Tetrahedron. Vol. 31, pp. 13 to 19 Pergamon Press 1975. Printed in Great Britain

FAVORSKII REARRANGEMENT OF α,β-EPOXY KETONES

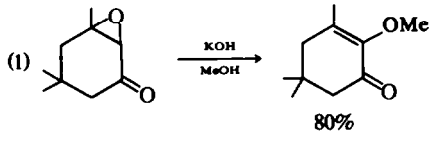
R. W. MOUK, K. M. PATEL and W. REUSCH*

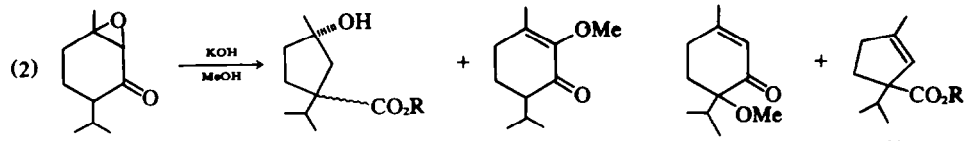
Department of Chemistry, Michigan State University, East Lansing, Michigan 48824

(*Received in USA* 24 *May* 1974; *Received in UK for publication* 20 *August* 1974)

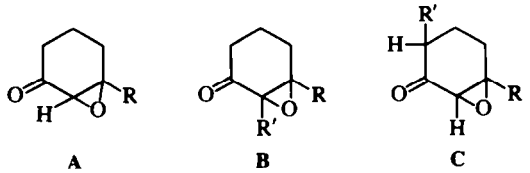
Abstract—Reactions of α,β-epoxy ketones with nucleophilic bases generally take one of two courses: (1) α-displacement followed by β-elimination of water or (2) Favorskii rearrangement *via* a cyclopropanone or zwitterion intermediate. Among the factors that appear to control these reactions, it is suspected that an α'-substituent effect may operate. Such an effect has been confirmed by observing the conversion of 3,5,5,6 - tetramethyl - 2,3 - epoxycyclohexanone (**1**) to the ring-contracted γ-lactone **3**, together with other Favorskii rearrangement products, on treatment with refluxing methanolic potassium hydroxide. The α'-methyl substituted steroid **2** under similar reaction conditions was transformed into roughly equal amounts of **4**, **5** and **4** (all rationalized by a Favorskii-like mechanism). In each case the analogous epoxy ketone lacking an α'-Me substituent failed to give any Favorskii products.

Previous investigations of the base catalyzed reactions of α,βepoxyketones[1-4] have disclosed two distinct modes of reaction, a nucleophilic displacement-elimination process (illustrated for isophorone oxide in Eq 1) and a Favorskii rearrangement (shown in Eq 2 for piperitone oxide). The Favorskii reaction products are strongly solvent dependent[2] and clearly reflect the existence of a cyclopropanone intermediate and/or its zwitterionic equivalent. In agreement with this view of the reaction, the stereoisomeric pulegone oxides were observed to rearrange in a stereospecific manner.[4]



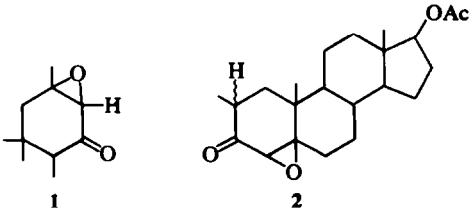


In considering the factors that might influence these epoxy ketone reactions, it is convenient to distinguish three different substitution patterns:



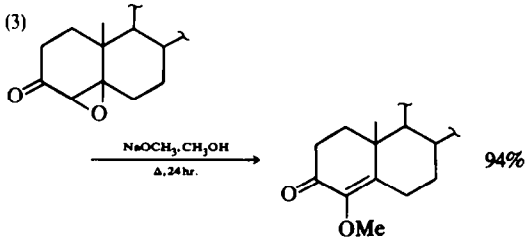
The results thus far reported suggest that cyclic epoxyketones of type **A** normally react by a displacement-elimination pathway. This mode of reaction is rendered unfavorable by further alkyl substitution of the α-C atom (as in **B**), due to increased steric hindrance to nucleophilic displacement and the impossibility of subsequent α-elimination; consequently, only the Favorskii rearrangement occurs with this class of substrate. The influence of an α'-alkyl substituent (as in **C**) remains a puzzling factor. A comparison of the reactions of isophorone oxide and piperitone oxide (Eqs 1 and 2) suggests that the α'-substituent somehow influences the competing reactions so as to favor Favorskii rearrangement, but a rationalization of this effect is not immediately apparent.

In this paper we report some recent investigations which confirm the existence of an α'-substituent effect in Favorskii-like reactions of α,β-epoxy ketones. Two different type **C** substrates were chosen for our study:



The first, 3,5,5,6 - tetramethyl - 2,3 - epoxycyclohexanone (**1**), enabled us to study the effect of an α'-Me substituent on the reaction of isophorone oxide (Eq 1). The second,* 2 - methyl - 17β - acetoxy - 4β,5β - epoxy - androstan - 3 - one (**2**), was selected to minimize any gross conformational changes that an alkyl substituent might impose on monocyclic systems, and because general stereospecific routes to nor-steroids are potentially useful in pharmacology. Previous work[3] has demonstrated that 4,5 - epoxy - 3 - keto - steroids and 1,2 - epoxy - 3 - ketosteroids (both type A compounds) react by the displacement-elimination path, as illustrated in Eq 3.

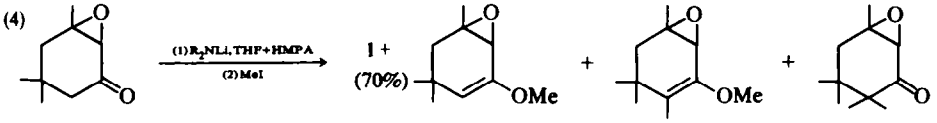
(3)



RESULTS AND DISCUSSION

Preparation of **1** was accomplished either by epoxidation of the corresponding α,β-unsaturated ketone with alkaline hydrogen peroxide (74% yield) or by direct methylation of isophorone oxide:

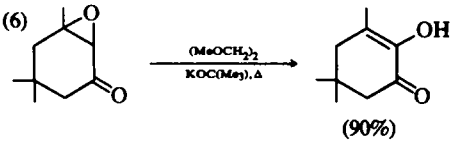
(4)



Compound **1** failed to react when treated with aqueous methanolic potassium hydroxide at 0° for 20 h. However, after 90 min at reflux, an equivalent reaction system was completely converted to a mixture of 1,4,5,5 - tetramethyl - 2 - oxabicyclo [2.2.1] heptan - 3 - one (**3**) and several incompletely characterized esters and ketones presumed to arise from a common Favorskii intermediate.

Reaction of **1** with potassium *t-butoxide* in glyme appeared to be sluggish compared with the corresponding rearrangement of piperitone oxide (Eq 2). Thus, reflux conditions were necessary to convert **1** to a mixture of 1,3,6,6 - tetramethyl - 2 - cyclohexene - 1 - carboxylic acid and **3** (Eq 5b); whereas, piperitone oxide is reported[2] to give the γ-lactone shown in Eq 2, after reacting 4 h at room temperature. Isophorone oxide again behaves quite differently, giving 2 - hydroxy - 3,5,5 - trimethyl - 2 - cyclohexenone after prolonged reflux:

(6)

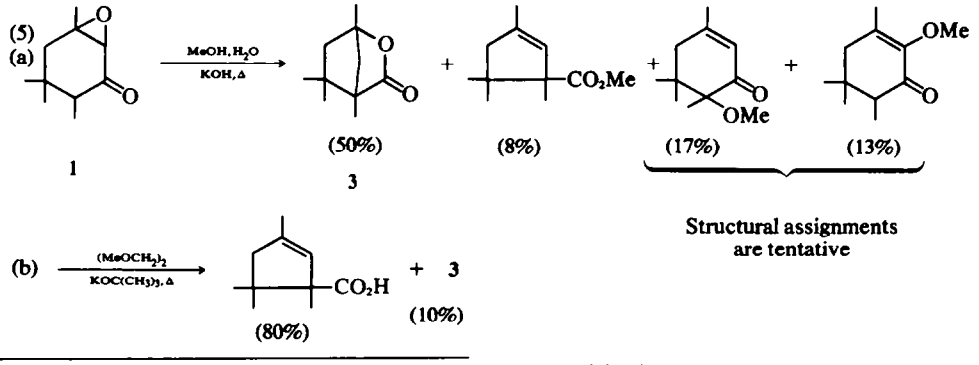


Preparation of **2** was also accomplished in two ways. Reduction of 2 - methylene - 4β,5β - epoxytestosterone,[5] using a Pd catalyst, gave the 2α-epimer of **2**, which was readily isomerized to the more stable 2β-epimer by the action of methanolic potassium hydroxide, as shown in Eq 7. Epimerization in a dioxane-D_2O solution gave **2** (2β-epimer) labeled with deuterium at C-2.

Direct methylation of testosterone epoxide (or its acetate derivative) is not efficient, apparently because the enolate-alkoxide double salt is poorly soluble. The dimethyl t-butylsilyl ether derivative of testosterone is not subject to double salt formation, and this derivative (or the corresponding 4β,5β-epoxycholesten - 3 - one) can be methylated in good yield (Eq 8).

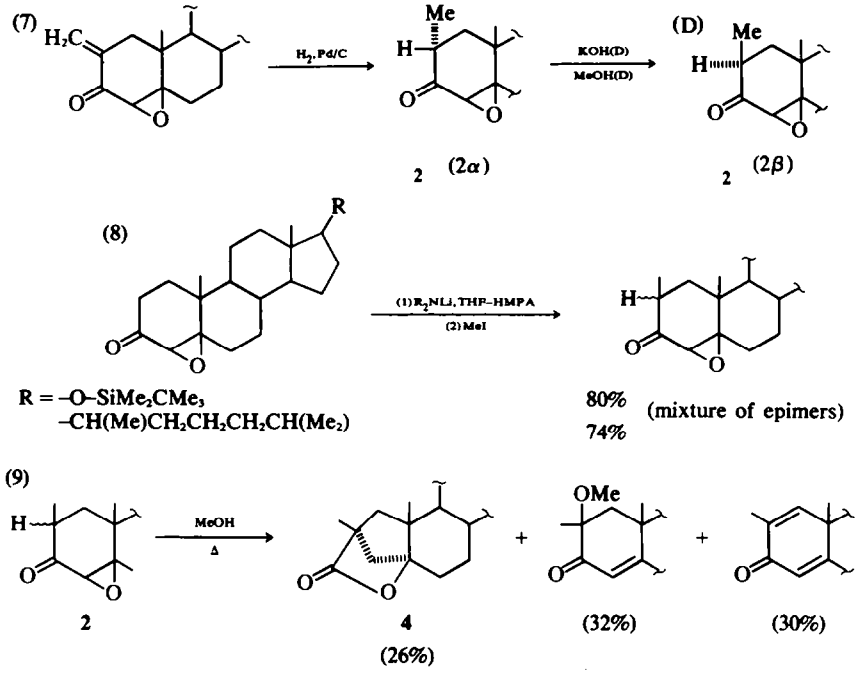
Treatment of **2** with refluxing methanolic potassium hydroxide for 2 to 3 h gave three crystalline products, identified as **4**, **5** and **6** (Eq 9). The spectroscopic and analytical evidence supporting these assignments is presented in the Experimental. The OMe group in **5** is located at C-2 on the strength of a sharp three proton singlet at δ 1·30 in the NMR spectrum (assigned to the

(5)

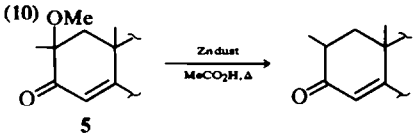


Structural assignments are tentative

*A preliminary report of some of this work was presented at the 160*th National Meeting of the American Chemical Society*, Chicago, Illinois September (1970).



2-Me group), and reduction of **5** to 2-methyltestosterone (Eq 10). Because the OMe protons appear at relatively high field (δ 3·02) this group is tentatively assigned a β-configuration (*i.e.*, it is axial and in the π-electron shielding region).

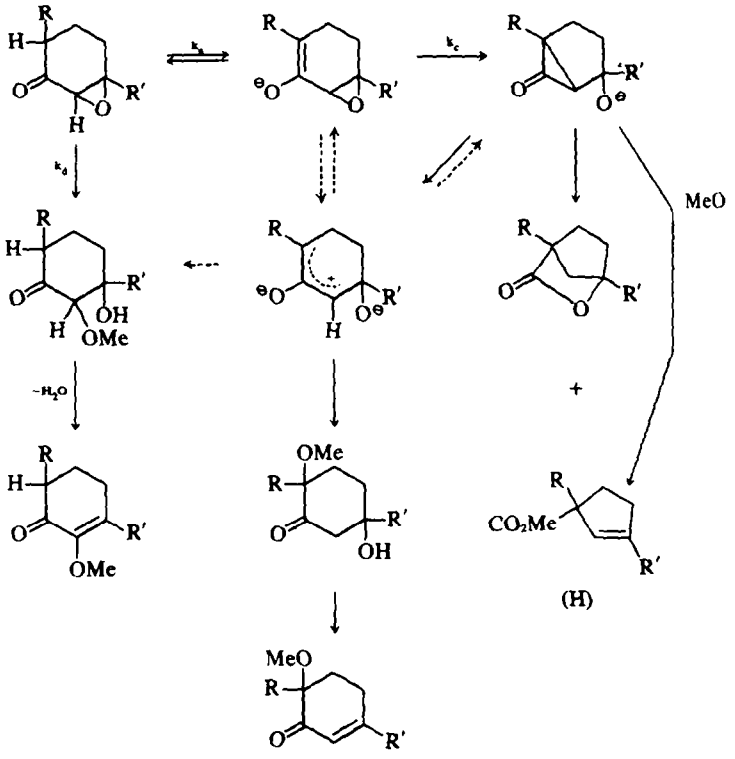


The products from this base catalyzed rearrangement as well as those from the rearrangement of **1** (Eq 5) are clearly derived from Favorskii intermediates (Schemes I and II), thus confirming the previously noted α′-alkyl substituent effect. A clue to the source of this effect is found in the relative rates of the base catalyzed reactions of **1** or **2** and their unsubstituted precursors.

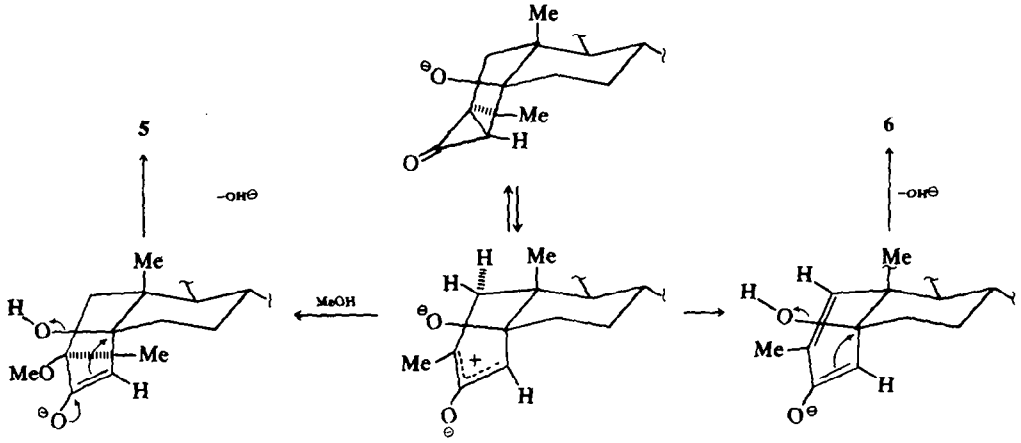
To begin with, the rate of enolate base formation (k_e in Scheme I) must be relatively large to explain the facile epimerization, isotope exchange and alkylation reactions at the α′-position. The products formed in base-catalyzed epoxy ketone reactions should therefore reflect the relative rates of first order transformations of the enolate anion (*i.e.*, to cyclopropanone or zwitterion intermediates) compared with the second order displacement-elimination process. Since compounds **1** and **2** react about ten times more rapidly than isophorone oxide or testosterone oxide respectively, and since it is unlikely that an α′-substituent would significantly affect the rate of nucleophilic epoxide ring opening (k_d), the influence of the Me substituents in **1** and **2** is probably due primarily to an increase in the steady state concentration of the enolate base and/or to an increase in the rate constant (k_c) for enolate base cyclization to cyclopropanone* (the Thorpe–Ingold effect). In short, when the epoxy ketone substrate does not have an α′-alkyl substituent (R = H in scheme I), enolate base formation is rapid but cyclization to a cyclopropanone intermediate is very slow, allowing the moderate displacement step (k_d) to successfully compete with the Favorskii pathway. When an α′-alkyl substituent is present, however, the rate of cyclopropanone formation is enhanced and Favorskii products predominate.

At this point it seemed to us that α′-unsubstituted epoxy ketones such as isophorone oxide and testosterone oxide could be forced to give Favorskii products by simply converting them irreversibly to their enolate conjugate bases. In practice, however, this event has not been realized. Both isophorone oxide and 4β,5β-epoxycholestan - 3 - one were recovered unchanged after their respective lithium enolates were subjected to reflux temperatures in THF and glyme for periods of time that exceeded those required for rearrangement of **1** and **2**. The addition of tetramethylethylenediamine to these reactions effected no change; however, isophorone oxide was converted to the diosphenol shown in Eq 6 on treatment with sodium hydride in a refluxing THF–HMPA solution. We suggest that this unexpected failure to react may be due to the solvent changes instituted here in order to avoid the presence of nucleophilic alkoxides. A H-bonding solvent such as methanol may substantially assist

*Aside from the fact that Favorskii ring contraction is at least as fast in glyme as it is in methanol, we have no evidence to favor initial cyclopropanone formation as contrasted to zwitterion formation. The dashed arrows in Scheme I denote alternative pathways.



SCHEME 1. (R = H or Me)



SCHEME 2.

the opening of the epoxide ring by solvating the incipient alkoxide leaving group.

EXPERIMENTAL

All reactions involving strong bases have been conducted under dry N_2 or argon, using solvents purified by distillation from suitable drying agents. Magnetic stirring devices were used in all cases. Organic extracts were always dried over $MgSO_4$ before being concentrated or distilled.

Analysis by GLPC was conducted with model A-90 or 1200 Varian-Aerograph instruments; preparative TLC was carried out with 2 mm silica gel F-254 absorbent on 20 × 20 cm glass plates. M.ps were determined with a Koefler hot stage and are uncorrected. IR spectra were recorded on a Perkin–Elmer 237B grating spectrophotometer using NaCl cells. NMR spectra were taken with Varian A-60 and T-60 high resolution spectrometers, using TMS as an internal standard in both $CDCl_3$ and CCl_4 solns. Mass spectra were obtained with Hitachi RMU 6 or LKB 9000 mass spectrometers. Optical rotations were measured with a Perkin–Elmer 141 Polarimeter.

Microanalyes were performed by Spang Microanalytical Labs, Ann Arbor, Michigan.

Methylation of isophorone. To a cold soln of isopropylcyclohexylamine, (22 ml; 120·7 mmol) in 20 ml dry THF was added 66 ml of 1·9 M BuLi (125·4 mmol) in hexane. After the reaction was stirred at 0° for 15 min, isophorone (13·00 gm; 94·2 mmol) in 100 ml THF was slowly added and the resulting soln maintained at 0° for 90 min. Following a rapid addition of MeI (20·00 ml; 320·0 mmol), the mixture was allowed to warm to room temp. After standing overnight, the mixture was mixed with water and extracted several times with ether. The combined ether extracts were washed, dried and distilled under reduced pressure. The yield of 3,5,5,6 - tetramethylcyclohex - 2 - enone was 11·50 gm (81%), b.p. 60–62°/1 mm.; IR (CCl_4) 1670, 1635, 1375 cm^{-1}; NMR (CCl_4) δ 5·73 (m, 1H)=CH, δ 2·10 (m, 3H) ring CH_2, δ 1·90 (s, 3H) = CCH_3, δ 0·93 (9H). (Found: C, 78·78; H, 10·60. Calcd. for $C_{10}H_{16}O$: C, 78·90; H, 10·59).

Preparation of 2,3 - *epoxy* - 3,5,5,6 *tetramethylcyclohexanone* (1) *by epoxidation of* 3,5,5,6 - *tetramethylcyclohex* - 2 - *enone.* A soln of 3,5,5,6 - tetramethylcyclohex - 2 - enone (10·00 g; 64·93 mmol) and 30% aqueous H_2O_2 (19·1 ml; 168·52 ml) in MeOH (65 ml) was cooled to 15° while 6N NaOH (5·5 ml; 33·0 mmol) was added over a period of 15 min. The resulting mixture was stirred for 3 h, the temp being maintained at 20–25°, and then poured into 150 ml water. The product was extracted with ether and the combined ether extracts were washed twice with water, dried and distilled under reduced pressure. The yield of 1 was 8·1 g (74%), b.p. 61–64°/1·6 mm. (Found: C, 71·25; H, 9·65. Calcd. for $C_{10}H_{16}O_2$: C, 71·39; H, 9·59%).

Spectroscopic properties consistent with the assigned structure and identical with those reported in the next section were observed for 1. The aqueous phase was acidified, extracted with ether, and the extracts washed twice with water, dried over $MgSO_4$ and concentrated. An ether soln of the acidic residue (1·0 g) was esterified by treatment with excess diazomethane. Analysis by GLPC (4% SE 30 90°, 4% QF-1, 100°) showed at least 7 components. The major product was collected by preparative GLPC and tenatively identified as the δ-lactone methyl ester of 2 - hydroxy - 2,4,4,5 - tetramethyladipic acid on the strength of the following spectroscopic evidence: IR (CCl_4), broad absorption at 1735 cm^{-1}; NMR (CCl_4) δ 3·63 (s, 3H) CO_2CH_3, δ 2·6 (m, 1H) ring CH, δ 2·2 and 2·6 (ABq, J 14 Hz, 2H) ring CH_2, δ 2·06 (s, 3H), δ 1·36 to 0·96 (9H); mass spectrum, *m/e* (rel. intensity) 214(<5), 199(<5), 184(<5), 172(<5), 155(11), 129(51), 110(19), 99(40).

Preparation of 1 *by methylation of isophorone oxide.* To a chilled (0°) soln of lithium isopropylcyclohexylamide (LiICA) (4·55 mmol) in 20 ml of THF was added, over a 10 min period, a soln of isophorone oxide (0·54 g; 3·57 mmol) in 25 ml THF. A 20 ml portion of dry hexamethylphosphoric triamide (HMPA) was then added and, following a 90 min period of stirring at 0°, the mixture was quenched by the rapid addition of excess MeI. After standing at 25° for 3 h, the resulting mixture was poured into ice water and extracted several times with ether. The combined ether extract was washed (twice each) with 5% HCl, water and brine, dried and concentrated under reduced pressure. Analysis of the product mixture by GLPC (4% QF-1 at 135°) showed it to be composed of: 1 (70%); 5,6 - epoxy - 2,3,5 - trimethyl - 1 - methoxycyclohexene (10%); 5,6 - epoxy - 2,3,3,5 - tetramethyl - 1 - methoxycyclohexene (5%); 2,3 - epoxy - 3,5,5,6,6 - pentamethylcyclohexanone (3%) and isophorone oxide (4%).

Pure samples of each component of this mixture were obtained by preparative GLPC. Identification of each compound rested on the following evidence: Compound 1; IR (CCl_4) 1720 cm^{-1}; NMR (CCl_4) δ 3·0 (s, 1H) oxirane CH, δ 2·7 (q, J 7 Hz, 1H) ring CH, δ 2·1 and 1·6 (ABq, J 14 Hz, 2H) ring CH_2, δ 1·40 (s, 3H), δ 0·96 (s, 3H), δ 0·86 (d, J 7 Hz, 3H), δ 0·73 (s, 3H); MS (70 eV), *m/e* (rel. intensity) 168(20·8), 153(21·5), 139(37·5), 125(40·0), 97(99·8), 83(35·3), 70(99·4).

5,6 - *Epoxy* - 3,3,5 - *trimethyl* - 1 - *methoxycyclohexene*; IR (CCl_4). 1660, 1237, 1200 cm^{-1}; NMR (CCl_4) δ 4·33 (d, J 2·5 Hz, 1H) = CH, δ 3·53 (s, 3H)OCH_3, δ 2·86 (d, J 2·5 Hz, 1H) oxirane CH, δ 1·82 and 1·48 (ABq, J 14 Hz, 2H) ring CH_2, δ 1·36 (s, 3H), δ 1·06 (s, 3H), δ 1·00 (s, 3H); MS (70 eV), *m/e* (rel. intensity) 168(44·6), 153(82·3), 137(10·6), 125(37·8), 112(66·7), 111(56·6), 95(21·7), 93(32·3), 77(20·7). (Found: C, 71·25; H, 9·63. Calcd. for $C_{10}H_{16}O$: C, 71·39; H, 9·59%).

5,6 - *Epoxy* - 2,3,3,5 - *tetramethyl* - 1 - *methoxycyclohexene*; IR (CCl_4) 1665, 1100 cm^{-1}; NMR (CCl_4) δ 3·43 (s, 3H)OCH_3, δ 2·86 (s, 1H)oxirane H, δ 1·53 (m, 2H) ring CH_2, δ 1·3 (s, 6H), δ 0·90 (6H); MS (70 eV), *m/e* (rel. intensity) 182(2), 123(5), 99(100).

2,3 - *Epoxy* - 3,5,5,6,6 - *pentamethylcyclohexanone*; IR (CCl_4). 1710 cm^{-1}; NMR (CCl_4) δ 2·93 (s, 1H) oxirane CH, δ 2·18 and 1·58 (ABq, J 15 Hz, 2H) ring CH_2, δ 1·40 (s, 3H), δ 1·10 (s, 3H); δ 0·93 6(H); MS (70 eV), *m/e* (rel. intensity) 182(5·8), 154(14·4), 139(20·5), 97(53·2), 84(99·4), 69(95·0).

When the methylation described above was conducted with 4·8 mmoles of tetramethylethylenediamine replacing the HMPA, the conversion to 1 was slower and less favorable. A mixture consisting chiefly of recovered isophorone oxide (34%), 1 (30%) and 2,3 - epoxy - 3,5,5,6,6 - pentamethylcyclohexanone (15%) was obtained.

When the methylation in a THF/HMPA solvent mixture was conducted as described above, with a 1 h reflux of the isophorone conjugate base soln preceding the addition of MeI, no significant changes in product composition were noted (*i.e.*, the product distribution given in Eq 6 remained unchanged).

Reaction of 1 *with hot methanolic potassium hydroxide.* A soln of 2,3 - epoxy - 3,5,5,6 - tetramethylcyclohexanone (1·38 g; 8·18 mmol) and KOH (0·8 g; 14·6 mmol) in MeOH (20 ml) was refluxed for 90 min. Following dilution with 80 ml ice water, the mixture was extracted with ether, and the combined ether extracts were washed and dried. Concentration of the ether extracts yielded 1·18 g crude product, which GLPC analysis (4% QF-1, 150°) showed to be a mixture of 3 (45%) and three other products tentatively identified as 6 - methoxy - 3,5,5,6 - tetramethyl - 2 - cyclohexenone (17%), 2 - methoxy - 3,5,5,6 - tetramethyl - 2 - cyclohexenone (13%), and methyl 1,3,5,5 - tetramethyl - 2 - cyclopentene - 1 - carboxylate (8%).

A pure sample of 3 was obtained by preparative GLPC: 3; IR (CCl_4) 1785 cm^{-1}; NMR (CCl_4) δ 1·63 to 2·03 (4H), δ 1·50 (s, 3H), δ 1·10 (s, 3H), δ 1·06 (s, 3H), δ 1·00 (s, 3H); *m/e* (rel. intensity) 153 (0·9, M-15), 126(11, M-42), 124(9, M-44), 112(100), 109(94). (Found: C, 71·43; H, 9·51. Calcd. for $C_{10}H_{16}O_2$: C, 71·39; H, 9·59%).

The structural assignments for the other three components rest on their mass spectra, which have been compared with related homologs.

6 - Methoxy - 3,5,5,6 - tetramethyl - 2 - cyclohexeneone, *m/e* (rel. intensity) 182(very weak), 152(8), 137(5), 123(59), 112(32), 107(13), 101(47), 85(13), 82(100).

2-Methoxy - 3,5,5,6 - tetramethyl - 2 - cyclohexenone, *m/e* (rel. intensity) 182(61), 167(12), 112(54), 96(11), 84(42), 69(100).

Methyl 1,3,5,5 - tetramethyl - 2 - cyclopentene - 1 - carboxylate, *m/e* (rel. intensity) 182(2·2), 167(2·1), 123(100, M-$C_2H_3O_2$), 107(14). The mass spectrum and GLPC retention time of this compound were identical with those of the following product.

Reaction of 1 *with potassium* t-*butoxide.* To a soln of t-BuOK, prepared from K (0·55 g; 0·014 g atom) and t-BuOH (1·05 g; 0·014 mol) in 1,2 - dimethoxyethane (40 ml) was added a soln of 3,5,5,6 - tetramethyl - 2,3 - epoxycyclohexanone in (2·0 g; 0·0119 mol) of 1,2 - dimethoxyethane (10 ml). The resulting mixture was refluxed for 4 h, concentrated under reduced pressure and then poured into a mixture of ice and water. The ethereal extract of this mixture gave 425 mg of crude neutral product, which was analyzed by gas chromatography and proved to be composed of equal amounts of 3 (described earlier) and starting material. Acidification of the aqueous phase gave, after extraction

and the usual work-up, 1·60 g (80%) of an acid, which was then esterified with diazomethane. This ester was identified as methyl 1,3,5,5 - tetramethyl - 2 - cyclopentene - 1 - carboxylate; b.p. 56–58°/2·8 mm; IR (CCl_4) 1725 cm^{-1}; NMR (CCl_4) δ 5·2 (brd. s, 1H) = CH, δ 3·5 (s, 3H) OCH_3, δ 1·9 and 2·0 (ABq, J 7·5 Hz, 2H) ring CH_2, δ 1·67 (brd. s, 3H), δ 1·07 (s, 3H), δ 0·87 (s, 3H); NMR (C_6D_6) 5·44 (brd. s, 1H), δ 3·33 (s, 3H), δ 1·9 and 2·0 (ABq, J 7·5 Hz, 2H), δ 1·54 (brd. s, 3H), δ 1·17 (s, 3H), δ 1·10 (s, 3H), δ 1·0 (s, 3H). (Found: C, 72·45; H, 10·05. Calcd. for $C_{11}H_{18}O_2$: C, 72·49; H, 9·95%).

Reaction of isophorone oxide with sodium hydride. A soln of isophorone oxide (2·95 g; 19·1 mmol) in THF (45 ml) was treated with 26 mmol sodium hydride (from 1·2 g of 52% oil dispersion washed several times with pentane). A 15 ml portion dry HMPA was added and the resulting suspension was refluxed for 4 h. After cooling, the mixture was quenched with ice water and extracted with ether. The usual work-up of the ether extracts gave 2·53 g crude product, which GLPC analysis showed to be a 3:1 mixture of 2 - hydroxy - 3,5,5 - trimethyl - 2 - cyclohexenone and isophorone oxide. Acidification of the aqueous phase followed by ether extraction yielded an additional 200 mg of the diosphenol. The overall yield of diosphenol was 72%. Sublimation of the crude product gave crystalline diosphenol, m.p. 92–93° (lit. 92–92·5°).

2 - *Methylene* - 17β - *Acetoxy* - 4β,5β - *Epoxyandrostan* - 3 - *one.* To 4β,5β - epoxytestosterone acetate (4·59 g; 13·3 mmol) dissolved in EtOH (125 ml) was added 25 ml of 37% formaldehyde soln and 4 g AcOK (in 15 ml of H_2O). The soln was heated to reflux for 5½ h. After cooling, 2·4 ml glacial AcOH was added and about one half of the total volume of the soln was removed on the rotary evaporator (room temp). The remaining liquid was poured into 300 ml water and placed in the refrigerator. The crystals which deposited were filtered and recrystallized from acetone to yield 3·72 g (77%) of 2 - methylene - 4β,5β - epoxytestosterone acetate: m.p. 227–229°, (lit.[5] 226–227°); IR ($CHCl_3$) 1725, 1685 and 1615 cm^{-1}; NMR ($CDCl_3$) δ 6·11 (t, J 2 Hz, 1H), δ 5·21 (t, J 2 Hz, 1H), δ 4·55 (t, J 7 Hz, 1H) 17-H, δ 3·10 (s, 1H) 4-H, δ 2·00 (s, 3H) acetate, δ 1·17 (s, 3H), δ 0·80 (s, 3H).

2α - *Methyl* - 17β - *Acetoxy* - 4β,5β - *Epoxyandrostan* - 3 - *one*, **2** (2α). A suspension of 10% Pd/C (0·021 g) in dioxane (20 ml) was purged and equilibrated with H_2. A 0·267 g sample of 2 - methylene - 17β - acetoxy - 4β,5β - epoxyandrostan - 3 - one (0·755 mmol) in 10 ml dioxane was added, and an uptake of 0·75 mmol H_2 was noted after stirring at 25° for 10 min. Following filtration of the catalyst, the dioxane soln yielded, on evaporation of the solvent and crystallization of the residue from MeOH, 0·265 g (98·7%) of **2** (2α): m.p. 208–210°; IR ($CHCl_3$) 1720 cm^{-1}; NMR ($CDCl_3$) δ 4·60 (t, J 7 Hz, 1H)17-H, δ 3·02 (s, 1H)4-H, δ 2·11 (s, 3H) acetate, δ 1·20 (s, 3H) 19-H_3, δ 0·92 (d, J 7 Hz, 3H)2-CH_3, δ 0·82 (s, 3H)18-H_3; NMR (pyridine) δ 3·37 (s, 1H), δ 2·11 (s, 3H), δ 1·18 (s, 3H), δ 1·00 (d, J 7 Hz, 3H), δ 0·82 (s, 3H); $[\alpha]_D$ (0·05 g/10 ml $CHCl_3$) + 75·8°.

2β - *Methyl* - 17β - *acetoxy* - 4β,5β - *epoxyandrostan* - 3 - *one*, **2** (2β). A soln of **2** (2α) (1·57 g; 4·30 mmol) and NaOH (0·6 g) in MeOH (600 ml) was maintained at 23° for 3 h. Roughly 70% of the solvent was evaporated at reduced pressure, and the concentrated soln was added to an equal volume of water, chilled and filtered. The crude product, a mixture of **2** and the corresponding deacetylated compounds, was acetylated (Ac_2O in pyridine soln) and crystallized from hexane. This procedure yielded **2** 1·46 g (93%) of **2** (2β); m.p. 212–213°; IR ($CHCl_3$) 1720 cm^{-1}: NMR ($CDCl_3$) δ 4·59 (t, 7 Hz, 1H)17-H, δ 2·97 (s, 1H)4-H, δ 2·02 (s, 3H) acetate, δ 1·14 (s, 3H)19-H_3, δ 1·10 (d, J 7 Hz, 3H)2-CH_3, δ 0·82 (s, 3H)18-H_3; NMR (pyridine) δ 3·22 (s, 1H), δ 2·02 (s, 3H), δ 1·10 (d, J 7 Hz, 3H), δ 1·09 (s, 3H), δ 0·82 (s, 3H); $[\alpha]_D$ (0·042 g/10 ml $CHCl_3$) + 118·9°.

If the epimerization of **2** (2α) was conducted in a 20% dioxane-heavy water soln to which Na_2O had been added, the recovered **2** (2β) proved to be the 2α-deuterio derivative: NMR ($CDCl_3$), Me signal at δ 1·10 changes to a broad singlet, remaining spectrum unchanged.

Methylation of 4β,5β - *epoxycholestan* - 3 - *one.* To a chilled (0°) soln of lithium ICA (1·09 mmol) in 5 ml THF was added 4β,5β - epoxycholestan - 3 - one (250 mg; 0·62 mmol) in 15 ml THF. A 10 ml portion of dry HMPA was then added and, following a 90 min period of stirring at 0°, the mixture was quenched by the rapid addition of excess MeI. After standing at 25° for 3 h, the resulting mixture was poured into water and extracted with ether. The combined ether extracts were washed, dried and concentrated under reduced pressure, yielding 263 mg crude product. Preparative TLC on 2 mm silica gel plates (15% EtOAc in cyclohexane elutant) gave 190 mg (74%) of **2**; m.p. 100–101°; IR (KBr) 1715 cm^{-1}; $[\alpha]^D$ + 117·53° (0·015 g/10 ml $CHCl_3$). (Found: C, 81·01; H, 11·23. Calcd. for $C_{28}H_{46}O_2$: C, 81·10; H, 11·18%).

17β - t - *Butyldimethylsiloxy* -4β,5β - *epoxyandrostan* - 3 - *one.* 4β,5β - Epoxytestosterone (2·36 g, m.p. 158–159°) was treated with t-butyldimethylchlorosilane (1·40 g; 9·3 mmol) and imidazole (1·32 g; 19·41 mmol) in 20 ml DMF (dry) for 15 h at 35°. The usual work-up gave 2·750 g (85%) of 17β - t - butyldimethylsiloxy - 4β,5β - epoxyandrostan - 3 - one, m.p. 127–128°. (Found: C, 71·67; H, 10·12. Calcd for $C_{25}H_{42}O_3Si$; C, 71·71; H, 10·11%).

Methylation of 17β - t - *butyldimethylsiloxy* - 4β,5β - *epoxyandrostan* - 3 - *one.* To a chilled (0°) soln of lithium ICA (2·95 mmol) in THF (5 ml) was added 17β - t - *butyldimethylsiloxy* - 4β,5β - epoxyandrostan - 3 - one (1·00 g; 2·4 mmol) in THF (15 ml). A 10 ml portion of HMPA was then added and, following a 90 min period of stirring at 0°, the mixture was quenched by the rapid addition of MeI (16 mmol). After standing at room temp for 4 h, the resulting mixture was poured into water and extracted with ether. The usual washing, drying and concentration of the combined ether extract yielded 950 mg of a crystalline product. Recrystallization from hexane gave an 80% yield of 17β - t - butyldimethylsiloxy - 2 - methyl - 4β,5β - epoxyandrostan - 3 - one; m.p. 131–133°; IR (KBr) 1710 cm^{-1}; NMR ($CDCl_3$) δ 3·57 (m, 1H)17-H, δ 2·97 (s, 1H)4-H, δ 1·13 (s, 3H)19-H_3, δ 1·08 (d, J 7 Hz, 3H)2-CH_3, δ 0·87 (s, 9H), δ 0·72 (s, 3H)18-H_3, δ 0·00 (s, 6H). (Found: C, 72·30; H, 10·28. Calcd. for $C_{26}H_{44}O_3Si$: C, 72·16; H, 10·25%).

Reaction of 4β,5β - *epoxytestosterone acetate with methoxide.* 4β,5β - Epoxytestosterone acetate (6·8 gm, 22·4 mmol) was dissolved in dry MeOH (125 ml); NaOMe (3·4 g; 63·0 mmol) was added and the mixture was heated under reflux for 24 h. After the soln cooled to room temp, it was extracted with chloroform. Evaporation of the solvent gave 7·00 g (94%) of 4-methoxytestosterone, crystallization from EtOAc yielding fine white needles, m.p. 218–220° (lit.[3c] 218–220°).

Reaction of 2 - *methyl* - 4β,5β - *epoxytestosterone acetate* (**2**) *with methoxide.* To a soln of KOH (0·66 g, 10·2 mmol) in MeOH was added 2β (0·94 g; 2·6 mmol) dissolved in enough MeOH to bring the final volume to 40 ml. This soln was refluxed for 2·5 h, poured into ice cold 2N KOH, and extracted with ether. The ether extracts were washed, dried and evaporated, following which the residue was reacetylated by treatment with a mixture of pyridine and Ac_2O. Extraction of the pyridine mixture with ether yielded a solid mixture that did not respond to purification by crystallization. Preparative TLC on 2 mm silica gel plates gave two major products: **5**, 0·374 g (32%); and **6**, 0·267 g (30%).

Acidification of the alkaline extracts of the mixture to a congo red endpoint gave, after extraction with ether and reacetylation (Ac_2O in pyridine), the A-norsteroidal-γ-lactone **4**, 0·23 g (26%).

The properties of these compounds which lead to the above structural assignments are: **4**: m.p. 149–150·5°; IR ($CHCl_3$) 1770 and 1723 cm^{-1}; NMR (CCl_4) δ 4·50 (m, 1H)17-H, δ 1·98 (s, 3H) acetate, δ 1·20 (s, 3H), δ 0·98 (s, 3H), δ 0·79 (s, 3H) 18-H_3. (Found: C, 73·21; H, 9·02. Calcd. for $C_{22}H_{32}O_4$: C, 73·30; H, 8·95%).

5; m.p. 187–189°; IR ($CHCl_3$) 1723, 1665 and 1620 cm^{-1}; NMR (CCl_4) δ 5·2 (s, 1H)4-H, δ 4·49 (m, 1H)17-H, δ 3·02 (s, 3H)OCH_3, δ 1·97 (s, 3H)acetate, δ 1·30 (s, 3H)2-CH_3, δ 1·12 (s, 3H)19-H_3, δ 0·80 (s, 3H)18-H_3. (Found: C, 73·95; H, 9·21. Calcd. for $C_{23}H_{34}O_4$: C, 73·76; H, 9·15%).

6; m.p. 180–182° (lit[6] 180–182°); IR (CCl_4) 1730, 1670, 1645 and 1635 cm^{-1}; NMR (CCl_4) δ 6·64 (q, J 1·5 Hz, 1H)1-H, δ 5·87 (s, 1H)4-H, δ 4·48 (m, 1H)17-H, δ 1·97 (s, 3H) acetate, δ 1·80 (d, J 1·5 Hz, 3H)2-CH_3, δ 1·19 (s, 3H)19-H_3, δ 0·82 (s, 3H)18-H_3 (Found: C, 77·18; H, 8·86. Calcd. for $C_{22}H_{30}O_3$: C, 77·16; H, 8·83%).

Reaction of 2 - *methoxy* - 2 - *methyltestosterone acetate* (**5**) *with zinc in acetic acid.* A soln of **5** (100 mg) in glacial AcOH (15 ml) was refluxed with Zn dust (1·0 g) for 20 h. The cooled soln was filtered and evaporated under vacuum. An ether soln of the residue was washed with 5% NaOH followed by water, and the alkaline and aqueous washes were reextracted with ether. The combined ether extracts were dried, and evaporated, yielding 100 mg of crude product. Preparative TLC on 2 mm silica gel plates gave 37 mg (40%) of 2α-methyltestosterone acetate; m.p. 177–180° (lit[6] m.p. 179–180°); IR (CCl_4) 1675 (C=O), 1623 (C=C), 1740 cm^{-1} (ester C=O); NMR ($CDCl_3$), δ 5·66 (s, 1H)4-H, δ 4·7 (t, J 8 Hz, 1H)17-H, δ 1·96 (s, 3H) acetate, δ 1·2 (s, 3H)19-H_3, δ 1·06 (d, J 7 Hz, 3H)2-CH_3, δ 0·83 (s, 3H)18-H_3; mass spectrum (70 eV), *m/e* (rel. intensity), 344(30), 302(18), 288(26), 228(32), 147(41), 138(40), 91(29).

Reaction of 4β,5β - *epoxycholesten* - 3 - *one with LiICA in glyme.* To a cold soln of lithium ICA (0·876 mmol) in 1,2 - dimethoxyethane (4 ml) was added 4β,5β - epoxycholesten - 3 - one (260 mg; 0·65 mmol) in glyme (20 ml). Subsequently, tetramethylethylenediamine (0·22 ml; 1·1 mmol) was added and the soln was stirred at 0° for 30 min, followed by a 3 h reflux. Water and ether were added to the cold mixture, and the aqueous soln was extracted several times. The combined ether extracts were washed, and evaporated, giving 0·260 g crude product. TLC showed only one spot corresponding to starting material. This was supported by the IR and NMR of the product.

Acknowledgement—We are grateful to the National Institutes of Health for their generous support of this work through Grant AM 10849. We also thank Mrs. Lorraine Guile and Mr. Jack Harten for their assistance in obtaining mass spectra, and Dr. Duane Priddy for conducting an exploratory alkylation experiment.

REFERENCES

[1]W. Treibs, *Ber. Dtsch. Chem. Ges.* **66**, 610, 1483 (1933) and earlier papers
[2]H. O. House and W. Gilmore, *J. Am. Chem. Soc.* **83**, 3972 (1961)
[3a]W. Reusch and R. LeMahieu, *Ibid.* **85**, 1669 (1963); [b]W. Reusch and R. LeMahieu, *J. Org. Chem.* **28**, 2443 (1963); [c]B. Camerino, B. Patelli and R. Sciaky, *Gazz. Chim. Ital.* **92**, 709 (1962)
[4a]W. Reusch and P. Mattison, *Tetrahedron* **23**, 1953 (1967); [b]G. W. K. Cavill and C. D. Hall *Ibid.* **23**, 1119 (1967)
[5]I. Laos, *J. Org. Chem.* **32**, 1409 (1967)
[6]A. J. Liston and P. Toft, *Ibid.* **34**, 2288 (1969)