazocyclopropane gave the same mixture of products (g.l.c.) as was obtained from the reaction of diazocyclopropane with pregn-4-ene-3,20-dione (7) the four compounds (9)—(11a and b) must have formed as a result of attack of diazocyclopropane on the initially formed A-homo-compound (8), albeit to a much lesser extent. Compound (9) (M^+ $C_{27}H_{38}O_2$) shows i.r. carbonyl absorptions at 1710 and 1772 cm^{-1} for the 20-oxo-group and the four-membered ring ketone and compound (10) (M^+ $C_{27}H_{38}O_2$) i.r. carbonyl absorptions at 1690 and 1775 cm^{-1} for the seven- and four-membered ring ketones. The n.m.r. spectra of these two compounds (9) and (10) are consistent with their structures, showing three sharp singlets for the 18-, 19-, and 21-methyl groups and a broadened singlet for 4a-H; the compounds are homogeneous by g.l.c. and t.l.c. analysis and seem therefore to be single isomers at C-3 and C-20 respectively. Compounds (11a and b) (M^+ $C_{30}H_{42}O_2$) were not separable on a preparative scale but gave two peaks on g.l.c. The n.m.r. spectrum of this mixture shows three singlets for the 18-, 19-, and 21-methyl groups, but the olefinic 4a-H signal appears as two broadened singlets, so again these compounds are probably C(3) isomers.

In order to study the reaction of diazocyclopropane with one functional group only, the reaction of diazocyclopropane with cholest-4-en-3-one and with several 20-ketones was investigated. Reaction of diazocyclopropane with cholest-4-en-3-one, however, gave no further information as the reaction was not nearly so rapid as with (7) and even with a large excess of reagent only a 60% conversion (g.l.c.) into the A-homo-compound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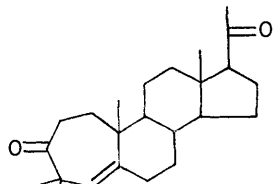
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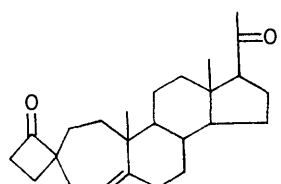
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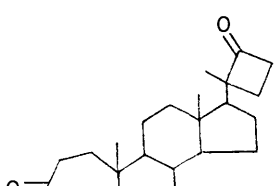
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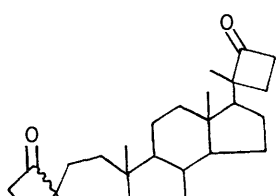
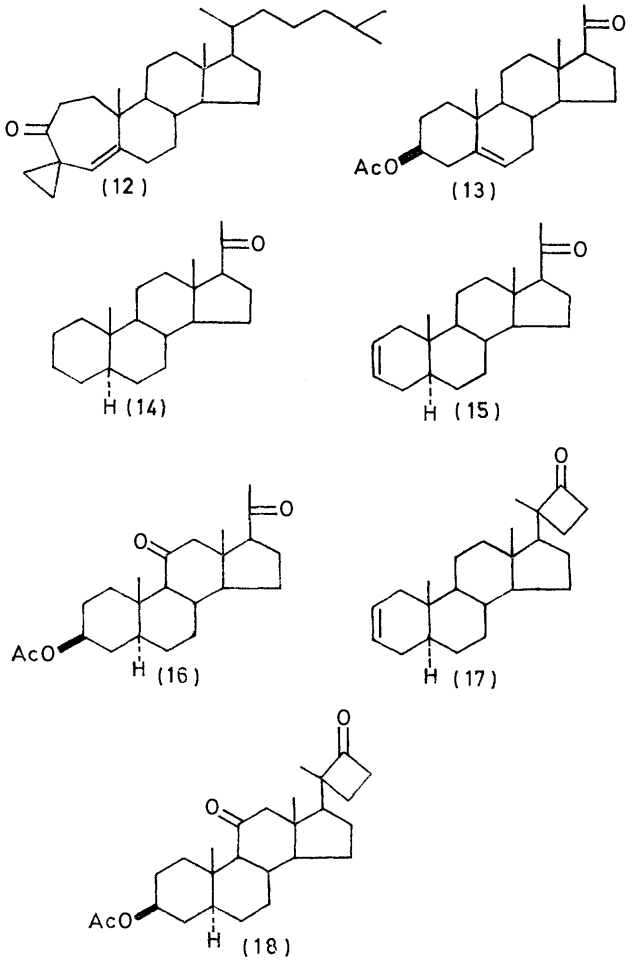

(11a and b)

Diazomethane has been reported not to react with Δ^4-3-oxo-steroids, although the Lewis acid catalysed reactions of diazoalkanes with Δ^4-3-ketones are known to give A-homo-steroids.[2] The reactions of diazocyclopropane with the 3-oxo-group of (3) and (7) can therefore be considered as uncatalysed, ring expansion reactions (12) occurred. Small amounts of cyclobutanone products were formed but owing to lack of material they were not isolated in a pure state.

[2] W. S. Johnson, N. Neeman, S. P. Birkeland, and N. A. Fedoruk, *J. Amer. Chem. Soc.*, 1962, **84**, 989; E. Muller, B. Zeeh, and R. Heischkeil, *Annalen*, 1964, **677**, 47.

Treatment of diazocyclopropane with 3β-acetoxypregn-5-en-20-one (13) and 5α-pregnan-20-one (14) resulted in no detectable reaction. Reaction with 5α-pregn-2-en-20-one (15) and 3β-acetoxy-5α-pregnane-11,20-dione (16), however, under similar conditions gave



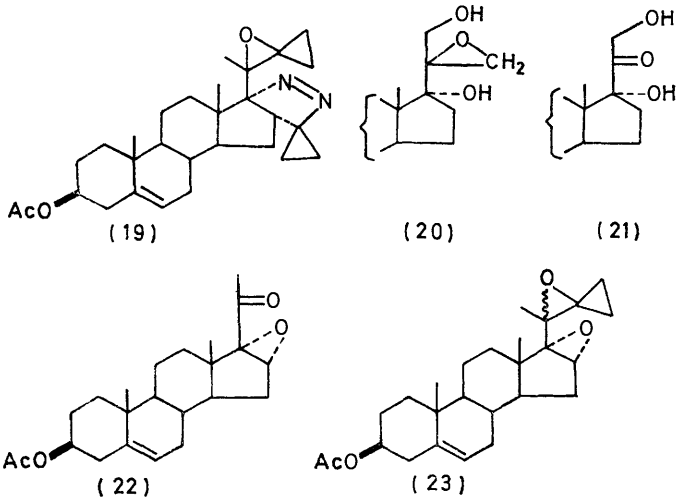
the two cyclobutanone products (17) and (18) in 20 and 60% yield respectively, the remaining unchanged starting material being recovered in both cases. Compound (17) (M^+ $C_{24}H_{36}O$) shows an i.r. carbonyl absorption at 1775 cm^{-1} for the cyclobutanone group and compound (18) (M^+ $C_{26}H_{38}O_4$) i.r. carbonyl absorptions at 1780, 1730, and 1700 cm^{-1} for the cyclobutanone, 3β-acetate, and 11-oxo-groups respectively. The n.m.r. spectra of both compounds (17) and (18) are consistent with their structures, the 21-methyl groups appearing as singlets at δ 1·23 and 1·25 respectively.

In the reactions in which only one of the two possible cyclobutanone derivatives has been isolated; *i.e.* compounds (9), (10), (11a and b) [for C(20)], (17), and (18), no conclusions could be made as to the stereochemistry at C-3 or C-20 in these compounds.

It would appear from the above reactions of diazocyclopropane that its reactivity is highly susceptible to the environment of the carbonyl group; small differences at remote parts of the molecule effect reaction rates considerably. This differing reactivity must be attributed to long range conformational transmission effects.[3]

Reaction of diazocyclopropane with 3β-acetoxypregn-5,16-dien-20-one (2) gave besides the [16α,17α-*c*]pyrazoline (4) another compound which was assigned the structure (19) on the basis of its spectroscopic properties. This compound (M^+ $C_{29}H_{40}N_2O_3$) shows only one carbonyl absorption at 1730 cm^{-1} for the 3β-acetate group and a weak absorption at 1522 cm^{-1} for the –N=N– group. The n.m.r. spectrum shows three methyl singlets at δ 1·03, 1·20, and 1·95 for the 18-, 19-, and 21-methyl groups respectively and a one-proton olefinic multiplet for 6-H. The formation of this product is not too surprising as ketones with electronegative α-substituents are much more reactive towards nucleophilic attack than the unsubstituted analogues and in general react with diazomethane to form the epoxide product.[4] A similar type of product has been reported by Naussbaum and Carlon [5] who isolated epoxides of type (20) from the reactions of diazomethane with 17α,21-dihydroxy-20-ketones (21).

3β-Acetoxy-16α,17α-epoxypregn-5-en-20-one (22) also reacts rapidly with diazocyclopropane to give a mixture of the two C(20) epimeric diepoxides (23) which were readily separated by chromatography. Both compounds have very similar spectroscopic properties; the i.r. spectra both show only acetate absorption in the carbonyl region and the n.m.r. spectra singlets at δ 1·02, 1·02, 1·63, and 3·5 (major isomer) and δ 0·80, 1·02, 1·56, and 3·45 (minor isomer) for the 18-, 19-, and 21-methyl groups and 16β-H respectively. The relative configuration of these two compounds was not determined. In a preliminary experiment the major epoxide was treated with boron trifluoride–ether complex, and



the i.r. spectrum of the crude product shows a carbonyl absorption at 1770 cm^{-1} indicating the formation of a cyclobutanone ring. The product was not isolated in a

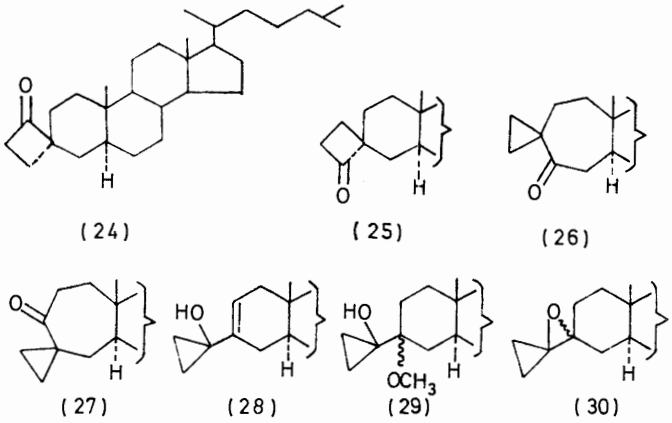
[3] D. H. R. Barton, A. J. Head, and P. J. May, *J. Chem. Soc.*, 1957, 935; C. Altona, H. J. Geise, and C. Romers, *Tetrahedron*, 1968, **24**, 13; M. E. Herr and F. W. Heyl, *J. Amer. Chem. Soc.*, 1953, **75**, 5927.

[4] C. D. Gutsche, *Org. Reactions*, 1954, **8**, 364.

[5] A. L. Naussbaum and F. E. Carlon, *J. Amer. Chem. Soc.*, 1957, **79**, 3831.

pure state. Further work concerning the rearrangement of such oxiranspirocyclopropanes will be the subject of a later paper.

The reaction of diazocyclopropane with 5α-cholestan-3-one gave several products which were separated by



(24) (25) (26)

(27) (28) (29) (30)

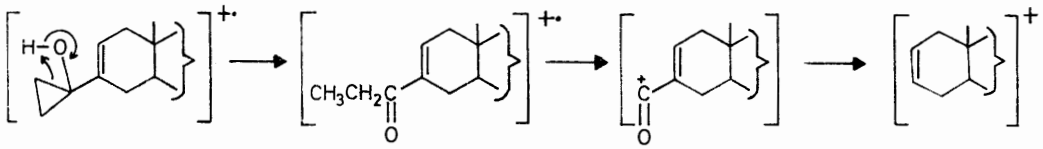
chromatography and assigned structures (24), (25), [(26) or (27)], (28), (29), and (30).

The major portion (40%) of the reaction product consisted of the two cyclobutanone isomers (24) (M^+ $C_{30}H_{50}O$), $\nu_{max.}$ 1762 cm^{-1}, and (25) (M^+ $C_{30}H_{50}O$), $\nu_{max.}$ 1770 cm^{-1}, which were isolated in an approximate ratio of 4 : 1 respectively. Compound (26) (24%) shows an i.r. carbonyl absorption at 1690 cm^{-1} typical of a seven-membered ring ketone. The alternative structure (27) cannot be discounted for this compound, although (26) is preferred on the basis of the preferential migration of the C(2)–C(3) bond in the ring expansion of cholestanone with diazomethane.[6] Compound (28) (M^+ $C_{30}H_{50}O$) (10%) has a hydroxy-absorption but no carbonyl absorption in the i.r. spectrum, and the n.m.r. spectrum shows a one proton multiplet for an olefinic proton. The mass spectral fragmentation is consistent with this structure, showing sequential loss of an ethyl radical and then carbon monoxide as outlined in Scheme 1. Metastable peaks support this fragmentation.

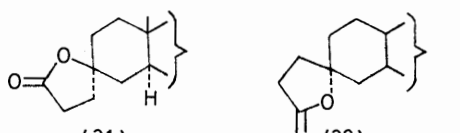
The oxiranspirocyclopropane (30) was not isolated, but a non-polar fraction eluted from the column probably having this structure gave a more polar compound on crystallisation from methanol which was assigned the structure (29). This compound (5% yield) shows a hydroxy-absorption and no carbonyl absorption in the i.r. spectrum, and the n.m.r. spectrum shows a signal for a methoxy-group, and no olefinic proton. The mass spectrum shows no molecular ion corresponding to this structure, but the cracking pattern is identical with that of a mixture of the two cyclobutanone derivatives (24) and (25), and it was found that distillation of the methoxy-derivative at reduced pressure gave, after crystallisation, a mixture of these two cyclobutanone compounds. It is probable that in this latter experiment and in the inlet system of the mass spectrometer the methoxy-compound (29) first reverts to the epoxide (30) by pyrolytic loss of methanol, and this then rearranges further to the two cyclobutanones.*

Baeyer–Villiger oxidation of the two cyclobutanones (24) and (25) gave the spiro-lactones (31) and (32) respectively which were reduced with lithium aluminium hydride to the two diols (33) and (34).

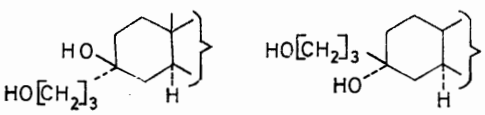
Axial hydroxy-groups are prone to lose water during mass spectral fragmentation to a far greater extent than equatorial hydroxy-groups.[7] The predominant fragmentation by loss of water seen in the mass spectrum of the diol (34) compared to the small loss of water in the spectrum of (33) is therefore a strong indication of the stereochemistry of these two isomers. In addition, compound (33) shows a large peak corresponding to the loss of C_3H_7O whereas its isomer (34) shows only a small peak corresponding to this loss and is in keeping with the greater ease of loss of an axial substituent during fragmentation.



Scheme 1



(31) (32)



(33) (34)

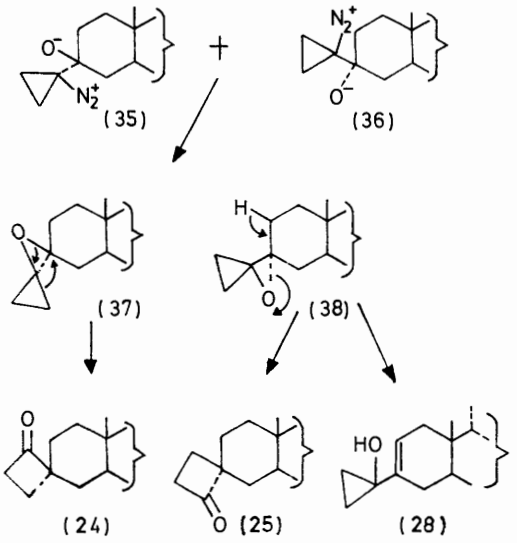
If we assume normal nucleophilic attack,[4] the addition of diazocyclopropane to cholestanone should give the two intermediates (35) and (36) (Scheme 2) which could either ring-close to the epoxides (37) and (38) or rearrange to the A-homo-steroid (26). Rearrangement of these two epoxides (37) and (38) would give the cyclobutanones (24) and (25) respectively. Thus the epoxide formed as a result of rear-side attack at the carbonyl group rearranges to give the major cyclobutane (24), this being the more likely on steric grounds.

* Neither of the two cyclobutanones forms a hemiacetal on refluxing in methanol.

[6] N. A. Nelson and R. N. Schut, *J. Amer. Chem. Soc.*, 1959, **81**, 6486.

[7] H. Budzikiewicz, C. Djerassi, and D H. Williams, 'Mass Spectrometry of Organic Compounds,' Holden-Day, San Francisco, 1967.

The cyclopropyl alcohol (28) is probably formed by the rearrangement of the epoxide (38) in which *trans*-diaxial elimination of the 2β-H and 3α-oxygen atom would be favoured over the *cis*- or *trans*-diequatorial elimination that would have to occur for the formation of (28) from



SCHEME 2

the isomeric epoxide (37). The A-homo-steroid (26) could also be a rearrangement product of one or both the epoxides or it could be formed from the initial intermediates (35) or (36).

EXPERIMENTAL

For general experimental procedures, see ref. 1.

General Procedure for the Reaction of Diazocyclopropane with Steroidal Ketones in situ.—To a solution containing ethyl *N*-cyclopropyl-*N*-nitrosocarbamate [1] [prepared from ethyl *N*-cyclopropylcarbamate (0·1 mol)] and the steroidal ketone (*ca.* 0·01 mol) in ether–methanol at −10° was added a methanolic solution of potassium hydroxide (25 ml; 20%) over 0·5 h keeping the temperature of the solution between 0 and −10°. The solution was left at 0° for 2 h, poured into water, and the ether layer washed and evaporated to give an oil which was dissolved in benzene and chromatographed on neutral alumina. In the reactions of compounds (2), (16), and (22) the oil formed on evaporation of the ether solution was first reacetylated with acetic anhydride in pyridine at room temperature before further purification. Compounds (3), (18), and (19) were isolated by direct crystallisation from the crude reaction product without resorting to chromatography.

Reaction of Diazocyclopropane with Pregna-1,16-diene-3,20-dione (1) (5 g).—Chromatography of the products from the above procedure was as follows. Elution with 3 : 1 benzene–light petroleum gave 4″β,5″-*dihydrotrispiro*{*cyclobutane*-1,3′-(A-*homopregn*-4a′-*eno*[17′α,16′-c]*pyrazole*)-4′,1‴:5″,1⁗-*dicyclopropane*}-2,20′-*dione* (6a and b) (200 mg) as a 1 : 1 mixture of epimers (g.l.c.), m.p. 230—235° (decomp.) (from ethyl acetate), $[\alpha]_D^{15}$ +3·54° ($CHCl_3$) (Found: C, 75·25; H, 8·5%; M^+, 460·3061. $C_{30}H_{40}N_2O_2$ requires C, 75·75; H, 8·3%; M^+, 460·3089). Elution with benzene gave 4″β,5″-*dihydrodispiro*{*cyclopropane*-1,4′-(A-*homopregn*-4a′-*eno*[17′α,16a′-c]*pyrazole*)-5″,1‴-*cyclopropane*}-3′,20′-*dione* (5) (1·3 g) as an oil, homogeneous on t.l.c., $[\alpha]_D^{25}$ −65·6° ($CHCl_3$) (Found: N, 6·7%; M^+, 420·2778. $C_{27}H_{36}N_2O_2$ requires N, 6·7%; M, 420·2776). Elution with 5% ether–benzene gave crystals which were recrystallised from ethyl acetate to give 4″β,5″-*dihydrospiro*{*cyclopropane*-1,5″-(*pregn*-4′-*eno*[17′α,16′-c]*pyrazole*)}-3′,20′-*dione* [1] (3) (1·5 g).

Reaction of Diazocyclopropane with Pregn-4-ene-3,20-dione (7) (5 g).—Chromatography of the products obtained as above was as follows. Elution with 1 : 1 benzene–light petroleum gave an oil which was crystallised from methanol to give *trispiro*[*cyclobutane*-1,3′-A-*homopregn*-4a′-*ene*-20′,1″-*cyclobutane*-4′,1‴-*cyclopropane*]-2,2″-*dione* (11a and b) (200 mg) as a 1 : 1 mixture of epimers (g.l.c.), m.p. 145—150°, $[\alpha]_D$ +83° ($CHCl_3$), δ 0·81, 1·01, and 1·27 (each 3H, s, 18-, 19-, and 21-H_3), and 4·99 and 5·02 (1H, 2 s, $W_{\frac{1}{2}}$ 2·5 Hz, 4a-H), o.r.d. (*c* 0·038, MeOH) $[\Phi]_{588}$ +202°, $[\Phi]_{323}$ +11,400° $[\Phi]_{278}$ −6,210°, and $[\Phi]_{256}$ −425° (Found: C, 83·2; H, 9·5%; M^+, 434·3175. $C_{30}H_{40}O_2$ requires C, 83·3; H, 9·3%, M, 434·3185). Elution with 3 : 1 benzene–light petroleum gave an oil which was crystallised from methanol to give *dispiro*-[*cyclobutane*-1,3′-A-*homopregn*-4a′-*ene*-4′,1″-*cyclopropane*]-2,20′-*dione* (9) (450 mg), m.p. 170—172°, $[\alpha]_D^{22}$ +121° ($CHCl_3$), δ 0·72, 1·01, and 2·10 (each 3H, s, 18-, 19-, and 21-H_3), and 4·97 (1H, s, $W_{\frac{1}{2}}$ 2·6 Hz, 4a-H), o.r.d. (MeOH) $[\Phi]_{588}$ +497°, $[\Phi]_{323}$ +15,100°, and $[\Phi]_{250}$ −26,400° (Found: 81·75; H, 9·7%; M^+, 394·2864. $C_{27}H_{38}O_2$ requires C, 81·3; H, 9·7%; M^+, 394·2872). Elution with benzene gave an oil (2 g) which was crystallised from methanol to give *spiro*-[*cyclopropane*-1,4′-A-*homopregn*-4a′-*ene*]-3′,20′-*dione* (8) (1 g); recrystallisation from ethyl acetate gave crystals, m.p. 104—105°, $[\alpha]_D^{22}$ +109° (*c* 0·98, $CHCl_3$), δ 0·72, 1·10, and 2·10 (each 3H, s, 18-, 19-, and 21-H_3), and 4·70 (1H, s, $W_{\frac{1}{2}}$, 2·6 Hz, 4a-H), o.r.d. (*c* 0·056, MeOH) $[\Phi]_{588}$ +372°, $[\Phi]_{307}$ +9300° $[\Phi]_{263}$ −11,200°, and $[\Phi]_{250}$ −10,500° (Found: C, 81·4; H, 9·7%; M^+, 354·2552. $C_{24}H_{34}O_2$ requires C, 81·3; H, 9·7%; M, 354·2559). The mother liquors from the above fractions were combined and rechromatographed on neutralised alumina. Elution with 1 : 1 benzene–light petroleum gave an oil (200 mg) which on crystallisation from methanol afforded a further 100 mg of the di-cyclobutanone derivatives (11a + b). Further elution with 1 : 1 benzene–light petroleum gave a further 300 mg of the spirocyclobutanone (9). Elution with 3 : 1 benzene–light petroleum gave an oil (200 mg) which on crystallisation from methanol gave *dispiro*[*cyclobutane*-1,20′-A-*homopregn*-4a′-*ene*-4′,1″-*cyclopropane*]-2,3′-*dione* (10) (100 mg), which with two further crystallisations afforded pure material, m.p. 142—145°, $[\alpha]_D^{20}$ +22·4° (*c* 0·49, $CHCl_3$), δ 0·81, 1·10, and 1·27 (each 3H, s, 18-, 19-, and 21-H_3), and 4·67 (1H, s, $W_{\frac{1}{2}}$ 2·5 Hz, 4a-H), o.r.d. (*c* 0·046, MeOH) $[\Phi]_{588}$ −2050°, $[\Phi]_{323}$ −6300°, $[\Phi]_{275}$ −3730°, and $[\Phi]_{256}$ −5400° (Found: M^+, 394·2861. $C_{27}H_{38}O_2$ requires M, 394·2872). A satisfactory elemental analysis was not obtained for this compound.

Reaction of Diazocyclopropane with Cholest-4-en-3-one (4 g).—Chromatography of the products obtained as above was as follows. Elution with 3 : 1 light petroleum–benzene gave impure fractions. Elution with 1 : 1 light petroleum–benzene gave a pure fraction which crystallised from methanol to give *spiro*[*cyclopropane*-1,4′-A-*homocholest*-4a′-*en*]-3-*one* (12) (1·2 g), m.p. 102—103°, $[\alpha]_D^{18}$ +22·8° ($CHCl_3$) (Found: C, 85·2; H, 11·4. $C_{30}H_{48}O$ requires C, 84·8; H, 11·4%). Elution with 3 : 1 benzene–light petroleum gave impure crystals (100 mg), $\nu_{max.}$ (KCl) 1780 cm^{-1}. Elution with benzene gave unchanged cholestenone (1 g).

Reaction of Diazocyclopropane with 5α-Pregn-2-en-20-one

(15) (1 g).—Chromatography of the products obtained as above was as follows. Elution with 3 : 1 light petroleum–benzene gave crystals (150 mg) which were recrystallised from methanol to give *spiro*[*cyclobutane*-1,20′-5′α-*pregn*-2′-*en*]-2-*one* (17), m.p. 126°, $[\alpha]_D^{20}$ +51·2° (*c* 0·45, $CHCl_3$), δ 0·72, 0·75, and 1·23 (each 3H, s, 18-, 19-, and 21-H_3), o.r.d. (*c* 0·026, MeOH) $[\Phi]_{588}$ +192°, $[\Phi]_{323}$ +1395°, $[\Phi]_{286}$ +347°, and $[\Phi]_{256}$ +1150° (Found: M^+, 340·2719. $C_{24}H_{36}O$ requires *M*, 340·2767). A satisfactory elemental analysis was not obtained for this compound.

Reaction of Diazocyclopropane with 3β-*Acetoxy*-5α-*pregnane*-11,20-*dione* (16) (500 mg).—The product from the general procedure above was reacetylated and crystallised from methanol to give 3′β-*acetoxyspiro*[*cyclobutane*-1,20′-5′α-*pregnane*]-2,11′-*dione* (18) (200 mg), m.p. 159—162°, $[\alpha]_D^{16}$ +26·6° (*c* 0·49, $CHCl_3$), δ 0·72, 1·01, and 1·25 (each 3H, s, 18-, 19-, and 21-H_3) (Found: M^+, 414·2762. $C_{26}H_{36}O_2$ requires *M*, 414·2769). A satisfactory analysis was not obtained for this compound.

Reaction of Diazocyclopropane with 3β-*Acetoxy*-16α,17α-*epoxypregn*-5-*en*-20-*one* (22) (1·2 g).—Chromatography of the products obtained as above was as follows. Elution with 3 : 1 benzene–light petroleum gave crystals (700 mg) which were recrystallised from ethyl acetate to give 3″β-*acetoxy*-16″α,17″α-*epoxydispiro*[*cyclopropane*-1,2′-*oxiran*-3′,20″-*pregn*-5″-*ene*] (23) (isomer A) (620 mg), m.p. 154—156°, $[\alpha]_D^{16}$ −28° (*c* 0·68, $CHCl_3$), δ 1·02 (6H, s, 18- and 19-H_3) and 1·62 (3H, s, 21-H_3) (Found: C, 75·3; H, 8·5. $C_{26}H_{36}O_4$ requires C, 75·7; H, 8·8%). Elution with 3 : 1 benzene–ether gave crystals, which on recrystallisation from ethyl acetate gave the *epimeric diepoxide* (23) (isomer B) (300 mg), m.p. 170—171°, $[\alpha]_D^{16}$ −12·6° (*c* 0·95, $CHCl_3$), δ 0·80, 1·0, and 1·57 p.p.m. (each 3H, s, 18-, 19-, and 21-H_3) (Found: C, 75·2; H, 8·6. $C_{26}H_{36}O_4$ requires C, 75·7; H, 8·8%).

Isomerisation of the Diepoxide (23) (*Isomer A*) *with* BF_3–Et_2O.—The diepoxide (200 mg) was dissolved in dry benzene (10 ml) and BF_3–Et_2O (0·1 ml) was added. The solution was left at room temperature for 5 min then poured into ether. Work-up gave an oil which crystallised from ethyl acetate (110 mg), m.p. 130—160°, $\nu_{max.}$ (KCl) 1735 (AcO−) and 1775 cm^{-1} (C=O).

Reaction of Diazocyclopropane with 3β-*Acetoxypregna*-5,16-*dien*-20-*one* (2) (5 g).—Following the above general procedure, the oil formed on reacetylation crystallised from ethyl acetate to give 3′β-acetoxy-4″β,5″-dihydrospiro{cyclopropane-1,5″-(pregn-5′-eno[17′α,16′-*c*]pyrazol)}-20′-one (4) (3·8 g) (see ref. 1 for physical constants). The mother liquors gave material which was 3β-*acetoxy*-4″β,5″-*dihydrotrispiro*{*cyclopropane*-1,5″-(*preg*-5′-*eno*[17′α,16′-c]*pyrazole*)-20′,2‴-*oxiran*-3‴,1⁗-*cyclopropane*} (19) (1 g), m.p. 195—233° (decomp.), $[\alpha]_D^{16}$ −59·5° ($CHCl_3$), δ 1·04, 1·20, and 1·95 (each 3H, s, 18-, 19-, and 21-H_3) (Found: C, 74·5; H, 8·4; N, 6·35%; M^+, 464·3203. $C_{29}H_{40}N_2O_3$ requires C, 75·0; H, 8·7; N, 6·0%; *M*, 464·3038).

Reaction of Diazocyclopropane with 5α-*Cholestan*-3-*one* (8·5 g).—Chromatography of the products from the general procedure was as follows. Elution with 3 : 1 light petroleum–benzene gave an oil (5 g) which was crystallised from methanol to give crystals (4·1 g), m.p. 130—150° (fraction A); the mother liquors were evaporated to give an oil (600 mg) (fraction B). Elution with 1 : 1 benzene–light petroleum gave crystals (1·9 g) which were recrystallised from methanol to give spiro[cyclopropane-1,3′(or 4′)-A-homo-5′α-cholestane]-4′(or 3′)-one (26) or (27), m.p. 97—98°, $[\alpha]_D^{16}$ +19·4° (*c* 0·62, $CHCl_3$) (Found: C, 84·3; H, 11·7. Calc. for $C_{30}H_{50}O$: C, 84·4; H, 11·8%). Elution with benzene gave crystals (20 mg) which were recrystallised from methanol to give an unidentified product (10 mg), m.p. 100—103°, $\nu_{max.}$ (CCl_4) 3600 and 3510 cm^{-1} (unchanged on dilution) (Found: M^+, 458·4127. Calc. for $C_{31}H_{54}O_2$: *M*, 458·4123). Further elution with benzene gave crystals (680 mg) which were recrystallised from methanol to give 3-(1-*hydroxycyclopropyl*)-5α-*cholest*-2-*ene* (28) (600 mg), m.p. 107—109°, $[\alpha]_D^{16}$ +56·7° (*c* 0·6, $CHCl_3$), $\nu_{max.}$ (CCl_4) 3595 cm^{-1} (Found: C, 84·7; H, 11·3%; M^+, 426·3850. $C_{30}H_{50}O$ requires C, 84·4; H, 11·3%; *M*, 426·3861).

Fraction A was rechromatographed on neutralised alumina. Elution with 5 : 1 light petroleum–benzene gave crystals which were recrystallised from petroleum ether (b.p. 60—80°) to give (3R)-*spiro*-[5α-*cholestane*-3,1′-*cyclobutan*]-2′-*one* (24) (2·5 g), m.p. 154—155°, $[\alpha]_D^{20}$ +37·1°, o.r.d. (*c* 0·052 EtOH) $[\Phi]_{588}$ +121°, $[\Phi]_{320}$ +1365°, $[\Phi]_{278}$ −170°, and $[\Phi]_{263}$ +290° (Found: C, 84·1; H, 11·6%; M^+, 426·3878. $C_{30}H_{50}O$ requires C, 84·4; H, 11·3%; *M*, 426·3861). Elution with 5 : 1 light petroleum–benzene gave crystals which were recrystallised from petroleum ether (b.p. 60—80°) to give (3S)-*spiro*-[5α-*cholestane*-3,1′-*cyclobutan*]-2′-*one* (25) (700 mg), m.p. 166—168°, $[\alpha]_D^{18}$ +38·4 (*c* 0·86, $CHCl_3$), o.r.d. (*c* 0·052, EtOH) $[\Phi]_{588}$ +83·5° $[\Phi]_{318}$ +2180°, $[\Phi]_{286}$ −1120°, and $[\Phi]_{238}$ 0° (Found: C, 84·6; H, 11·5%; M^+, 426·3877. $C_{30}H_{50}O$ requires C, 84·4; H, 11·3%; *M*, 426·3861).

Fraction B was rechromatographed on neutralised alumina. Elution with 5 : 1 light petroleum–benzene gave the cyclobutanone (24) (50 mg), and the cyclobutanone (25) (50 mg). Elution with 5 : 1 benzene–ether gave crystals of 3-(1-hydroxycyclopropyl)-5α-cholest-2-ene (28) (100 mg), m.p. 107—109° (from acetone). Elution with 5 : 1 benzene–ether gave crystals, which were recrystallised from acetone to give 3-(1-*hydroxycyclopropyl*)-3-*methoxy*-5α-*cholestane* (29) (350 mg), m.p. 114—116°, $[\alpha]_D$ +37·3° (*c* 0·51, $CHCl_3$), $\nu_{max.}$ (CCl_4) 3610w and 3560s cm^{-1} (unaffected on dilution) (Found: C, 82·1; H, 11·9. $C_{31}H_{54}O_2$ requires C, 81·2; H, 11·9%).

Distillation of the Methoxy-alcohol (29).—The alcohol (15 mg) was heated at 0·04 mmHg in a horizontal tube contained in a heated aluminium block at 220 °C. The distillate solidified and was crystallised from methanol to give a mixture of the two cyclobutanones (24) and (25) (10 mg), m.p. 130—150°, $\nu_{max.}$ (KCl) 1770 and 1762 (shoulder) cm^{-1}.

(3R)-3′,4′-*Dihydrospiro*-[5α-*cholestane*-3,2′-*furan*]-5′-*one*.—To a solution of the cyclobutanone (24) (2·4 g) in chloroform (36 ml), was added glacial acetic acid (15 ml), 30% hydrogen peroxide (2 ml), and 10% w/v sulphuric acid (1 ml) and the solution was left at room temperature, with occasional shaking, for 3 weeks. Evaporation of the chloroform solution gave a solid which was crystallised from light petroleum (b.p. 60—80°) to give the *spiro-lactone* (31) (2·02 g), m.p. 202—206°, $[\alpha]_D^{18}$ +6·6° (*c* 0·91, $CHCl_3$), $\nu_{max.}$ (KCl) 1760 cm^{-1} (Found: C, 80·9; H, 11·35%; M^+, 442·3832. $C_{30}H_{50}O_2$ requires C, 81·3; H, 11·4%; *M*, 442·3810).

(3S)-3′,4′-*Dihydrospiro*-[5α-*cholestane*-3,2′-*furan*]-5′-*one* (32).—By a similar procedure to that described for compound (24), the cyclobutanone (25) (400 mg) gave the *spiro-lactone* (32) (280 mg), m.p. 217—222°, $[\alpha]_D$ +21·7° (*c* 0·60, $CHCl_3$), $\nu_{max.}$ (KCl) 1790 cm^{-1} (Found: C, 81·55; H, 11·4%; M^+, 442·3793. $C_{30}H_{50}O_2$ requires C, 81·3; H, 11·4%; *M*, 442·3810).

3-(3-*Hydroxypropyl*)-5α-*cholestan*-3β-ol (33).—To a solution of the lactone (31) (200 mg) in sodium-dried tetrahydrofuran (25 ml) was added lithium aluminium hydride (400 mg)

and the mixture refluxed for 2 h. The solution was cooled, the excess of lithium aluminium hydride was destroyed by ethyl acetate, and the mixture poured into water. The ether extract gave a solid which was crystallised from methanol to give the *diol* (33) (170 mg), m.p. 141—142°, $[\alpha]_D$ +45° (*c* 0·60, C_5H_5N), *m/e* 446·4126 ($C_{30}H_{54}O_2$, M^+, 1·5%), 428·4012 ($C_{30}H_{52}O$, $M^+ - H_2O$, 10%), and 387·3631 ($C_{27}H_{47}O$, $M^+ - C_3H_7O$, 100%) (Found: C, 80·8; H, 12·3. $C_{30}H_{54}O$ requires C, 80·65; H, 12·2%).

3-(3′-*Hydroxypropyl*)-5α-*cholestan*-3α-*ol* (34).—By a similar procedure to that described for compound (31), the lactone (32) gave the *diol* (34) (110 mg), m.p. 164—170°, $[\alpha]_D$ +24·4° (*c* 0·41, C_5H_5N), *m/e* 446·4131 ($C_{30}H_{54}O_2$, M^+, 8%), 428·4021 ($C_{30}H_{52}O$, $M^+ - H_2O$, 100%), and 387·3624 ($C_{27}H_{47}O$, $M^+ - C_3H_7O$, 45%) (Found: C, 80·2; H, 12·4. $C_{30}H_{54}O_2$ requires C, 80·65; H, 12·2%).

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