882. *Aspects of Stereochemistry. Part XVIII.* Synthesis of the 10-Methyldecalin-2,9-diols.*

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The four geometrical isomers of 10-methyldecalin-2,9-diol have been prepared from 10-methyl-$\Delta^{1(9)}$-octalone, the *cis*-diaxial *trans*-fused diol (IX) being required for study of the hydrolysis of its monoesters.

Hydrolysis of esters can be assisted by intramolecular participation of a suitably placed nucleophilic or electrophilic substituent. Neighbouring hydroxyl groups are the most important examples of the latter type, and acceleration of hydrolysis has been noted with monoesters of cholestane-*cis*-3,5-diols [1] and with some hydroxy-esters derived from cevine and germine.[2] The hydroxyl group of a neighbouring carboxyl group apparently assists the hydrolysis of the hydrogen succinate of salicylic acid.[3]

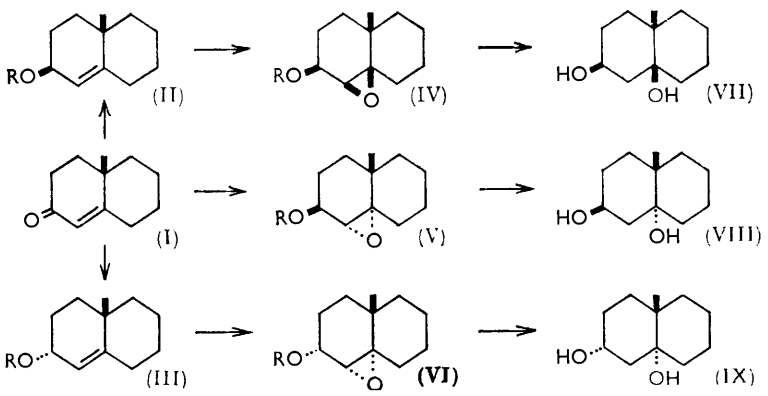
The infrared spectra of the monoacetates of the two steroid *cis*-diaxial diols showed [1] hydrogen bonding between the 5-hydroxyl group and the alkyl-oxygen of the 3-acetate, whereas hydroxyl groups normally form bonds with the carbonyl-oxygen of esters when there are no stereochemical restrictions. Intramolecular hydrogen bonding does not occur in the more flexible monoesters of acyclic 1,3-diols. Pronounced hydrogen bonding to the ether-oxygen and acceleration of ester hydrolysis may therefore be confined to compounds in which the two groups are held close together by the molecular structure.

Serine constitutes part of the active site of chymotrypsin and some other hydrolytic enzymes, and the hydroxyl group of this amino-acid may be involved in the reactions

* Part XVII, *J.*, 1960, 3575.

[1] Henbest and Lovell, *Chem. and Ind.*, 1956, 278; *J.*, 1957, 1965.
[2] Kupchan and Johnson, *J. Amer. Chem. Soc.*, 1956, **78**, 3864; Kupchan and Narayanan, *ibid.*, 1959, **81**, 1913.
[3] Morawetz and Oreskes, *J. Amer. Chem. Soc.*, 1958, **80**, 259.

catalysed by these enzymes.[4] The assistance given to the hydrolysis of steroid axial acetates by neighbouring hydroxyl groups may therefore be a process related to, but simpler than, those occurring in enzyme-catalysed reactions. In order to be able to make physicochemical comparisons, particularly kinetic studies in aqueous media, the synthesis of monoesters of bicyclic diols related to the 3,5-dihydroxy-steroids was undertaken. Esters of the particularly rigid diaxial diol (IX) were especially required.



Yields of diols from (II + III)	
R = H	R = Ac
58%	27%
19%	45%
8%	9%

The bicyclic ketone (I), prepared from 2-methylcyclohexanone, was reduced by lithium aluminium hydride to a mixture of alcohols (II and III). Reduction of relatively unhindered unsaturated ketones often yields the quasiequatorial alcohol as the main product. Application of this rule to the reduction of ketone (I) is made difficult by the fact that both alcohols (II and III; R = H) can assume conformations in which the hydroxyl groups are quasiequatorial. The further reactions of the alcohol mixture showed that the ratio of (II) : (III) was about 9 : 1.

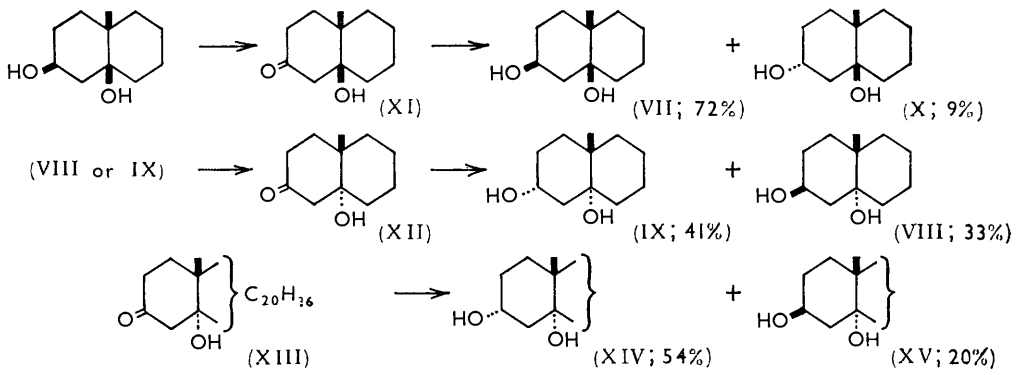
The allylic alcohol mixture (II and III; R = H) was treated with perbenzoic acid, and the epoxide product was reduced with lithium aluminium hydride to a mixture of diols. Chromatography gave three of the four possible diols in crystalline form. The same three diols (two of them in different proportions, see below) were obtained from the mixed acetates (II and III; R = Ac) by successive reactions with peracid and lithium aluminium hydride. The yields of diols are given alongside the structures (VII, VIII, and IX) which are based on the following chemical and spectroscopic evidence.

The steroid (cholestane) analogues of compounds (II; R = H and Ac) give, on epoxidation and reduction, cholestane-3β,5β- and -3β,5α-diol, respectively.[5] The bicyclic alcohol and acetate mixtures did not give the same isomer as major product. The two major products here differ in configuration at $C_{(9)}$ because they gave different ketols on oxidation, but they do not differ in configuration at $C_{(2)}$ (see below), both being derived ultimately from the alcohol (II; R = H). This evidence and the analogy with the steroid series suggest that these two diols have structures (VII) and (VIII). The ketols, obtained by oxidation with chromic acid, must then be formulated as (XI) and (XII), respectively.

The third diol, obtained in similar small yield starting from either the allylic alcohol or the allylic acetate mixture, had the same configuration as diol (VIII) at the angular position $C_{(9)}$ as it was oxidised to the same ketol (XII); structure (IX) is assigned to this diol. The yields of diol (IX) by the alcohol and the acetate route were almost identical, as they depend only on the proportion of the 2α-alcohol (III; R = H) in the original mixture obtained by reduction of ketone (I). The combined yields of the diols (VII and VIII), 77% from the alcohol mixture and 72% from the acetate mixture, represent the proportion of 2β-alcohol (II; R = H) in the original mixture.

[4] Westheimer, *Proc. Nat. Acad. Sci. U.S.A.*, 1957, **43**, 969.
[5] Henbest and Wilson, *J.*, 1957, 1958.

Reduction of ketol (XII) with lithium aluminium hydride gave the diols (VIII) and (IX) in 33 and 41% yield, respectively. Reduction of ketol (XI) gave a high yield of diol (VII) and a small amount of the fourth isomer (X). The compounds with *cis*-hydroxyl groups were the major products from each of these reductions. [The sequence (VIII) ⟶ (XII) ⟶ (IX) gave a method for obtaining more of this required diaxial compound; it



was only obtained in small yield from the epoxy-alcohol mixture (IV, V, VI; R = H).] Similarly, reduction of 5α-hydroxycholestan-3-one (XIII) yielded the *cis*-3α,5α-diol (XIV) as the chief product, although in the absence of the 5α-hydroxyl group, reduction (of cholestanone) gives the 3β-alcohol in 79% yield.[6] The effect of the angular hydroxyl group may be steric, its bulk (possibly as an aluminohydride complex), relative to hydrogen, inhibiting α-approach of reagent. Alternatively, an intramolecular polar effect may be operating of the kind recently discovered in the study of reduction of chloro-ketones by complex hydrides.[7]

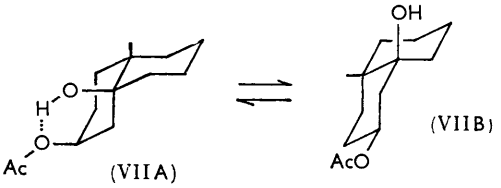
The configurations of the 9-hydroxyl groups in the diols rest largely, as discussed above, on the analogy between the formation of the different main products and the corresponding reactions established in the steroid series. In steroids, the configuration at $C_{(5)}$ of 5-hydroxy-3-ketones may be established by their different rates of dehydration (5β faster) under alkaline conditions, but the method could not be applied to the bicyclic ketols (XI and XII) as they were dehydrated at very similar rates. However, the ease of dehydration of the two ketols (XI) and (XII) provides confirmatory evidence for the assigned structures [containing O=C–CH–C(OH)< groups], and hence for the configuration of the hydroxyl groups at $C_{(2)}$ and $C_{(9)}$ in the original diols. As expected from the given structures, acetylation of each of the four diols under mild conditions gave a (crystalline) monoacetate.

Intramolecular hydrogen bonding in diols should reduce the strength of their adsorption on alumina. Thus, on chromatography, the *cis*-diols, (VII) and (IX), were eluted before the *trans*-compound (VIII). The 2α,9α-diol (IX), containing the strongest hydrogen bond (infrared evidence below), was eluted before the 2β,9β-diol (VII).

We thank Mr. F. Dalton and Dr. G. D. Meakins (Oxford) for determining the infrared spectra of compounds described in this paper. The results, which they will be reporting in detail later, are in accord with the structures assigned above to the diols and ketols. The *trans*-compound (VIII) does not give a peak below 3600 cm.$^{-1}$ but both *cis*-diols (VII and IX) give well-defined peaks (at 3522 and 3532 cm.$^{-1}$, respectively) due to intramolecular hydrogen bonding. The acetates of the *cis*-diols show significant differences: the acetate from (IX) can only exist in one all-chair conformation and gives a single hydroxyl peak (at 3598 cm.$^{-1}$) due to chelation,[1] but the acetate from (VII) gives two

[6] Nace and O'Connor, *J. Amer. Chem. Soc.*, 1951, **73**, 5824.
[7] Combe and Henbest, unpublished work.

hydroxyl peaks, one chelated (at 3599 cm.$^{-1}$) and one unchelated (at 3622 cm.$^{-1}$), corresponding to the two possible conformations, diaxial (VIIA) and diequatorial (VIIB), that this compound can adopt.



(VIIA) (VIIB)

Kinetic studies, being carried out in collaboration with Dr. D. T. Elmore, show that the axial acetate of diol (IX) is hydrolysed more rapidly than the equatorial acetate of diol (VII) under alkaline conditions. Details will be reported later.

Experimental

M. p.s were determined on a Kofler block. Light petroleum refers to the fraction of b. p. 40—60°. Alumina (Spence, type H) was deactivated with dilute acetic acid.[8] The αβ-system of nomenclature [9] is used for denoting geometrical configuration of compounds, all of which are racemic.

Reduction of 10-*Methyl*-$\Delta^{1(9)}$-2-*octalone* (I).—The ketone (10·2 g.) in dry ether (25 ml.) was heated under reflux with stirring for 3 hr. with lithium aluminium hydride (2·4 g.) in dry ether (25 ml.), and then stirred overnight at 20°. Water was slowly added; the ether and the aqueous layer were decanted from the residual slurry which was washed with ether, and the combined ether extracts were dried ($MgSO_4$) and evaporated. Distillation in a short-path still gave the alcohol mixture (II and III; R = H) that was redistilled into fractions (total 9·1 g., 90%), b. p. 73·5—76°/0·2 mm., n_D^{23} 1·5130—1·5140 (Found: C, 79·5; H, 10·6. Calc. for $C_{11}H_{18}O$: C, 79·45; H, 10·9%).

The alcohol (5·75 g.) and acetic anhydride (5 ml.) in dry pyridine (20 ml.) were kept overnight at 20°. Ice-cold 5% sulphuric acid was slowly added until the mixture was acid. The product was isolated with ether and distilled to give the acetate mixture (II and III; R = Ac) (6·65 g., 92%), b. p. 68·5—71°/0·07 mm., n_D^{24} 1·4906—1·4913 (Found: C, 75·15; H, 9·65. Calc. for $C_{13}H_{20}O_2$: C, 74·95; H, 9·7%).

Reaction of the 10-*Methyl*-$\Delta^{1(9)}$-*octalin*-2-*ols* (II *and* III; R = H) *with Perbenzoic Acid*.—The alcohol mixture (3·0 g.) in dry ether (20 ml.) and ethereal 0·48M-perbenzoic acid (45 ml.) were mixed at 0°. After 30 hr. at 0°, reaction was complete. Calcium hydroxide (40 g.) was added, and the mixture was shaken till neutral. The product (2·8 g.) was isolated with ether and distilled in the presence of a trace of calcium hydroxide, to give the mixture of epoxy-alcohols (2·46 g., 74%), b. p. 69—71°/0·04 mm., n_D^{25} 1·4990—1·5000 (Found: C, 72·6; H, 9·9. Calc. for $C_{11}H_{18}O_2$: C, 72·5; H, 9·95%).

Reaction of the Acetates (II *and* III; R = Ac) *with Perbenzoic Acid*.—The acetate mixture (6·5 g.) in dry benzene (20 ml.) was mixed at 0° with a 0·46M-solution (80 ml.) of perbenzoic acid in benzene. After 24 hr. at 0°, reaction was complete. The solution was shaken with calcium hydroxide (60 g.) until neutral, and the product was isolated with benzene. Distillation in the presence of a trace of calcium hydroxide gave the epoxy-acetate mixture (6·1 g.), b. p. 83—86°/0·2 mm., n_D^{20} 1·4840—1·4850 (Found: C, 69·8; H, 8·85. Calc. for $C_{13}H_{20}O_3$: C, 69·6; H, 9·0%).

Reduction of the Epoxy-alcohol Mixture.—The mixture (2·25 g.) in dry ether (25 ml.) was heated under reflux with stirring for 3 hr. with lithium aluminium hydride (0·5 g.) in dry ether (25 ml.), and then stirred overnight at 20°. Ethyl acetate (50 ml.) was slowly added, followed by ice-cold 5% sulphuric acid. The aqueous layer was saturated with sodium chloride, and the product was extracted with ethyl acetate. These extracts were washed and dried ($MgSO_4$), to give the diols (2·13 g.). This was dissolved in light petroleum (b. p. 60—80°) (6 ml.) and adsorbed on deactivated alumina (250 g.). Elution with light petroleum–benzene gave a gum (150 mg.). Elution with benzene–ether (9 : 1) gave 10β-*methyldecalin*-2α,9α-*diol* (IX) (168 mg.,

[8] Farrar, Hamlet, Henbest, and Jones, *J.*, 1952, 2657.
[9] Henbest, Smith, and Thomas, *J.*, 1958, 3293.

9%), m. p. 124—128° (m. p. 130—131·5° after crystallisation from isopropyl ether) (Found: C, 71·5; H, 10·85. $C_{11}H_{20}O_2$ requires C, 71·7; H, 10·95%) and then the 2β,9β-*diol* (VII) (1·225 g., 68%), m. p. 93—97° (m. p. 98·5—100° after crystallisation from isopropyl ether) (Found: C, 72·0; H, 10·75%). Ether eluted the 2β,9α-*diol* (VIII) (415 mg., 22%), m. p. 154—159° (m. p. 161·5—162·5° after crystallisation from ethyl acetate) (Found: C, 71·7; H, 10·95%). For analyses of these diols and the fourth diol, samples were dried in a high vacuum at 40° immediately before weighing.

Reduction of the Epoxy-acetate Mixture.—The mixture (6 g.) in dry ether (40 ml.) was heated under reflux with stirring for 3 hr. with lithium aluminium hydride (1·0 g.) in dry ether (40 ml.). The diols (4·85 g.) were isolated with ethyl acetate as in the preceding experiment. Part (1·15 g.) was stirred with light petroleum–benzene (1 : 1) (4 ml.) to give the relatively insoluble *trans*-diol (VIII) (421 mg.), m. p. 160—162°. The soluble part was adsorbed on deactivated alumina (100 g.) and separated into *cis*-diol (IX) (107 mg., 11%), *cis*-diol (VII) (313 mg., 33%), and *trans*-diol (VIII) (96 mg.; total yield 517 mg., 56%) as in the previous experiment. The pure diols obtained by crystallisation had the same m. p.s as those previously obtained.

Oxidation of 10β-*Methyldecalin*-2β,9α-*diol* (VIII).—Chromic acid (*ca.* 8N; [10] 0·30 ml.) was added in 2 min., with swirling, to the diol (200 mg.) in " AnalaR " acetone (20 ml.) at 20°. After a minute water was added and the product (180 mg.) was isolated with methylene chloride. Two crystallisations from isopropyl ether gave 9α-*hydroxy*-10β-*methyl*-2-*decalone* (XII) (134 mg., 67%), m. p. 162—163° (mixed m. p. with starting material, 140—147°) (Found: C, 72·5; H, 9·8. $C_{11}H_{18}O_2$ requires C, 72·5; H, 9·95%).

Oxidation of 10β-*Methyldecalin*-2β,9β-*diol* (VII).—The diol (360 mg.) in " AnalaR " acetone (30 ml.) was treated with 8N-chromic acid (0·55 ml.) as in the previous experiment. The product (328 mg.) was isolated as before and crystallised from isopropyl ether, to give 9β-*hydroxy*-10β-*methyl*-2-*decalone* (XI) (202 mg., 56%), m. p. 124—125° (Found: C, 72·6; H, 9·85%).

Dehydration of the Ketols (XI) *and* (XII).—Solutions of the ketols (1 mg.) in pure dioxan (100 ml.) were dehydrated at 20° with 0·1% methanolic potassium hydroxide (100 ml.) to 10-methyl-$\Delta^{1(9)}$-2-octalone, rates being followed by the rise in intensity at 2420 Å. The dehydrations proceeded at similar rates; after 24 hr. the solutions from the ketols (XI and XII) showed ε_{2420} of 10,280 and 10,370 respectively [pure (I) has ε_{2420} 14,900]. Under the same conditions 5α-hydroxycholestan-3-one gave a solution with ε_{2420} 11,400 (pure cholest-4-en-3-one has ε_{2420} 16,000).

Reduction of 9α-*Hydroxy*-10β-*methyl*-2-*decalone* (XII).—The ketol (245 mg.) in dry ether (25 ml.) was heated under reflux for 3 hr. with lithium aluminium hydride (25 mg.). The excess of hydride was decomposed with wet ether, and the product (225 mg.) was isolated with ether. It was warmed with light petroleum–benzene (1 : 1) (2 ml.), leaving the 2β,9α-diol (VIII) (55 mg.), m. p. and mixed m. p. 160—163°. The soluble portion (170 mg.) was chromatographed on deactivated alumina (20 g.); elution with benzene–ether (9 : 1) gave the 2α,9α-diol (IX) (93 mg., 41%), m. p. 127—130°; and elution with ether gave more of the 2β,9α-diol (VIII) (20 mg.; total yield 75 mg., 33%), m. p. 155—159°. Gummy material (50 mg.) was eluted before the diols.

Reduction of 9β-*Hydroxy*-10β-*methyl*-2-*decalone* (XI).—The ketol (140 mg.) in dry ether (25 ml.) was heated under reflux for 3 hr. with lithium aluminium hydride (20 mg.). The product (124 mg.) was isolated with ether as in the preceding experiment and chromatographed on deactivated alumina (15 g.). Elution with benzene–ether (9 : 1) gave the 2β,9β-diol (VII) (73 mg.), m. p. and mixed m. p. 97—99°. Elution with ether gave a mixture (31 mg.), m. p. 96—112°, which, on chromatography on deactivated alumina (3 g.), gave on elution with benzene–ether (9 : 1) the 2β,9β-diol (VII) (15 mg.; total yield 88 mg., 72%), m. p. 95—98°, and with ether the 2α,9β-*diol* (X) (12 mg., 9%), m. p. 141—142° (after sublimation at 100°/0·5 mm.) (Found: C, 71·3; H, 10·55%). Viscous material (19 mg.) was eluted with benzene before the diols appeared.

Reduction of 5α-*Hydroxycholestan*-3-*one* (XIII).—The keto-steroid (250 mg.) in dry ether (25 ml.) was heated under reflux for 3 hr. with lithium aluminium hydride (15 mg.). The excess of hydride was decomposed with wet ether, and the residual slurry was washed with ether. The combined ether extracts were dried ($MgSO_4$), and the resulting product (236 mg., 94%) was chromatographed on deactivated alumina (30 g.). Elution with benzene–ether (9 : 1) gave cholestane-3α,5α-diol (XIV) (135 mg., 54%), m. p. and mixed m. p. 195—198°. Elution

[10] Bowden, Heilbron, Jones, and Weedon, *J.*, 1946, 39.

with ether gave cholestane-3β,5α-diol (XV) (50 mg., 20%), m. p. and mixed m. p. 223—224° (crystallised from isopropyl ether). Viscous material (43 mg.) was eluted with benzene before the steroid diols.

2α-*Acetoxy*-10β-*methyldecalin*-9α-*ol*.—The diol (IX) (350 mg.) in dry pyridine (7 ml.) with acetic anhydride (2·1 ml.) was kept overnight at 40°. Ice was added and the product was isolated with ether. Sublimation at 60°/0·2 mm. gave the *acetoxy-alcohol* (397 mg., 92%), m. p. 40·5—41·5° (Found: C, 68·65; H, 10·1. $C_{13}H_{22}O_3$ requires C, 69·0; H, 9·8%). Similar acetylation of the diol (X) gave 2α-*acetoxy*-10β-*methyldecalin*-9β-*ol* (65%), m. p. 53° (from isopropyl ether) (Found: C, 69·2; H, 9·65%).

2β-*Acetoxy*-10β-*methyldecalin*-9α-*ol*.—The diol (VIII) (1·0 g.) in dry pyridine (20 ml.) with acetic anhydride (6 ml.) was kept overnight at 20°. The product was isolated with ether and sublimed at *ca.* 100°/0·5 mm., to give the *acetoxy-alcohol* (1·12 g., 92%), m. p. 103·5—104·5° (Found: C, 68·6; H, 9·55%).

Similar acetylation of the diol (VII) (660 mg.) gave 2β-*acetoxy*-10β-*methyldecalin*-9β-*ol* (736 mg., 91%), m. p. 91·5—92·5° (Found: C, 69·0; H, 9·7%). The mixed m. p. with diol (VIII) was 77—88°.

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