

Boron Trifluoride-catalysed Rearrangements of Some Tetrasubstituted A-Norcholestane Epoxides. Evidence for the Formation of an Oxetan Intermediate in a Novel Fragmentation Reaction

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3',3'-Dimethyl-(3*R*)-spiro[A-norcholestane-3,2'-oxiran] (1) and its 3*S*-isomer (2) give, on treatment with boron trifluoride-ether, acetone and A-norcholest-3(5)-ene (11). The oxetan (10), formed together with the allylic alcohol (9) during the chromatographic separation over alumina of (1) and (2), shows a similar behaviour when submitted to the action of the same reagent. Similar treatment of 3-(1-deuterio-1-methylethyl)-3,5β-epoxy-A-norcholestane (15) leads to acetone and 3-deuterio-A-norcholest-3(5)-ene (12). These results suggest a mechanism for all fragmentation reactions involving an oxetan intermediate such as (10).

We have previously described a fragmentation reaction undergone by 3-(1-methylethyl)-3,5β-epoxy-A-norcholestane (14),¹ and proposed a mechanism involving an oxetan intermediate. It has now been possible to establish that this fragmentation is peculiar also (and especially) of epoxides derived from isopropylidene olefins of the A-norsteroid series.† It will be shown here that our hypothesis about the fragmentation of (14) through an oxetan intermediate also appears to be correct.

RESULTS AND DISCUSSION

3-(1-Methylethylidene)-A-norcholestane,² on treatment with *m*-chloroperbenzoic acid in chloroform, gave two α- and β-epoxides (1) and (2) in the ratio 7 : 3 (g.l.c.), which were partially separated by column chromatography over alumina. The stereochemistry of (1) and (2) was determined by a method used previously for similar compounds.³ In fact, whilst (1) was not reduced by lithium aluminium hydride either in boiling ether or in tetrahydrofuran, (2) was smoothly converted into a mixture of alcohols, conceivably having structures (3) and (4). This appears to be in agreement with the fact that in epoxide (2) the α-side is unhindered for hydride attack on oxiran carbons. Treatment of mixture (3) + (4) with phosphorus oxychloride in pyridine led to olefins (5) and (6) and 3-(1-methylethylidene)-A-norcholestane. As the retention times of (5) and (6) on g.l.c. were the same, the composition of the mixture was determined in part by g.l.c., and in part by i.r. Olefin (6) can obviously derive from dehydration of (4) only.

Epoxides (1) and (2) were converted into dienes (7) and (8) by the action of pyridinium chloride, a reagent which has been shown to produce little or no rearrangement in epoxide dehydration.³ Both compounds gave (8), the thermodynamically most stable diene, on treatment with hydrochloric acid in ethanol.

During the chromatographic separation of (1) and (2), an allylic alcohol and a new ether were also obtained. These two compounds were not present in the original

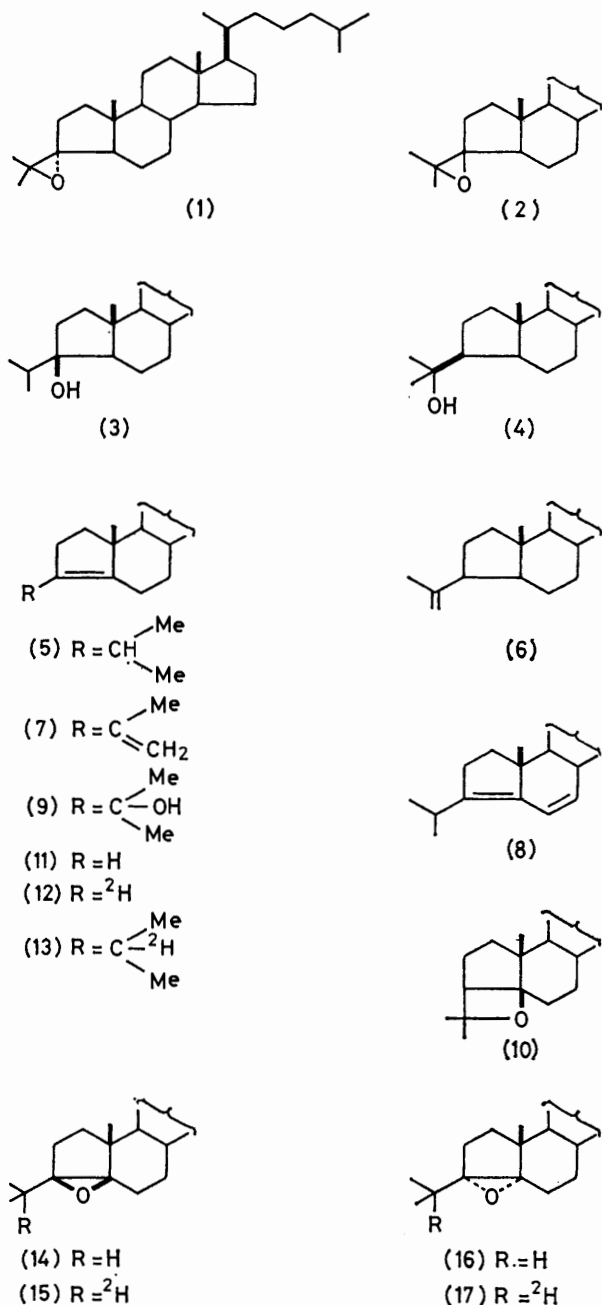
mixture, which was shown to contain the two epoxides (in the ratio indicated) and traces of 3-(1-methylethylidene)-A-norcholestane. The amounts of (1), (2), allylic alcohol, and new ether, obtained after the chromatographic separation, appeared to be about equal. Structure (9) was attributed to the allylic alcohol because, in addition to the presence in it of a tetrasubstituted double bond, it afforded the conjugated diene (7) as the only product of dehydration with phosphorus oxychloride in pyridine. This diene was converted into the most stable one (8) by hydrochloric acid in ethanol. On the basis of spectroscopic characteristics (see Experimental section) structure (10) appeared to be very likely for the new ether. Moreover, fragmentation to A-norcholest-3(5)-ene (11) and acetone occurred on treatment with boron trifluoride-ether and by the action of hydrochloric acid in ethanol the diene (8) (85% by g.l.c.), in addition to (11), was also obtained.

The formation of the allylic alcohol (9) and the oxetan (10) could be rationalised as follows. First, the fact that approximately equal amounts of (1), (2), (9), and (10) were obtained from a mixture originally containing only epoxides (1) and (2) in the ratio 7 : 3 should mean that the allylic alcohol and the oxetan must arise only from epoxide (1), the major component before chromatography. If one considers that, whereas the oxiran carbon atoms in this latter compound are sterically more hindered than the corresponding atoms of (2), the oxygen, on the contrary, must be less hindered for α-attack by acidic reagents. It appears therefore very likely that the attack may primarily give rise to a carbocation intermediate, formed by interaction of the epoxide with hydrated alumina, having a structure such as (18a).

The mechanism outlined involves either elimination of a proton from C-5 of (18a) (formation of the allylic alcohol), or a 1,2-shift of hydride from C-5 to C-3, leading to the carbocation (18b), which could be attacked intramolecularly by oxygen to give the oxetan. Formation of this product could be stereochemically controlled by the well-known fact that 1,2-shifts occur on the same face of the molecule,⁴ and favoured because the *cis*-hydrindan junction thus formed between rings A and B should have a much lesser strain than a *trans* one.⁵

† Olefins of the A'-neotriterpene series seem to behave similarly and give acetone and very probably a rearranged olefin (work in progress at this laboratory).

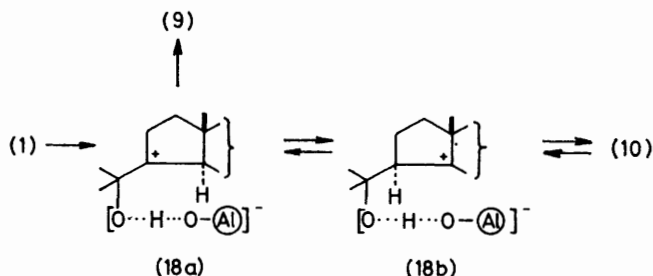
When either epoxide (1) or (2) was treated with boron trifluoride-ether, Δ -norcholest-3(5)-ene (11) and acetone were formed.



This last result, and the data reported, suggest for the fragmentation a mechanism involving an oxetan intermediate such as (10), possibly followed by formation of an open-chain carbocation such as (18b). The configuration of these intermediates (at C-3 and C-5, and, respectively, at C-3) should depend only on the stereochemistry of the 1,2-shift of hydride from C-5 to C-3, and therefore should be the same, either if originated from (1) or from (2).

In order to obtain some evidence that also the frag-

mentation of epoxide (14) follows a mechanism analogous to that proposed for (1) and (2), the deuteriated olefin (13) was prepared by treatment of 3-(1-methylethylidene)- Δ -norcholestane with *O*-deuteriated trichloroacetic acid.⁶ Epoxidation of (13) with *p*-nitroperbenzoic acid gave (15) and (17), which were separated by chromatography.



The action of boron trifluoride-ether on (15) led to olefin (12), which contained deuterium in sufficient amount to permit the deduction that in this case an oxetan like (10) is also to be invoked as the most likely intermediate. Thus, the sequence leading from (15) to (12) could possibly be the following: (i) attack of oxygen by BF₃, (ii) fission of the C-3-O bond, (iii) shift of deuterium from C-4 to C-3, (iv) formation of the oxetan (10) (deuteriated at C-3), (v) fission of the C-5-O bond, and (vi) fragmentation, with formation of acetone and 3-deuterio- Δ -norcholest-3(5)-ene (12). This olefin contained a lesser percentage of deuterium than the epoxide (15), possibly owing to acid-catalysed exchange with protonated species in the reaction medium.

It should be mentioned here that other cases of formation of oxetans in the treatment of epoxides with boron trifluoride-ether have been reported.⁷

Finally, the fact that only epoxide (14) [and (15)] undergo fragmentation, whereas (16) shows a different behaviour,⁸ seems to us in striking agreement with both the mechanism and the stereochemistry proposed above.

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus, i.r. spectra were recorded for Nujol mulls with a Perkin-Elmer 137 spectrophotometer, u.v. spectra for solutions in cyclohexane with a Beckman D.U. spectrophotometer, n.m.r. spectra for solutions in deuteriochloroform with a JEOL C-60 HL spectrometer (Me₄Si as internal standard), and specific rotations for 1% solutions in chloroform at 25 °C with a Perkin-Elmer 141 photoelectric polarimeter; g.l.c. analyses were performed with a Carlo Erba Fractovap 2300 gas-chromatograph (3% OV 17 silicone rubber on Gas-Chrom Q 80-100 mesh at 220 °C, injection block temperature 270 °C, carrier gas N₂, flow rate 50 ml min⁻¹); mass spectra were measured with a Varian CH7 instrument at 70 eV using a direct inlet system. Organic solutions were dried with magnesium sulphate. Light petroleum refers to the fraction of b.p. 40-60 °C.

The following compounds have been already described: (5),⁸ (6),² (8),⁸ (11),^{1,9} (14),⁸ and (16).⁸ The identity of all compounds was determined by comparison of i.r., n.m.r., and g.l.c. The results of the g.l.c. analyses of the mixtures

were confirmed by comparison with mixtures prepared from pure compounds.

Treatment of 3-(1-Methylethylidene)-A-norcholestone with m-Chloroperbenzoic Acid.—A solution of 3-(1-methylethylidene)-A-norcholestone (1.5 g) in chloroform (150 ml) was treated with 75% *m*-chloroperbenzoic acid (1.2 g). After 2 h at 5 °C the solution was washed with aqueous sodium carbonate and water, dried, and evaporated. The residue [1.5 g, 7 : 3 mixture of epoxides (1) and (2) (g.l.c.)] was chromatographed over neutral alumina (grade II—III, 190 g, 2 × 56 cm column), collecting 30 ml fractions. Light petroleum eluted (1) (0.28 g), (2) (0.27 g), and (10) (0.32 g), respectively. Ether eluted polar compounds containing (9) (0.26 g). 3',3'-Dimethyl-(3R)-spiro[A-norcholestone-3,2'-oxiran] (1) had m.p. 113—114.5 °C (from acetone), $[\alpha]_D -22.3^\circ$, ν_{\max} 862 cm^{-1} (epoxide), δ 1.25 (3 H, s) and 1.36 (3 H, s) (Found: C, 84.15; H, 12.35. $\text{C}_{29}\text{H}_{50}\text{O}$ requires C, 84.0; H, 12.15%). 3',3'-Dimethyl-(3S)-spiro[A-norcholestone-3,2'-oxiran] (2) had m.p. 104—105 °C (from acetone), $[\alpha]_D +36.8^\circ$, ν_{\max} 892 and 873 cm^{-1} (epoxide), δ 1.25 (3 H, s) and 1.32 (3 H, s) (Found: C, 83.8; H, 12.0. $\text{C}_{29}\text{H}_{50}\text{O}$ requires C, 84.0; H, 12.15%). 4',4'-Dimethyl-(3R : 5S)-A-norcholestone[5,3b]oxetane (10) had m.p. 92—95 °C (from acetone), $[\alpha]_D -4.8^\circ$, ν_{\max} 952 cm^{-1} (oxetane), δ 1.26 (6 H, s) (Found: C, 83.5; H, 12.1. $\text{C}_{29}\text{H}_{50}\text{O}$ requires C, 84.0; H, 12.15%). 3-(1-Hydroxy-1-methylethyl)-A-norcholestone-3(5)-ene (9) had m.p. 127—129 °C (from acetone), $[\alpha]_D +22.4^\circ$ (Found: C, 84.3; H, 11.9. $\text{C}_{29}\text{H}_{50}\text{O}$ requires C, 84.0; H, 12.15%).

Reaction of Epoxides (1) and (2) with Lithium Aluminium Hydride.—(a) A solution of (1) (150 mg) in dry ether (20 ml) was refluxed for 8 h with lithium aluminium hydride (50 mg). Addition of water and evaporation of the ethereal layer gave a residue identical with the starting material. When the reaction was performed in boiling tetrahydrofuran for 12 h, the unchanged epoxide was recovered.

(b) A solution of (2) (150 mg) in dry ether was treated as described under (a). Usual work-up gave a mixture (120 mg) of (3) and (4). No attempts were made to separate the two components, but the mixture (100 mg), dissolved in pyridine (3 ml), was treated with phosphorus oxychloride (0.4 ml) and heated on a steam-bath for 1 h. The solution was diluted with water and extracted with light petroleum. The organic layer, washed with 2N-hydrochloric acid, water, dried, and filtered over neutral alumina, afforded a 1 : 3 mixture (g.l.c.) of 3-(1-methylethyl)-A-norcholestone-3(5)-ene (5), and 3-(1-methylethylidene)-A-norcholestone. The presence of 3-(1-methylethenyl)-A-norcholestone (6) in the mixture was only qualitatively deduced from the i.r. spectrum (weak bands at 1636 and 892 cm^{-1}).

3-(1-Methylethenyl)-A-norcholestone-3(5)-ene (7).—Alcohol (9) (100 mg) in pyridine (6 ml) was treated with phosphorus oxychloride (0.6 ml) and heated on a steam-bath for 1.5 h. Usual work-up and filtration of the light petroleum solution of the reaction product over neutral alumina afforded the diene (7) (65 mg), m.p. 57—59 °C (from acetone), $[\alpha]_D +29.0^\circ$, ν_{\max} 1623 and 883 cm^{-1} (C=CH₂), λ_{\max} 240 (ϵ 15 000), 248 (15 200), and 256 nm (9 200), δ 1.88 (3 H, s) and 4.8 (2 H, m) (Found: C, 87.9; H, 12.3. $\text{C}_{29}\text{H}_{48}$ requires C, 87.8; H, 12.2%).

Hydrogenation of Diene (7).—A solution of (7) (60 mg) in cyclohexane (60 ml) and acetic acid (40 ml) was hydrogenated at room temperature and pressure over 10% Pt-C (0.1 g). After 4 h the catalyst was filtered off and the filtrate was washed with water, 2N-sodium hydroxide, dried,

and filtered over neutral alumina. The residue obtained on evaporation (40 mg) was identical with 3-(1-methylethyl)-A-norcholestone-3(5)-ene (5).

3-(1-Methylethyl)-A-norcholestone-3(5),6-diene (8).—Treatment of the diene (7) with hydrochloric acid in ethanol in the conditions described below for oxides (1), (2), and (10), caused quantitative conversion into the diene (8).

Treatment of Epoxides (1) and (2) with Pyridinium Chloride.—Epoxides (1) and/or (2) (0.3 g), dissolved in a 0.35M-solution of pyridinium chloride in pyridine (30 ml), were refluxed for 2 h. The mixture was then diluted with water and extracted with light petroleum. Usual work-up, filtration over neutral alumina, and evaporation left a residue (0.22 g) which was identical with diene (7).

Treatment of the Oxides with Hydrochloric Acid.—The oxide (1 part by weight) was heated under reflux for 1.5 h with 1M-hydrochloric acid in 90% ethanol (400 parts by volume). The mixture was diluted with water and extracted with light petroleum. Usual work-up and filtration over neutral alumina gave the following results: from epoxides (1) and (2) (250 mg) pure diene (8) was obtained (210 mg); from oxetan (10), a mixture of (8) and A-norcholestone-3(5)-ene (11), in the relative amounts (g.l.c.) 85 : 15, was obtained.

Treatment of the Oxides with Boron Trifluoride-Ether.—The oxide (1 part by weight) in dry chloroform (50 parts by volume) was treated with 48% boron trifluoride-ether (5 parts by volume), freshly distilled over calcium hydride. After 1 min at room temperature the solution was washed with aqueous sodium carbonate and water, dried, and evaporated. The residue was chromatographed over neutral alumina. Light petroleum eluted hydrocarbons; no products were eluted by ether. From epoxides (1), (2), or from their mixture, only (11) was formed (average yield, 90%); oxetan (10) (50 mg) afforded (11) (35 mg). When the reaction mixtures were treated with sodium carbonate and steam-distilled into 2,4-dinitrophenylhydrazine solution, acetone-2,4-dinitrophenylhydrazone was obtained, m.p. (ethanol) 124—126 °C.

3-(1-Deuterio-1-methylethyl)-A-norcholestone-3(5)-ene (13).—A solution of 3-(1-methylethylidene)-A-norcholestone (1.2 g) in anhydrous carbon tetrachloride (30 ml) was stored at 5 °C for 15 h with *O*-deuteriotrichloroacetic acid (1.3 g). After evaporation at reduced pressure the residue, dissolved in light petroleum, was chromatographed over neutral alumina. Elution with light petroleum and evaporation of the solvent afforded 1.1 g of 3-(1-methylethyl)-A-norcholestone-3(5)-ene (5) and (13) in the ratio 35 : 65 (m.s.).*

Treatment of Compounds (5) and (13) with p-Nitroperbenzoic Acid.—The mixture of olefins (5) and (13) (1.0 g) and 98% *p*-nitroperbenzoic acid (0.5 g) in chloroform (50 ml) was stirred at 5 °C for 30 min. The precipitated *p*-nitrobenzoic acid was filtered off and the filtrate was washed with aqueous sodium carbonate, dried, and evaporated. The residue (1.0 g) was chromatographed over neutral alumina (grade II—III). Elution with light petroleum afforded fractions containing 3-(1-methylethyl)-3,5 α -epoxy-A-norcholestone (16),⁸ and 3-(1-deuterio-1-methylethyl)-

* This ratio was calculated by comparing the peaks at *m/e* 398 (*M*⁺) and 399 (*M* + 1)⁺, and at *m/e* 383 (*M*⁺ - CH₃) and 384 [(*M* + 1)⁺ - CH₃], respectively, in the spectra of pure (5) and of (5) + (13). Both spectra showed the same pattern and intensities of the peaks around *m/e* 355 [*M*⁺ - Me₂C¹⁸H for (5), and *M*⁺ - Me₂C²H for (13)]. This permitted us to deduce that the deuterium atom in (13) is located in the isopropyl group at C-3).

3,5 α -epoxy-A-norcholestane (17) (0.5 g) and a mixture of (16), (17), 3-(1-methylethyl-3,5 β -epoxy-A-norcholestane (14),¹ and 3-(1-deuterio-1-methylethyl)-3,5 β -epoxy-A-norcholestane (15) (0.45 g). The latter mixture was again chromatographed over p.l.c. plates (silica gel Merck F₂₅₄, 20 × 20 cm, thickness 2 mm, eluant light petroleum). The less polar epoxides (14) and (15) (0.1 g) in the ratio 32 : 68 (m.s.) were separated from the more polar ones (16) and (17).

Treatment of (14) and (15) with Boron Trifluoride-Ether.—The mixture of epoxides (14) and (15) was treated with boron trifluoride-ether as described above. Usual work-up afforded (11) and 3-deuterio-A-norcholest-3(5)-ene (12) in the ratio 65 : 35 (m.s.). The composition of the mixture, as deduced from the n.m.r. spectrum (ratio between the intensity of the olefinic signal at δ 6.0, and the intensity of one proton, calculated from the aliphatic signals) was ca. 60 : 40.

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