Synthesis of 16-Substituted 17-Nor-13α-steroids and Skeletal Rearrangement of 17-Nor-5α,13α-androstane-16α-carbonyl *m*-Chlorobenzoyl Peroxide†

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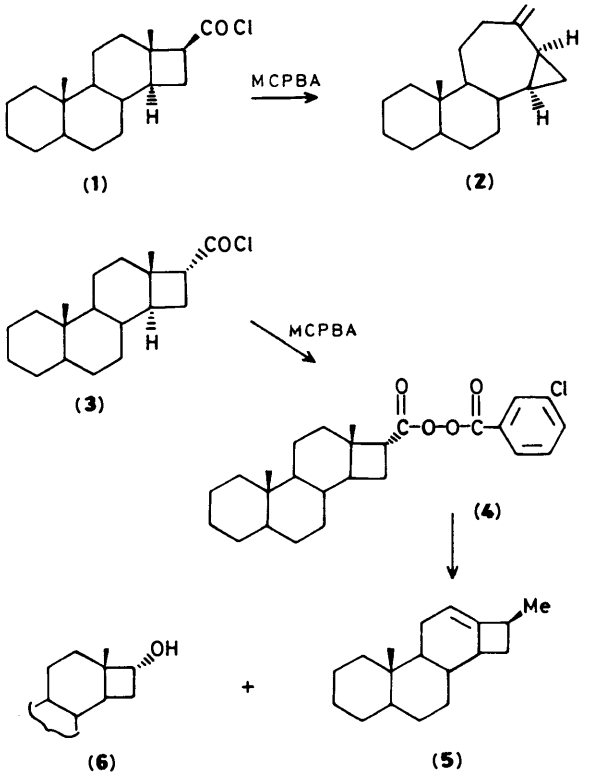
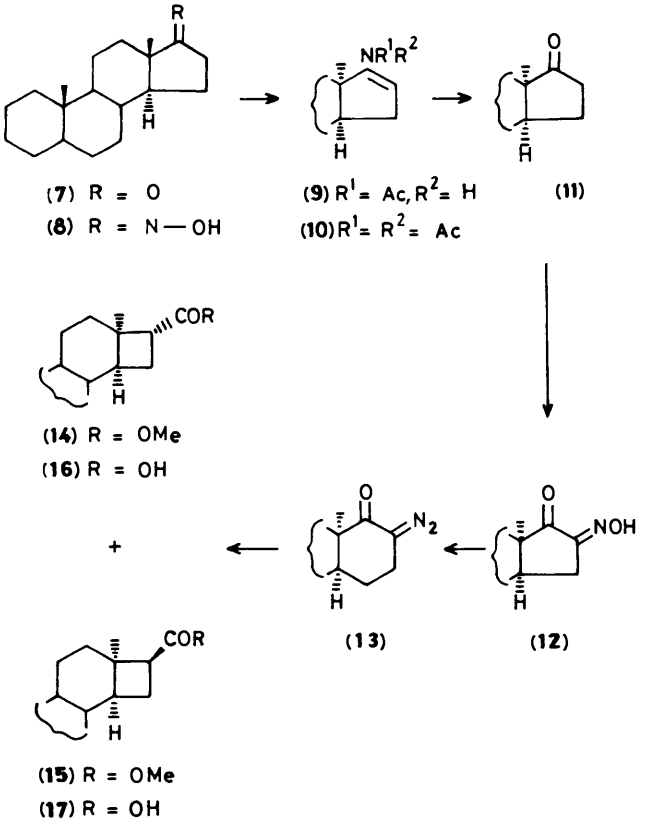
The reaction of 17-nor-5α,13α-androstane-16β-carbonyl chloride with *m*-chloroperbenzoic acid led to a skeletal rearrangement that resulted in an *abeo* homodinorsteroid identical with one obtained by the reaction of 17-nor-5α-androstane-16β-carbonyl chloride with MCPBA, while the reaction of the isomeric 16α-carbonyl chloride with MCPBA gave 17-nor-5α,13α-androstan-16α-yl *m*-chlorobenzoate *via* a carboxy inversion of the initially formed acyl aroyl peroxide followed by decarboxylation. Several 16-substituted 13-epi-D-ring-norsteroids, including 16-nor-5α,13α-pregnan-20-one and its 17α-epimer, 17-nor-5α,13α-androstan-16α- and -16β-ol, and 17-nor-5α,13α-androstan-16-one, were synthesized, for the first time, from 5α,13α-androstan-17-one.

In a previous paper,[1] one of us reported that the reaction of 17-nor-5α-androstane-16β-carbonyl chloride (**1**) with *m*-chloroperbenzoic acid (MCPBA) led to the exclusive formation of an *abeo* homodinorsteroid (**2**) *via* a rearrangement, while the reaction of the 16α-isomer (**3**) with MCPBA gave the corresponding acyl aroyl peroxide (**4**), which was then transformed into 16β-methyl-17,18-dinor-5α-androst-12-ene (**5**) and 17-nor-5α-androstan-16α-ol (**6**) on thermolysis (Scheme 1). We



Scheme 1.

concluded that the rearrangement of acid chloride (**1**) into product (**2**) was triggered by the heterolysis of the O–O bond of the first formed acyl aroyl peroxide, and that compound (**2**) is formed without the intervention of the intermediary mixed carbonate arising from the carboxy inversion. It is thus clear



Scheme 2.

that the geometry of the D-ring and the relevant substituents affect the outcome of the reaction considerably. We decided, therefore, to study in further detail the influence of the geometry of the cyclobutyl moiety and the relative configurations of the relevant substituents.

In this paper, we describe the first synthesis of 16-substituted 5α,13α-androstanes including 16-nor-5α,13α-pregnanes, and the results of the reactions of 17-nor-5α,13α-androstane-16α- and 16β-carbonyl chlorides having a C/D *cis* ring junction with *m*-chloroperbenzoic acid.

† These compounds were previously designated as D-norsteroids (ref. 1).

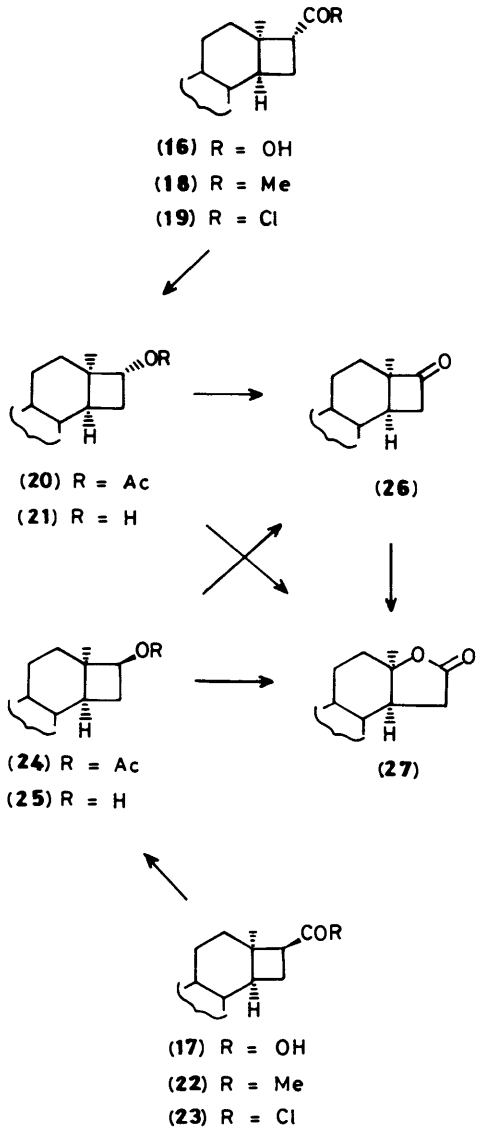
Results

Synthesis of 17-Nor-5α,13α-androstan-16α- and -16β-carboxylic Acids and their Transformations into 17-Nor-5α,13α-androstan-16-ols (**21**) *and* (**25**) *and -16-one* (**26**).—The 17-nor-5α,13α-steroids used in this study were prepared by the photolytic rearrangement of α-diazo ketones.[2–4] 5α,13α-Androstan-17-one (**11**) was prepared for this purpose by epimerization of the 13β-substituent of 5α-androstan-17-one (**7**) more or less according to the procedure devised by Barton and co-workers.[5] Thus, treatment of 5α-androstan-17-one oxime (**8**)[6] with refluxing acetic anhydride and pyridine gave a mixture of enamide (**9**) and enimide (**10**). Hydrolysis of this mixture with 2M-hydrochloric acid in methanol gave 5α,13α-androstan-17-one (**11**). The yield from the oxime was 41.9%. Nitrosation of the C-17 ketone (**11**) under standard conditions gave 16-hydroxyimino-5α,13α-androstan-17-one (**12**) (69% yield), which was then oxidized with alkaline sodium hypochlorite in methanol to give 16-diazo-5α,13α-androstan-17-one (**13**) in 80% yield.

Irradiation of 16-diazo ketone (**13**) in tetrahydrofuran (THF)–methanol under nitrogen by a 450-W Hanovia high-pressure Hg arc through a Pyrex filter for 74 h gave a 1:1 mixture of methyl 17-nor-5α,13α-androstane-16α- (**14**) and -16β-carboxylates (**15**) in 65.7% yield. The isomers were separated by column chromatography. Hydrolysis of the methyl esters (**14**) and (**15**) gave respectively 17-nor-5α,13α-androstane-16α-(**16**) and -16β-carboxylic acid (**17**) (Scheme 2). All the electron-impact (e.i.) mass spectra of the epimeric 16-carboxylic acids (**16**) and (**17**) and methyl esters (**14**) and (**15**) exhibited their base peak at *m/z* 218; this arose from the elimination of acrylic acid or its methyl ester from the D-ring of their molecular ion.[4,7] The configuration of the 16-carboxyl group of the higher melting isomer (**14**) was assigned to be α and that of the lower melting isomer (**15**) to be β from their transformation into the corresponding 16α-(**21**) and 16β-alcohol (**25**) and by determination of the configuration of their 16-hydroxy group by ^{1}H n.m.r. spectroscopy with the aid of a shift reagent[8] and nuclear Overhauser enhancement (n.O.e.). The 16ξ-carboxylic acid (**16**) in benzene was thus treated with methyl-lithium to give 16-nor-5α,13α,17ξ-pregnan-20-one (**18**) in 85% yield. Baeyer–Villiger oxidation of 16-nor-5α,13α,-17α-pregnan-20-one (**18**) with MCPBA afforded 17-nor-5α,13α-androstan-16α-yl acetate (**20**) in 78% yield. The acetate was then hydrolysed with methanolic KOH to give 17-nor-5α,13α-androstan-16α-ol (**21**) as outlined in Scheme 3.

A similar series of reactions of the 16β-carboxylic acid (**17**) gave the isomeric 16-nor-5α,13α-pregnan-20-one (**22**), 17-nor-5α,3α-androstan-16β-yl acetate (**24**), and 17-nor-5α,13α-androstan-16β-ol (**25**). The 16α-alcohol (**21**) was identical with the 16β-alcohol obtained *via* the carboxy-inversion reaction of acid chloride (**19**) (*vide infra*).[9] Oxidation of either alcohol (**21**) or its isomer (**25**) with Jones' reagent resulted in the formation of a lactone, 17-oxa-5α,13α-androstan-16-one (**27**). Oxidation of either alcohol, (**21**) or (**25**), with pyridinium chlorochromate (PCC), however, gave 17-nor-5α,13α-androstan-16-one (**26**). We found that further oxidation of ketone (**26**) with Jones' reagent readily gave the lactone (**27**), as has been reported for the oxidation of the simpler cyclobutanone with potassium dichromate in dilute sulphuric acid.[10] The reaction of 17-nor-5α,13α-androstan-16-one (**26**) with $LiAlH_4$ afforded a mixture of the corresponding C-16 alcohols (**21**) and (**25**) in the ratio 2.7:7.2.

The effects on the chemical shifts of 18-H_3 and 19-H_3 in the ^{1}H n.m.r. for each alcohol in $CDCl_3$ on addition of increasing amounts of Eu(dpm)$_3$* is shown in the Figure. It can be seen



Scheme 3.

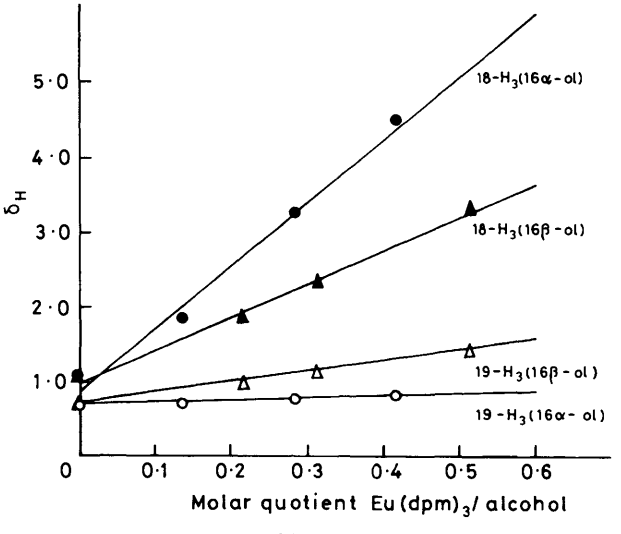
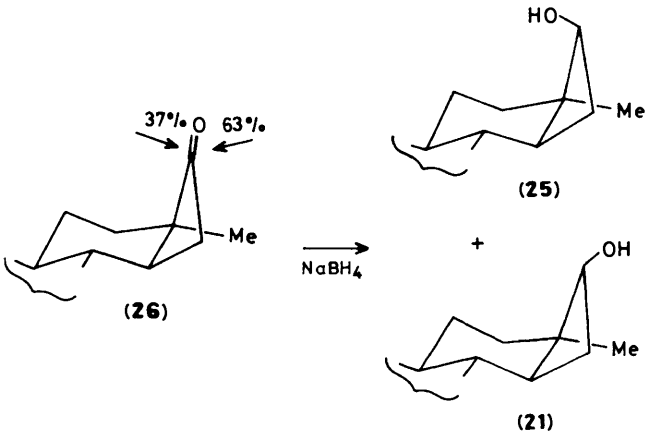


Figure.

* Tris(dipivaloylmethanato)europium(III).

that although the chemical shifts of 18-H_3 in both alcohols move linearly to lower field on addition of the paramagnetic shift reagent, the slope of the least-squares concentration line obtained from 16α-alcohol (**21**) is much steeper than that obtained from the 16β-alcohol (**25**). The reverse effect is true for the chemical shifts of the 19-H_3, also shown in the Figure. On the basis of these results, it is concluded that the 16-hydroxy group of compounds (**25**) and (**21**) is respectively 16β- and 16α-oriented. These assignments are further supported by n.O.e. studies. Thus, saturation of the signal due to 16-H of compound (**25**) resulted in an enhancement of the signal of 18-H_3, while for the isomer (**21**) similar irradiation gave virtually no enhancement of the 18-H_3 signal.

The predominant formation of 16β-alcohol (**25**) in the reduction of 17-nor-5α,13α-androstan-16-one (**26**) with $LiAlH_4$ thus shows that the approach of the complex metal hydride to the carbonyl group of the puckered cyclobutanone ring[11] from the β-face is hindered more appreciably than that from the α-face (Scheme 4).



Scheme 4.

On the basis of the well established stereochemistry of Baeyer–Villiger oxidation, the establishment of the stereochemistry of the 16α-(**21**) and 16β-alcohol (**25**) suggested that the acetyl and carboxylic acid groups of compounds (**18**) and (**16**) are α-oriented while those of their epimers (**22**) and (**17**) are β-oriented.

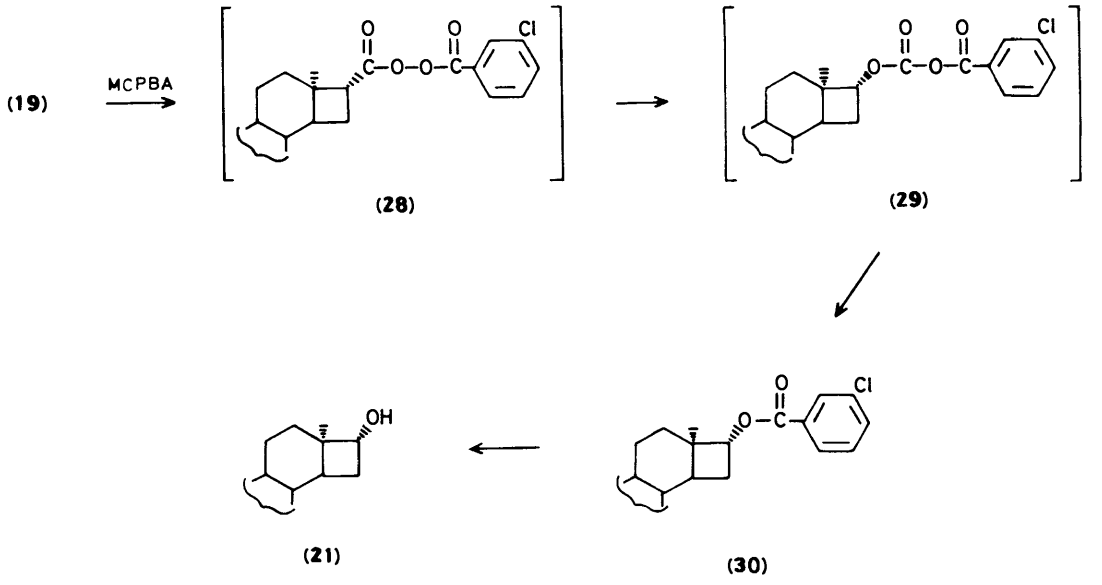
All the e.i. mass spectra of the epimeric C-16 alcohols (**21**) and (**25**), their acetates (**20**) and (**24**), and the C-16 ketone (**26**) showed their base peak at *m/z* 218.[4,7] This ion derives from the respective elimination of the elements of acetaldehyde, vinyl acetate, or ketene from the D-ring of their molecular ion. The e.i. mass spectra of epimeric 16-nor-5α,13α-pregnan-20-ones (**18**) and (**22**) also showed the *m/z* 218 ion as prominent peaks (55 and 81%).

The Reactions of 17-*Nor*-5α,13α-*androstane*-16α- *and* -16β-*Carbonyl Chlorides* (**19**) *and* (**23**).—17-Nor-5α,13α-androstane-16α-carboxylic acid (**16**) was transformed into the corresponding acid chloride (**19**). Reaction of the acid chloride (**19**) with MCPBA gave 17-nor-5α,13α-androstan-16α-yl *m*-chlorobenzoate (**30**), a product deriving from a carboxy-inversion reaction[8] *via* acyl aroyl peroxide (**28**) and mixed carbonate (**29**), in 51% yield. Basic hydrolysis of the ester (**30**) gave 17-nor-5α,13α-androstan-16α-ol (**21**), identical with the product obtained *via* Baeyer–Villiger oxidation of the 16α-acetyl derivative (**18**) (Scheme 5).

17-Nor-5α,13α-androstane-16β-carboxylic acid (**17**) was similarly transformed into the corresponding crystalline acid chloride (**23**) on treatment with thionyl chloride. In contrast to the 16α-isomer (**19**), treatment of acid chloride (**23**) with MCPBA in the presence of pyridine led to the formation of compound (**2**) as the virtually exclusive product, which was identical with the compound obtainable on treatment of 17-nor-5α-androstane-16β-carbonyl chloride (**1**) with MCPBA (Scheme 1).[1]

Discussion

The reaction of acid chlorides with MCPBA has been studied by Denney and Sherman.[9] They found that mixed peroxides derived from MCPBA rearrange by carboxy inversion[12,13] to the mixed carbonates which decompose to some extent under the conditions of the reaction to give alkyl *m*-chloroperbenzoates. They proposed a polar transition state followed by ion-pair(s) formation for the path of the rearrangement of mixed peroxides into mixed carbonates. Walling *et al.* subsequently proposed that polar and radical products in the decomposition of diacyl peroxides derive *via* a single rate-



Scheme 5.

determining transition state, and that product distributions are determined by the partitioning of a subsequent ion pair–radical pair.[14]

In our case both products (**2**) and (**30**) undoubtedly derive from the ionic decomposition of the initially formed 17-nor-5α,13α-androstane-16α-carbonyl *m*-chlorobenzoyl peroxide (**28**) and its 16β-epimer (**31**).

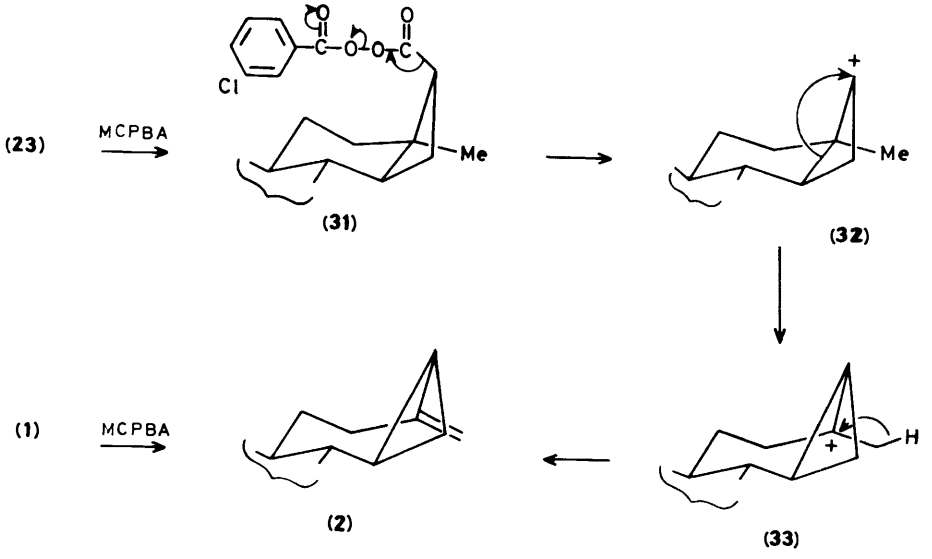
Both our present and previous results, however, indicate that the configuration and conformation of the cyclobutane moieties appreciably influences the outcome of the decompositions of the initially formed mixed peroxides; although 16α-carbonyl chloride (**19**) with MCPBA gives ester (**30**) arising from a normal carboxy inversion, the reaction of 16β-isomer (**23**) with MCPBA leads to a rearranged product (**2**).

The anomalous outcome found in the reaction of 16β-isomer (**23**) can be interpreted on consideration of the conformations of the cyclobutane ring. Although the puckered conformation of conformationally rigid cyclobutane rings of D-ring-norsteroids has been determined by *X*-ray crystallography,[10,15] no exact *X*-ray analysis of the conformation of the cyclobutane rings of D-ring-nor-13α-steroids, where the C/D rings are *cis*-fused, has been carried out. Nevertheless, a puckered conformation such as the one depicted in Scheme 6 can be assumed to be the C-13 epimeric acid chlorides (**1**) and (**23**) (16β-series) with MCPBA give an identical rearranged steroid (**2**) regardless of the configuration of their 13-Me group, while the reactions of the 13-epimeric acid chlorides (**3**) and (**19**) (16α-series) with MCPBA do not lead to the loss of

$$-\overset{\overset{O}{\|}}{C}-O-O-\overset{\overset{O}{\|}}{C}-C_6H_4Cl.$$

and instead give an isolable peroxide (**4**) or a product deriving from a carboxy inversion of the initially formed peroxide (**28**).

As in the case of the decomposition of 17-nor-5α,13α-androstane-16β-carbonyl *m*-chlorobenzoyl peroxide (**31**), the driving force that turns this 13β-epimer (**1**) into product (**2**) appears to be the relief of the steric compression deriving from an interaction between the 16β-substituent and the hydrocarbon framework with the 13β-Me group. The results of the 13β-series indicate that a special relative geometry between the C(13)–C(14) bond and the C(16) substituent, such as we previously considered for the rearrangement of a mixed peroxide formed from acid chloride (**1**) and MCPBA, is not necessarily required for the generation of carbonium ion (**32**), and that the formation of rearranged olefin (**2**) from the reaction



Scheme 6.

conformation of the 13a-D-ring-nor-13α-steroids. The extent of destabilization of the initially formed 17-nor-5α,13α-androstan-16β-carbonyl *m*-chlorobenzoyl peroxide (**31**) is likely to be greater than that of its 16α-epimer because of a greater interaction between the 16-substituent and the hydrocarbon framework. Heterolysis of the O–O bond of the peroxide (**31**) would thus take place under the conditions of the reaction to give a four-membered-ring carbonium ion (**32**) following the loss of CO_2. The relief of steric compression thus appears to be the driving force which leads to the carbonium ion (**32**). A Wagner–Meerwein rearrangement of ion (**32**) then generates another carbonium ion (**33**), from which a proton is lost to afford compound (**2**).

The present results have shown that the results of the reactions of 17-nor-5α-androstan-16α- and -16β-carbonyl chlorides (**1**) and (**3**), both with a C/D *trans* junctions with MCPBA and those of 17-nor-5α,13α-androstan-16α- and -16β-carbonyl chlorides (**19**) and (**23**), both with a C/D *cis* junction, with MCPBA are broadly parallel. Namely, the reactions of the of acid chloride (**1**) with MCPBA may well involve a cyclobutyl carbonium ion.

With regard to the reaction of acid chlorides of the 16α-series, the foregoing results show that a rearrangement of mixed peroxide (**28**) into mixed carbonate (**29**) takes place in a stereospecific manner, such as has already been reported by several investigators for other peroxides.[16] While peroxide (**4**) can be isolated in the reaction of acid chloride (**3**) with MCPBA, the product in the reaction of acid chloride (**19**) with MCPBA is an ester (**30**) which arises from a decarboxylation. The reason is not clear at present.

Experimental

M.p.s were recorded with a Yanagimoto micro m.p. apparatus and are uncorrected. I.r. spectra were determined for Nujol mulls with a Hitachi Model 285 i.r. spectrometer unless otherwise stated. ^{1}H N.m.r. spectra were determined with a JEOL PS200 high-resolution f.t.-n.m.r. spectrometer (200 MHz)

(solvent $CDCl_3$; $SiMe_4$ as internal standard) (Faculty of Pharmaceutical Sciences of this University). T.l.c. was carried out on Merck Kieselgel 60 PF_{254}. The high- and low-resolution mass spectra were determined with a JEOL JMA-D 300 spectrometer (70 eV) (Faculty of Agriculture of this University). Elemental analysis was performed by the staff of the Laboratory for microanalysis of the Faculty of Pharmaceutical Sciences of this University. Field desorption (F.D.) mass spectra were determined with a JEOL JMS 01SG-2 spectrometer (Faculty of Agriculture of this University).

Synthesis of 5α,13α-*Androstan*-17-*one* (**11**).—A solution of 5α-androstan-17-one oxime[6] (**8**) (21 g), prepared from 5α-androstan-17-one (**7**), in dry pyridine (800 ml) containing acetic anhydride (500 ml) was heated under reflux for 12 h. After removal of the solvent, the black residual oil was dissolved in diethyl ether and the solution was filtered through Celite to remove insoluble material. The filtrate was washed successively with 5% aq. sodium carbonate, water, and brine, and dried over anhydrous magnesium sulphate. Evaporation of the solvent gave a light brown oily mixture of enamide (**9**) and enimide (**10**). The mixture was dissolved in methanol (1 500 ml), treated with 2M-hydrochloric acid (500 ml), and heated under reflux for 1 h. After removal of methanol, the residue was extracted with diethyl ether. The extract was washed successively with 5% aq. sodium hydrogen carbonate, water, and brine, and dried over anhydrous magnesium sulphate. Evaporation of the solvent gave a crude 5α,13α-androstan-17-one (**11**) (17.05 g) containing a small amount of the 13β-isomer (**7**). The crude 13α-isomer (**11**) was subjected to column chromatography (Merck Kieselgel 60; 70—230 mesh; 500 g). Elution with a 1:2 mixture of dichloromethane–hexane gave two fractions. The first fraction, A (1.9 g), was an unidentified oil, while the second fraction, B (1.55 g), was a mixture of an unidentified oil and 5α,13α-androstan-17-one. Further elution with a 1:1 mixture of dichloromethane–hexane gave 5α,13α-androstan-17-one (6.91 g), a mixture of 13α- and 13β-isomers (0.22 g), and 5α-androstan-17-one (1.68 g) successively. Fraction B was again subjected to column chromatography to give pure 5α,13α-androstan-17-one (1.28 g). The mixture of 13α- and 13β-isomer was subjected to preparative t.l.c. (p.l.c.) with a 2:1 mixture of dichloromethane–hexane as developer to give a further crop of 5α,13α-androstan-17-one (155 mg). The total amount of the 13α-isomer (**11**) obtained was 8.43 g (41.9%), m.p. 120—122 °C; δ_H 0.62 (3 H, s, 19-H_3) and 0.96 (3 H, s, 18-H_3); *m/z* 274 (M^+, 100%), 124 (94.5), 110 (71.7), and 97 (93.9).

Preparation of 16-*Hydroxyimino*-5α,13α-*androstan*-17-*one* (**12**).—Potassium t-butoxide (11.2 g) was dissolved in anhydrous t-butyl alcohol (190 ml) under nitrogen. After the ketone (**11**) (3.5 g) had been dissolved in this solution at 30—35 °C, butyl nitrite (6 ml) was added dropwise. The solution was stirred for 6 h at 30—35 °C and then poured into ice–water. After the addition of 2M-hydrochloric acid, the solution was extracted with dichloromethane. The extract was worked up as usual. The yellow oily product (3.71 g) was subjected to column chromatography (300 g). Elution with 5:1 benzene–diethyl ether gave a fraction, which was recrystallized from methanol to yield the *oxime* (**12**) (6.345 g), m.p. 169.5—170.5 °C (Found: C, 74.8; H, 9.6; N, 4.65. $C_{19}H_{29}NO_2$ requires C, 75.20; H, 9.63; N, 4.62%); $\nu_{max.}$($CHCl_3$) 3 216 (OH), 1 731 (C=O), 1 633 (C=N), 1 292—1 162, 942, 908, and 901 cm^{-1}; δ_H 0.59 (3 H, s, 19-H_3) and 1.04 (3 H, s, 18-H_3); *m/z* 303 (M^+, 2.1%), 258 (67.7), and 56 (100).

16-*Diazo*-5α,13α-*androstan*-17-*one* (**13**).—To a solution of 16-hydroxyimino-5α,13α-androstan-17-one (**12**) (6.35 g) in methanol (165 ml) containing 5M-sodium hydroxide was added conc. ammonium hydroxide (15 ml). To the solution, cooled in a water-bath, was added dropwise an alkaline aq. sodium hypochlorite (active chlorine 5%) (90 ml). The solution was stirred for 5 h and further aq. sodium hypochlorite (20 ml) was added; the solution was then stirred for 15.5 h. Yellow crystals of diazo steroid, which had crystallized out from the solution, were collected by filtration. The crystals (4.637 g) were washed with water and dried. The filtrate was extracted with dichloromethane and the extract was worked up as usual to give crystals of diazo steroid (**13**) (0.685 g). These crystals were purified once by p.l.c. to give pure *diazo steroid* (**13**) (0.403 g). An analytical specimen was obtained by recrystallization from methanol, m.p. 153—155 °C (Found: M^+, 300.2203. $C_{19}H_{28}N_2O$ requires *M*, 300.2202); $\nu_{max.}$ 2 082 (N≡N), 1 661 (C=O), 1 343, 1 251, and 976 cm^{-1}; δ_H 0.65 (3 H, s, 19-H_3), 1.04 (3 H, s, 18-H_3), 2.66 (1 H, d, *J* 13.3 Hz, 15α-H), and 3.16 (1 H, dd, *J* 13.3 and 6.1 Hz, 15β-H); *m/z* 300 (M^+, 4.6), 272 ($M^+ - N_2$, 19.3), 257 ($M^+ - N_2$ – Me, 14.6), 217 (M^+ – D-ring, 52.9), and 109 (100%).

Methyl 17-*Nor*-5α,13α-*androstane*-16α- *and* -16β-*carboxylate* (**14**) *and* (**15**).—A solution of diazo ketone (**13**) (5.04 g) in a mixture of dry THF (215 ml) and methanol (65 ml) was irradiated under nitrogen with a 450-W Hanovia lamp through a Pyrex filter for 74 h. The reaction mixture was filtered to remove colourless solids, and the solvent was removed from the filtrate on a rotary evaporator to give an oily product (5.28 g). The product was subjected to column chromatography (Silica gel; 160 g). Elution with 1:1 benzene–hexane gave three fractions, A, B, and C in order of elution. Fraction A (650 mg) gave the oily 13α,16β-isomer (**15**) of the title ester. The second oily fraction (2.31 g) was a 51:4 mixture of 13α,16β- (**15**) and 13α,16α-isomer (**14**). The final fraction, C (398 mg), gave a crystalline 13α,16α-isomer (**14**). The 13α,16β-*isomer* (**15**) was crystallized from aq. methanol, m.p. 53.5—54.5 °C (Found: C, 78.7; H, 10.6. $C_{20}H_{32}O_2$ requires C, 78.90; H, 10.95%); $\nu_{max.}$ 1 737 (C=O), 1 183, and 1 174 cm^{-1}; δ_H 0.71 (3 H, s, 19-H_3), 1.19 (3 H, s, 18-H_3), 2.75 (1 H, t, *J* 8.6 Hz, 16α-H), and 3.65 (3 H, s, OMe); *m/z* 304 (M^+, 5.0%), 218 (100), 203 (40.5), 175 (32.7), 148 (40.7), 109 (68.3), and 108 (56.7).

The 13α,16α-isomer (**14**) was recrystallized from methanol, m.p. 89.5—91.0 °C (Found: C, 78.6; H, 10.7. $C_{20}H_{32}O_2$ requires C, 78.9; H, 10.6%); $\nu_{max.}$ 1 728 (C=O), 1 191, and 1 176 cm^{-1}; δ_H 0.74 (3 H, s, 19-H_3), 1.03 (3 H, s, 18-H_3), 2.56 (1 H, dt, *J* 6.84 and 10.74 Hz, 15-H), 3.12 (1 H, dd, *J* 7.81 and 1.96 Hz, 16β-H), and 3.64 (3 H, s, OMe); *m/z* 304 (M^+, 3.8%), 219 (100), 203 (41.9), 175 (29.3), 148 (40.1), 109 (81.7), and 108 (55.0). The combined yield of 16α- and 16β-isomer was 65.7%, and the calculated yields of 16α- and 16β-isomer were 32.2 and 33.5% respectively.

17-*Nor*-5α,13α-*androstane*-16α- *and* -16β-*carboxylic Acids* (**16**) *and* (**17**).—A solution of methyl 17-nor-5α,13α-androstane-16α-carboxylate (**14**) (398 mg) in a mixture of methanol (90 ml) and water (25 ml) containing potassium hydroxide (5.2 g) was heated under reflux for 3.5 h. The solution was then neutralized with 2M-hydrochloric acid (45 ml) and extracted with dichloromethane (3 ×). The combined extracts were worked up as usual to yield a crude carboxylic acid (371 mg), which was recrystallized from methanol to afford the *acid* (**16**), m.p. 211—213 °C (Found: C, 78.2; H, 10.4. $C_{19}H_{30}O_2$ requires C, 78.57; H, 10.41%); $\nu_{max.}$ 1 702 cm^{-1} (CO_2H); δ_H 0.75 (3 H, s, 19-H_3), 1.11 (3 H, s, 18-H_3), 2.42 (1 H, dt, *J* 7.32 and 10.74 Hz, 15-H), and 3.15 (1 H, dd, *J* 7.32 and 2.45 Hz, 16β-H); *m/z* 290 (M^+, 8.64%), 275 (M^+ – Me, 8.2), 218 (100), 203 (47.8), 175 (32.0), 148 (35.9), 109 (72.2), and 108 (59.4).

Methyl 17-nor-5α,13α-androstane-16α-carboxylate (**15**) was similarly hydrolysed to give the corresponding *carboxylic acid* (**17**), m.p. 116—124 °C (from aq. methanol) (Found: C, 78.19; H, 10.32%); $\nu_{max.}$ 1 698 cm^{-1} (CO_2H); δ_H 0.72 (3 H, s, 19-H_3), 1.21 (3

H, s, 18-H_3), 2.27 (1 H, dt, *J* 5.37 and 11.72 Hz, 15-H), and 2.80 (1 H, t, *J* 8.79 Hz, 16α-H); *m/z* 290 (M^+, 15.8%), 275 (M^+ − Me, 8.9), 218 (100), 203 (36.6), 175 (28.6), 148 (34.1), 109 (60.3), and 108 (50.8).

17-*Nor*-5α,13α-*androstane*-16α- *and* -16β-*carbonyl Chlorides* (**19**) *and* (**23**).—17-Nor-5α,13α-androstane-16α-carboxylic acid (**16**) (51 mg) was dissolved in freshly distilled thionyl chloride (4 ml) at room temperature. To this solution was added a catalytic amount of pyridine, and the solution was stirred at room temperature for 4 h. To the reaction mixture was added benzene, and the excess of the reagent and pyridine were removed by distillation under reduced pressure to yield an oily chloride (**19**) (53 mg, 98%), $\nu_{max.}$ 1 793 (COCl), 1 062, 908, and 785 cm^{-1}. This chloride was immediately subjected to reaction with MCPBA (see below).

The 16β-carboxylic acid (**17**) (53 mg) was similarly transformed into the corresponding crystalline chloride (**23**) (55 mg, 98%), $\nu_{max.}$ 1 797 (COCl), 1 062, 877, 865, 796, and 786 cm^{-1}. This chloride was immediately subjected to the next step.

Reaction of 17-*Nor*-5α,13α-*androstane*-16β-*carbonyl Chloride* (**23**) *with MCPBA*.—To a solution of the 16β-carbonyl chloride (23) (55 mg) in dry hexane (1.5 ml) at 0 °C was added a solution of MCPBA (60 mg) in a mixture of cyclohexane (0.4 ml) and dry pyridine (0.1 ml). The solution was stirred for 1.5 h at 0 °C, benzene was added, and the solution was washed successively with 5% aq. $Na_2S_2O_3$, water, and brine, and then dried. Removal of the solvent gave a rearranged steroid (**2**), which was purified by p.l.c. with hexane as developer to afford a gum (24 mg, 55%), δ_H 0.26 (1 H, dd, *J* 4.88 and 9.77 Hz, cyclopropyl proton), 0.58 (1 H, m, cyclopropyl proton), and 0.73—1.00 (2 H, m, cyclopropyl protons).

Reaction of 17-*Nor*-5α,13α-*androstane*-16α-*carbonyl Chloride* (**19**) *with MCPBA*.—The 16α-carbonyl chloride (**19**) (53 mg) was subjected to reaction with MCPBA as in the case of the 16β-carbonyl chloride (**23**). T.l.c. examination of the crude product (80 mg) indicated that it was almost a single product, contaminated with some minor polar products. The major ester was purified by p.l.c. with hexane as developer to give oily 17-*nor*-5α,13α-*androstan*-16α-*yl* m-*chlorobenzoate*(**30**) (35 mg, 51%), which crystallized after treatment with methanol, m.p. 56.5—58.5 °C (Found: M^+, 400.2177. $C_{25}H_{33}ClO_2$ requires *M*, 400.2168); $\nu_{max.}$ 1 723 cm^{-1} (C=O), 1 575, 1 288, 1 250, 1 130, 1 072, and 752 cm^{-1}; δ_H 0.75 (3 H, s, 19-H_3), 1.16 (3 H, s, 18-H_3), 2.02 (1 H, dd, *J* 11.23 and 7.33 Hz, 15α-H), 2.33 (1 H, dd, *J* 11.23 and 8.30 Hz, 15β-H), 5.29 (1 H, t, *J* 8.30 Hz, 16β-H), 7.33—7.55 (2 H, m, ArH), and 7.88—8.00 (2 H, m, ArH); *m/z* (f.i.m.s.) 400 (M^+, 100%) and 245 (M^+ − *m*-chlorobenzoyl, 6.4).

17-*Nor*-5α,13α-*androstan*-16α-*ol* (**21**).—A mixture of the *m*-chlorobenzoyl ester (**30**) (10 mg), methanol (1.2 ml), water (0.3 ml), and diethyl ether (0.3 ml) containing sodium hydroxide (80 mg) was stirred for 2 h at room temperature. The solvent was removed under diminished pressure, and the residue was neutralized with 2M-hydrochloric acid; the solution was extracted with diethyl ether. Work-up as usual gave the 16α-*alcohol* (**21**) (8 mg), which was recrystallized from aq. methanol, m.p. 125.5—127.5 °C (Found: C, 82.4; H, 11.55. $C_{18}H_{30}O$ requires C, 82.38; H, 11.52%); $\nu_{max.}$ 3 317 cm^{-1} (OH); δ_H 0.71 (3 H, s, 19-H_3), 1.04 (3 H, s, 18-H_3), and 4.19 (1 H, t, *J* 7.82 Hz, 16β-H); *m/z* 262 (M^+, 0.3%), 218 (100), 203 (18.3), 175 (15.8), 148 (19.4), 109 (30.7), and 108 (20.1).

Preparation of 16-*Nor*-5α,13α,17β-*pregnan*-20-*one* (**22**).—To a stirred solution of the 16β-carboxylic acid (**17**) (100 mg) in dry benzene (8.5 ml) was added dropwise 0.58M-methyl-lithium in diethyl ether (0.6 ml). Three further amounts of the methyl-lithium solution (each of 0.6 ml) were added to the stirred solution at 30 min intervals at room temperature. The solution was then poured into ice–water and extracted with diethyl ether, and the extract was worked up as usual. The crude product was purified by p.l.c. (87 mg) (30:1 benzene–diethyl ether) and was then recrystallized from methanol to yield 16-*nor*-5α,13α,17α-*pregnan*-20-*one* (**22**), m.p. 84.5—86.5 °C (Found: M^+, 288.2455. $C_{20}H_{32}O$ requires *M*, 288.2454); $\nu_{max.}$ 1 710 cm^{-1} (Ac); δ_H 0.70 (3 H, s, 19-H_3), 1.29 (3 H, s, 18-H_3), 2.01 (3 H, s, Ac), and 2.92 (1 H, t, *J* 8.70 Hz, 17α-H); *m/z* 288 (M^+, 3.5%), 230 (71.2), 218 (80.9), 109 (100), 81 (74.1), 67 (71.5), and 55 (52.6).

Preparation of 17-*Nor*-5α,13α-*androstan*-16α-*yl Acetate* (**24**).—16-Nor-5α,13α,17β-pregnan-20-one (**22**) (37 mg), MCPBA (35 mg), and toluene-*p*-sulphonic acid (PTSA) (0.7 mg) were dissolved in dichloromethane (3 ml) in a vessel covered by aluminium foil, and the solution was stirred for 72 h at room temperature. Further amounts of the reagents were added after 20 h and 69 h [MCPBA (5 mg), PTSA (0.1 mg) each]. The excess of peracid was then decomposed by addition of 5% aq. sodium thiosulphite. The solution was washed successively with 10% aq. sodium hydrogen carbonate and water, and dried (Na_2SO_4). The solution was worked up as usual to give an oily acetate (41 mg), which was purified by p.l.c. (50:1 benzene–diethyl ether) to give the *title compound* (Found: M^+, 304.2423. $C_{20}H_{32}O_2$ requires *M*, 304.2402); $\nu_{max.}$(neat) 1 738 (C=O) and 1 240 cm^{-1} (C–O); δ_H 0.74 (3 H, s, 19-H_3), 1.14 (3 H, s, 18-H_3), 2.03 (3 H, s, Ac), 2.62 (1 H, m, 15-H), and 4.68 (1 H, t, *J* 8.0 Hz, 16α-H); *m/z* 304 (M^+, 0.01%), 244 (0.38, $M^+ - CH_3CO_2H$), 218 (100), 203 (30.5), 175 (29.4), 148 (37.4), and 109 (64.1).

17-*Nor*-5α,13α-*androstan*-16β-*ol* (**25**).—The acetate (**24**) (20 mg) was dissolved in methanol (10 ml) containing water (3 ml) and was hydrolysed with potassium hydroxide (550 mg), the solution being stirred for 2 h at room temperature. The solution was extracted with diethyl ether, and the extract was washed successively with 2M-hydrochloric acid and water, and dried ($MgSO_4$). The crude product was recrystallized from aq. methanol to yield the 16β-*alcohol* (**25**), m.p. 114.5—116.0 °C (Found: M^+, 262.2331. $C_{18}H_{30}O$ requires *M*, 262.2296); $\nu_{max.}$ 3 300 cm^{-1} (OH); δ_H 0.74 (3 H, s, 19-H_3), 1.06 (3 H, s, 18-H_3), 2.60 (1 H, m, 15-H), and 3.84 (1 H, t, *J* 7.8 Hz, 16α-H); *m/z* 262 (M^+, 0.01%), 218 (100), 203 (13.2), 148 (11.0), 109 (8.5), and 108 (6.7).

Preparation of 16-*Nor*-5α,13α,17α-*pregnan*-20-*one* (**18**).—This *compound* was prepared from the 16α-carboxylic acid (**16**) by the same procedure as for the preparation of 16-nor-5α,13α.17α-pregnan-20-one (**22**), and was recrystallized from methanol, m.p. 87.0—88.5 °C (Found: M^+, 288.2456. $C_{20}H_{32}O$ requires *M*, 288.2453); $\nu_{max.}$ 1 703 cm^{-1} (Ac); δ_H 0.76 (3 H, s, 19-H_3), 0.98 (3 H, s, 18-H_3), 2.47 (1 H, m, 15-H), and 3.23 (1 H, dd, *J* 7.8 and 2.0 Hz, 17β-H); *m/z* 288 (M^+, 8.2%), 273 (M^+ − Me, 6.4), 230 (61.6), 218 (54.6), 203 (42.1), 175 (35.4), 148 (45.3), 109 (88.4), 108 (60.7), 93 (48.0), 81 (66.5), 79 (59.6), 67 (70.9), and 43 (100).

Preparation of 17-*Nor*-5α,13α-*androstan*-16α-*yl Acetate* (**20**).—This acetate was prepared from 16-nor-5α,13α,17α-pregnan-20-one (**18**) by Baeyer–Villiger oxidation following the same procedure as for oxidation of the 17β-isomer (**22**). The *acetate* (**20**) had m.p. 67.5—68.0 °C (from methanol) (Found: C, 78.8; H, 10.5. $C_{20}H_{32}O_2$ requires C, 78.9; H, 10.6%); $\nu_{max.}$ 1 738 (Ac), 1 244 (C–O), and 1 066 cm^{-1}; δ_H 0.72 (3 H, s, 19-H_3), 1.05 (3 H, s, 18-H_3), 2.02 (3 H, s, Ac), 2.20 (1 H, m, 15-H), and 5.05 (1 H, t, *J* 6.0 Hz, 16β-H); *m/z* 304 (M^+, 0.02%), 244 ($M^+ + CH_3CO_2H$, 0.53), 218 (100), 203 (27.8), 175 (24.3), 148 (30.7), and 109 (54.4).

17-*Nor*-5α,13α-*androstan*-16α-*ol* (**21**).—Hydrolysis of the acetate (**20**) by standard procedure gave the 16α-alcohol (**21**), which was identical with the specimen obtained by hydrolysis of 17-nor-5α,13α-androstan-16α-yl *m*-chlorobenzoate (**30**).

Oxidation of 17-*Nor*-5α,13α-*androstan*-16-*ols,* (**21**) *and* (**25**).—(a) *With PCC.* To a solution of PCC (11 mg) in dichloromethane (2 ml) at room temperature was added a solution of the 16β-alcohol (**25**) (12 mg) in dichloromethane (2 ml). The solution was stirred for 4.5 h, then filtered, and the filtrate was neutralized with 5% aq. sodium hydrogencarbonate. After removal of dichloromethane the residue was extracted with diethyl ether. The extract was worked up as usual to yield the crude ketone (**26**) (13 mg), which was purified once by p.l.c. (10:1 benzene–diethyl ether) to give oily 17-*nor*-5α,13α-*androstan*-16-*one* (**26**) (8 mg), and which crystallized on the addition of chloroform, m.p. 79—83 °C [Found: M^+(f.i.m.s.), 260.2154. $C_{18}H_{28}O$ requires *M*, 260.2141]; $\nu_{max.}$ 1 774 (C=O) and 1 054 cm^{-1}; δ_H 0.68 (3 H, s, 19-H_3), 1.21 (3 H, s, 18-H_3), 2.46 (1 H, dd, *J* 3.1 and 16.7 Hz, 15α-H), and 3.40 (1 H, dd, *J* 8.8 and 16.7 Hz, 15β-H); *m/z* (f.i.m.s) 260 (M^+, 29.4%) and 218 (100). Oxidation of the 16α-alcohol (**21**) gave analogous results.

(b) *With Jones' Reagent.* To a solution of the 16α-alcohol (**21**) (10 mg) in acetone (5 ml) at room temperature was added Jones' reagent dropwise; the mixture was stirred for 4.5 h, and then worked up as usual to yield 17-oxa-5α,13α-androstan-16-one (**27**) (9 mg); this is identical with a specimen obtained by the Baeyer–Villiger oxidation of the ketone (**26**).

Reduction of 17-*Nor*-5α,13α-*androstan*-16-*one* (**26**) *with Lithium Aluminium Hydride.*—Lithium aluminium hydride (10 mg) was added to a THF solution of the ketone (**26**) (8 mg in 4 ml) at room temperature. After the solution had been stirred for 45 min, water was added and the solution was filtered. After removal of the solvent, the residue was extracted with diethyl ether. The extract was worked up as usual. ^1H N.m.r. spectroscopy of the residue showed that the crude product was a 37:63 mixture of the 16α- and 16β-alcohol (**21**) and (**25**).

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References

1 H. Suginome and T. Uchida, *J. Chem. Soc., Perkin Trans. 1*, 1980, 943. Errata on page 945, right column, line 39 and lines 43—45.
2 J. Meinwald, *Rec. Chem. Prog.*, 1961, **22**, 39.
3 M. P. Cava and E. Moroz, *J. Am. Chem. Soc.*, 1962, **84**, 115; J. L. Mateos and O. Chao, *Bol. Inst. Quim. Univ. Nac. Auton. Mex.*, 1961, **13**, 3; G. Muller, C. Huyuh, and J. Mathiew, *Bull. Soc. Chim. Fr.*, 1962, 296; J. Meinwald, L. Labana, and T. Wheeler, *J. Am. Chem. Soc.*, 1970, **92**, 1006.
4 G. Eadon, S. Popov, and C. Djerassi, *J. Am. Chem. Soc.*, 1972, **94**, 1282.
5 R. B. Boar, F. K. Jetnah, J. F. McGhie, M. S. Robinson, and D. H. R. Barton, *J. Chem. Soc., Perkin Trans. 1*, 1977, 2163.
6 J. Hora, *Collect. Czech. Chem. Commun.*, 1965, **30**, 70.
7 H. Suginome, T. Uchida, K. Kizuka, and T. Masamune, *Bull. Chem. Soc. Jpn.*, 1980, **53**, 2285.
8 J. K. M. Saunders and D. H. Williams, *Nature*, 1972, **240**, 485 and refs. cited therein; 'Nuclear Magnetic Resonance Shift Reagents,' ed. R. S. Sievers, Academic Press, New York, 1973.
9 D. B. Denney and N. Sherman, *J. Org. Chem.*, 1965, **30**, 3760 and papers cited therein.
10 R. Jeanne-Carlier and F. Bourelle-Wargnier, *Tetrahedron Lett.*, 1075, 1841; *Bull. Soc. Chim. Fr.*, 1976, 297.
11 For a review of the conformation of the four-membered ring see R. M. Moriarty in 'Topics in Stereochemistry,' eds. E. L. Eliel and N. L. Allinger, Wiley, New York, 1974, vol. 8, p. 271.
12 J. E. Leffler, *J. Am. Chem. Soc.*, 1950, **72**, 67; J. E. Leffler and C. C. Petropoulos, *ibid.*, 1957, **79**, 3068.
13 For a review see R. Hiatt, 'Organic Peroxides,' ed. D. Swern, Wiley, New York, 1971, vol. 2, p. 799.
14 C. Walling, H. P. Waits, J. Milovanovic, and C. G. Pappiannou, *J. Am. Chem. Soc.*, 1970, **92**, 4927.
15 P. Coggon and A. T. McPhail, *Chem. Commun.*, 1971, 1133.
16 H. H. Lau and H. Hart, *J. Am. Chem. Soc.*, 1959, **81**, 4897; F. D. Green, H. P. Stein, C. C. Chu, and F. M. Vane, *ibid.*, 1964, **86**. 2080; C. Walling, H. N. Moulden, J. H. Waters, and R. C. Neuman, *ibid.*, 1965, **87**, 518.

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