CYCLOHEXANE COMPOUNDS

III. THE 1-METHOXY- AND 1-ETHOXY-2-HYDROXY-3-BROMOCYCLOHEXANES[1, 2]

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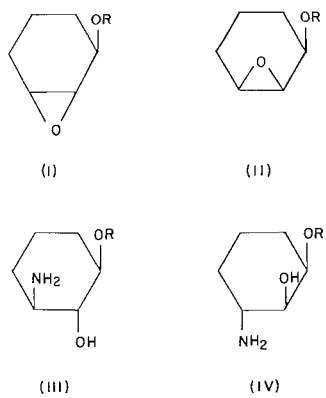
ABSTRACT

1α-Methoxy-2β-hydroxy-3α-bromocyclohexane and 1α-methoxy-2α-hydroxy-3β-bromocyclohexane have been prepared by the action of hydrobromic acid on 1β-methoxy-2α,3α-epoxycyclohexane and 1α-methoxy-2α,3α-epoxycyclohexane respectively. Assignment of stereochemical configuration to 1α-methoxy-2β-hydroxy-3α-bromocyclohexane was made by catalytic debromination of the phenyl- and 1-naphthyl-urethanes to derivatives of 2β-methoxy-1α-cyclohexanol. An alternative proof of structure was obtained by de-etherification of the bromohydrin to 3α-bromo-1α,2β-cyclohexanediol, which was catalytically debrominated to 1α,2β-cyclohexanediol and oxidized via periodate to 2-bromoadipaldehyde, isolated as the bis-2,4-dinitrophenylhydrazone. The structure of 1α-methoxy-2α-hydroxy-3β-bromocyclohexane was established by de-etherification to 3β-bromo-1α,2α-cyclohexanediol, which was oxidized by periodate 10 times more rapidly than its isomer. The corresponding ethoxy compounds were prepared and their structures were elucidated in a completely analogous manner.

In an earlier paper (1) the mixtures of bromohydrins resulting from the action of aqueous N-bromosuccinimide on 1-methoxy- and 1-ethoxy-cyclohexene-2 were utilized for synthesis of the stereoisomeric 1-methoxy- and 1-ethoxy-2,3-epoxycyclohexanes I and II (R = CH_3 or C_2H_5) and led ultimately by ammonolysis of the latter to the 1-methoxy- and 1-ethoxy-2-hydroxy-3-aminocyclohexanes III and IV (R = CH_3 or C_2H_5). The formation of two oxides by the action of aqueous sodium hydroxide on each 1-alkoxy-cyclohexene-2 bromohydrin demonstrated the presence in each of at least two trans-oriented bromohydrins (2, 3), but the possibility existed that all four bromohydrins V–VIII were present. Attempts to separate the bromohydrin mixtures by fractionation *in vacuo* were unsuccessful, and attention was, therefore, directed toward preparation of pure bromohydrins from the pure oxides by the action of hydrobromic acid, since it was anticipated that knowledge gained concerning the physical and chemical characteristics of any of the possible components of the mixtures would facilitate the development of a method for separation and identification of all the components.



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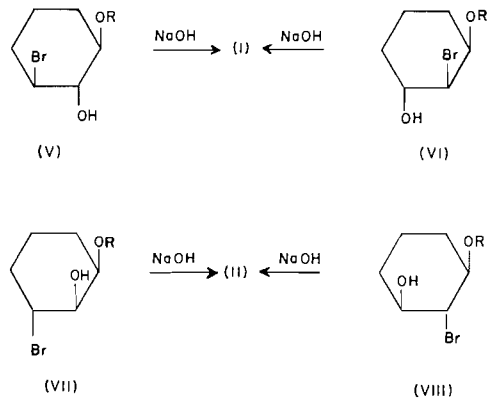
Issued as D.R.C.L. Report No. 312.
[2]*For Part II of this series see reference 1.*



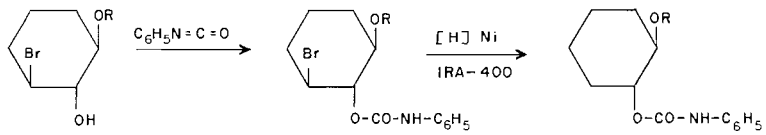
Theoretically, two bromohydrins can be formed from each oxide if ring scission occurs in both possible directions (4). However, our previous experience with ammonolysis of the oxides, in which derivatives of 3-amino-1,2-cyclohexanediol were formed exclusively (1), together with the results obtained by Lemieux, Kullnig, and Moir (5) on methanolysis of the oxides, suggested that 1-alkoxy-2-hydroxy-3-bromocyclohexanes would probably be the only bromohydrins formed. The work now to be described is concerned only with the synthesis and proof of structure of the 1-methoxy- and 1-ethoxy-2-hydroxy-3-bromocyclohexanes. Application of the information gained therefrom to solution of the problem of the composition of the bromohydrin mixtures referred to above is reserved for a subsequent communication.

1β-Methoxy-2α,3α-epoxycyclohexane (I, R = CH_3) on treatment with hydrobromic acid gave a solid bromohydrin, m.p. 68.5–69°, in 63% yield. The liquid fraction isolated from the reaction was shown to consist of 27% bromohydrin (by isolation of the 1-naphthylurethane, m.p. 185–186°) and 19% of a 1-methoxy-2,3-cyclohexanediol (identified by periodate cleavage followed by isolation of the bis-2,4-dinitrophenylhydrazone of 2-methoxyadipaldehyde, m.p. 192–193.5°, and by isolation of a 1-methoxy-2,3-cyclohexanediol bis-1-naphthylurethane, m.p. 224–226°) leaving approximately 50% of the oil unidentified. No further attempt was made to characterize this portion of the product but the suggestion is offered that it could well be a 2-methoxy-3-bromocyclohexanol formed by methoxyl migration (6). In support of this suggestion is the observation (see below) that the action of hydrobromic acid on the cis oxide II produces the corresponding bromohydrin in 93% yield with formation of only a very minor quantity of methoxydiol. The absence of a large fraction of unknown structure is to be expected in this instance because facile migration of the methoxyl group is hindered by virtue of the cis relationship of the methoxyl and its neighboring hydroxyl group.

The bromohydrin was characterized by preparation of its phenylurethane, m.p. 133–134° (86%), 1-naphthylurethane, m.p. 185–186° (94%), and its acetyl derivative, m.p. 56–56.5° (90%), and its structure was established as 1α-methoxy-2β-hydroxy-3α-bromocyclohexane (V, R = CH_3) by the following methods.

The phenylurethane of the bromohydrin (IX, R = CH_3) was debrominated according to the method of McCasland and Horswill (7) using hydrogen, Raney nickel, and an anion exchange resin, producing 2β-methoxy-1α-cyclohexanol phenylurethane (X, R = CH_3), m.p. 66–67.5°, in 78% yield. The identity of the latter compound was established by comparison with an authentic specimen obtained from 2β-methoxy-1α-cyclohexanol (8).

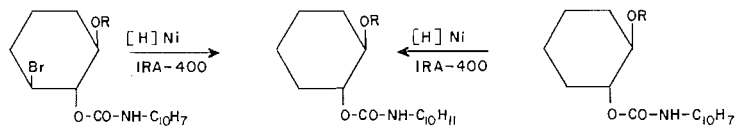
Prior to use of the debromination method it was shown that no concomitant reduction of the benzene or urethane groups occurred under the conditions employed, since debromination of 2β-bromo-1α-cyclohexanol phenylurethane, m.p. 85–87° (9) gave cyclohexanol phenylurethane, m.p. 83–84.5° (10), in 86.5% yield. The bromine atom must have occupied a position trans to the hydroxyl group in the original bromohydrin since the latter yields the oxide I (R = CH_3) on treatment with alkali (2, 3) and it therefore follows that the bromohydrin must be 1α-methoxy-2β-hydroxy-3α-bromocyclohexane (V, R = CH_3).



(V) (IX) (X)

R = CH_3, m.p. 68.5–69° R = CH_3, m.p. 133–134° R = CH_3, m.p. 66–67.5°
R = C_2H_5, m.p. 46–47.5° R = C_2H_5, m.p. 132–133.5°

A similar proof of structure was obtained using the 1-naphthylurethane (XI, R = CH_3) rather than the phenylurethane. During debromination, however, simultaneous reduction of one of the benzenoid rings occurred, leading to the tetralin derivative (XII, R = CH_3). The latter substance was identified by comparison with an authentic specimen prepared by reduction of 2β-methoxy-1α-cyclohexanol 1-naphthylurethane (XIII, R = CH_3) under the same conditions as used for debromination.



(XI) (XII) (XIII)

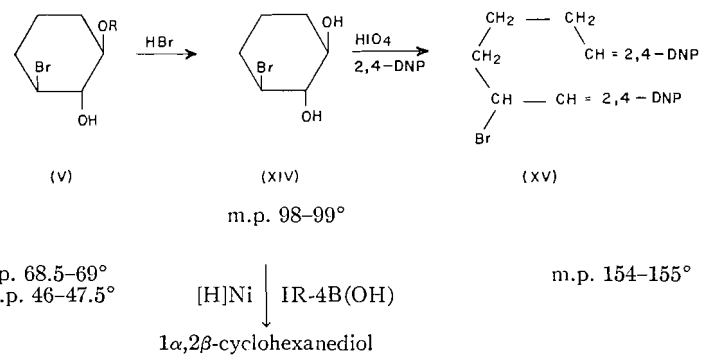
R = CH_3, m.p. 185–186° R = CH_3, m.p. 89.5–91° R = CH_3, m.p. 111–112°
R = C_2H_5, m.p. 196–197° R = C_2H_5, m.p. 71–72.5° R = C_2H_5, m.p. 131–132°

It was also shown that debromination of 2β-bromo-1α-cyclohexanol 1-naphthylurethane by the hydrogen – Raney nickel method leads to a cyclohexanol tetrahydro-1-naphthylurethane identical with that obtained by reduction of cyclohexanol 1-naphthylurethane under the same conditions. These experiments did not establish which benzenoid ring was reduced. However, by analogy with work reported by Papa and Schwenk (11) it seems probable that reduction occurred in the unsubstituted ring.

The urethanes were used rather than the bromohydrin V (R = CH_3) itself to avoid the possibility of intermediate oxide formation, which would invalidate any structural assignment based on the debromination experiments since the oxide I (R = CH_3) could result just as readily from VI as from V (R = CH_3). It will be demonstrated in the sequel, however, that the use of derivatives is unnecessary because oxide formation is readily preventable and, moreover, if it is forced to occur the oxide is not reduced under the conditions of debromination.

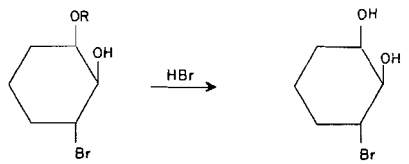
De-etherification of the bromohydrin with fuming hydrobromic acid gave a bromodiol, m.p. 98–99°, in 89% yield, which was further characterized via its bis-1-naphthylurethane, m.p. 210–210.5°, and diacetate, m.p. 65.5–66.5°, and was shown to be a

derivative of 1,2-cyclohexanediol, since periodate oxidation followed by treatment with 2,4-dinitrophenylhydrazine gave a 97% yield of the bis-2,4-dinitrophenylhydrazone of 2-bromoadipaldehyde (XV). The steric orientation of the 1,2-diol group was shown to be trans since debromination in the presence of Amberlite IR-4B (OH) resin gave *dl*-1α,2β-cyclohexanediol in 91% yield. Since the bromine and its adjacent hydroxyl group in the original bromohydrin are in a trans orientation, it follows that the bromodiol must be *dl*-3α-bromo-1α,2β-cyclohexanediol (XIV) and the bromohydrin must be *dl*-1α-methoxy-2β-hydroxy-3α-bromocyclohexane (V, R = CH_3) in agreement with the structural assignment reached on the basis of debromination of the urethanes. This proof of structure is based on two assumptions. First, that no inversion of configuration occurs during de-etherification and second, that elimination of bromine is not assisted by intermediate oxide formation. The first assumption was shown to be valid by de-etherification of 2β-methoxy-1α-cyclohexanol under conditions identical with those used for the bromohydrin, when 1α,2β-cyclohexanediol was obtained in 92% yield. It was also shown that the oxide cannot be an intermediate in the debromination reaction since 1β-methoxy-2α,3α-epoxycyclohexane and other oxides are not reduced by Raney nickel and hydrogen under the conditions used. In complete agreement with this result is the observation that debromination of the bromodiol XIV does not proceed in the presence of Amberlite IRA-400 (OH) resin, whereas the use of identical conditions with the phenyl- and 1-naphthyl-urethanes IX and XI (R = CH_3) had furnished high yields of the debrominated compounds X and XII (R = CH_3). Debromination of XIV is readily achieved, however, in the presence of Amberlite IR-4B (OH). This behavior was explained when the action of the two anion exchange resins on 1α-methoxy-2β-hydroxy-3α-bromocyclohexane (V, R = CH_3) was examined. In the presence of the weakly basic resin, IR-4B, the bromohydrin remains unchanged, but in the presence of the strongly basic resin it is converted to the oxide I (R = CH_3), which does not undergo reduction to a diol under the conditions used. These results underline the efficacy of the protection afforded against intermediate oxide formation by the presence of urethane groups in the earlier debromination experiments in which the strongly basic resin was used.



1α-Methoxy-2α,3α-epoxycyclohexane II (R = CH_3) on treatment with hydrobromic acid gave a 93% yield of a liquid bromohydrin VII (R = CH_3) b.p. 62–63° at 0.01 mm. This substance was quite different from the solid bromohydrin V (R = CH_3) obtained from the isomeric oxide, as demonstrated by comparison of their derivatives and infrared spectra. Conversion of the liquid bromohydrin to a 1-naphthylurethane, m.p. 122–124°, in 86% yield and to a liquid acetyl derivative, b.p. 63–65° at 0.01 mm in 95% yield

suggested that the compound was sterically pure. The proof of structure of this bromohydrin was not as exhaustively pursued as that of its stereoisomer and the simplicity of the de-etherification approach led us to follow this method. Ether cleavage of the bromohydrin gave a bromodiol, m.p. 70.5–71°, in 74% yield together with 8% of unchanged starting material. The new compound gave a liquid diacetyl derivative, b.p. 85–86° at 0.1 mm, in 95% yield and a bis-1-naphthylurethane, m.p. 176–178°, in 95% yield. The bromodiol was shown to be a 3-bromo-1,2-cyclohexanediol since periodate oxidation followed by treatment with 2,4-dinitrophenylhydrazine gave the bis-2,4-dinitrophenylhydrazone of 2-bromoadipaldehyde (XV) which had been obtained earlier from similar treatment of its isomer XIV. The orientation of the hydroxyl groups in the lower-melting bromodiol was shown to be cis since its rate of oxidation by periodate at 20° was 10 times more rapid than that of its isomer. Since the liquid bromohydrin yields the oxide II (R = CH_3) on treatment with alkali, it follows (2, 3) that the structure of the bromohydrin must be *dl*-1α-methoxy-2α-hydroxy-3β-bromocyclohexane (VII, R = CH_3) and the corresponding bromodiol must be *dl*-3β-bromo-1α,2α-cyclohexanediol (XVI).



(VII) (XVI)

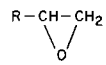
A solid bromohydrin, m.p. 46–47.5°, was obtained in 61% yield by the action of hydrobromic acid on the trans oxide I (R = C_2H_5) and was further characterized by preparation of the phenylurethane, m.p. 132.5–133.5° (75%), 1-naphthylurethane, m.p. 196–197° (97%), and acetyl derivative, m.p. 29.5–30.5° (92%). Its structure was established as *dl*-1α-ethoxy-2β-hydroxy-3α-bromocyclohexane (V, R = C_2H_5) by debromination of the 1-naphthylurethane XI (R = C_2H_5) to the tetrahydronaphthylurethane of *dl*-2β-ethoxy-1α-cyclohexanol XII (R = C_2H_5) in 88% yield and by de-etherification of the bromohydrin to the bromodiol XIV in 86% yield.

As in the case of the cis methoxy oxide II (R = CH_3), the action of hydrobromic acid on the ethyl homologue produced a liquid bromohydrin, b.p. 71–72° at 0.01 mm, in 82% yield. This bromohydrin failed to yield a solid 1-naphthylurethane and gave a liquid acetyl derivative, b.p. 72–74° at 0.05 mm, in 90% yield. The substance was assigned the structure 1α-ethoxy-2α-hydroxy-3β-bromocyclohexane VII (R = C_2H_5) since de-etherification with hydrogen bromide gave the bromodiol XVI in 51% yield together with 26% of unreacted bromohydrin.

The n.m.r. spectra of the bromohydrin acetates and bromodiol diacetates were measured by Dr. R. R. Fraser of Ottawa University. Interpretation of these spectra according to the principles elaborated by Lemieux, Kullnig, Bernstein, and Schneider (12) fully confirmed the structural assignments made above on the basis of chemical evidence. An additional check on the purity of the two liquid bromohydrins (VII, R = CH_3 and C_2H_5) and their corresponding liquid acetyl derivatives was thereby provided, since there were no abnormalities in the spectra indicative of contamination of any of these substances with positional isomers or stereoisomers.

In recent years considerable attention has been focused upon mechanisms of oxide

ring scissions and the mode of addition of nucleophiles to unsymmetrically substituted oxides. The results of these investigations have been summarized by Winstein and Henderson (4) and Parker and Isaacs (13) in extensive review articles, but no unifying theory capable of accurately predicting the products of such reactions has emerged. The stereoisomeric 1-alkoxy-2,3-epoxycyclohexanes I and II (R = CH_3 or C_2H_5), which were first prepared by McRae, Moir, and co-workers (14, 15, 16), provided, during and after elucidation of their structures (5, 1), useful models for examination of certain aspects of the mechanisms of oxide ring cleavages by careful product analysis. Investigations by McRae *et al.* (14), Lemieux, Kullnig, and Moir (5), and Bannard and Hawkins (1) made it evident that under alkaline conditions these oxides are attacked by nucleophiles such as methanol, water, and ammonia predominantly at position 3 (yields in excess of 70%). Although some work on the opening of the oxides under acidic conditions by water (17) and *p*-toluenesulphonic acid (5) was also reported earlier, yields of isolated products were not sufficiently high to permit a definite conclusion to be drawn regarding the preferred position of attack. The results of the present work make it quite clear, however, that position 3 is still the preferred point of attack under acidic conditions and that there is apparently no tendency toward reversal of the mode of opening of the oxide ring in 1-alkoxy-2,3-epoxycyclohexanes as has frequently been observed for unsymmetrical oxides of the type XVII (18, 13, 15, 21).



(XVII)

In the reactions cited above, opening of the oxide ring was attended by Walden inversion at position 3, which is suggestive that an S_N2 mechanism is operating (19). This result agrees with the majority of evidence in the literature (13, 15, 20, 21), which supports the S_N2 mechanism for oxide scissions. No indication of the presence of products formed by ring opening with retention of configuration was obtained in any of the work summarized above. This observation makes improbable the intervention of an S_N1 process as a major feature of the mechanism (see references 18, 4, 13, 20, 21) since under such circumstances at least some cis-2,3-oriented products would be expected (13, 19, 20, 21). The latter mechanism may occur to a minor extent, however, because in none of the reactions under consideration was a total material balance of completely characterized products obtained. The results of Lemieux, Kullnig, and Moir (5), obtained when the ring was opened with water under alkaline conditions and arrived at by a method of product analysis which was sensitive enough to reveal minor products formed by attack at position 2, suggests that further careful product analysis is required in all these reactions before intervention of the S_N1 mechanism to a minor extent can be ruled out. No clear picture of the role of polar and steric effects in determining the point of attack of nucleophiles on the 1-alkoxy-2,3-epoxycyclohexanes has resulted. On the basis of simple polar effects and the view that the important feature in S_N2 processes is the facilitation of reagent approach (18, 19, 20) (which is adequate for explanation of the mode of addition to oxides of type XVII), it would be predicted that attack should occur at position 2, which is not the case. Lemieux, Kullnig, and Moir (5) have pointed out however, that the observed result is in agreement with prediction if the governing factor in S_N2 mechanisms is ease of development of carbonium ion character in the transition state (22, 13, 20). Also, there is no uniformity in prediction of the position

of attack by the nucleophile on the basis of Angyal's (23) extension of the Fürst–Plattner rule (24) which visualizes the more stable conformer undergoing reaction to produce a chair form by diaxial ring opening. This theory predicts the observed result for the cis oxides but not for the trans oxides. If the view is taken that steric ease of approach of the nucleophile determines the point of attack, the observed products are predicted for the trans oxides because attack at position 2 is inhibited by the presence of the methoxyl group at position 1 in a cis relationship to the entering nucleophile, as indicated by Lemieux, Kullnig, and Moir (5). However, such an effect would be absent from reactions involving the cis oxides and it might have been expected that attack would occur at positions 2 and 3 with equal facility. It seems evident from these observations that much work still remains to be done before the mechanisms of oxide ring openings can be placed on a firm basis.

EXPERIMENTAL*†

dl-1α-Methoxy-2β-hydroxy-3α-bromocyclohexane (V, R = CH_3)

dl-1β-Methoxy-2α,3α-epoxycyclohexane (42.5 g, 0.332 mole) was dissolved in acetone (100 ml) and the solution was cooled with mechanical stirring to −10°. Hydrobromic acid (48%, 56.0 g, 0.332 mole) was added dropwise at −10° to 0°, the solution was allowed to come to room temperature, the excess acid was neutralized by addition of sodium carbonate, the precipitated salt was removed by filtration, and the solution was evaporated to dryness *in vacuo*. The residue was recrystallized from ether, yielding 43.9 g (63.3%) of *dl*-1α-methoxy-2β-hydroxy-3α-bromocyclohexane, as colorless needles, m.p. 68.5–69°. Calc. for $C_7H_{13}O_2Br$: C, 40.22; H, 6.27; Br, 38.22%. Found: C, 40.10; H, 6.25; Br, 38.10%. A liquid fraction (13.1 g), b.p. 65–67° at 0.03 mm, was also obtained which was shown to contain more of the bromohydrin V (R = CH_3) and a 1-methoxy-2,3-dihydroxycyclohexane (see below).

Derivatives of dl-1α-Methoxy-2β-hydroxy-3α-bromocyclohexane

The phenylurethane (IX, R = CH_3) was obtained in 86.1% yield, m.p. 133–134°, after recrystallization from 95% ethanol. Calc. for $C_{14}H_{18}O_3NBr$: C, 51.23; H, 5.53; N, 4.27; Br, 24.35%. Found: C, 51.13; H, 5.35; N, 4.21; Br, 24.72%.

The 1-naphthylurethane (XI, R = CH_3) was obtained in 94.4% yield, m.p. 185–186°, after recrystallization from ether. Calc. for $C_{18}H_{20}O_3NBr$: C, 57.15; H, 5.33; N, 3.70; Br, 21.13%. Found: C, 57.16; H, 5.28; N, 3.91; Br, 21.12%.

The acetyl derivative was obtained in 90.0% yield as colorless needles, m.p. 56–56.5°, after recrystallization from ether–heptane. Calc. for $C_9H_{15}O_3Br$: C, 43.04; H, 6.02; Br, 31.82%. Found: C, 42.99; H, 6.13; Br, 32.08%.

dl-1α-Methoxy-2β,3α-cyclohexanediol Bis-1-naphthylurethane

A sample (1.00 g) of the liquid fraction from preparation of 1α-methoxy-2β-hydroxy-3α-bromocyclohexane was treated with 1-naphthylisocyanate (2.00 g) at 70°. The crude mixture of resultant 1-naphthylurethanes was washed with petroleum ether, then fractionally crystallized from ether, yielding 0.43 g (27%) of *dl*-1α-methoxy-2β-hydroxy-3α-bromocyclohexane 1-naphthylurethane, m.p. 185–186°—identified by mixed melting point and infrared spectrum, and 0.41 g (13%) of *dl*-1α-methoxy-2β,3α-cyclohexanediol bis-1-naphthylurethane, m.p. 224–226°. Calc. for $C_{29}H_{28}O_5N_2$: C, 71.88; H, 5.82; N, 5.78%. Found: C, 71.72; H, 5.84; N, 5.94%.

**All melting points are uncorrected.*
†Microanalyses by J. G. Helie of these laboratories.

2-Methoxyadipaldehyde Bis-2,4-dinitrophenylhydrazone

A second portion (1.00 g) of the above-mentioned liquid fraction was dissolved in ethanol (20 ml) and treated with sodium metaperiodate (3 g in 50 ml water). The solution was kept for 4 hours at room temperature, evaporated to dryness *in vacuo*, and extracted with ether. After evaporation, the residue from the ether extract was treated with 2,4-dinitrophenylhydrazine reagent (25). The bis-2,4-dinitrophenylhydrazone of 2-methoxyadipaldehyde separated as a yellow solid and after recrystallization from ethyl acetate had m.p. 192–193.5°. Yield, 0.64 g (19%). Calc. for $C_{19}H_{20}O_9N_8$: C, 45.24; H, 4.00; N, 22.22%. Found: C, 45.31; H, 4.17; N, 21.80%.

Debromination of dl-2β-Bromo-1α-cyclohexanol Phenylurethane

dl-2β-Bromo-1α-cyclohexanol phenylurethane (cf. Bedos (9)), m.p. 85–87° (0.900 g, 3.02×10^{-3} mole), was debrominated by the same method as described below for *dl*-1α-methoxy-2β-hydroxy-3α-bromocyclohexane phenylurethane. The crude product after recrystallization from ethanol–heptane furnished 0.57 g (86.5%) of cyclohexanol phenylurethane, m.p. 83–84.5°, alone and in admixture with an authentic sample (cf. Stengl *et al.* (10)).

dl-2β-Methoxy-1α-cyclohexanol Derivatives

dl-2β-Methoxy-1α-cyclohexanol was prepared by the method of Winstein and Henderson (8) and converted to the phenylurethane in 82% yield, m.p. 66–67.5°, after recrystallization from aqueous ethanol. Calc. for $C_{14}H_{19}O_3N$: C, 67.45; H, 7.68; N, 5.62%. Found: C, 67.40; H, 7.54; N, 5.70%. The 1-naphthylurethane was obtained in 77% yield, m.p. 111–112°, after recrystallization from ether–heptane. Calc. for $C_{18}H_{21}O_3N$: C, 72.22; H, 7.07; N, 4.69%. Found: C, 72.31; H, 7.09; N, 4.74%.

Debromination of dl-1α-Methoxy-2β-hydroxy-3α-bromocyclohexane Phenylurethane

dl-1α-Methoxy-2β-hydroxy-3α-bromocyclohexane phenylurethane (0.900 g, 2.74×10^{-3} mole) was dissolved in ethanol (50 ml), Raney Nickel W-7 (26) catalyst (10 g) and Amberlite IRA-400 (OH) resin (2 ml) were added, and the mixture was shaken for 24 hours at room temperature at 40 p.s.i. hydrogen pressure. The mixture was filtered and the filtrate was evaporated to dryness *in vacuo* yielding a crystalline residue, which, after recrystallization from ether–heptane, furnished 0.53 g (78%) of *dl*-2β-methoxy-1α-cyclohexanol phenylurethane (X, R = CH_3), m.p. 66–67.5°, alone and in admixture with an authentic specimen. The infrared spectra of the two samples (KBr pellet) were also identical.

dl-2β-Methoxy-1α-cyclohexanol Tetrahydro-1-naphthylurethane (XII, R = CH_3)

dl-2β-Methoxy-1α-cyclohexanol 1-naphthylurethane (0.200 g, 6.7×10^{-4} mole) was reduced by the same method as described for *dl*-1α-methoxy-2β-hydroxy-3α-bromocyclohexane phenylurethane except that ethanol–benzene (2:1, v/v; 30 ml) was used as solvent. Recrystallization of the crude product from aqueous ethanol gave 0.199 g (98.5%) of fine colorless needles, m.p. 89.5–91°. Calc. for $C_{18}H_{25}O_3N$: C, 71.25; H, 8.31; N, 4.62%. Found: C, 71.26; H, 8.27; N, 4.67%.

Debromination of dl-1α-Methoxy-2β-hydroxy-3α-bromocyclohexane 1-Naphthylurethane

dl-1α-Methoxy-2β-hydroxy-3α-bromocyclohexane 1-naphthylurethane (1.00 g, 2.65×10^{-3} mole) was debrominated by the same method as given for *dl*-2β-methoxy-1α-cyclohexanol 1-naphthylurethane. The crude product was recrystallized from aqueous ethanol yielding 0.690 g (86%) of *dl*-2β-methoxy-1α-cyclohexanol tetrahydro-1-naphthylurethane,

m.p. 89.5–91°, alone and in admixture with an authentic specimen. The infrared spectra (KBr pellet) of the two substances were also identical.

dl-2β-Bromo-1α-cyclohexanol 1-Naphthylurethane

This compound was obtained in 75% yield from *dl*-2β-bromo-1α-cyclohexanol (27) after recrystallization from ether, m.p. 177–177.5°. Calc. for $C_{17}H_{18}O_2NBr$: C, 58.63; H, 5.21; N, 4.03; Br, 22.95%. Found: C, 58.54; H, 5.19; N, 4.19; Br, 22.74%.

Cyclohexanol Tetrahydro-1-naphthylurethane

Cyclohexanol 1-naphthylurethane (cf. Bickel and French (28)), m.p. 131–132.5° (1.10 g, 4.07×10^{-3} mole), was reduced by the same method as described for 2β-methoxy-1α-cyclohexanol 1-naphthylurethane. Recrystallization of the crude product from aqueous ethanol gave 1.01 g (90.2%) of cyclohexanol tetrahydro-1-naphthylurethane as fine colorless needles, m.p. 105–106.5°. Calc. for $C_{17}H_{23}O_2N$: C, 74.69; H, 8.48; N, 5.12%. Found: C, 74.77; H, 8.48; N, 5.15%.

Debromination of dl-2β-Bromo-1α-cyclohexanol 1-Naphthylurethane

dl-2β-Bromo-1α-cyclohexanol 1-naphthylurethane (0.340 g, 9.77×10^{-4} mole) was debrominated by the same procedure as described for *dl*-2β-methoxy-1α-cyclohexanol 1-naphthylurethane. Recrystallization of the crude product from aqueous ethanol gave 0.250 g (93.7%) of cyclohexanol tetrahydro-1-naphthylurethane as colorless needles, m.p. 105–106.5°, alone and in admixture with an authentic specimen. The infrared spectra (KBr pellet) of the two samples were also identical.

Conversion of dl-1α-Methoxy-2β-hydroxy-3α-bromocyclohexane to dl-1β-Methoxy-2α,3α-epoxycyclohexane via Amberlite IRA-400 (OH) Resin

dl-1α-Methoxy-2β-hydroxy-3α-bromocyclohexane (4.18 g, 0.02 mole) was placed in a 500-ml pressure bottle together with Amberlite IRA-400 (OH) resin (40 ml) and ether (200 ml) and the mixture was shaken for 24 hours at atmospheric pressure. The resin was collected, washed with ether (100 ml), and the filtrate and washings dried over anhydrous sodium sulphate. The ether was removed by distillation at atmospheric pressure, after which the residue was fractionated *in vacuo* yielding 2.18 g (85.1%) of *dl*-1β-methoxy-2α,3α-epoxycyclohexane as a colorless oil, b.p. 60–61° at 12 mm, n_D^{25} 1.4511. The substance was identified by its infrared spectrum (1).

Attempted Reduction of dl-1β-Methoxy-2α,3α-epoxycyclohexane with Raney Nickel and Hydrogen

dl-1β-Methoxy-2α,3α-epoxycyclohexane (6.00 g, 4.68×10^{-2} mole), dissolved in ether (100 ml), was shaken with Raney nickel catalyst (10 ml) at room temperature under 40 p.s.i. hydrogen pressure for 24 hours. The mixture was filtered, the filtrate was concentrated by removal of the ether at atmospheric pressure, and the residue was distilled *in vacuo* yielding 5.60 g (93.4%) of unchanged starting material, b.p. 54–55° at 10 mm, which was identified via its infrared spectrum (1).

Action of Amberlite IR-4B (OH) Resin on dl-1α-Methoxy-2β-hydroxy-3α-bromocyclohexane (V, R = CH_3)

dl-1α-Methoxy-2β-hydroxy-3α-bromocyclohexane (1.00 g, 4.78×10^{-3} mole), dissolved in 95% ethanol (100 ml), was shaken for 24 hours with Amberlite IR-4B (OH) resin. The mixture was filtered, and the filtrate was allowed to evaporate to dryness at room temperature in an evaporating dish. The residual crystals were collected, recrystallized from ether, and identified as *dl*-1α-methoxy-2β-hydroxy-3α-bromocyclohexane by their melting

point of 68–69°, alone and in admixture with an authentic specimen. Recovery, 0.925 g (92.5%).

De-etherification of dl-1α-Methoxy-2β-hydroxy-3α-bromocyclohexane (V, R = CH_3) to dl-3α-Bromo-1α,2β-cyclohexanediol (XIV)

dl-1α-Methoxy-2β-hydroxy-3α-bromocyclohexane (1.05 g, 5.0×10^{-3} mole) was finely ground and heated for 1.5 hours in a sealed tube at 65° with fuming hydrobromic acid (1.0 ml, 68%, 1.57×10^{-2} mole). The pale yellow solution was transferred quantitatively to a 250-ml, round-bottomed flask (in ca. 50 ml of water), the excess acid was neutralized by addition of solid sodium bicarbonate, and the solution was evaporated to dryness *in vacuo*. The residue was transferred to a Soxhlet extractor, extracted for 4 hours with anhydrous ether, and the extract evaporated to dryness. Crystallization of the product from ether gave 0.861 g (88.8%) of *dl*-3α-bromo-1α,2β-cyclohexanediol as colorless prisms, m.p. 98–99°. Calc. for $C_6H_{11}O_2Br$: C, 36.94; H, 5.68; Br, 40.97%. Found: C, 36.96; H, 5.64; Br, 41.07%.

Derivatives of dl-3α-Bromo-1α,2β-cyclohexanediol (XIV)

The bis-1-naphthylurethane was obtained in 84.5% yield as fine colorless needles, m.p. 210–210.5°, after recrystallization from acetone. Calc. for $C_{28}H_{25}O_4N_2Br$: C, 63.04; H, 4.72; N, 5.25; Br, 14.98%. Found: C, 62.89; H, 4.93; N, 5.49; Br, 14.68%.

The diacetate was obtained in 95.1% yield as fine colorless needles, m.p. 65.5–66.5°, after recrystallization from ether–heptane. Calc. for $C_{10}H_{15}O_4Br$: C, 43.03; H, 5.42; Br, 28.63%. Found: C, 43.17; H, 5.62; Br, 28.73%.

dl-1α,2β-Cyclohexanediol from dl-2β-Methoxy-1α-cyclohexanol

dl-2β-Methoxy-1α-cyclohexanol (0.650 g, 5.0×10^{-3} mole) was heated for 1 hour at 75° with fuming hydrobromic acid (3.0 ml, 68%, 4.70×10^{-2} mole) in a sealed tube. The product was isolated by the same procedure as described for the de-etherification of *dl*-1α-methoxy-2β-hydroxy-3α-bromocyclohexane, except that final purification was effected by sublimation *in vacuo*. In this manner, 0.533 g (92.0%) of colorless crystals, m.p. 104.5–105.5°, alone and in admixture with an authentic specimen of *dl*-1α,2β-cyclohexanediol, were obtained.

Debromination of dl-3α-Bromo-1α,2β-cyclohexanediol (XIV)

dl-3α-Bromo-1α,2β-cyclohexanediol (0.400 g, 2.05×10^{-3} mole) was placed in a 500-ml pressure bottle together with ethanol (100 ml), Amberlite IR-4B (OH) resin (3 g), and Raney nickel catalyst and shaken for 24 hours under 40 p.s.i. hydrogen pressure at room temperature. The mixture was filtered and the crystalline residue, which resulted from evaporation to dryness of the filtrate, was sublimed *in vacuo*, yielding 213 mg (90.3%) of colorless crystals, m.p. 104.5–105.5°, alone and in admixture with an authentic specimen of *dl*-1α,2β-cyclohexanediol. The infrared spectra of the two specimens (KBr pellet) were also identical.

2-Bromoadipaldehyde Bis-2,4-dinitrophenylhydrazone (XV) from dl-3α-Bromo-1α,2β-cyclohexanediol (XIV)

dl-3α-Bromo-1α,2β-cyclohexanediol (1.00 g, 5.12×10^{-3} mole) and sodium metaperiodate (4.18 g, 2×10^{-2} mole) were dissolved in water and the solution was kept overnight at 25°, then evaporated to dryness *in vacuo* at room temperature. The residue was extracted with ether and the latter was removed *in vacuo*. The product was dissolved in ethanol and treated with 2,4-dinitrophenylhydrazine reagent (25). The yellow precipitate

was collected and washed three times with hot ethanol yielding 2.75 g (96.8%) of 2-bromoadipaldehyde bis-2,4-dinitrophenylhydrazone, m.p. 154–155° (with decomposition). Calc. for $C_{18}H_{17}O_8N_8Br$: C, 39.07; H, 3.10; N, 20.25; Br, 14.44%. Found: C, 39.35; H, 3.09; N, 19.90; Br, 14.41%.

dl-1α-Methoxy-2α-hydroxy-3β-bromocyclohexane (VII, R = CH_3)

The procedure was identical with that used for the preparation of *dl*-1α-methoxy-2β-hydroxy-3α-bromocyclohexane (V, R = CH_3) except that the cis oxide II (R = CH_3) (12.0 g, 9.37×10^{-2} mole) was employed as starting material. The crude liquid product was fractionated *in vacuo* yielding 18.3 g (93.3%) of a colorless viscous oil, b.p. 62–63° at 0.01 mm; n_D^{25} 1.5080. Calc. for $C_7H_{13}O_2Br$: C, 40.22; H, 6.27; Br, 38.22%. Found: C, 40.01; H, 6.17; Br, 38.27%.

Derivatives of dl-1α-Methoxy-2α-hydroxy-3β-bromocyclohexane

The 1-naphthylurethane was obtained in 86.5% yield, m.p. 122–124°, after recrystallization from acetone – petroleum ether (65–110°). Calc. for $C_{18}H_{20}O_3NBr$: C, 57.15; H, 5.33; N, 3.70; Br, 21.13%. Found: C, 57.27; H, 5.16; N, 3.80; Br, 20.83%.

The acetyl derivative was obtained in 95.5% yield as a colorless liquid, b.p. 63–65° at 0.01 mm; n_D^{25} 1.4828. Calc. for $C_9H_{15}O_3Br$: C, 43.04; H, 6.02; Br, 31.82%. Found: C, 43.00; H, 5.94; Br, 32.07%.

De-etherification of dl-1α-Methoxy-2α-hydroxy-3β-bromocyclohexane to dl-3β-Bromo-1α,2α-cyclohexanediol (XVI)

dl-1α-Methoxy-2α-hydroxy-3β-bromocyclohexane (2.09 g, 1.0×10^{-2} mole) was subjected to ether cleavage under conditions identical with those used for its stereoisomer. The resultant mixture of oil and crystals (1.82 g) was washed with anhydrous ether to dissolve the oil, and recrystallization of the residue from anhydrous ether gave 1.44 g (73.8%) of *dl*-3β-bromo-1α,2α-cyclohexanediol as colorless prisms, m.p. 70.5–71°. This substance was shown to be quite different from its stereoisomer, by comparison of their infrared spectra (KBr pellet). Calc. for $C_6H_{11}O_2Br$: C, 36.94; H, 5.68; Br, 40.97%. Found: C, 37.11; H, 5.43; Br, 40.78%. The oil fraction from this preparation was distilled in an air bath at 25–30° at 0.001 mm pressure yielding 170 mg (8.1%) of colorless oil, n_D^{25} 1.5085, identified via its infrared spectrum as *dl*-1α-methoxy-2α-hydroxy-3β-bromocyclohexane (VII, R = CH_3).

Derivatives of dl-3β-Bromo-1α,2α-cyclohexanediol

The bis-1-naphthylurethane was obtained in 95.3% yield as colorless crystals, m.p. 176–178°, after recrystallization from ethyl acetate. Calc. for $C_{28}H_{25}O_4N_2Br$: C, 63.04; H, 4.72; N, 5.25; Br, 14.98%. Found: C, 63.20; H, 4.73; N, 5.15; Br, 15.14%.

The diacetyl derivative was obtained in 95.0% yield as a colorless viscous oil, b.p. 85–86° at 0.1 mm pressure; n_D^{25} 1.4810. Calc. for $C_{10}H_{15}O_4Br$: C, 43.03; H, 5.42; Br, 28.63%. Found: C, 43.02; H, 5.20; Br, 28.93%.

2-Bromoadipaldehyde Bis-2,4-dinitrophenylhydrazone (XV) from dl-3β-Bromo-1α,2α-cyclohexanediol (XVI)

The procedure used was identical with that given for the periodate oxidation and subsequent 2,4-dinitrophenylhydrazone formation from *dl*-3α-bromo-1α,2β-cyclohexanediol (XIV). The bis-2,4-dinitrophenylhydrazone was obtained in 95% yield, m.p. 154–155°, and had an infrared spectrum (KBr pellet) identical with that of an authentic specimen of XV.

Periodate Oxidation of dl-3α-Bromo-1α,2β-cyclohexanediol (XIV) and dl-3β-Bromo-1α,2α-cyclohexanediol (XVI)

The experimental procedure used for periodate oxidation of the bromodiols XIV and XVI was identical with that described earlier for oxidation of the *p*-nitrobenzoyl derivatives of the 3-amino-1,2-cyclohexanediols (1), except that the determinations were performed at 20° and 14-mg samples of the bromodiols were used. The results showed uptake of 1 mole of periodate by the cis diol in 15 minutes and by the trans diol in 180 minutes. Comparison of the $t_{\frac{1}{4}}$ values (1.75 minutes for XVI and 18.0 for XIV) indicated that the rate of oxidation of the cis diol is approximately 10 times that of the trans diol.

dl-1α-Ethoxy-2β-hydroxy-3α-bromocyclohexane (V, R = C_2H_5)

dl-1β-Ethoxy-2α,3α-epoxycyclohexane (I, R = C_2H_5) (14.2 g, 0.100 mole) on treatment with hydrobromic acid in the same manner as described for its lower homologue gave 13.6 g (61.0%) of *dl*-1α-ethoxy-2β-hydroxy-3α-bromocyclohexane as colorless needles, m.p. 46–47.5°, after recrystallization from ether. Calc. for $C_8H_{15}O_2Br$: C, 43.07; H, 6.78; Br, 35.82%. Found: C, 42.91; H, 6.58; Br, 35.61%.

Derivatives of dl-1α-Ethoxy-2β-hydroxy-3α-bromocyclohexane

The phenylurethane (IX, R = C_2H_5) was obtained as fine needles in 75.3% yield, m.p. 132.5–133.5°, after recrystallization from ether–heptane. Calc. for $C_{15}H_{20}O_3NBr$: C, 52.64; H, 5.89; N, 4.09; Br, 23.35%. Found: C, 52.68; H, 5.84; N, 4.16; Br, 23.38%.

The 1-naphthylurethane (XI, R = C_2H_5) was obtained in 96.6% yield as fine needles, m.p. 196–197°, after recrystallization from ethyl acetate. Calc. for $C_{19}H_{22}O_3NBr$: C, 58.17; H, 5.65; N, 3.57; Br, 20.37%. Found: C, 58.32; H, 5.46; N, 3.88; Br, 20.04%.

The acetate was obtained as fine colorless needles in 92.4% yield, m.p. 29.5–30.5°, after recrystallization from *n*-hexane. Calc. for $C_{10}H_{17}O_3Br$: C, 45.29; H, 6.46; Br, 30.14%. Found: C, 45.28; H, 6.28; Br, 30.31%.

dl-2β-Ethoxy-1α-cyclohexanol 1-Naphthylurethane (XIII, R = C_2H_5)

dl-2β-Ethoxy-1α-cyclohexanol (b.p. 75–77° at 11 mm; n_D^{25} 1.4538) was prepared in 73% yield by the same method (8) as used for the corresponding methoxy compound (cf. Mousseron *et al.* (29)) and was converted in 94.2% yield to the 1-naphthylurethane, which was obtained as fine needles, m.p. 131–132°, after recrystallization from ethyl acetate. Calc. for $C_{19}H_{23}O_3N$: C, 72.81; H, 7.40; N, 4.47%. Found: C, 73.08; H, 7.39; N, 4.67%.

dl-2β-Ethoxy-1α-cyclohexanol Tetrahydro-1-naphthylurethane (XII, R = C_2H_5)

dl-2β-Ethoxy-1α-cyclohexanol 1-naphthylurethane (0.830 g, 2.66×10^{-3} mole) was reduced by the same method as described for *dl*-2β-methoxy-1α-cyclohexanol 1-naphthylurethane. Recrystallization of the crude product from aqueous ethanol gave 0.760 g (90.3%) of fine colorless needles, m.p. 71–72.5°, of the tetrahydro-1-naphthylurethane. Calc. for $C_{19}H_{27}O_3N$: C, 71.88; H, 8.57; N, 4.41%. Found: C, 71.80; H, 8.67; N, 4.58%.

Debromination of dl-1α-Ethoxy-2β-hydroxy-3α-bromocyclohexane 1-Naphthylurethane (XI, R = C_2H_5)

dl-1α-Ethoxy-2β-hydroxy-3α-bromocyclohexane 1-naphthylurethane (0.900 g, 2.88×10^{-3} mole) was debrominated by the same method as described for *dl*-2β-methoxy-1α-cyclohexanol 1-naphthylurethane. The crude product was recrystallized from aqueous ethanol yielding 0.640 g (87.9%) of *dl*-2β-ethoxy-1α-cyclohexanol tetrahydro-1-naphthylurethane as colorless needles, m.p. 71–72.5°, alone and in admixture with an authentic sample. The infrared spectra (5% in carbon tetrachloride) were also identical.

dl-3α-Bromo-1α,2β-cyclohexanediol (XIV) from dl-1α-Ethoxy-2β-hydroxy-3α-bromocyclohexane (V, R = C_2H_5)

dl-1α-Ethoxy-2β-hydroxy-3α-bromocyclohexane (1.12 g, 5.0×10^{-3} mole) was subjected to ether cleavage under conditions identical with those described for the lower homologue. The crude product was recrystallized from ether yielding 831 mg (85.7%) of colorless prisms, m.p. 98–99°, alone and in admixture with an authentic specimen of *dl*-3α-bromo-1α,2β-cyclohexanediol.

dl-1α-Ethoxy-2α-hydroxy-3β-bromocyclohexane (VII, R = C_2H_5)

dl-1α-Ethoxy-2α,3α-epoxycyclohexane (II, R = C_2H_5) (14.2 g, 0.100 mole) was treated with hydrobromic acid in the same manner as described for *dl*-1β-methoxy-2α,3α-epoxycyclohexane. The crude liquid product was fractionated *in vacuo* yielding 18.3 g (82.0%) of *dl*-1α-ethoxy-2α-hydroxy-3β-bromocyclohexane, b.p. 70–71° at 0.01 mm; n_D^{25} 1.4971. Calc. for $C_8H_{15}O_2Br$: C, 43.07; H, 6.78; Br, 35.82%. Found: C, 43.11; H, 6.85; Br, 35.69%.

dl-1α-Ethoxy-2α-acetoxy-3β-bromocyclohexane

dl-1α-Ethoxy-2α-hydroxy-3β-bromocyclohexane (2.23 g, 1.00×10^{-2} mole) was heated under reflux for 1 hour with acetic anhydride (10 ml). The excess anhydride was removed by distillation *in vacuo* and the residue was distilled *in vacuo* yielding 2.39 g (90.2%) of colorless mobile oil, b.p. 64–64.5° at 0.01 mm; n_D^{25} 1.4760. Calc. for $C_{10}H_{17}O_3Br$: C, 45.29; H, 6.46; Br, 30.14%. Found: C, 45.13; H, 6.13; Br, 30.25%.

De-etherification of dl-1α-Ethoxy-2α-hydroxy-3β-bromocyclohexane to dl-3β-Bromo-1α,2α-cyclohexanediol (XVI)

dl-1α-Ethoxy-2α-hydroxy-3β-bromocyclohexane (2.23 g, 1.0×10^{-2} mole) was subjected to ether cleavage under conditions identical with those described for its homologue, yielding a mixture of oil and crystals (1.67 g) which, after recrystallization from anhydrous ether, gave 988 mg (50.6%) of colorless prisms, m.p. 70.5–71°, alone and in admixture with an authentic sample of *dl*-3β-bromo-1α,2α-cyclohexanediol (XVI). The residual oil was distilled in an air bath at 28–33° at 0.001 mm pressure yielding 588 mg (26.4%) of colorless oil, n_D^{25} 1.4981, which was identified as *dl*-1α-ethoxy-2α-hydroxy-3β-bromocyclohexane (VII, R = C_2H_5) via its infrared spectrum.

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