Preparation and Decomposition of Some Steroidal 4'β,5'-Dihydro-[17α,16-*c*]pyrazoles

By **Peter Bladon, Duncan R. Rae,*† and Alexander D. Tait,** Department of Chemistry, University of Strathclyde, Glasgow G1 1XL

Reaction of a series of aliphatic diazo-compounds with Δ^{16}-20-oxo-steroids has given the corresponding 4',5'-dihydro-[17α,16α-*c*]pyrazoles ([17α,16α-*c*]pyrazolines). Pyrolysis of the pyrazolines gave in the cases where the substituent on the heterocyclic ring is unsaturated, the 1'β,3'-dihydrocyclopropa[16,17α]-compounds (8) and (9). Pyrolysis of the pyrazolines with a saturated substituent on the heterocyclic ring gave a mixture of the Δ^{16}-16-alkyl- and the 1'β,3'-dihydrocyclopropa[16,17α]-compounds. Photolytic decomposition of the pyrazolines gave only the cyclopropa[16α,17α]-compounds.

Δ^{16}-20-OXO-STEROIDS react with diazomethane to yield 4'β,5'-dihydro-[17α,16-*c*]pyrazoles ([17α,16α-*c*]pyrazolines); subsequent loss of nitrogen from these compounds in pyrolytic, photolytic, or chemically induced reactions have been used to prepare 1'β,3'-dihydrocyclopropa-[16,17α]- and 16-methyl-Δ^{16}-steroids.[1-3] A systematic extension of the reaction to derivatives of diazomethane is lacking although there are a small number of references to the use of diazoethane[3] and ethyl diazoacetate.[4] This paper describes the reaction of several substituted diazomethanes with Δ^{16}-20-oxo-steroids and the subsequent way in which the [17α,16α-*c*]pyrazolines so formed decompose under thermal and photolytic conditions.

Formation of Pyrazolines.—Diazopropene, diazopropyne, 2-diazopropane, and diazocyclopropane were prepared by conventional or by slightly modified conventional methods and when allowed to react with 3β-acetoxypregna-5,16-dien-20-one (1) and pregna-4,16-diene-3,20-dione (2) gave the [16α,17α-*c*]pyrazolines (3a—e) and (4a—d) respectively. The reaction of diazopropene with (1) gave a mixture of the two 5'-vinyl isomers, obtained as two crystalline fractions; the minor fraction consisting of the 5'α-vinyl isomer (3b) containing 25% of the 5'β-isomer (as seen from the n.m.r. spectrum),

† *Present address:* Organon Scientific Development Group, Newhouse, Lanarkshire.

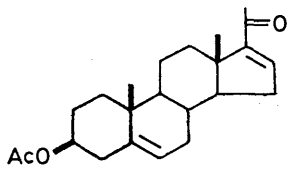
[1] A. Wettstein, *Helv. Chim. Acta*, 1944, **27**, 1803; A. Sandoval, G. Rosenkranz, and C. Djerassi, *J. Amer. Chem. Soc.*, 1951, **73**, 2383; H. L. Slates and N. L. Wendler, *ibid.*, 1959, **81**, 5472; K. Kocsis, P. G. Ferrini, D. Arigoni, and O. Jeger, *Helv. Chim. Acta*, 1960, **43**, 2178.

[2] G. Nominé and D. Bertin, *Bull. Soc. chim. France*, 1960, 550.

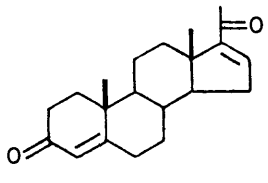
[3] D. Burns, J. W. Ducker, B. Ellis, A. K. Hiscock, A. P. Leftwick, C. M. Peach, V. Petrow, and D. M. Williamson, *J. Chem. Soc.*, 1963, 4242.

[4] G. P. Mueller and B. Riegel, *J. Amer. Chem. Soc.*, 1954, **76**, 3686.

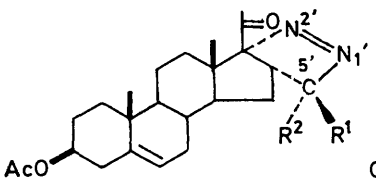
and the major fraction consisting predominantly of the 5′β-isomer (3a) from which the pure 5′β-vinyl isomer was obtained by recrystallisation. The 5′α-vinyl isomer could not be further purified. From the reaction of



(1)



(2)



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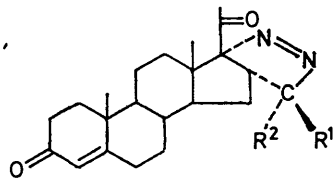


(4)

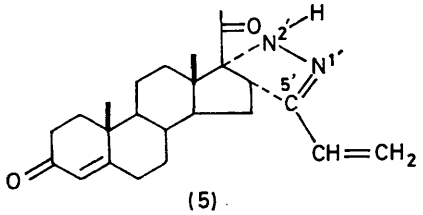
a; R^1 = —CH=CH_2, R^2 = H
b; R^1 = H, R^2 = —CH=CH_2
c; R^1 = —C≡CH, R^2 = H
d; R^1 = R^2 = Me
e; R^1R^2 = —CH_2CH_2—

a; R^1 = —CH=CH_2, R^2 = H
b; R^1 = —C≡CH, R^2 = H
c; R^1 = R^2 = Me
d; R^1 R^2 = —CH_2CH_2—
e; R^1 = H, R^2 = —C≡CH

diazopropene with (2) and the reactions of diazopropyne with (1) and (2) only the 5′β-substituted pyrazolines were isolated.

Diazocyclopropane in addition to giving the [16α,17α-*c*]pyrazolines (3e) and (4d) reacted further with both the 3- and 20-carbonyl groups; these reactions and others of diazocyclopropane will be the subject of a later paper.

The dihydropyrazole (5) was isolated on one occasion when the crude vinylpyrazoline (4a) was passed through an alumina column. The spectral data of this compound

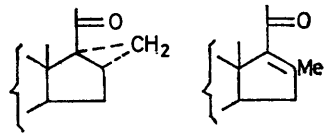


(5)

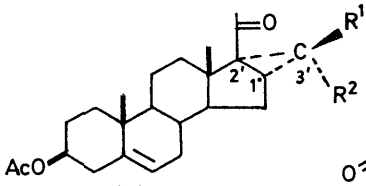
are consistent with its structure (see Experimental section)

The structures of the pyrazolines follow from their spectroscopic properties (see Table 1) and ensuing chemistry. The assignment of the configuration at C-5′ of the vinyl- and ethynyl-pyrazolines follows from inspection of the n.m.r. spectra. In the ethynylpyrazolines (3c) and (4b) the 5′-protons appear as doublets at δ 4·82 and 5·00 respectively (*J* 2·5 Hz) (the 5′-H signals in the vinylpyrazolines are masked by the vinylic protons). The 16β-protons of the 5′β-isomers (3a), (3c), (4a), and (4b) appear as doubled pseudo-triplets (*J* 2·5, 2·5, and 8 Hz) and the 16β-proton in the 5′α-vinylpyrazoline appears as a doubled pseudo-triplet (*J* 8·5, 8·5, and 2 Hz) and it therefore follows that $J_{16\beta\text{-H},5'\alpha\text{-H}}$ is *ca.* 2·5 and $J_{16\beta\text{-H},5'\beta\text{-H}}$ is *ca.* 8 Hz which is consistent with the assigned structures.

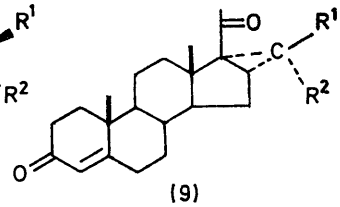
Decomposition of the Pyrazolines.—It has been well established [1-3] that pyrazolines of type (3) and (4) where $R^1 = R^2 = H$ decompose photochemically to give the



(6) (7)



(8)



(9)

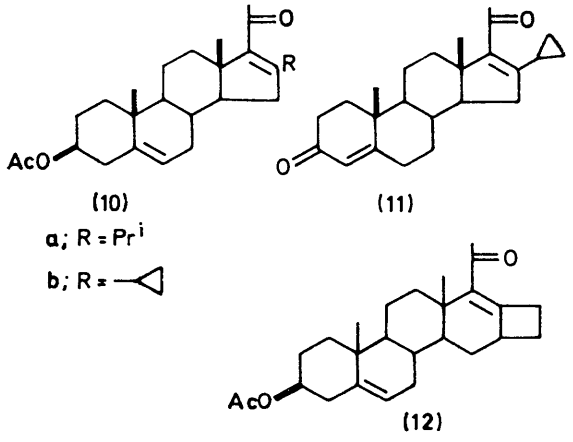
a; R^1 = —CH=CH_2, R^2 = H
b; R^1 = H, R^2 = —CH=CH_2
c; R^1 = —C≡CH, R^2 = H
d; R^1 = R^2 = Me
e; R^1R^2 = —CH_2CH_2—

a; R^1 = —CH=CH_2, R^2 = H
b; R^1 = H, R^2 = —CH=CH_2
c; R^1 = —C≡CH, R^2 = H
d; R^1 = H, R^2 = —C≡CH
e; R^1 = R^2 = Me
f; R^1R^2 = —CH_2CH_2—

cyclopropa[16α,17α]-steroids [partial structure (6)] and decompose pyrolytically to give mainly the 16-methyl-Δ^{16}-steroids [partial structure (7)] as well as a small amount of (6). Interestingly therefore it was found that the vinyl- and ethynyl-pyrazolines (3a—c) and (4a and b)

decompose pyrolytically to give in greater than 90% yields the substituted cyclopropanes (8a—c) and (9a—c); no other products were isolated. Photolytic decomposition of the vinylpyrazoline (3a) also gave only the cyclopropyl derivatives, but the yield of crystalline material was lower than that obtained by pyrolysis. Pyrolytic decomposition of both the 5′β-vinylpyrazoline (3a) and the 5′α-vinylpyrazoline (3b) (containing 25% of the 5′β-isomer) gave the same mixture of the two vinylcyclopropane compounds (8a and b) in an approximate ratio of 2 : 1 (t.l.c.), from which the two pure components were separated by fractional crystallisation. Pyrolysis of the 5′β-vinylpyrazoline (4a) also gave a mixture of the two vinylcyclopropane compounds (9a and b) (n.m.r. evidence) but only the predominant 3′β-vinyl isomer (9a) could be obtained from the mixture. The low melting 3′α-vinyl isomer (9b) was obtained, however, in low yield by hydrolysis and oxidation [5] of compound (8b).

Pyrolytic decomposition of the 5′β-ethynylpyrazoline (4b) gave the 3′β-ethynylcyclopropane (9c) in 95% yield; the 3′α-ethynyl isomer (9d) was not isolated from this reaction although it was obtained as a by-product in the reaction of diazopropyne with (2). Since only the 3′α-ethynylcyclopropane was isolated from this reaction, its formation must have occurred *via* the spontaneous decomposition of the 5′α-pyrazoline (4e); none of the 3′β-isomer was detected (g.l.c.).



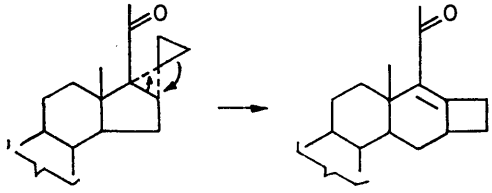
Pyrolysis of the dimethylpyrazoline (3d) gave in a similar manner to the unsubstituted pyrazolines,[1-3] the 16-isopropyl-Δ^{16}-steroid (10a), and a small amount of the dimethylcyclopropane (8d); pyrolysis of the dimethylpyrazoline (4c) gave an inseparable mixture of products containing, however, mainly the Δ^{16}-16-isopropyl compound, as seen from a spectroscopic examination of the mixture. Photolytic decomposition of the dimethylpyrazolines (3d) and (4c) gave the dimethylcyclopropanes (8d) and (9e) as the only isolable products in *ca.* 50 and 25% yields respectively.

Pyrolytic decomposition of the cyclopropylpyrazolines (3e) and (4d) gave mixtures consisting mainly of the spirocyclopropane compounds (8e) and (9f) and a little of the 16-cyclopropyl-Δ^{16}-compounds (10b) and (11). Photolytic decomposition of (3e) gave a mixture of (8e) and (10b) in approximately the same ratio as obtained by pyrolysis, along with a small amount of the cyclobuteno-compound (12). This compound (12) was shown to be a secondary irradiation product since irradiation of the spirocyclopropane compound (8e), under the same conditions as used for the decomposition of the pyrazoline, gave (12) as the only isolable product (Scheme 1).

TABLE 1

Physical data of pyrazolines (3a—e) and (4a—d)

Compound	M.p. (°C)	$[\alpha]_D$ (°)	$\nu_{max.}$ (KCl)/cm^{-1} 20-Oxo	$\nu_{max.}$ (KCl)/cm^{-1} N=N	N.m.r. (δ values) Me groups 18	19	21	5′-H	16-H	$J_{5',16}$ (Hz)	Analyses Found (%) C	H	N	Required (%)	C	H	N
(3a)	127—130	−195	1710	1540	0·80	1·01	2·44		2·79	3	73·1	8·5	6·7	$C_{26}H_{36}N_2O_3$	73·5	8·55	6·6
(3b)			1710	1540	0·83	1·01	2·42		3·05	8·5	Not obtained pure						
(3c)	130—135	−194	1710	1545	0·80	1·00	2·43	4·82	3·10	2·5	73·9	8·0	6·55	$C_{26}H_{34}N_2O_3$	73·9	8·1	6·6
(3d)	172—173	−32·3	1705	1540	0·82	0·92	2·40				73·1	8·8	6·6	$C_{26}H_{38}N_2O_3$	73·2	9·0	6·6
(3e)	248—249	−85·4	1705	1515	0·82	0·91	2·38				73·2	8·6	6·6	$C_{26}H_{36}N_2O_3$	73·5	8·55	6·6
(4a)	138—140	−156	1705	1540	0·83	1·17	2·43		2·78	2·5	75·8	8·7	7·4	$C_{24}H_{32}N_2O_2$	75·7	8·4	7·4
(4b)	205—208	−203	1705	1550	0·83	1·14	2·42	5·0		3·0	76·2	7·9	7·4	$C_{24}H_{30}N_2O_2$	76·2	8·0	7·45
(4c)	160—172	+71·5	1708	1556	0·82	1·18	2·42				75·6	9·0	7·3	$C_{24}H_{34}N_2O_2$	75·3	9·0	7·3
(4d)	230—235	+3·54	1708	1522	0·82	1·18	2·43				75·3	8·5	7·4	$C_{24}H_{32}N_2O_2$	75·7	8·4	7·4



SCHEME 1

The structures of the compounds obtained from decomposition of the pyrazolines were established from their spectroscopic properties (see Table 2) and chemical evidence. The cyclopropa[16α,17α]-compounds have i.r. absorptions at *ca.* 1680—1690 cm^{-1} corresponding to a 20-ketone in conjugation with a cyclopropane ring; the 16-alkyl-Δ^{16}-compounds have i.r. carbonyl absorptions at *ca.* 1660 cm^{-1} and typical u.v. absorptions. The n.m.r. spectra of all the compounds are consistent with their structures (see Table 2) and in addition they enabled the assignment of configuration of the 3′-vinylcyclopropane isomers. The n.m.r. spectrum of the 3′α-vinyl compound (8b) shows a normal ABMX pattern for the vinylcyclopropane group, the $-CH{=}CH_2$ appearing

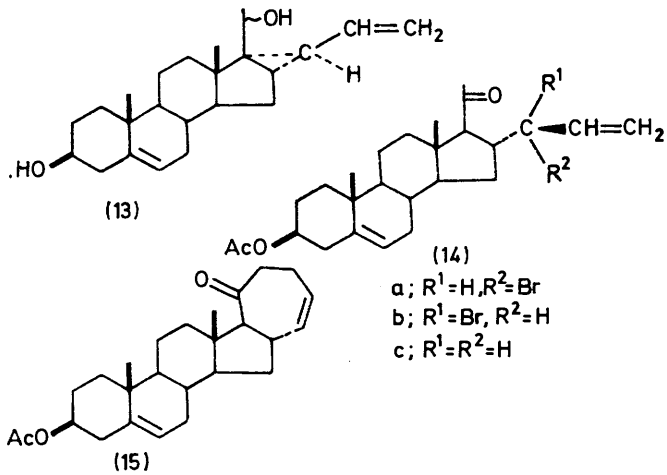
[5] K. E. Pfitzner and J. G. Moffatt, *J. Amer. Chem. Soc.*, 1963, **85**, 3027.

as 8 lines at δ 6·08 and $-CH=CH_2$ at 5·25 and 5·12. The n.m.r. spectrum of the 3′β-vinyl isomer shows the three vinylic protons as a multiplet at δ 5·1. Dreiding models indicated that the $-CH=CH_2$ proton in this isomer is located within the shielding cone of the 20-carbonyl group and this therefore accounts for its upfield shift. In the corresponding 20-hydroxy-compound (13) [prepared by reduction of (8a) with lithium aluminium hydride] a normal ABMX pattern similar to that seen for the 3′α-vinylcyclopropane isomer (8b) is observed for the vinyl group.

TABLE 2

Physical data of compounds (8a—e) and (9a—f)

Compound	M.p. (°C)	$[\alpha]_D$ (°) ($CHCl_3$)	$\nu_{max.}$ (KCl)/ cm^{-1} 20-Oxo	N.m.r. (δ values) Methyl groups 18	19	21	Analyses Found (%) C	H		Required (%) C	H
(8a)	144—146	−36·4	1690	0·85	1·03	2·14	78·9	9·1	$C_{26}H_{36}O_3$	78·7	9·15
(8b)	109—113	+8·6	1670	0·92	1·02	2·08	78·8	9·1	$C_{26}H_{36}O_3$	78·7	9·15
(8c)	197—199	+12	1690	0·86	1·03	2·26	79·1	8·5	$C_{26}H_{34}O_3$	79·1	8·7
(8d)	178—180	−16·5	1690	0·81	1·03	2·18	78·3	9·4	$C_{26}H_{38}O_3$	78·3	9·6
(8e)	125—127	−16·0	1675	0·95	1·02	2·02	78·4	9·2	$C_{26}H_{36}O_3$	78·7	9·15
(9a)	186—189	+125	1690	0·89	1·19	2·14	81·4	8·95	$C_{24}H_{32}O_2$	81·8	9·15
(9b)	95—97	+160	1685	0·95	1·19	2·07	81·7	9·25	$C_{24}H_{32}O_2$	81·8	9·15
(9c)	218	+217	1690	0·88	1·17	2·19	82·1	8·7	$C_{24}H_{30}O_2$	82·2	8·6
(9d)	194—196	+65	1685	0·95	1·20	2·14	82·1	8·65	$C_{24}H_{30}O_2$	82·2	8·6
(9e)	170	+142	1690	0·83	1·18	2·18	81·6	9·6	$C_{24}H_{34}O_2$	81·3	9·8
(9f)	142—145	+157	1673	0·98	1·19	1·97	81·5	9·15	$C_{24}H_{32}O_2$	81·8	9·15



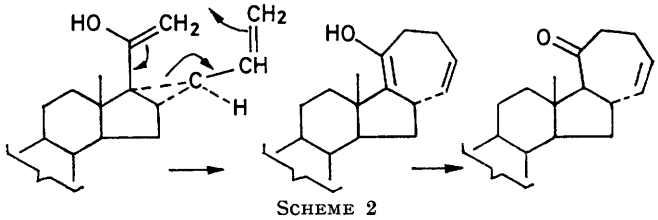
The two vinyl cyclopropane compounds (8a) and (8b) were shown to be isomeric by treating them with hydrogen bromide in acetic acid; from each was obtained a different 16α-(1-bromoallyl) compound, (14a) and (14b) respectively, consistent with *trans*-opening of the cyclopropane ring. Zinc reduction of both these bromo-compounds gave the 16α-allylpregnene (14c).

Further evidence to support the assignment of configuration of the two isomers (8a) and (8b) was obtained when the 3′α-vinyl compound (8b) was heated for a short time at a higher temperature than required for its formation from the pyrazoline (3a). Two compounds were isolated; the 3′β-vinyl isomer (8a) and a compound assigned structure (15). Pyrolysis of the 3′β-vinyl compound (8a) at this temperature gave only the cycloheptenone (15). The structure of this compound follows from its spectroscopic properties (see below) and its probable formation *via* a Cope [6] rearrangement of the initially formed 20-enol (Scheme 2) which is only sterically feasible for the 3′β-vinyl isomer. The 3′α-vinyl compound (8b) must therefore rearrange to the 3′β-isomer (8a) before rearranging further to (15). The thermal rearrangement of *cis*- to *trans*-divinylcyclopropane prior to further rearrangement to cycloheptadiene has been shown to occur.[6]

The n.m.r. spectrum of the cycloheptenone (15) shows a total of three olefinic protons and no signal for the 21-CH_3 group, and the i.r. absorption for the 20-carbonyl group appears at 1700 cm^{-1} indicating the absence of the cyclopropane ring. The configuration at C-17 is not certain, but it is thought that the extra ring bond has the 17β-configuration, this having more equatorial character than a 17α-bond.

Catalytic reduction of the 3′β-ethynyl compound (9c) gave the 3′β-vinyl compound (9a); thus the two isomers are isosteric. Unfortunately a similar reduction of the 3′α-ethynyl compound (9d) gave an inseparable mixture of products, produced by (*inter alia*) reduction of the cyclopropane ring.

As already mentioned pyrolysis of the dimethylpyrazoline (3d) gave a mixture of the 16-isopropyl-Δ^{16}-compound (10a) (major component) and the dimethylcyclopropane (8d) (minor component). This reaction was carried out on 100 mg of material and when it was

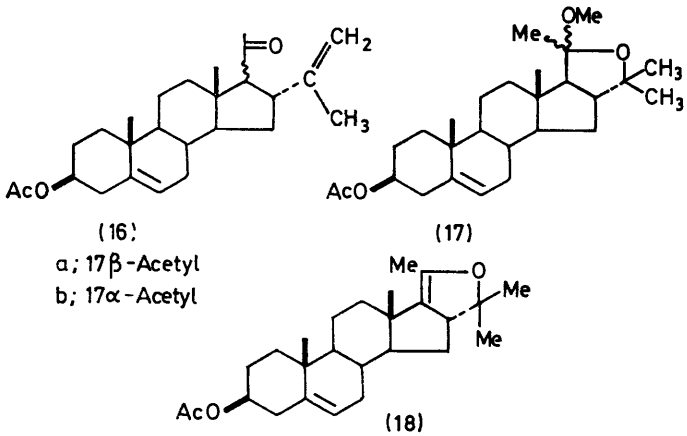


SCHEME 2

repeated using a relatively larger amount of the pyrazoline (3·7 g) none of the dimethylcyclopropane was obtained; three other compounds were isolated which were separated by chromatography and assigned structures (16a), (16b), and (17). The methoxy-compound (17) isolated in small yield was presumably formed when the

[6] E. Vogel, *Angew. Chem. Internat. Edn.*, 1963, **2**, 1.

dihydrofuran (18) initially formed on decomposition of the pyrazoline was recrystallised from methanol; the larger scale of reaction enabled its isolation in this

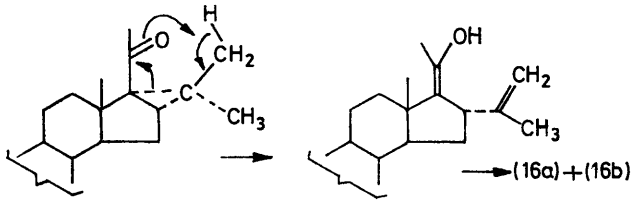


(16)
a; 17β-Acetyl
b; 17α-Acetyl

(17)

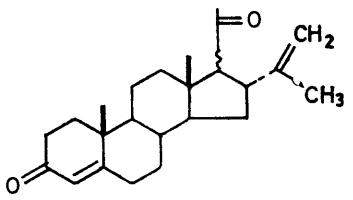
(18)

instance. The two 16α-isopropenyl compounds (16a) and (16b) probably result from the decomposition of the dimethylcyclopropane (8a) during the longer time at higher temperature required to decompose a larger amount of the pyrazoline. The driving force for the reaction could be relief in steric interaction between the



SCHEME 3

3'α-methyl group and the 14α-proton, and the rearrangement can be envisaged as a Cope type (Scheme 3). This proposal is partly supported by the fact that two similar products (19a) and (19b) were obtained, together with the dimethylcyclopropane (9e) after Oppenauer oxidation of the 3β-hydroxy-derivative of (8d).



(19)
a; 17β-Acetyl
b; 17α-Acetyl

The n.m.r. spectra of the four compounds (16a), (16b), (19a), and (19b) show typical absorptions for the isopropenyl groups. The i.r. spectra show saturated carbonyl absorptions at 1705 cm^{-1} for the acetyl groups. Compound (16a) shows a strong positive Cotton effect curve, thus establishing the 16α,17β-configuration.[7] Compound (16b) shows a negative Cotton effect curve,[7] and a 16-H–17-H coupling[8] of 3 Hz in the n.m.r. spectra of both (16b) and (19b) indicate the 17α-acetyl and 16α-isopropenyl groupings.

[7] P. Crabbé, F. McCapra, F. Comer, and A. I. Scott, *Tetrahedron*, 1964, **20**, 2455.

EXPERIMENTAL

U.v. spectra were obtained using a Perkin-Elmer 137 instrument using ethanol as solvent, and i.r. spectra using Perkin-Elmer 125, 237, or 257 instruments using either KCl discs or carbon tetrachloride solutions. Mass spectra were obtained using an A.E.I. MS9 instrument; mass measurements, accurate to ±5 p.p.m., were made by the peak matching technique using heptacosafluorotributylamine as reference. N.m.r. spectra were obtained using a Perkin-Elmer R10 instrument operating at 40 MHz, using deuteriochloroform as solvent, and tetramethylsilane as an internal standard, unless otherwise stated. A few spectra were obtained on Varian A60 and HA100 instruments. Optical rotations were determined in chloroform solution at room temperature, and o.r.d. spectra were obtained using a Bendix Polarmatic 62 spectropolarimeter using either methanol or ethanol as solvent.

All compounds were checked for purity where possible by use of g.l.c. on a Perkin-Elmer F11 machine, with columns packed with silicone Gum Rubber E-301 (2·5) on AW-DMCS 80—100 mesh Chromosorb G (97·5 parts). M.p.s were determined on a Kofler hot-stage. Spence's Grade H alumina was used for column chromatography and was neutralised with 10% aqueous acetic acid (5 ml per 100 g) before use. Kieselgel G nach Stahl was used for t.l.c., and the chromatograms were developed by use of sulphuric acid. Light petroleum was the fraction which had b.p. 40—60°.

Preparation of a Solution of 2-Diazopropane.—Acetone (20 g) was added slowly to an ice-cooled solution of hydrazine hydrate (20 g) and the resulting solution of acetone hydrazone added, over 30 min, to a stirred suspension of yellow mercuric oxide (100 g) in ether (300 ml), containing an ethanolic solution of potassium hydroxide (5 ml; 10%) at 15°. The solution was stirred for a further 10 min and the red solution of 3-diazopropane produced was filtered through glass wool, dried over potassium hydroxide pellets, and was then ready for use.

Preparation of an Ethereal Solution of Ethyl N-Cyclopropyl-N-nitrosocarbamate.[9]—Anhydrous sodium acetate (45 g) was slowly added to a solution of nitrogen dioxide (50 g) in ether (300 ml) at −40°, and the resulting solution was allowed to warm to −10°. Ethyl *N*-cyclopropylcarbamate (15 g) was added over 30 min, keeping the temperature of the solution at −10°. The solution was allowed to stand with occasional stirring at −10° for a further 30 min, and then washed with ice–water, followed by a sodium hydrogen carbonate solution at 0°.

The resulting ethereal solution of ethyl *N*-cyclopropyl-*N*-nitrosocarbamate was used immediately.

General Method of Preparation of Steroidal Pyrazolines (3) *and* (4).—An ethereal solution of the diazo-compound was added to a solution of the Δ^{16}-20-oxo-steroid in ether–methanol, and the resulting solution allowed to stand in the dark, generally at room temperature, until either complete reaction occurred, or the solution was decolourised, indicating the absence of the diazo-compound. If in this latter instance the reaction had not gone to completion, a further amount of the diazo-compound was added to effect complete

[8] A. D. Cross and P. Crabbé, *J. Amer. Chem. Soc.*, 1964, **86**, 1221.

[9] E. H. White, *J. Amer. Chem. Soc.*, 1955, **77**, 6008.

reaction. Evaporation of the solvent to a small bulk and crystallisation gave the [16α,17α-*c*]pyrazoline derivatives (see Table 1 for physical data).

Analytical samples were prepared by recrystallising the products from ethyl acetate.

In the preparation of the pyrazoline compounds (3e) and (4d), diazocyclopropane was prepared by decomposing a solution of ethyl *N*-cyclopropyl-*N*-nitrosocarbamate with alcoholic potassium hydroxide (10% solution) at −10° and allowing it to react *in situ* with the Δ^{16}-20-ketones (1) and (2). Working up (and in the former case reacetylation) gave crude material from which the pyrazoline compounds (3e) and (4d) were isolated by crystallisation (see Table 1).

Reaction of Diazopropene with 3β-*Acetoxypregna*-5,16-*dien*-20-*one* (1).—An ethereal solution of diazopropene [prepared in the usual way [10] from *N*-allyl-*N*-nitrosourea (100 g)] was added to a solution of the steroid (1) (50 g) in methanol–methylene chloride, and allowed to stand at 4° until the solution was decolourised. The crystalline solid formed (10 g) was a 3 : 1 mixture of the 5′α- (3b) and 5′β-vinylpyrazoline (3a) (see Table 1). The mother liquors were reduced in volume and gave a further two crops of crystals (40 g in total) which were recrystallised from methanol–methylene chloride to give 3β-*acetoxy*-4′β,5′-*dihydro*-5′β-*vinylpregn*-5-*eno*[17α,16-c]*pyrazol*-20-*one* (3a) (see Table 1).

Reaction of Diazopropyne with Pregna-4,16-*diene*-3,20-*dione* (2).—An ethereal solution of diazopropyne [prepared in the usual way [10] from *N*-nitroso-*N*-(prop-2-ynyl)urea (50 g)] was added to a solution of the dione (2) (10 g) in methanol (50 ml) and ether (200 ml) and the solution was allowed to stand at room temperature in the dark for 1 week. The solution was evaporated to a small volume and allowed to crystallise to give 5′β-*ethynyl*-4′β,5′-*dihydropregn*-4-*eno*-[17α,16-c]*pyrazole*-3,20-*dione* (4b) (3·5 g) (see Table 1). The mother liquors were evaporated to dryness, and the residual oil was dissolved in benzene and chromatographed on alumina. Elution with benzene gave unchanged dione (2) (2 g), followed by a fraction (1·5 g) consisting of a 1 : 1 mixture of two compounds (g.l.c.). Fractional recrystallisation of this mixture gave a further amount of (2) (500 mg) and 3′α-*ethynyl*-1′β,3′-*dihydrocyclopropa*[16,17α]*pregn*-4-*ene*-3,20-*dione* (9d) (500 mg) (see Table 2).

Isomerisation of the 5′-*Vinylpyrazoline* (4a).—The pyrazoline (4a) (2 g) in ethyl acetate (50 ml) was eluted through an non-neutralised alumina column (40 g), and the eluant evaporated to a small volume and allowed to crystallise to give 2′,4′β-*dihydro*-5′-*vinylpregn*-4-*eno*[17α,16-c]*pyrazole*-3,20-*dione* (5) (1·5 g), m.p. 195° (decomp.) $\nu_{max.}$ (KCl) 3310 (N–H), 1685 (20-oxo), 1870 and 1610 (C=C–C=O), and 1620 cm^{-1} (N=C), $\lambda_{max.}$ (EtOH) 240 and 280 nm (ε 19,000 and 9400), δ 0·81, 1·18, and 2·22 (each 3H, s, 18-, 19-, and 21-H_3), 5·47 (1H, s, 4-H), 6·55 (1H, m, NCH), and 5·3 (2H, m, $=CH_2$) (Found: C, 75·4; H, 8·3; N, 7·4. $C_{24}H_{32}N_2O_2$ requires C, 75·5; H, 8·4; N, 7·4%).

Pyrolysis of the 5′-*Vinylpyrazolines* (3a) *and* (3b).—A mixture of the two pyrazolines (100 g) was dissolved in dimethyl sulphoxide (1 l) and the solution heated at 110—120° for 1 h. The solution was cooled and poured into water, and the solid formed was collected, dried, and crystallised from methanol to give 3β-*acetoxy*-1′β,3′-*dihydro*-3′β-*vinylcyclopropa*[16,17α]*pregn*-5-*en*-20-*one* (8a) (54 g). A further crop from the mother liquors was 3β-*acetoxy*-1′β,3′-*dihydro*-3′α-*vinylcyclopropa*[16,17α]*pregn*-5-*en*-20-*one* (8b) (14 g), which was also recrystallised from methanol (see Table 2).

Pyrolysis of the Pyrazolines (3c), (4a), *and* (4b).—The pyrazolines were heated at their m.p. under vacuum until evolution of nitrogen had ceased. The products were crystallised from methanol to give the *cyclopropane derivatives* (8c) in 95% yield, (9a) in 70% yield, and (9c) in 95% yield respectively (see Table 2).

Pyrolysis of the Pyrazolinespirocyclopropane (3e).—The pyrazoline (1 g) was heated at its m.p. under vacuum until evolution of nitrogen had ceased, and the oil formed was dissolved in benzene and chromatographed on alumina. Elution with 3 : 1 benzene–light petroleum gave a solid which was crystallised from methanol to give 3β-*acetoxy*-(1′β,3′-*dihydrocyclopropa*[16,17α]*pregn*-5-*ene*)-3′-*spirocyclopropan*-20-*one* (8e) (700 mg) (see Table 2). Elution with benzene gave a solid which was crystallised to give 3β-*acetoxy*-16-*cyclopropylpregna*-5,16-*dien*-20-*one* (10b) (200 mg), m.p. 177—180° (from methanol), $[\alpha]_D$ −149° ($CHCl_3$), $\nu_{max.}$ (KCl) 1665 cm^{-1} (20-oxo), $\lambda_{max.}$ (EtOH) 270 nm (ε 10,100), δ 1·01, 1·05, and 2·34 (each 3H, s, 18-, 19-, and 21-H_3) (Found: C, 78·55; H, 8·85. $C_{26}H_{36}O_3$ requires C, 78·75; H, 9·15%).

Pyrolysis of the Pyrazolinespirocyclopropane (4d).—The pyrazoline (1·5 g) was heated under vacuum at 240° for 5 min and the resulting oil was dissolved in benzene and chromatographed on alumina. Elution with benzene gave a fraction which was crystallised from methanol to give (1′β,3′-*dihydrocyclopropa*[16,17α]*pregn*-4-*ene*)-3′-*spirocyclopropane*-3,20-*dione* (9f) (1 g) (see Table 2). Elution with 9 : 1 benzene–ether gave a solid which was crystallised to give 16-*cyclopropylpregna*-4,16-*diene*-3,20-*dione* (11) (100 mg), m.p. 152—155° (from ethyl acetate), $[\alpha]_D^{25}$ +12° ($CHCl_3$), $\nu_{max.}$ (KCl) 1659 cm^{-1} (20-oxo), $\lambda_{max.}$ (EtOH) 244 and 252 nm (ε 15,900 and 10,900), δ 1·0, 1·20, and 2·32 (each 3H, s, 18-, 19-, and 21-H_3) (Found: C, 81·65; H, 8·8. $C_{24}H_{32}O_2$ requires C, 81·8; H, 9·15%).

Pyrolysis of the Dimethylpyrazoline (3d).—(*a*) The pyrazoline (3·7 g) was heated at its m.p. under reduced pressure until evolution of nitrogen had ceased and the resulting oil was crystallised from methanol to give 3β-*acetoxy*-16-*isopropylpregna*-5,16-*dien*-20-*one* (10a) (2 g), m.p. 169—171°, $[\alpha]_D$ −103° ($CHCl_3$), $\nu_{max.}$ (KCl) 1670 cm^{-1}, $\lambda_{max.}$ (EtOH) 254 nm (ε 6640), δ 0·99, 1·05, and 2·25 (each 3H, s, 18-, 19-, and 21-H_3) (Found: C, 77·95; H, 9·35. $C_{26}H_{38}O_3$ requires C, 78·35; H, 9·6%). After removal of a second crop of (10a) (500 mg), the mother liquors were evaporated giving an oil (1 g) which was dissolved in benzene and chromatographed on alumina. Elution with 1 : 1 benzene–light petroleum gave a solid which was crystallised from methanol to give 2′,3′β,4′α,5′-*tetrahydro*-5′-*methoxy*-2′,2′,5′-*trimethylandrost*-5-*eno*[16,17-c]*furan*-3β-*yl acetate* (17) (40 mg) m.p. 138—142°; recrystallisation from methanol gave crystals, m.p. 140—142°, $[\alpha]_D^{16}$ −116° (*c* 0·5, $CHCl_3$), δ 0·80 and 1·01 (both 3H, s, 18- and 19-H_3), 1·27 (6H, s, 2 × Me), 1·32 (3H, s, Me), and 3·15 (3H, s, OMe) (Found: M^+ − MeOH, 398·2868. $C_{28}H_{38}O_3$ requires 398·2821). A satisfactory analysis was not obtained for this compound. Elution with 3 : 1 benzene–light petroleum gave crystals (15 mg) which were crystallised twice from methanol to give 3β-*acetoxy*-16α-*isopropenylpregn*-5-*en*-20-*one* (16a), m.p. 140—141°, o.r.d. (0·02 methanol) $[\Phi]_{588}$ −318°, $[\Phi]_{309}$ +5370°, $[\Phi]_{263}$ −12,030°, and $[\Phi]_{244}$ −9380° (Found: M^+, 398·2842. $C_{26}H_{38}O_3$ requires *M*, 398·2821). Elution with benzene gave a gum which was crystallised from methanol to give 3β-*acetoxy*-16α-*isopropenyl*-17α-*pregn*-5-*en*-20-*one* (16b), m.p. 158—161°, o.r.d. (0·064 ethanol) $[\Phi]_{588}$ −311°, $[\Phi]_{313}$ −5780°,

[10] F. Arndt, *Org. Synth.*, Coll. Vol. II, 1943, p. 461; W. W. Hartman and R. Phillips, *Org. Synth.*, 1953, **13**, 84.

$[\Phi]_{270}$ +3480°, and $[\Phi]_{250}$ +2020 (Found: M^+, 398·2884. $C_{26}H_{36}O_3$ requires M, 398·2821).

(*b*) The pyrazoline (3d) (100 mg) was heated under reduced pressure until evolution of nitrogen had ceased and the product crystallised from methanol to give the isopropyl compound (10a) (50 mg) identical with that prepared above. The mother liquors gave a second crop of crystals (10 mg) which were recrystallised from methanol to give the dimethylcyclopropane (8d), which was identical (i.r. spectrum) with that prepared by photolytic decomposition of the pyrazoline (3d) (see below).

Photolytic Decomposition of Pyrazoline (3d).—The pyrazoline (20 g) in dioxan (500 ml) in a glass flask was irradiated for 10 h with two 125 W medium pressure mercury lamps placed 4 cm on either side of the flask. Crystallisation of the product resulting from two such reactions gave 3β-*acetoxy*-1′β,3′-*dihydro*-3′,3′-*dimethylcyclopropa*[16,17α]-*pregn*-5-*en*-20-*one* (8d) (20 g) (see Table 2).

Photolytic Decomposition of the Dimethylpyrazoline (4c).—The pyrazoline (4c) (200 mg) in dioxan (50 ml) in a glass flask was irradiated for 45 min with a medium pressure mercury lamp placed 4 cm from the flask. Evaporation and crystallisation of the resulting oil gave 1′β,3′-*dihydro*-3′,3′-*dimethylcyclopropa*[16,17α]*pregn*-4-*ene*-3,20-*dione* (9e) (50 mg) (see Table 2).

Photolytic Decomposition of the Pyrazolinespirocyclopropane (3e).—The pyrazoline (3·7 g) in dioxan (100 ml) in a quartz flask was irradiated for 2 h with a medium pressure mercury lamp, placed 6 cm from the flask. The solvent was evaporated off and the unchanged pyrazoline removed by crystallisation from methanol and re-irradiated as above for a further 2 h. The combined products were evaporated giving an oil which was crystallised from methanol to give the spirocyclopropane compound (8e) (1·2 g), identical with the sample prepared by pyrolytic decomposition of the pyrazoline (3e). The mother liquors were evaporated to dryness, dissolved in benzene, and chromatographed on alumina. Elution with 1 : 1 benzene–light petroleum gave more compound (8e) (1 g). Further elution with this solvent mixture gave a solid which was crystallised from methanol to give 3β-*acetoxy*-3′,4′-*dihydro*-16ξH-*cyclobuteno*-[16,17]-D-*homopregna*-5,17-*dien*-20-*one* (12) (70 mg), m.p. 143—145°, $[\alpha]_D^{16}$ −92·5° (*c* 0·53, $CHCl_3$), $\lambda_{max.}$ (EtOH) 250 nm (ε 7500), δ 1·00 (6H, s, 18- and 19-H_3) and 2·15 (3H, s, 21-H_3) (Found: C, 78·65; H, 9·25%; M^+, 396·2664. $C_{26}H_{36}O_3$ requires C, 78·75; H, 9·15%; M, 396·2664). Elution with benzene gave a fraction which was crystallised from methanol to give the Δ^{16}-16-cyclopropyl compound (10b), identical with the sample prepared by pyrolytic decomposition of the pyrazoline (3e).

Photolysis of the Spirocyclopropane Compound (8e).—The spiro-compound (500 mg) in dioxan was irradiated in a quartz flask with a medium pressure mercury lamp, placed 6 cm from the flask, for 5 h in which time all the starting material had disappeared, as indicated by t.l.c. Evaporation of the solvent gave an oil, which crystallised from methanol to give the D-homo-steroid (12), identical with that prepared above.

Isomerisation of the 3′α-*Vinyl Compound* (8b).—The compound (100 mg) was heated in a sealed, evacuated tube at 200° for 10 min and the resulting oil was crystallised from methanol to give two products. The first crop was recrystallised from methanol to give 3β-*acetoxy*-1′β,2′α,4′,5′-*tetrahydrocyclohepta*[16,17]*androsta*-5,16-*dien*-3′-*one* (15), m.p. 195—198°, $[\alpha]_D^{20}$ −80° (*c* 0·60, $CHCl_3$), $\nu_{max.}$ (KCl) 1700 cm^{-1} (20-oxo), δ 0·85 and 1·01 (both 3H, s, 18- and 19-H_3), 5·75 (2H, m, CH=CH), and 5·35 (1H, m, 6-H) (Found: C, 78·9; H, 9·1. $C_{26}H_{36}O_3$ requires C, 78·7; H, 9·1). The second crop was recrystallised from methanol to give the 3′β-vinyl compound (8a), identical with a previously prepared sample.

Isomerism of the 3′β-*Vinyl Compound* (8a).—The compound (8a) (2 g) was heated in a sealed, evacuated tube at 200° for 1 h and the crystals formed on cooling were recrystallised from acetone to give the cycloheptenone (15) (1·5 g), identical with the sample prepared above.

Reaction of the 3′β-*Vinyl Compound* (8a) *with* HBr.—To a solution of the compound (8a) (500 mg) in acetic acid (2 ml) was added a solution (50% w/v) of HBr in acetic acid (0·6 ml) and the reaction was allowed to stand at room temperature for 30 min and then poured into water. The solid formed was crystallised from petroleum (b.p. 60—80°) to give 3β-*acetoxy*-16α-[(R)-1-*bromoprop*-2-*enyl*]*pregn*-5-*en*-20-*one* (14a), m.p. 163—165°, $[\alpha]_D$ +23·8° (*c* 0·63, $CHCl_3$), δ 0·66, 1·01, and 2·10 (each 3H, s, 18-, 19-, and 21-H_3) (Found: C, 66·0; H, 7·85; Br, 14·9. $C_{26}H_{37}BrO_3$ requires C, 65·5; H, 7·85; Br, 16·8%).

3β-*Acetoxy*-16α-*allylpregn*-5-*en*-20-*one* (14c).—To a solution of the foregoing bromo-compound in acetic acid (10 ml) was added an excess of zinc powder and the mixture was shaken at room temperature for 1 h, filtered, and the filtrate poured into water to give a solid which was dried and crystallised from methanol to give the 16α-*allyl compound* (14c), m.p. 130—132°, $[\alpha]_D$ −26·2° (*c* 0·57, $CHCl_3$) (Found: C, 78·2; H, 9·6. $C_{26}H_{38}O_3$ requires C, 78·3; H, 9·6%).

Reaction of the 3′α-*Vinyl Compound* (8b) *with* HBr.—The vinyl methylene compound (70 mg) was treated as above with HBr in acetic acid. The reaction mixture was poured into water and the solid was crystallised from light petroleum (b.p. 60—80°) to give 3β-*acetoxy*-16α-[(S)-1-*bromoprop*-2-*enyl*]*pregn*-5-*en*-20-*one* (14b) (50 mg), m.p. 159—161°, $[\alpha]_D$ −14·1° (*c* 0·71, $CHCl_3$) (Found: C, 65·6; H, 7·8; Br, 16·6. $C_{26}H_{37}BrO_3$ requires C, 65·6; H, 7·85; Br, 16·8%).

Treatment of this bromo-compound with zinc in the manner described above gave the 16α-allyl compound (14c), identical with that prepared from the isomeric bromo-compound.

Catalytic Hydrogenation of the 3′β-*Ethynyl Compound* (9c).—The ethynyl compound (9c) (100 mg) was dissolved in pyridine (10 ml), 10% palladium in calcium carbonate (50 mg) was added, and the mixture was shaken in the presence of hydrogen for 8 min in which time the uptake of hydrogen had stopped. The solution was filtered and the pyridine solution taken to dryness. The resulting oil was taken up in ether, washed in the usual manner to remove traces of pyridine, and evaporated to dryness giving a solid which was crystallised from methanol to give the 3′β-vinyl compound (9a) (50 mg), identical with a previously prepared sample.

Reduction of the 3′β-*Vinyl Compound* (8a) *with Lithium Aluminium Hydride*.—The vinyl compound (8a) (1 g) was dissolved in tetrahydrofuran, a solution of lithium aluminium hydride (200 mg) in tetrahydrofuran was added, and the solution stirred at room temperature for 1 h. The solution was poured into water and the solid formed crystallised from acetone to give 1′β,3′-*dihydro*-3′β-*vinylcyclopropa*-[16,17α]*pregn*-5-*ene*-3β,20ξ-*diol* (13), m.p. 195—201°, $[\alpha]_D$ −114° ($CHCl_3$), δ 0·95 and 1·02 (both 3H, s, 18- and 19-H_3), 1·28 (3H, d, *J* 6·5 Hz, 21-H_3), 6·10 (1H, m, *J* 8·5, 9·5, and 17 Hz; $-CH=$), and 5·01 and 4·91 (2H, m, $=CH_2$) (Found: M^+, 356·2724. $C_{24}H_{36}O_2$ requires, M, 356·2715).

Oppenauer Oxidation of the Dimethylcyclopropane Compound.—The compound (8d) (31 g) was heated under reflux for 30 min in a methanolic solution of potassium hydroxide, the solution was poured into water, and the solid collected and dried to give the 3β-hydroxy-derivative. This was added to toluene (1 l) and cyclohexanone (150 ml) and the solution was distilled to remove water; aluminium isopropoxide (9 g) was then added and the mixture refluxed for 1·5 h. A saturated solution of sodium potassium tartrate was added and the mixture steam-distilled for 5 h. The residue taken up in chloroform, dried, and evaporated to give an oil, which was dissolved in benzene and chromatographed on alumina. Elution with 9 : 1 benzene–ether gave an oil (20 g), which was crystallised from methanol to give 1′β,3-*dihydro*-3′,3′-*dimethylcyclopropa*[16,17a]*pregn*-4-*ene*-3,20-*dione* (9e) (8 g) (see Table 2).

The remaining fractions from the column were combined and crystallised from methanol to give: first crop (5 g), m.p. 115—125°; second crop (200 mg), m.p. 145—165°; third crop (500 mg), m.p. 130—165°. The first crop was recrystallised from methanol to give 16α-isopropenylpregn-4-en-3,20-dione (19a) containing 20% (n.m.r.) of the dimethylcyclopropane (9e), m.p. 118—121° (4·6 g). Further recrystallisation failed to improve the purity.

The third crop was repeatedly recrystallised from methanol to give 16α-*isopropenyl*-17α-*pregn*-4-*ene*-3,20-*dione* (19b) (150 mg), m.p. 175—178°, $[\alpha]_D$ +3·0° ($CHCl_3$), $\nu_{max.}$ (CH_2Cl_2) 1705 (20-oxo), and 1675 and 1620 cm^{-1} (Δ^4-3-oxo), δ 1·03 and 1·18 (both 3H, s, 18- and 19-H_3), 1·65 (3H, s, CH_3–C=), 3·12 (1H, d, *J* 3 Hz, 17β-H), and 4·82 (2H, m, CH_2=) (Found: C, 81·0; H, 9·7. $C_{24}H_{34}O_2$ requires C, 81·3; H, 9·65%).

16α-*Isoproprenylpregn*-4-*ene*-3,20-*dione* (19a).—A 1 : 1 mixture of the dimethylcyclopropane compound (9e) and the 16α-isopropenyl compound (19a) (600 mg) isolated from the mother liquors of the previous experiment was heated under nitrogen for 1 h at 200°. Crystallisation of the resulting melt gave the 16α-*isopropenyl compound* (450 mg), m.p. 124—126°, $[\alpha]_D$ +128° ($CHCl_3$), $\nu_{max.}$ (CH_2Cl_2) 1705 (20-oxo), and 1675 and 1620 cm^{-1} (Δ^4-3-oxo), δ 0·74 and 1·18 (both 3H, s, 18- and 19-H_3), 1·69 (3H, s, CH_3–C=), 2·57 (1H, d, *J* 10 Hz, 17α-H), and 4·66 (2H, m, CH_2=) (Found: C, 81·0; H, 9·7. $C_{24}H_{34}O_2$ requires C, 81·3; H, 9·7%).

1′β,3′-*Dihydro*-3′α-*vinylcyclopropa*[16,17α]*pregn*-4-*ene*-3,20-*dione* (9b).—To a suspension of 3β-acetoxy-1′β,3′-dihydro-3′α-vinylcyclopropa[16,17α]pregn-5-en-20-one (8b) (15 g) in methanol (200 ml) was added a methanolic solution of potassium hydroxide (10 ml; 10%) and the mixture stirred at room temperature for 1 h. The mixture was poured into water, and the solid formed was collected, dried, and dissolved in a mixture of dimethyl sulphoxide (120 ml) and sodium-dried benzene (50 ml). To this solution were added dry pyridine (4 ml), trifluoroacetic acid (1·8 ml), and dicyclohexylcarbodi-imide (30 g), and the mixture was stirred at room temperature for 3 h. Ethyl acetate (200 ml) and oxalic acid (1 g) were then added, and the mixture allowed to stand at room temperature overnight. The mixture was filtered, and the filtrate washed with water, dried, and evaporated to give an oil which was chromatographed on silica gel. Elution with 3 : 1 benzene–ethyl acetate gave a fraction which was treated with dilute hydrochloric acid in acetone. Watering out gave a solid which was crystallised from methanol to give the *dione* (9b) (2 g) (see Table 2).

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