Synthesis and Configurational and Conformational Study of the Diastereoisomeric 2-(α-Hydroxybenzyl)- and 2-(α-Methoxybenzyl)-cyclohexanols and Some of Their Derivatives

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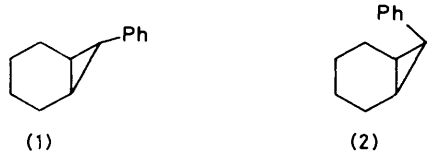
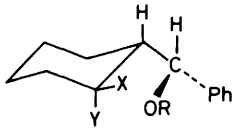
All the diastereoisomeric 2-(α-hydroxybenzyl)- (3), (4), (13), and (14) and 2-(α-methoxybenzyl)cyclohexanols (5), (6), (15), and (16) have been synthesized and some of their derivatives prepared as model compounds of the products of ring opening of some cyclopropanes with electrophiles. The *cis–trans* configuration and the *erythro–threo* relationship for all the title compounds have been unequivocally determined by ^{1}H n.m.r. spectroscopy and by i.r. investigations in the 3 700—3 400 cm^{-1} range in dilute solution. These studies also give information about the conformational equilibria around the bond between the benzylic carbon and the cyclohexane ring in this class of products.

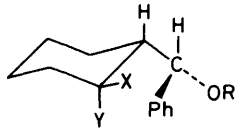
THE ring opening of cyclopropane and its derivatives with electrophiles is interesting both from a synthetic and mechanistic point of view.[1] In continuation of our work on the mechanism and the stereochemistry of the electrophilic ring opening of arylcyclopropanes [2] we have extended the investigation to cyclopropanes (1) and (2) in which the stereochemistry of the electrophilic and nucleophilic steps of the ring opening can be examined separately and related to each other. In order to achieve this it was necessary to prepare and characterize the diols (3), (4), (13), and (14), the corresponding methoxy-alcohols (5), (6), (15), and (16) and some their derivatives



(1) (2)



(3) R = H, X = H, Y = OH
(4) R = H, X = OH, Y = H
(5) R = CH_3, X = H, Y = OH
(6) R = CH_3, X = OH, Y = H
(7) R = Ac, X = H, Y = OAc
(8) R = Ac, X = OAc, Y = H
(9) R = CH_3, X = H, Y = OAc
(10) R = CH_3, X = OAc, Y = H
(11) R = H, X,Y = OCH_2CH_2O
(12) R = CH_3, X,Y = OCH_2CH_2O



(13) R = H, X = H, Y = OH
(14) R = H, X = OH, Y = H
(15) R = CH_3, X = H, Y = OH
(16) R = CH_3, X = OH, Y = H
(17) R = Ac, X = H, Y = OAc
(18) R = Ac, X = OAc, Y = H
(19) R = CH_3, X = H, Y = OAc
(20) R = CH_3, X = OAc, Y = H
(21) R = CH_3, X = H, Y = OPNB
(22) R = CH_3, X = OPNB, Y = H
(23) R = H, X,Y = OCH_2CH_2O
(24) R = CH_3, X,Y = OCH_2CH_2O

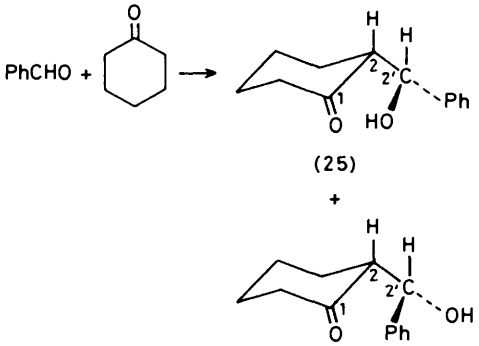
TABLE 1

^{1}H N.m.r. and i.r. spectroscopic data for *erythro*-compounds

Compd.	δ (p.p.m.) CHC_6H_5 [J(Hz)]	δ (p.p.m.) CXY [$W_{\frac{1}{2}}$(Hz)]	$\nu_{max.}$ (cm^{-1}) OH free	$\nu_{max.}$ (cm^{-1}) OH · · · O
(3)	4.82 (2.1)	4.22 (5.7)	3 622	3 527
(4)	4.88 (3.0)	3.46 (24.0)	3 620	3 528
(5)	4.44 (3.8)	4.03 (6.7)	3 625	3 510
(6)	4.56 (3.3)	3.63 (16.5)	3 629	3 519
(7)	5.56 (9.2)	4.38 (7.5)		
(8)	6.07 (3.1)	4.72 (18.9)		
(9)	3.93 (7.0)	4.40 (10.0)		
(10)	4.40 (4.0)	4.93 (22.0)		
(11)	5.41 (2.4)			3 530
(12)	4.55 (2.4)			

(see Tables 1 and 2), as possible products from the ring opening of cyclopropanes (1) and (2) with thallic salts, and as models for a configurational and conformational investigation of the products of ring opening of the same cyclopropanes with mercuric salts.[1]

The condensation of benzaldehyde with cyclohexanone in the presence of NaOH and $MgSO_4$ according to the



(25) + (26)

procedure of House [3] gave a *ca.* 7 : 3 mixture of the two diastereoisomeric hydroxy-ketones, the *erythro*- (25) and *threo*-isomer (26),† from which the *erythro*-isomer (25) was obtained by fractional crystallisation from hexane–

† In order to define the steric relationship between C-2 and C-2′ in compounds (3)—(10), (13)—(22), (25), and (26) and in their derivatives we have used, according to previous authors,[3,4] the nomenclature *erythro–threo*. The steric relationship between the substituents on C-1 and C-2 in compounds (3)—(10) and (13)—(22) and their derivatives is defined, as usual, by the *cis–trans* nomenclature.

diethyl ether or CCl_4. Recrystallisation of the residue of the mother liquor from Et_2O yielded the *threo*-isomer (26). Even when the condensation was carried out without $MgSO_4$ a 3 : 1 mixture of the isomers (25) and (26) was obtained in good yields, contrary to previous reports.[5,6]

The diols (3) and (4), and (13) and (14) were previously prepared [4] *via* the reduction of the *erythro*-ketol (25) with diborane, and *via* hydroboration of *trans*-benzylidenecyclohexanone, respectively. However, only the diols (4) and (13) were obtained in a pure state.[4] Therefore, we examined some reduction reactions of compounds (25) and (26) in order to find better routes to the diols (3), (4), (13), and (14). Reduction of compound (25) with $LiAlH_4$ yielded a mixture of (3) and (4) (see Table 3) in

TABLE 2

^1H N.m.r. and i.r. spectroscopic data for *threo*-compounds

	δ (p.p.m.)		$\nu_{max.}$ (cm^{-1})	
Compd.	CHC_6H_5 [J(Hz)]	CXY [$W_{\frac{1}{2}}$(Hz)]	OH free	OH · · · O
(13)	4.55 (5.5)	3.95 (7.5)	3 618	3 514
(14)	4.47 (9.0)	3.56 (24.0)	3 610	3 520
(15)	4.27 (6.0)	4.16 (10.0) [a]	3 632	3 533
(16)	4.11 (9.0)	3.63 (18.0)	3 615 [b]	3 496
(17)	5.50 (10.5)	5.37 (8.0)		
(18)	5.95 (4.7)	4.50 (20.7)		
(19)	3.77 (9.0)	5.57 (7.0)		
(20)	4.30 (5.6)	4.63 (20.0)		
(21)	3.87 (8.9)	5.92 (7.5)		
(22)	4.34 (5.8)	5.03 (19.0)		
(23)	4.83 (9.3)			3 505
(24)	4.38 (6.6)			

[a] The half-band width cannot be precisely measured because of the partial overlapping of this signal with that of the benzyl proton. [b] Very weak band.

which the former predominated and could be purified by crystallisation. When the reduction was carried out with BH_3·SMe_2 complex the *cis* : *trans* ratio was almost inverted and the *trans*-isomer (4) could be obtained pure by preparative t.l.c. When the *threo*-isomer (26) was reduced with $LiAlH_4$ the *trans*-diol (14) predominated strongly. Reduction with BH_3·SMe_2 gave even higher stereoselectivity. From these mixtures the *trans*-diol (14) was obtained by crystallisation. Reduction with a more bulky agent [$LiAlH(Bu^tO_3)$] afforded larger amounts of the *cis*-diol (13), resulting from an equatorial attack by the hydride. From this last mixture, however, it was not possible to isolate compound (13) in a pure state by t.l.c. or by crystallisation but only by manual separation of the two crystalline forms precipitated after recrystallisation from hexane (see Scheme 1).

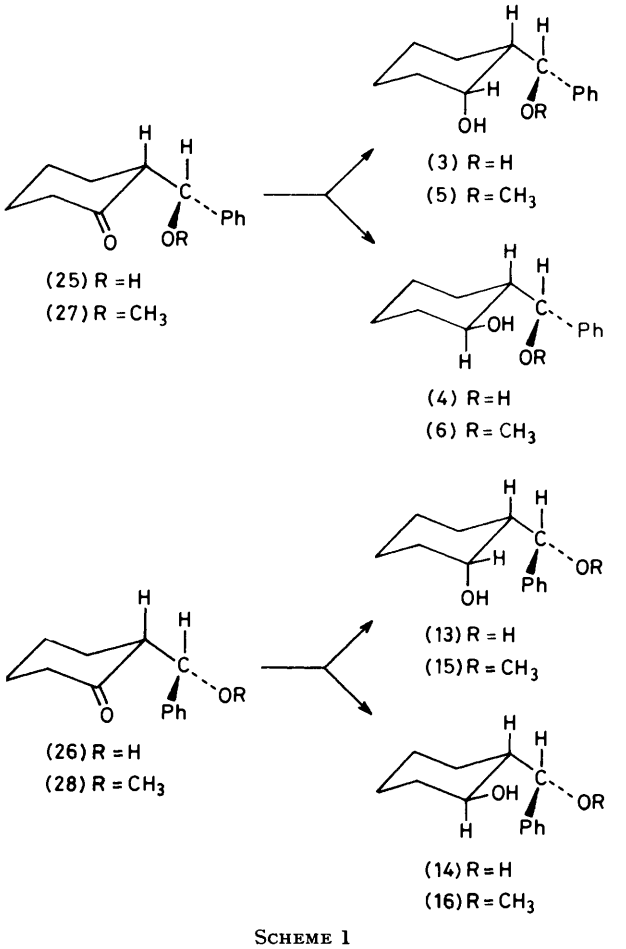
The methoxy-alcohols (5), (6), (15), and (16) could not be simply obtained through selective methylation of the corresponding diols (3), (4), (13), and (14) because of the fact that both the secondary hydroxy-groups are likely to have similar reactivities. The reduction of the methoxy-ketones, *erythro*- (27) and *threo*-isomers (28), appeared to be a promising route to compounds (5), (6), (15), and (16). However, attempts to prepare compounds (27) and (28) by direct methylation were fruitless because of the instability of the starting products under the reaction conditions; they were only obtained after protection of the carbonyl group. Compounds (25) and (26) were converted into the corresponding ethylene acetals (11) and (23) (see Scheme 2)

TABLE 3

cis–trans Ratio of products from the reduction of ketols (25) and (26), and of methoxy-ketones (27) and (28) with different reducing agents

	Ratio of *cis* : *trans* isomers [starting ketol]			
Reducing agent	(3) : (4) [(25)]	(13) : (14) [(26)]	(5) : (6) [(27)]	(15) : (16) [(28)]
$LiAlH_4$	79 : 21	23 : 77	66 : 34	37 : 63
$NaBH_4$			65 : 35	
BH_3·SMe_2	36 : 64	14 : 86	68 : 32	62 : 38
$LiAlH(Bu^tO)_3$		49 : 51	93 : 7	48 : 52

by reaction with ethylene glycol in the presence of malonic acid. They were then treated with sodium hydride–methyl iodide in tetrahydrofuran (THF) to give the corresponding methoxy-derivatives (12) and (24), which

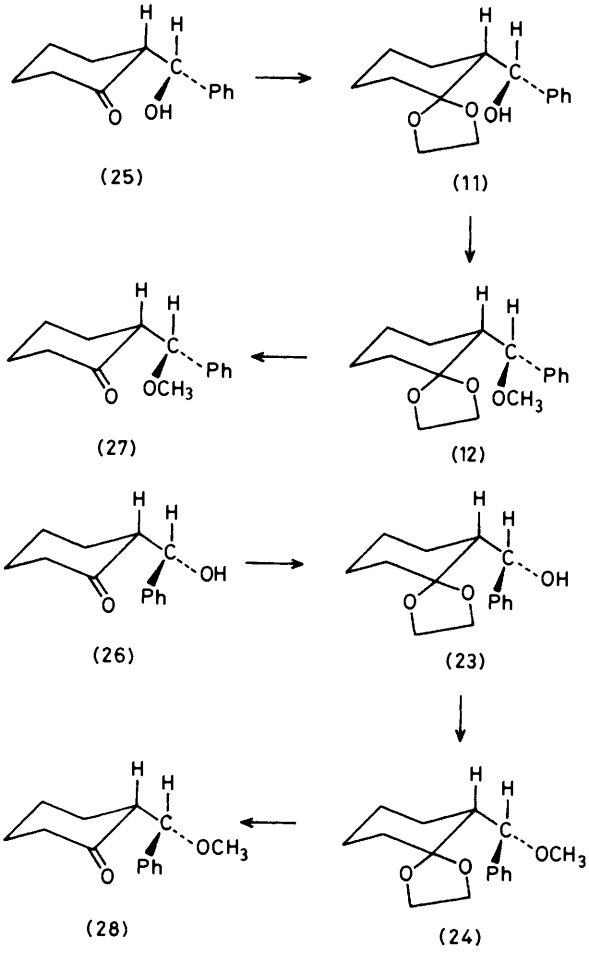


SCHEME 1

were converted into compounds (27) and (28) by reaction with acetone in the presence of toluene-*p*-sulphonic acid.

We then examined some reduction reactions of the methoxy-derivatives (27) and (28). Reduction of the *erythro*-compound (27) with $LiAlH_4$, $NaBH_4$, and BH_3·SMe_2 complex gave *ca.* 2 : 1 mixtures of the *cis*- (5) and

trans-product (6) (see Table 3), from which the pure compounds could be isolated by preparative t.l.c. The reduction of compound (27) with $LiAlH(Bu^tO)_3$ was still more selective, affording almost exclusively the *cis*-product (5). Reduction of the *threo*-methoxy-ketone (28) with $LiAlH_4$ gave a slight excess of the *trans*-compound (16). The *cis*-isomer (15) predominated in

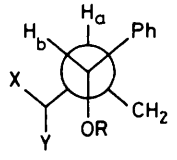


SCHEME 2

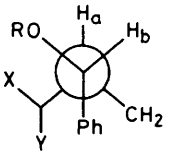
the reduction of (28) with $BH_3{\cdot}SMe_2$ complex. From these mixtures, however, it was not possible to obtain the methoxy-alcohols (15) and (16) pure by crystallisation or by chromatographic techniques. The separation of (15) and (16) was accomplished by converting the mixtures into the corresponding *p*-nitrobenzoates (21) and (22). Crystallisation gave pure *cis*-product (21), whereas preparative t.l.c. yielded the pure *trans*-isomer (22). Reduction of the *p*-nitrobenzoates (21) and (22) with $LiAlH_4$ gave the pure methoxy-alcohols (15) and (16), respectively. The methoxy-alcohols (5), (6), (15), and (16) were also transformed into the corresponding acetates (9), (10), (19), and (20), and the diols (3), (4), (13), and (14) into the diacetates (7), (8), (17), and (18).

While the *erythro*- and *threo*-configuration of the compounds under examination could be deduced, on the basis of their synthesis, from the relative configurations of the keto-alcohols (25) and (26), the steric relationship between the substituents on the cyclohexane ring was not so clear. The *cis–trans* configuration between the substituents on C-1 and C-2 has been determined through their n.m.r. spectra. Tables 1 and 2 list the n.m.r. and the i.r. data of the *erythro*- and *threo*-compounds, respectively. The half-band widths of the signals of the methynic proton on C-1 in compounds (3), (5), (7), (9), (13), (15), (17), (19), and (21) ($W_{\frac{1}{2}}$ 5.7, 6.7, 7.5, 10.0, 7.5, 10.0, 8.0, 7.0, and 7.5 Hz, respectively) are consistent with an equatorial proton, whereas those observed for the same proton in compounds (4), (6), (8), (10), (14), (16), (18), (20), and (22) ($W_{\frac{1}{2}}$ 24.0, 16.5, 18.9, 22.0, 24.0, 18.0, 20.7, 20.0, and 19.0 Hz, respectively) are in agreement with an axial proton.[7-9] Under the logical assumption that the α-hydroxy-, α-acyloxy- and α-methoxy-benzyl groups must occupy an equatorial position in the preferred conformation of these compounds, this defines the relative configuration between the substituents on C-1 and C-2. As can be observed, the coupling constant between the protons on C-2 and C-2′ changes markedly in most cases on passing from the *erythro* to the *threo* series and it also varies noticeably in the same series for different compounds. Consideration of the molecular models of the *erythro*- and *threo*-compounds, however, explains the differences observed and affords interesting information about the conformational equilibria around the C(2)–C(2′) bond in the compounds examined. These observations also give further confirmation of the relative *erythro–threo* configuration in these compounds. Structures (29a—c) and (30a—c) show the Newman projections of the three staggered conformations around the C(2)–C(2′) bond of the *erythro*- and *threo*-compounds, respectively. As pointed out above, the cyclohexane ring in these compounds is considered to be in a chair conformation with the bulky α-hydroxy-, α-methoxy-, and α-acetoxy-benzylic group equatorial. The coupling constants (J_{ab}) between the protons in C-2 (H_a) and C-2′ (H_b) observed for compounds of types (29) and (30) are the result of the weighted average of the coupling constants (J_{ab}) in the corresponding staggered conformations (a—c). The relative importance of conformations (a—c) in the *erythro*- (29) and in the *threo*-derivatives (30) can therefore be related to the experimental J_{ab} values The relative stability of the conformations (a—c) is affected by steric and dipole–dipole interactions, and by intramolecular hydrogen bonding. As for the hydroxy-compounds (diols, hydroxy-ethers) of the *erythro-cis* series, in which an OH · · · O hydrogen bond is possible [compounds (3), (5)] conformation (29a) should be strongly favoured because of the hydrogen bonding and the smaller steric interaction with the phenyl. Accordingly (3) and (5) exhibit very low J_{ab} values. In compounds of the same series in which the hydrogen bond is not possible [(7) and (9)], the dipole–dipole interaction between the OR and the Y groups and the steric interaction with the phenyl favour conformation (29c) in which, as observed, a higher value for J_{ab} results.

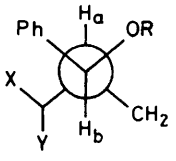
As for the *erythro-trans* series, for compounds in which an OH · · · O bond is possible [such as (4) and (6)], both conformations (29a) and (29b) should have a lower energy,* whereas in the compounds (8) and (10) conformation (29a) appears to be more favoured. Conformations (29b) and (29c) exhibit strong negative gauche–gauche [10] interaction (O–O and O–Ph respectively); low J_{ab} values are observed for all of these compounds. As for the compounds of the *threo-trans* series in which an OH · · · O bonding is possible [(14) and (16)] the hydrogen bonding and the steric factors should markedly favour



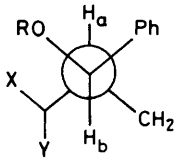
(29a)



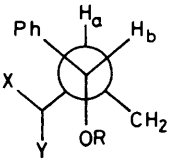
(29b)



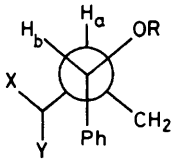
(29c)



(30a)



(30b)



(30c)

conformation (30a); in the other products [(18), (20), and (22)] no conformation is strongly favoured and intermediate values for J_{ab} are consequently observed. The *threo-cis*-compounds, in which an OH · · · O bond is possible [(13) and (15)] exhibit intermediate values of J_{ab}. Disregarding conformation (30c), which appears to be the most unfavourable one, these data indicate an equilibrium between (30a) and (30b); as the steric interactions of the phenyl group are equal in the two conformers, the two different OH · · · O interactions which are possible in (30a) and (30b) must be roughly equivalent energetically. In the other compounds of the same series [(17), (19), and (21)] conformer (30a) should definitely be the preferred one, and as expected high J_{ab} values are found.

For the dioxolan derivatives (11), (12), (23), and (24), the conformational aspect is more complex. However, for the hydroxy-*erythro*-compound (11), steric considerations and the absence, in (29c), of an OH · · · O bond lead to the exclusion of this conformation from the conformational equilibria, in agreement with the low J_{ab} observed. On the other hand, the presence of an OH · · · O interaction and the reduced interaction of the phenyl suggest that (30a) is the preferred conformation in the *threo*-hydroxy-derivative (23), in accordance with the experimental data. For the methoxy-derivatives (12) and (24), however, it is more difficult to evaluate the balance of the interactions. Bearing in mind that conformation (29b) appears to be by far the most crowded one in the *erythro*-compound (12), the low J_{ab} value indicates that the O–Ph interaction in (29c) is higher than the O–O interaction in (29a). No clear preference appears, however, in the conformational equilibrium of the *threo*-derivative (24). For both the keto-methoxy-derivatives (27) and (28), conformation (29b) and (30b), respectively, should be excluded because of the unfavourable interactions CO–O and CO–Ph. The high J_{ab} value for the *threo*-compound (28) (8.7 Hz) indicates conformation (30a) as the preferred one, whereas in the *erythro*-derivative (27) there can be no marked preference between conformations (29a) and (29c), as shown by the intermediate value of J_{ab} (4.2 Hz).

* A hydrogen bond between OH and O, even if lower in energy, is possible also in conformation (29a).

EXPERIMENTAL

M.p.s were determined on a Kofler apparatus and are uncorrected. I.r. spectra for comparison between compounds were taken on paraffin mulls on a Perkin-Elmer Infracord Model 137 instrument, and those for the determination of OH-stretching bands were taken with a Perkin-Elmer Model 225 double-beam grating spectrophotometer in dried (P_2O_5) CCl_4 using the indene band at 3 110 cm^{-1} as the calibration standard; a quartz cell of 2-cm optical length was employed, and the concentration of the solution was 5×10^{-3} M or lower to prevent intermolecular association. N.m.r. spectra were determined for *ca.* 10% $CDCl_3$ solutions with a Varian CFT-20 spectrometer using tetramethylsilane as internal standard. G.l.c. analyses of the mixtures of diols (3), (4), (13), and (14) were run on a Carlo Erba Fractovap 2300 apparatus with a flame ionization detector with glass columns (1.5 m × 2.5 mm) packed with 10% diethylene glycol succinate on 80—100 mesh silanized Chromosorb W (column 190 °C, evaporator and detector 250 °C; nitrogen flow rate 30 ml/min). G.l.c. analyses of methoxy-alcohols (5), (6), (15), and (16) were run on a Carlo Erba GV apparatus with a flame ionization detector with a glass column (1.5 m × 2.5 mm) packed with 10% diethylene glycol succinate on 80—100 mesh silanized Chromosorb W (column 140 °C, evaporator and detector 200 °C; nitrogen flow rate 30 ml/min). Preparative t.l.c. was performed on 2-mm layer silica-gel plates (Merck F_{254}) containing a fluorescent indicator. All comparisons between compounds were made on the basis of i.r. and n.m.r. spectra and g.l.c. $MgSO_4$ was always used as the drying agent. Evaporations were carried out under reduced pressure (rotating evaporator). Unless otherwise stated, light petroleum refers to the fraction boiling at 40—70 °C.

erythro- *and* threo-2-(α-*Hydroxybenzyl*)*cyclohexanone* (25) *and* (26).—These compounds were prepared as previously described [3] from benzaldehyde and cyclohexanone.

erythro-c-2-(α-*Hydroxybenzyl*)*cyclohexan*-r-1-*ol* (3).—A stirred suspension of $LiAlH_4$ (0.80 g, 21.1 mmol) was treated dropwise with the ketone (25) (0.80 g, 3.9 mmol) in anhydrous diethyl ether (40 ml) and the resulting mixture was refluxed for 2 h. After cooling, diethyl ether was added and the excess of hydride was decomposed with water and 10% aqueous NaOH; evaporation of the filtered and dried ether solution gave a solid residue (0.77 g) consisting of a mixture of the two diols (3) and (4) in the ratio 79 : 21; from this mixture pure *compound* (3) (0.40 g) was obtained by crystallisation from benzene–light petroleum, m.p. 97—99 °C, $\nu_{max.}$ (CCl_4) 3 622 (free OH), and 3 527 cm^{-1} (OH · · · O); δ 4.22 (1 H, m, $W_{\frac{1}{2}}$ 5.7 Hz, C*H*OH) and 4.82 (1 H, d, *J* 2.1

Hz, C*H*C$_6$H$_5$) (Found: C, 75.8; H, 8.75. $C_{13}H_{18}O_2$ requires C, 75.69; H, 8.79%).

erythro-t-2-(α-*Hydroxybenzyl*)*cyclohexan*-r-1-*ol* (4).—A solution of the cyclohexanone (25) (0.70 g, 3.43 mmol) in anhydrous-diethyl ether (70 ml) was treated with borane–methyl sulphide complex (0.9 ml of a solution 10.0M in BH_3) and the resulting mixture was stirred at room temperature for 2 h. Methanol was added at 0 °C and the mixture was left overnight at room temperature. Evaporation gave a residue consisting of the diols (3) and (4) in the ratio 36 : 64 which was subjected to preparative t.l.c.; a 7 : 3 mixture of light petroleum–diethyl ether was used as the eluant and the elution was repeated three times. Extraction with CH_2Cl_2 of the slower moving band afforded compound (4) (0.24 g), smoothly impure, which was further purified by crystallisation from benzene–light petroleum (b.p. 80—100 °C) to give pure diol (4) (0.180 g), m.p. 106—107.5 °C (lit.,[4] m.p. 100—101 °C).

threo-c-2-(α-*Hydroxybenzyl*)*cyclohexan*-r-1-*ol* (13).—A solution of compound (26) (0.30 g, 1.47 mmol) in anhydrous diethyl ether (30 ml) was treated with lithium t-butoxy-aluminium hydride (1.0 g, 3.93 mmol) and the resulting mixture was stirred for 2 h at room temperature. After the usual treatment, as for isomer (3), evaporation of the solvent afforded a solid residue (0.29 g) consisting of the diols (13) and (14) in the ratio 49 : 51. Recrystallisation from hexane afforded two different crystalline forms which were manually separated to give pure compound (13) (0.060 g), m.p. 88—90 °C (lit.,[4] m.p. 84—85 °C).

threo-t-2-(α-*Hydroxybenzyl*)*cyclohexan*-r-1-*ol* (14).— Reduction of the ketone (26) (0.50 g, 2.5 mmol) with lithium aluminium hydride, as described for the isomer (25) afforded a solid residue (0.49 g) essentially consisting of a mixture of the diols (13) and (14) in the ratio 23 : 77; from this *mixture* pure *compound* (14) was obtained by crystallisation from benzene–light petroleum (b.p. 80—100 °C) (0.20 g), m.p. 125—127 °C, $\nu_{max.}$ (CCl_4) 3 610 (free OH) and 3 520 cm^{-1} (OH · · · O); δ 3.56 (1 H, m, $W_{\frac{1}{2}}$ 24.0 Hz, C*H*OH) and 4.47 (1 H, d, *J* 9.0 Hz, C*H*C$_6$H$_5$) (Found: C, 75.85; H, 8.8. $C_{13}H_{18}O_2$ requires C, 75.69; H, 8.79%).

erythro-1,1-*Ethylenedioxy*-2-(α-*hydroxybenzyl*)*cyclohexane* (11).—A mixture of the ketone (25) (8.25 g, 0.040 mol), dry benzene (400 ml), ethylene glycol (30 ml), and malonic acid (2.18 g, 0.021 mol) was heated under reflux for 3 h while water was azeotropically removed using a Dean–Stark apparatus. After cooling, the mixture was washed (saturated aqueous sodium hydrogen carbonate and water), filtered and evaporated to give an oily residue (9.5 g) which spontaneously crystallised. Recrystallisation from light petroleum gave pure *compound* (11) (7.45 g), m.p. 80—82 °C, $\nu_{max.}$ (CCl_4) 3 530 cm^{-1} (OH · · · O); δ 4.13 (4 H, m, OCH_2CH_2O) and 5.41 (1 H, s, *J* 2.4 Hz, C*H*C$_6$H$_5$) (Found: C, 72.8; H, 8.1. $C_{15}H_{20}O_3$ requires C, 72.55; H, 8.11%).

erythro-1,1-*Ethylenedioxy*-2-(α-*methoxybenzyl*)*cyclohexane* (12).—A stirred suspension of sodium hydride (6.2 g of a 55% dispersion in oil, 0.14 mol), washed twice with anhydrous light petroleum, in anhydrous tetrahydrofuran (250 ml) was heated under a slow stream of nitrogen at 50 °C and then treated with drops of methyl iodide (27.3 g, 12 ml, 0.19 mol) followed by a solution of the hydroxy-compound (11) (11.5 g, 0.046 mol) in anhydrous tetrahydrofuran (50 ml), over 30 min. The resulting mixture was left at 50—55 °C for 80 min and then cooled: sufficient water was added as drops to dissolve any precipitate. The aqueous layer was separated and extracted twice with diethyl ether; the combined organic solutions were washed (water) and dried, and then evaporated to give an oily residue (12.5 g) consisting of the methoxy-compound (12) which was chromatographed on a silica-gel column (2 × 38 cm), eluting successively with light petroleum (800 ml), and mixtures of light petroleum–diethyl ether (9 : 1, 1 800 ml; 8.5 : 1.5, 700 ml; and 8 : 2, 500 ml). Elution with the 9 : 1 and the 8.5 : 1.5 mixtures afforded pure *compound* (12) (10.5 g) as an oil; $\nu_{max.}$ (Nujol) 1 430, 1 180, and 1 070 cm^{-1}; δ 3.25 (3 H, s, OCH_3), 3.93 (4 H, m, OCH_2CH_2O), and 4.55 (1 H, d, *J* 2.4 Hz, C*H*C$_6$H$_5$) (Found: C, 72.85; H, 8.7. $C_{16}H_{22}O_3$ requires C, 73.25; H, 8.45%).

erythro-2-(α-*Methoxybenzyl*)*cyclohexanone* (27).—A solution of the ethylenedioxy-compound (12) (7.20 g, 27.5 mmol) in acetone (370 ml) was treated with toluene-*p*-sulphonic acid monohydrate (1.40 g, 7.36 mmol) and then left at room temperature for 20 h. Solid sodium hydrogen carbonate was added and the mixture was diluted with water and extracted with diethyl ether; the combined ether extracts were washed (saturated aqueous sodium hydrogen carbonate and water) and dried, and then evaporated to give pure *compound* (27) as an oil (5.65 g); $\nu_{max.}$ (Nujol) 1 700 and 1 090 cm^{-1}; δ 3.40 (3 H, s, OCH_3) and 4.97 (1 H, d, *J* 4.2 Hz, C*H*C$_6$H$_5$) (Found: C, 76.9; H, 8.2. $C_{14}H_{18}O_2$ requires C, 77.03; H, 8.31%).

threo-1,1-*Ethylenedioxy*-2-(α-*hydroxybenzyl*)*cyclohexane* (23).—The same procedure as described for the preparation of compound (11) was followed, starting from the ketone (26) (0.35 g). Work-up gave a solid residue (3.9 g) which was recrystallised from hexane to give pure *compound* (23) (3.1 g), m.p. 95—97 °C; $\nu_{max.}$ (CCl_4) 3 505 cm^{-1} (OH · · · O); δ 4.13 (4 H, m, OCH_2CH_2O) and 4.83 (1 H, d, *J* 9.3 Hz, C*H*C$_6$H$_5$) (Found: C, 72.8; H, 8.15. $C_{15}H_{20}O_3$ requires C, 72.55; H, 8.11%).

threo-1,1-*Ethylenedioxy*-2-(α-*methoxybenzyl*)*cyclohexane* (24).—Treatment of compound (23) (2.8 g) with sodium hydride and methyl iodide following the procedure described for the methoxy-compound (12), gave an oily residue which was purified by chromatography on a silica-gel column (2 × 20 cm). After light petroleum (150 ml), elution with mixtures of light petroleum–diethyl ether (9 : 1, 250 ml; and 8 : 2, 200 ml) afforded pure *compound* (24) (2.7 g) as an oil; $\nu_{max.}$ (Nujol) 1 430, 1 210, and 1 090 cm^{-1}; δ 3.19 (3 H, s, OCH_3), 4.08 (4 H, m, OCH_2CH_2O), and 4.38 (1 H, d, *J* 6.6 Hz, C*H*C$_6$H$_5$) (Found: C, 72.8; H, 8.4. $C_{16}H_{22}O_3$ requires C, 73.25; H, 8.45%).

threo-2-(α-*Methoxybenzyl*)*cyclohexanone* (28).—As described for the methoxy-compound (27), treatment of compound (24) (2.4 g) with toluene-*p*-sulphonic acid monohydrate gave pure *cyclohexanone* (28) (1.85 g) as an oil; $\nu_{max.}$ (Nujol) 1 720 and 1 090 cm^{-1}; δ 3.27 (3 H, s, OCH_3) and 4.63 (1 H, d, *J* 8.7 Hz, C*H*C$_6$H$_5$) (Found: C, 7.6.7; H, 8.2. $C_{14}H_{18}O_2$ requires C, 77.03; H, 8.31%).

Reduction of the Methoxybenzyl-cyclohexanone (27) *with Borane–Methyl Sulphide Complex*.—Borane–methyl sulphide complex (1.36 ml of a solution 10.0M in BH_3) was added dropwise to a stirred solution of compound (27) (1.0 g, 4.6 mmol) in anhydrous diethyl ether (100 ml), as described for the diol (4). The usual work-up gave an oily residue (0.98 g) consisting of a 68 : 32 mixture of methoxy-compounds (5) and (6) which was separated by preparative t.l.c., eluting with a mixture of light petroleum–diethyl ether (7 : 3): elution was repeated three times. Extraction of the band with the higher R_F gave pure erythro-c-2-(α-*methoxybenzyl*)-*cyclohexan*-r-1-*ol* (5) (0.54 g) as an oil, $\nu_{max.}$ (CCl_4) 3 625 (free

OH) and 3 510 cm^{-1} (OH · · · O); δ 3.33 (3 H, s, OCH_3), 4.03 (1 H, m, $W_{\frac{1}{2}}$ 6.7 Hz, C*H*OH), and 4.44 (1 H, d, *J* 3.8 Hz, C*H*C_6H_5) (Found: C, 76.75; H, 9.25. $C_{14}H_{20}O_2$ requires C, 76.32; H, 9.15%). Extraction of the lower moving band gave erythro-t-2-(α-*methoxybenzyl*)*cyclohexan*-r-1-*ol* (6) (0.22 g) as an oil which crystallised. Recrystallisation from light petroleum at −15 °C gave pure (6), m.p. 57—59 °C; $\nu_{max.}$ (CCl_4) 3 629 (free OH) and 3 519 cm^{-1} (OH · · · O); δ 3.33 (3 H, s, OCH_3), 3.63 (1 H, m, $W_{\frac{1}{2}}$ 16.5 Hz, C*H*OH), and 4.56 (1 H, d, *J* 3.3 Hz, C*H*C_6H_5) (Found: C, 76.7; H, 9.2. $C_{14}H_{20}O_2$ requires C, 76.32; H, 9.15%).

The reduction of compound (27) (0.10 g, 0.46 mmol) was also performed with lithium aluminium hydride (0.15 g) in anhydrous diethyl ether (12 ml), with lithium tri-t-butoxyaluminium hydride (0.25 g) in anhydrous diethyl ether (10 ml), and with sodium borohydride (0.10 g) in ethanol (5 ml). The crude reaction mixture from each of these had the relative (5) : (6) composition shown in Table 3.

Reduction of the Cyclohexanone (28) *with Borane–Methyl Sulphide Complex*.—A solution of compound (28) (1.5 g) was treated with borane methyl sulphide complex (2.1 ml) as described for the analogous reduction of the isomer (27). Work-up gave an oily residue (1.45 g) consisting of the two isomers (15) and (16) in the ratio 62 : 38. All the attempts to separate these isomers by column chromatography or by preparative t.l.c. were unsuccessful.

The reduction of compound (28) was also performed with lithium aluminium hydride and with lithium tri-t-butoxyaluminium hydride in anhydrous diethyl ether as described for the analogous reactions of the isomer (27) to give the relative (15) : (16) composition shown in Table 3.

p-*Nitrobenzoyl Derivatives of Compounds* (15) *and* (16).—Recrystallised (CCl_4) *p*-nitrobenzoyl (PNB) chloride (0.64 g, 3.4 mmol) was added in portions to a stirred solution of the crude mixture of methoxy-alcohols (15) and (16) (0.63 g, 2.9 mmol), obtained in the reaction described above, keeping the temperature at 0 °C. The mixture was stirred for 30 min at 0 °C and then left overnight at room temperature. Addition of brine and extraction with CH_2Cl_2 gave, after evaporation of the washed (dilute hydrochloric acid, water, saturated aqueous sodium hydrogen carbonate and water) and dried organic extracts, a solid residue (0.96 g) which was carefully recrystallised from hexane to give the pure p-*nitrobenzoyl derivative* of (15) [(21)] (0.13 g), m.p. 167—169 °C; $\nu_{max.}$ (Nujol) 1 700, 1 265, and 1 101 cm^{-1}; δ 3.06 (3 H, s, OCH_3), 3.87 (1 H, d, *J* 8.9 Hz, C*H*C_6H_5), and 5.92 (1 H, m, $W_{\frac{1}{2}}$ 7.5 Hz, CHOCO) (Found: C, 68.5; H, 6.45; N, 3.4. $C_{21}H_{23}NO_5$ requires C, 68.27; H, 6.27; N, 3.79%).

The mother liquors contained essentially the *p*-nitrobenzoyl derivative of (16) [(22)]. Purification by preparative t.l.c., eluting with light petroleum–diethyl ether (8.5 : 1.5; ×4), gave, after extraction of the most intense band, a solid residue (0.15 g) which was recrystallised from light petroleum to give pure *compound* (22) (0.095 g), m.p. 69—71 °C; $\nu_{max.}$ (Nujol) 1 718, 1 250, and 1 086 cm^{-1}; δ 3.15 (3 H, s, OCH_3), 4.34 (1 H, d, *J* 5.8 Hz, C*H*C_6H_5), and 5.03 (1 H, m, $W_{\frac{1}{2}}$ 19.0 Hz, CHOCO) (Found: C, 68.55; H, 6.45; N, 3.5. $C_{21}H_{23}NO_5$ requires C, 68.27; H, 6.27; N, 3.79%).

threo-c-2-(α-*Methoxybenzyl*)*cyclohexan*-r-1-*ol* (15).—Lithium aluminium hydride (0.20 g, 5.3 mmol) was added in portions to a stirred solution of the *p*-nitrobenzoyl compound (21) (0.11 g, 0.30 mmol) in anhydrous diethyl ether (12 ml) and the resulting mixture was stirred for 1 h at room temperature, then refluxed for 15 min. After cooling, diethyl ether, water, and dilute sodium hydroxide solution were added in succession in order to destroy the excess of hydride. Evaporation of the washed (dilute hydrochloric acid, water, saturated aqueous sodium hydrogen carbonate, and water) and dried diethyl ether solution gave pure *compound* (15) as an oil; $\nu_{max.}$ (CCl_4) 3 632 (free OH) and 3 533 cm^{-1} (OH · · · O); δ 3.26 (3 H, s, OCH_3), 4.16 (1 H, m, $W_{\frac{1}{2}}$ was *ca.* 10.0 Hz and could not be precisely measured because of the partial overlapping of this signal with that of the benzyl proton), and 4.27 (1 H, d, *J* 6.0 Hz, C*H*C_6H_5) (Found: C, 76.55; H, 9.4. $C_{14}H_{20}O_2$ requires C, 76.32; H, 9.15%).

threo-t-2-(α-*Methoxybenzyl*)*cyclohexan*-r-1-*ol* (16).—Following the procedure described for compound (15), reduction of the *p*-nitrobenzyl derivative (22) (0.080 g) with lithium aluminium hydride gave pure *compound* (16) as an oil; $\nu_{max.}$ (CCl_4) 3 615 (free OH) and 3 496 cm^{-1} (OH · · · O); δ 3.20 (3 H, s, OCH_3), 3.63 (1 H, m, $W_{\frac{1}{2}}$ 18.0 Hz, C*H*OH), and 4.11 (1 H, d, *J* 9.0 Hz, C*H*C_6H_5) (Found: C, 76.75; H, 9.15. $C_{14}H_{20}O_2$ requires C, 76.32; H, 9.15%).

erythro-c-2-(α-*Acetoxybenzyl*)-r-1-*cyclohexyl Acetate* (7).—Acetic anhydride (3.6 ml) was added at 0 °C to a solution of the diol (3) (0.55 g) in dry pyridine (1.8 ml) and the reaction mixture was left at room temperature for 24 h. Ice and two drops of dilute hydrochloric acid were added and the reaction mixture left at room temperature for 24 h, and then extracted with diethyl ether. Evaporation of the washed (dilute hydrochloric acid, water, saturated aqueous sodium hydrogen carbonate and water) and dried ether extracts gave a solid residue which was recrystallised from hexane affording pure *compound* (7) (0.20 g), m.p. 106—108 °C; $\nu_{max.}$ (Nujol) 1 708, 1 365, and 1 230 cm^{-1}; δ 2.02 and 2.05 (3 H, s, $OCOCH_3$ each), 4.38 (1 H, m, $W_{\frac{1}{2}}$ 7.5 Hz, C*H*O$COCH_3$), and 5.56 (1 H, d, *J* 9.2 Hz, C*H*C_6H_5) (Found: C, 70.4; H, 7.6. $C_{17}H_{22}O_4$ requires C, 70.32; H, 7.63%).

erythro-t-2-(α-*Acetoxybenzyl*)-r-1-*cyclohexyl Acetate* (8).—Following the procedure described for the isomer (7), acetylation of the diol (4) (0.27 g) with acetic anhydride in dry pyridine gave a crude product (0.32 g) which was recrystallised from hexane to give pure *compound* (18) (0.14 g), m.p. 96—97 °C; $\nu_{max.}$(Nujol) 1 710, 1 360, and 1 220 cm^{-1}; δ 2.02 and 2.11 (3 H, s, $OCOCH_3$ each), 4.72 (1 H, m, $W_{\frac{1}{2}}$ 18.9 Hz, C*H*O$COCH_3$), and 6.07 (1 H, d, *J* 3.1 Hz, C*H*C_6H_5) (Found: C, 70.1; H, 7.9. $C_{17}H_{22}O_4$ requires C, 70.32; H, 7.63%).

threo-c-2-(α-*Acetoxybenzyl*)-r-1-*cyclohexyl Acetate* (17).—In a similar manner, reaction of the diol (13) (0.10 g) in dry pyridine with acetic anhydride gave a solid residue (0.11 g) which was recrystallised from light petroleum at 5 °C to give pure *compound* (17) (0.060 g), m.p. 105—107 °C; $\nu_{max.}$ (Nujol) 1 705, 1 360, and 1 240 cm^{-1}; δ 1.98 and 2.08 (3 H, $OCOCH_3$ each), 5.37 (1 H, m, $W_{\frac{1}{2}}$ 8.0 Hz, C*H*O$COCH_3$), and 5.50 (1 H, d, *J* 10.5 Hz, C*H*C_6H_5) (Found: C, 70.15; H, 7.5. $C_{17}H_{22}O_4$ requires C, 70.32; H, 7.63%).

threo-t-2-(α-*Acetoxybenzyl*)-r-1-*cyclohexyl Acetate* (18).—Compound (14) (0.24 g) was acetylated as described for the diol (3) with acetic anhydride in dry pyridine to give an oily product which was purified by preparative t.l.c. (a 7 : 3 mixture of light petroleum–diethyl ether was used as eluant; the elution was repeated three times). Extraction of the unique visible band gave pure *compound* (18) (0.25 g) as a liquid; $\nu_{max.}$ (Nujol) 1 700, 1 350, and 1 220 cm^{-1}; δ 2.01 and 2.09 (3 H, s, $OCOCH_3$ each), 4.50 (1 H, m, $W_{\frac{1}{2}}$ 20.7 Hz, C*H*O$COCH_3$), and 5.95 (1 H, d, *J* 4.7 Hz, C*H*C_6H_5) (Found: C, 70.25; H, 7.85. $C_{17}H_{22}O_4$ requires, C, 70.32; H, 7.63).

erythro-c-(9) *and* -t-2-(α-*Methoxybenzyl*)-r-1-*cyclohexyl Acetate* (10).—A 68 : 32 mixture of methoxy-alcohols (5) and (6) (0.40 g) was acetylated, as previously described, with acetic anhydride and dry pyridine. After the usual work-up, the oily crude residue obtained was subjected to preparative t.l.c. (a 95 : 5 mixture of light petroleum–diethyl ether was used as eluant; elution was repeated six times). Extraction of the slower moving band gave pure *compound* (9) (0.11 g) as an oil; $\nu_{max.}$ (Nujol) 1 725 and 1 235 cm^{-1}; δ 2.03 (3 H, s, $OCOCH_3$), 3.13 (3 H, s, OCH_3), 3.93 (1 H, d, *J* 7.0 Hz, CHC_6H_5), and 4.40 (1 H, m, $W_{\frac{1}{2}}$ 10.0 Hz, $CHOCOCH_3$) (Found: C, 73.15; H, 8.3. $C_{16}H_{22}O_3$ requires C, 73.25; H, 8.45%). Extraction of the faster moving band afforded pure *compound* (10) (0.070 g) as an oil; $\nu_{max.}$ (Nujol) 1 740 and 1 225 cm^{-1}; δ 2.00 (3 H, s, $OCOCH_3$), 3.20 (3 H, s, OCH_3), 4.40 (1 H, d, *J* 4.0 Hz, CHC_6H_5), and 4.93 (1 H, m, $W_{\frac{1}{2}}$ 22.0 Hz, $CHOCOCH_3$) (Found: C, 73.1; H, 8.5. $C_{16}H_{22}O_3$ requires C, 73.25; H, 8.45).

threo-c-(19) *and* -t-2-(α-*Methoxybenzyl*)-r-1-*cyclohexyl Acetate* (20).—A 62 : 38 mixture of isomers (15) and (16) (0.40 g) was acetylated as described above. The crude oily product was subjected to preparative t.l.c. (a 95 : 5 mixture of light petroleum–diethyl ether was used as eluant; elution was repeated three times); extraction of the faster moving band gave pure *compound* (20) (0.060 g) as an oil; $\nu_{max.}$ (Nujol) 1 735 and 1 243 cm^{-1}; δ 2.07 (3 H, s, $OCOCH_3$), 3.18 (3 H, s, OCH_3), 4.30 (1 H, d, *J* 5.6 Hz, CHC_6H_5), and 4.63 (1 H, m, $W_{\frac{1}{2}}$ 20.0 Hz, $CHOCOCH_3$) (Found: C, 72.95; H, 8.2. $C_{16}H_{22}O_3$ requires C, 73.25; H, 8.45%). Extraction of the slower moving band gave pure *compound* (19) (0.10 g) as a solid, m.p. 68—70 °C; $\nu_{max.}$ (Nujol) 1 730 and 1 250 cm^{-1}; δ 2.10 (3 H, s, $OCOCH_3$), 3.08 (3 H, s, OCH_3), 3.77 (1 H, d, *J* 9.0 Hz, CHC_6H_5), and 5.57 (1 H, m, $W_{\frac{1}{2}}$ 7.0 Hz, $CHOCOCH_3$) (Found: C, 73.4; H, 8.55. $C_{16}H_{22}O_3$ requires C, 73.25; H, 8.45%).

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