Synchronous Skeletal Rearrangement of D-Nor-5α-androstane-16α- and -16β-carbonyl *m*-Chlorobenzoyl Peroxides

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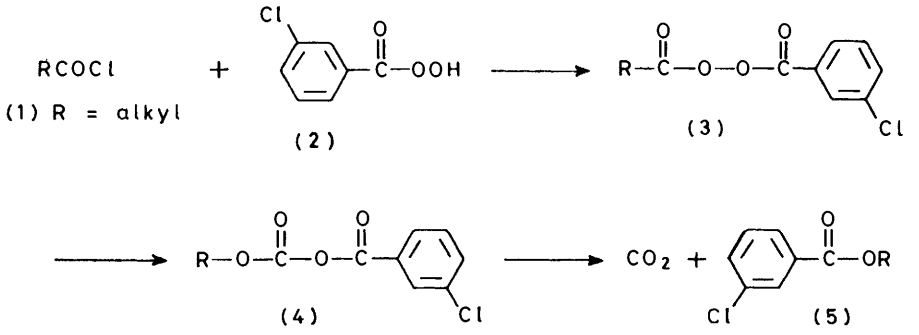
The reaction of D-nor-5α-androstan-16β-carbonyl chloride, a steroidal cyclobutanecarbonyl chloride, with *m*-chloroperbenzoic acid leads *via* rearrangement to a C-homo-D-bisnor-steroid. In contrast, the 16α-isomer with *m*-chloroperbenzoic acid afforded the corresponding stable acyl aroyl peroxide which underwent competitively a carboxy-inversion reaction and the migration of the 13β-methyl group upon reflux in benzene.

MIXED peroxides (3) derived from a reaction of acid chloride (1) with *m*-chloroperbenzoic acid (2), rearrange to the mixed carbonates (4) which further decompose to alkyl *m*-chlorobenzoates (5) [1,2] (Scheme 1). The reaction



SCHEME 1

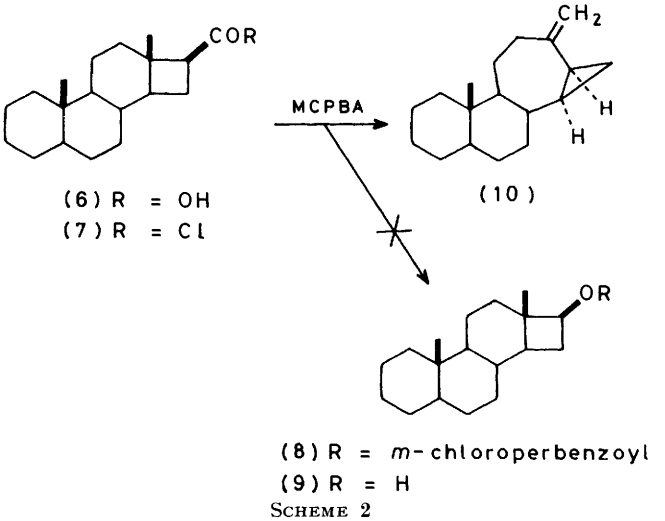
was examined for a number of acids and the generality of the transformation of an acid into an alcohol with the loss of one carbon atom was reported.[1] The carboxy-inversion reaction of acyl peroxides is catalysed by proton [3] and Lewis acids [4] and proceeds faster in polar solvents.[3] The rearrangement was shown to be stereospecific.[5] ^{18}O Labelling experiments [6] were also carried out in order to clarify the inversion step.

In the course of an investigation of the photoreaction of a steroidal cyclobutanol derivative,[7] we treated D-nor-5α-androstane-16β-carbonyl chloride (7), m.p. 232—233°, prepared by the reaction of the corresponding acid (6) with thionyl chloride, with *m*-chloroperbenzoic acid (MCPBA) in hydrocarbon solvents with the purpose of preparing D-nor-5α-androstan-16β-ol (9).

The product (10), obtained virtually as a sole product, was found not to be the expected 16β-ol *m*-chloroperbenzoate (8). The product, purified by preparative t.l.c., resisted all attempts at crystallization. The molecular formula $C_{18}H_{28}$ was determined by high-resolution mass spectrometry. The i.r. spectrum showed no hydroxy-band and exhibited bands at 1 640 and 895 cm^{-1} due to a terminal methylene group. The n.m.r. spectrum exhibited three cyclopropyl protons as a multiplet at τ 9.20—9.52 and one cyclopropyl proton as a double doublet at τ 9.77 (*J* 9 and 5 Hz). It also showed a three-proton singlet at τ 9.32 and two-proton broad singlet at τ 5.22 ascribable to 19-H_3 and the terminal methylene protons. The ^{13}C n.m.r. spectrum of the product (10) which exhibited two signals due to sp^2 carbons at δ 111.2 and 151.3 p.p.m. confirmed this. These signals were assignable to a carbon bearing two protons and a tertiary carbon in the terminal methylene group by the aid of an off-resonance decoupled spectrum.

The C-homo-D-bisnor-steroid (10), which is analogous to the product from the thermal decomposition of D-nor-steroid-16α-*N*-nitrosoacetamide,[8] is fully consistent with these spectral properties.

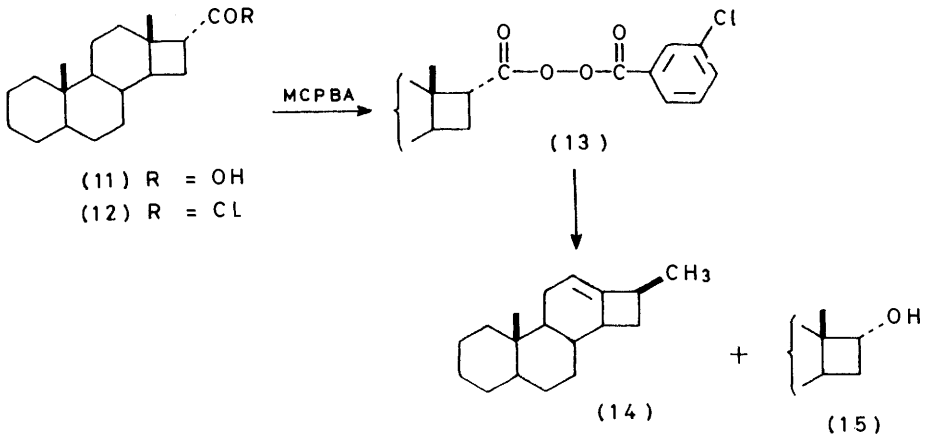
In contrast with the 16β-isomer (7), the reaction of



SCHEME 2

the acid chloride (12), derived from the D-nor-5α-androstane-16α-carboxylic acid, with *m*-chloroperbenzoic acid led to a stable acyl aroyl peroxide (13), m.p. 101—103°. No accompanying rearranged products, *i.e.* the

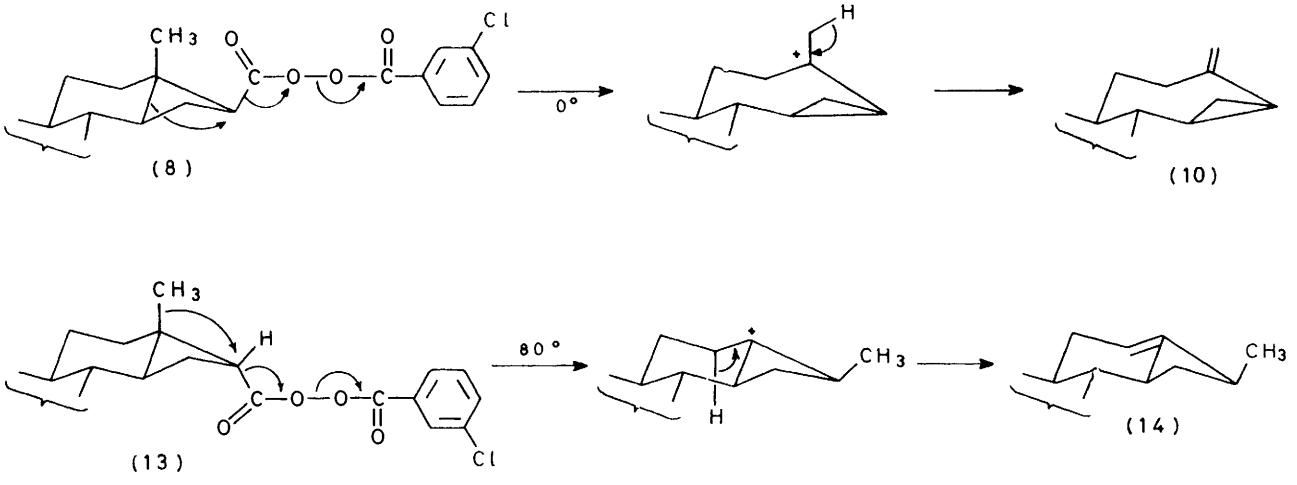
corresponding mixed carbonate, *m*-chlorobenzoate, or C-homo-D-bisnor-steroid (10), were found in this reaction as indicated by t.l.c. The acyl peroxide (13) was hydrolysed to the 16α-carboxylic acid (11) with methanolic sodium hydroxide and was transformed into a mixture of products when the benzene solution was collapse of the doublet into a singlet. All these spectral results can be accommodated in structure (14), *i.e.* 16β-methyl-18-nor-D-nor-5α-androst-12-ene. D-Nor-5α-androstan-16α-ol (15), resulting from a normal carboxy-inversion reaction, was also obtained in 44% yield as the least mobile compound in this thermal decomposition.



SCHEME 3

refluxed for 13.5 h. Separation by t.l.c. afforded a clear oil (14) (26%) as the most mobile compound, the molecular formula of which was determined as $C_{18}H_{28}$ by high-resolution mass spectrometry. The electron-impact mass spectrum of (14) exhibited an intense molecular-ion peak at *m/e* 244 (52.1%), an intense $M^+ - CH_3$ peak at *m/e* 229 (44.2%), and the base peak at *m/e* 134. The i.r. spectrum exhibited a medium absorption at 1 716 cm^{-1}, assignable to an exocyclic double bond attached to a strained ring,[9] and a strong absorption at 806 and 828 cm^{-1}, assignable to a trisubstituted double bond. The n.m.r. spectrum showed the presence of a singlet attributable to 19-H_3 at τ 9.26, a three proton doublet at τ 8.95 (*J* 6.6 Hz), and a one proton broad singlet at τ 4.83 ($W_{\frac{1}{2}}$ 12 Hz) due to an olefinic proton. In double-resonance experiments, irradiation at τ 7.06 caused a

It is apparent that the rearranged products (10) and (14) are formed before inversion to the mixed carbonates [type (4)] since stable 3β-methoxy-D-nor-5α-androstan-16β-ol toluene-*p*-sulphonate can be prepared.[8] Thus, it is believed that the observed rearrangements from (7) to (10) and (11) to (14) occur directly from acyl aroyl peroxides [*e.g.* (13)]. Since D-nor-5α-androstane-16β-carboxylic acid and its 16α-isomer respectively give



SCHEME 4

different rearranged products (10) and (14), the intervention of a common C-16 carbonium ion in both reactions is excluded, and the two rearrangements, the pathways of which are depicted in Scheme 4, are one-step processes. It is believed that the geometry of the conformationally rigid cyclobutane ring of the transition states in these rearrangements would permit the C(13)–C(14) or C(13)–C(18) bond to migrate immediately

to fill the developing *p*-orbital at the C(16) as was observed by Meinwald and his colleagues [8] for the rearrangements of 3β-methoxy-D-norandrostan-16β- and -16α-ylamine, their derivatives, and the 16β-toluene-*p*-sulphonate.[8]

It is of interest to note that in the case of the 16α-isomer, migration of the 13β-methyl group can compete with the carboxy-inversion reaction which leads directly to alcohol (15). This indicates that the geometry of the C(13)–C(18) bond for methyl migration in peroxide (13) is not as suitable as that for skeletal rearrangement of the 16β-isomer. It is also noteworthy that the carboxy-inversion reaction of the peroxide (13) resulted in a product with retention of the original configuration at the C(16) as found in the reaction of other peroxides.[2,5]

The present results may bear significance for fuller understanding of the nature of the carboxy-inversion reaction.

EXPERIMENTAL

Instruments and general procedures are described in ref. 10. The mass spectra of compounds (7), (10), and (12) were taken with a Hitachi RMU-6E spectrometer (source temperature 200°, ionizing voltage 80 eV) in the Faculty of Pharmaceutical Sciences of this University and the mass spectrum of compound (14) was taken with a Hitachi JMS-D 300 spectrometer (ionizing voltage 70 eV) in the Faculty of Agriculture of this University. The high-resolution mass spectra of the olefins (10) and (14) were measured with a Hitachi RMU 7MF double-focusing mass spectrometer (direct inlet system; ionizing voltage 70 eV) in the Coal Research Institute, Faculty of Engineering, Hokkaido University. ^{13}C N.m.r. spectra were taken with a JEOL JNM-FX 100 spectrometer (25 MHz; $CDCl_3$; Me_4Si as internal reference) in the Faculty of Pharmaceutical Sciences of this University. Rotations were measured with a JASCO DIP-SL automatic polarimeter.

D-*Nor*-5α-*androstane*-16β-*carbonyl Chloride* (7).—The carboxylic acid (6) (185 mg) in thionyl chloride (2 ml) was set aside for 3 h at 0°. After removal of thionyl chloride with added benzene, the residue (203 mg) was recrystallized from hexane to afford the *acid chloride* (7) (57 mg), m.p. 232—233° (Found: C, 73.4; H, 9.55; Cl, 10.4. $C_{19}H_{29}ClO$ requires C, 73.9; H, 9.4; Cl, 11.5%); $\nu_{max.}$ 1 798 (COCl), 1 007, 1 061, 1 046, 1 028, 770, and 715 cm^{-1}; *m/e* 308 (M^+, 3.5), 293 (8.2), 273 (6.5), 272 (8.8), 257 (10.0), 218 (80), 217 (100), 203 (36), 175 (47), 148 (48), 135 (25), 121 (26), 109 (72), 108 (50), 95 (45), 93 (30), 91 (21), 81 (45), 67 (41), 55 (48), and 36 (78); τ 8.89 (3 H, s, 18-H_3), 9.17 (3 H, s, 19-H_3), and 6.85 (1 H, dd, *J* 6.0 and 7.2 Hz, 16α-H).

Reaction of the Acid Chloride (7) *with* m-*Chloroperbenzoic Acid*.—To the acid chloride (7) (93 mg) and *m*-chloroperbenzoic acid (103 mg) in hexane (1 ml) was added pyridine (0.1 ml) in cyclohexane (0.4 ml) at 0°. The solution was set aside for 35 min. The solution was washed with 5% $Na_2S_2O_3$, 2N-hydrochloric acid, and water, and then dried over Na_2SO_4. After removal of the solvent, the residue was subjected to preparative t.l.c. with hexane to remove a small amount of polar material. The more mobile major portion (50 mg) was the *olefin* (10) as a gum (Found: *m/e*, 244.2215. $C_{18}H_{28}$ requires *M*, 244.2189); $[\alpha]_D^{24}$ +34.4° (*c* 0.3 $CHCl_3$); $\nu_{max.}$ (neat) 1 640 (C=CH_2), 1 447, 1 371, 1 028, and 895 cm^{-1} (C=CH_2); for n.m.r. spectrum see text; *m/e* 244 (M^+, 36), 299 (100), 216 (14), 215 (12), 201 (49), 187 (16), 175 (19), 161 (26), 133 (43), 119 (55), 109 (41), 107 (38), 105 (36), 95 (50), 93 (53), 91 (52), 81 (53), 79 (52), 77 (28), 67 (52), 55 (47), 41 (47), and 28 (57).

D-*Nor*-5α-*androstane*-16α-*carbonyl Chloride* (12).—The 16α-carboxylic acid (11) (200 mg) in thionyl chloride (1 ml) was set aside for 2 h at 0°. After removal of thionyl chloride with added benzene, the residue (172 mg) was recrystallized from hexane to afford the *acid chloride* (12) (36 mg), m.p. 83—85° (Found: C, 73.95; H, 9.45; Cl, 10.2. $C_{19}H_{29}ClO$ requires C, 73.9; H, 9.4; Cl, 11.5%); $\nu_{max.}$ 1 790 (COCl), 1 033, 1 018, 998, 859, 833, 780, and 715 cm^{-1}; *m/e* 308 (M^+, 4%), 293 (8), 272 (8), 219 (12), 218 (83), 217 (100), 203 (8), 202 (45), 189 (8), 175 (39), 163 (9), 162 (17), 161 (18), 149 (21), 148 (39), 147 (13), 135 (18), 122 (16), 121 (19), 108 (43), 95 (28), 93 (20), 81 (27), 79 (19), 67 (26), and 55 (27); τ 8.73 (3 H, s, 18-H_3), 9.20 (3 H, s, 19-H_3), and 6.76 (1 H, dd, *J* 1.5 and 6.0 Hz, 16β-H).

Reaction of the 16α-*Carbonyl Chloride with* m-*Chloroperbenzoic Acid*.—The 16α-acid chloride (82 mg) and *m*-chloroperbenzoic acid (100 mg) in hexane (1 ml) was stirred at 0°. To this solution were added pyridine (0.1 ml) and cyclohexane (0.4 ml) and the solution was stirred for a further 0.5 h at 0°. The solution was extracted with hexane and benzene and the organic layer was washed with water and dried (Na_2SO_4). After removal of the solvent, the residue (113 mg) was subjected to column chromatography (Wako gel C-200). The column was eluted with benzene to afford the crude acyl aroyl peroxide (13) (88 mg) and then the 16α-acid (11) (7 mg). The crude acyl aroyl peroxide (13) was subjected to preparative t.l.c. with 2 : 3 benzene–hexane (Wako gel B-5F) to afford pure *compound* (13) (63 mg). This was recrystallized from di-isopropyl ether, m.p. 101—103° (Found: C, 70.6; H, 7.5; Cl, 8.1. $C_{26}H_{33}ClO_4$ requires C, 70.25; H, 7.45; Cl, 7.9%); $\nu_{max.}$ 1 796 (CO_2 attached to four-membered ring), 1 765 (CO_2 of *m*-chloroperbenzoyl), 1 590 (aromatic C=C), 1 229 (C–O), 1 048, 860, and 732 cm^{-1}; *m/e* 400 ($M^+ - CO_2$, 0.1%), 358 (0.4), 296 (1.1), 294 (1.6), 218 (11), 148 (18), 139 ($ClC_6H_4CO_2^+$, 100), 109 (35), 95 (10), 93 (11), 91 (6), 81 (13), 67 (13), 55 (13), 44 (23), and 41 (11); τ 8.82 (3 H, s, 18-H_3), 9.21 (3 H, s, 19-H_3), 7.29 (1 H, dd, *J* 1 and 5 Hz, 16β-H), and 6.32 (3 H, s, CO_2CH_3).

Hydrolysis of Peroxide (13).—Peroxide (13) (17 mg) was dissolved in methanol (2 ml), diethyl ether (0.5 ml), and water (0.5 ml) containing sodium hydroxide (128 mg). The solution was stirred for 1.5 h at room temperature and was refluxed for 2 h. The solution was worked up in the usual manner. The residue was subjected to preparative t.l.c. with 3 : 2 benzene–diethyl ether (Wako gel B-5F) to afford the 16α-carboxylic acid (11) (6 mg), identical with an authentic specimen.

Thermal Decomposition of Peroxide (13) *in Benzene*.—Acyl aroyl peroxide (13) (23 mg) in dry benzene (3 ml) was refluxed for 13.5 h. After removal of the solvent, the residue was subjected to preparative t.l.c. (Wako gel B-5F) with 3 : 2 hexane–benzene to afford three fractions. The most mobile fraction (6 mg) was the oily *hydrocarbon* (14). This fraction was again purified by preparative t.l.c. (Whatman KC-18) with 9 : 1 methanol–water to afford an oil (3 mg) (Found: *m/e*, 244.2186. $C_{18}H_{28}$ requires *M*, 244.2189); *m/e* 244 (M^+, 52.1), 229 ($M^+ - CH_3$, 44.2), 149 (43.8), 148 (34.2), 134 (100), 119 (51.1), 109 (63.0), 105

(48.4), 95 (43.7), 93 (54.3), 91 (61.5), 81 (63.1), 79 (46.0), 67 (50.7), 55 (50.4), and 41 (45.1); $[\alpha]_D^{26}$ +3.8° (*c* 0.4 $CHCl_3$). The second mobile fraction (8 mg) was a mixture of three unidentified minor compounds. The least mobile fraction (11 mg) was again purified by preparative t.l.c. (Wako gel B-5F) with 1 : 1 benzene–diethyl ether to afford D-nor-5α-androstan-16α-ol (**15**) (6 mg).

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