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# REGIO- AND STEREOSELECTIVITY OF THE 3-MEMBERED RING OPENING OF SOME 3,4-EPOXYTETRAHYDROPYRANS AND OF THE CORRESPONDING EPIBROMONIUM IONS

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**Abstract**—The reactions of 3,4-epoxytetrahydropyran and of its *cis*- and *trans*-2-methyl derivatives with hydrogen halides and with lithium aluminum hydride have been investigated in order to assess the influence of an O atom in the $\beta$ position on the regioselectivity of the epoxide ring opening. All these reactions exhibit a high preference for nucleophilic attack at position 4, which decreases moderately only when the inductive effect of the O atom and the stereoelectronic requirements of the attack act in opposite directions. Similar trends are observed in the reactions of the 5,6-dihydro-2*H*-pyrans with NBA, which occur with preferential nucleophilic attack by water at position 4 of the intermediate epibromonium ions. A remarkably high preference (96%) for electrophilic attack *syn* to the 2-Me group is observed in the latter type of reaction, in accordance with a previous proposal of a mechanism in which the nucleophilic step is rate determining.

The regioselectivity of epoxide ring cleavage reactions is influenced by several factors of steric, stereoelectronic, polar and conjugative nature and it is usually difficult to assess the relative importance of each of these effects.[1] Other reactions involving 3-membered heterocycles as intermediates, such as many electrophilic additions to alkenes, are similarly influenced.[2] In order to ascertain the importance of the inductive effect we have chosen a simple substrate, as free from steric complications as possible. 3,4-Epoxytetrahydropyran (**1**), was subjected to some ring opening reactions and its reactivity compared with that of 5,6-dihydro-2*H*-pyran (**4**) reacting with N-bromoacetamide (NBA) in dioxane-water. The work has been extended to the corresponding 2-Me derivatives (**11**, **16** and **17**) in order to obtain some insight into the importance of stereochemical and conformational factors.

## RESULTS

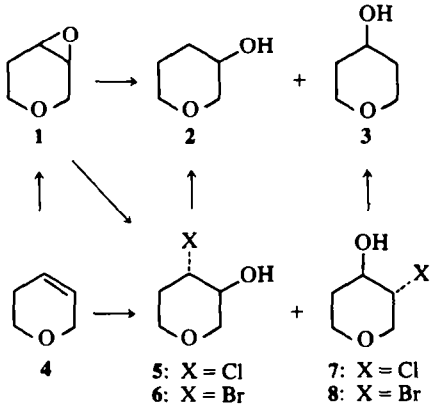
The reduction of epoxide **1** with LAH afforded a mixture of the alcohols **2** and **3** in a ratio of 93:7. Reference samples of these alcohols were obtained by modification of literature methods.[3,4] The epoxide ring openings of **1** with HCl and HBr were highly regioselective with a more than 9:1 prevalence of attack by the nucleophile at position 4, the main products being **5** and **6**.

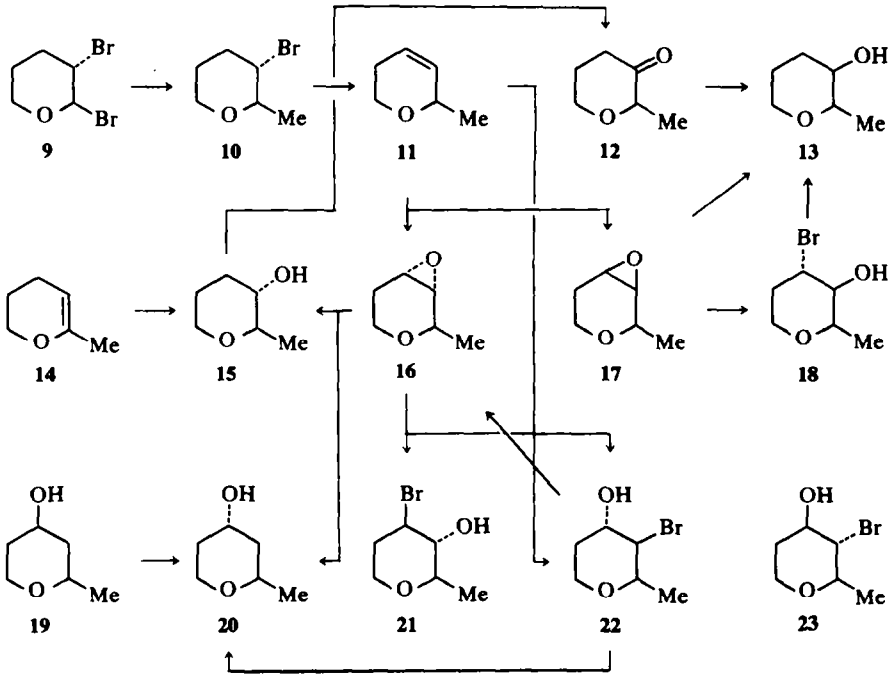
The bromohydrins **6** and **8** were also obtained by the action of NBA in dioxane-water on the unsaturated compound **4**, but in an inverted ratio of 20:80. The structures of these bromohydrins were demonstrated by their hydrogenolytic conversion[5] into **2** and **3**. Although no direct proof was secured for the *trans* configurations of the halohydrins, no doubt whatsoever can exist about this point, since *anti* opening of epoxide rings not directly substituted with groups capable of mesomeric electron release is a general rule.[1]

The epoxides **16** and **17** were obtained in a 55:45 ratio by reacting **11** with peroxybenzoic acid, and were separated by preparative GLC. Attempts to prepare **11** by the literature method[6] involving chlorination of dihydropyran, followed by Grignard methylation of the dichloride and by base catalyzed elimination, led to a very poor yield of **11** because the intermediate 2-methyl-3-chloro derivative contained an excess of the *cis* isomer, which was converted mostly into the unwanted isomer **14**, and because the conversion of the *trans* isomer into **11** required very drastic conditions. Much better results were achieved when the same sequence was followed with the bromo instead of the chloro derivatives. The bromination, in contrast with the chlorination, gives a large excess (*ca* 9:1) of the *trans* dibromide **9**,[7] and we found that the reaction of **9** with MeMgBr gives almost exclusively the *trans* isomer **10**, in a reaction exhibiting a remarkably high degree of retention. We are currently investigating the reasons for this unusual steric course, which may be related to the retention observed in the Grignard alkylation of 2-alkoxydioxanes.[8] The high selectivity with which the *trans* isomer **10** is formed is particularly useful for the subsequent *trans* elimination, which produces practically pure **11**, under conditions that are much milder than those required when starting from the chloro analogue.

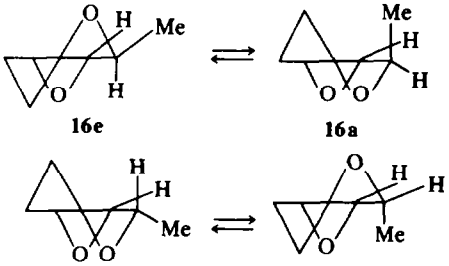
The configurations of epoxides **16** and **17**, which

could be inferred on the assumption that the major product was the *trans* isomer, in analogy with the similar reactions of 3-methyl- and 3-methoxycyclohexane,[2c] was confirmed by their NMR spectra, on the basis of the coupling constants between the protons in positions 2 and 3. Whereas in the *trans* isomer (**16**) the signals for H(2) and H(3) are, respectively a quartet (J 6·8 Hz) and a doublet (J 4·2) formed by lines which are only slightly broadened by long range couplings, in the *cis* isomer (**17**) these signals have the shape of a quartet of doublets (J 6·4 and 1·4 Hz) and a doublet of doublets (J 4·0 and 1·4 Hz). The assignments of the H(2) signals were confirmed by double resonance experiments. The data agree with the assumed configurations in the more stable half-chair conformations with equatorial methyl (**16e** and **17e**). In **16e** the dihedral angle H(2)–C(2)–C(3)–H(3) has a value of about 100°, which according to the modified Karplus equation for epoxycyclohexanes[9] corresponds to a $J_{2,3}$ of *ca* 0 Hz. In **17e** this angle is of about 50°, corresponding to a $J_{2,3}$ of *ca* 2 Hz. Although the application of the equation for epoxycyclohexanes may not give quantitatively exact J values in our case, because the vicinity of the tetrahydropyran ring oxygen may somewhat affect these values, the proposed configurations are not open to doubt, since similar values of J can be deduced from the abundant literature data on epoxy-2-alkoxytetrahydropyrans.[10] It must also be



pointed out that the above data clearly establish a high preference for conformation **17e** in the case of the *cis* epoxide, since in **17a**, with a dihedral angle of *ca* 20°, the value of $J_{2,3}$ should be substantially higher (4–4·5 Hz).[10] The situation is less clear cut for the *trans* epoxide, since conformation **16a**, with a dihedral angle of *ca* 70°, would be expected to have a $J_{2,3}$ of *ca* 0·5 Hz, which could not be visible even in the 100 MHz spectrum, because of the existance of small long-range couplings.[10a] However, whereas in the case of 2-alkoxy derivatives conformations corresponding to **16a** are the favoured ones because of the 'anomeric effect', no particular reasons can be seen for a Me group to prefer the axial conformation; equilibration[11] and chiroptical data[12] indicate that the preferences of a Me group for the equatorial orientation in position 2



**16e** **16a**



**17e** **17a**

of tetrahydropyran and on the cyclohexane ring are rather similar.

The reduction of the epoxides **16** and **17** with LAH took place with a regioselectivity for attack at C(4) which was almost complete (>98%) in the case of the *cis* isomer (**17**) and high (92%) for the *trans* isomer (**16**). Some alcohol **13** (2%) was formed in the reduction of **16**, and some alcohol **15** (4·5%) in the reduction of **17**. These products evidently derive from an 'oxidative inversion', which is less extensive than that observed in the reduction of cyclohexene oxides.[13]

The reactions of **16** and **17** with HBr exhibited a regioselectivity that was very similar to that found for the LAH reductions of the same compounds (Table 1).

The four reference alcohols **13**, **15**, **19** and **20** were prepared in the following manner. The *cis*-4-ol (**19**) was the main product of the Prins reaction between 3-buten-1-ol and acetaldehyde in aqueous $H_2SO_4$;[4] NMR analysis showed that the *trans* isomer **20** was present only in trace amounts. **19** was converted into the epimer **20** by reaction of its mesylate with sodium acetate, followed by LAH reduction. The *trans*-3-ol (**15**) was obtained as the main product of the hydroboration-oxidation of **14**,[3b] and the *cis*-3-ol (**13**) was prepared by oxidation of **15** to the ketone **12**, followed by reduction with Li-Selectride, which took place with

Table 1. Regioselectivity of epoxide ring opening

| Substrate X | Substrate R | Reagent | % Attack a | % Attack b |
|---|---|---|---|---|
| O | H(1) | HCl | 93 | 7 |
| | | HBr | 92 | 8 |
| | | LAH | 93 | 7 |
| | | $Me_2NH$[a] | 67 | 33 |
| O | *trans*-Me (**16**) | HBr | 80 | 20 |
| | | LAH | 92[b] | 8 |
| O | *cis*-Me (**17**) | HBr | >99 | <1 |
| | | LAH | >98[c] | <2 |
| O | *trans*-OMe | HCl;[d] LAH;[e] $Me_2NH$[f] | 100 | 0 |
| O | *cis*-OMe | HCl;[d] LAH;[e] $Me_2NH$[f] | 100 | 0 |
| $CH_2$ | *trans*-OMe | HBr[g] | 90 | 10 |
| | | LAH[h] | 52 | 48 |
| $CH_2$ | *cis*-OMe | HBr[g] | 100 | 0 |
| | | LAH[h] | 43 | 57 |
| $CH_2$ | *trans*-Me | HBr[i] | 36 | 64 |
| | | LAH[i] | 30 | 70 |
| $CH_2$ | *cis*-Me | HBr[i] | 90 | 10 |
| | | LAH[i] | 98 | 2 |

[a] Ref 15. [b] Including *ca* 2% of alcohol **13** (oxidative inversion). [c] Including 4·5% of alcohol **15** (oxidative inversion). [d] Ref 16a. [e] Ref 16b. [f] Ref 16c. [g] R. A. B. Bannard, A. A. Casselmann, E. J. Langstaff and R. Y. Moir, *Can. J. Chem.* **46**, 35 (1958). [h] Ref 20. [i] Ref 2c. [j] Ref 13.

the high selectivity (*ca* 99%), previously observed for the similar reduction of 2-methylcyclohexanone.[14] A mixture of the four alcohols **13**, **15**, **19** and **20** was also obtained in the hydroboration-oxidation of **11**.

The NMR spectra of the alcohols and of their esters (Table 2) were in good agreement with the assumed configurations. The width of the signals relative to the protons $\alpha$ to the hydroxy or acyloxy groups showed that the conformations with equatorial Me were the preferred ones, even in the esters of **13** and **20**.

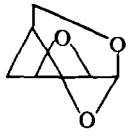
The three bromohydrins **18**, **21** and **22** were characterized by hydrogenolytic conversion into the corresponding alcohols.

The bromohydrin **22** was also obtained in an exceptionally selective way in the reaction of **11** with NBA in dioxane-water, since it constituted about 94% of the bromohydrin product of this reaction. Although the fourth bromohydrin **23** was not isolated and had almost the same retention time as **22**, it could not be present in the crude reaction product in an amount higher than 2·5%, as could be deduced by a comparison between the composition of this crude and that of the mixture of epoxides obtained from its treatment with base, in which **16** and **17** were present in a ratio of 96:4. Cyclization of pure **22** provided a good preparative method for obtaining pure **16**.

The NMR spectra of the bromohydrins **18**, **21**, **22** and of their *p*-nitrobenzoates (Table 2) confirmed the assigned structures and configurations and indicated that these molecules assume the conformation with an equatorial Me group.

## DISCUSSION

Table 1 summarizes our results on the epoxide ring openings together with some related literature data. The only previous reference to the oxirane ring opening of 3,4-epoxytetrahydropyran or of one of its alkyl derivatives concerns, to the best of our knowledge, the reaction of **1** with dimethylamine to give a 2:1 mixture of the two *trans* amino alcohols, with the prevalence of the one derived by nucleophilic attack at position 4.[15] There are more data on 2-alkoxy derivatives of **1**, which can be important intermediates in the synthesis of carbohydrates. Whereas simple *cis*- and *trans*-2-alkoxy-3,4-epoxytetrahydropyrans undergo mostly exclusively attack at C(4) both under basic and under acidic conditions,[16] the presence of additional ring substituents on the tetrahydropyran ring provides more complicated situations in which the regioselectivity depends also on the preferred conformation of the ring.[17] Particularly under basic conditions some diaxial attack can occure at C(3) [C(2), if carbohydrate numbering is used], and this becomes the main point of attack in conformationally rigid compounds, such as **24**, where the reactions with KOH and with LAH give over 50% of products derived from attack at C(3), notwithstanding the unfavourable inductive effect of the two adjacent O atoms; it should be noted, however, that the reaction of the same substrate with HI or $MgI_2$ produces exclusively the diequatorial iodohydrin.[18]



**24**

An electronegative substituent on the carbon $\alpha$ to the oxirane ring is expected to decrease the rate of nucleophilic attack on the epoxide carbon that is nearer to the substituent, provided that bond-breaking has progressed more than bond-making in the transition state, as usually assumed because of the 3-membered ring strain. This influence should be stronger in acid-catalyzed reactions, in which

Table 2. NMR data[a]

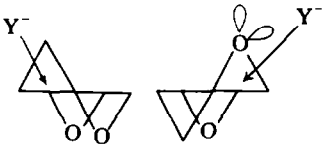
| Compound | H(2) | H(3) | H(4) |
|---|---|---|---|
| **13** PNB | — | 5·20, m, $W_{\frac{1}{2}}$ 6 Hz | — |
| **15** PNB | — | 4·7, m, W 33 Hz | — |
| **16** | 3·90, q, J 6·8 Hz | 3·00, d, J 4·2 Hz | — |
| **17** | 3·93, qd, J 6·4, 1·4 Hz | 3·01, dd, J 4·0, 1·4 Hz | — |
| **18** | — | 3·74, m, $W_{\frac{1}{2}}$ 7·5 Hz | 4·45, m, $W_{\frac{1}{2}}$ 7 Hz |
| **18** PNB | — | 5·25, m, $W_{\frac{1}{2}}$ 7 Hz | 4·6, m, $W_{\frac{1}{2}}$ 7 Hz |
| **19** PNB | — | — | 5·2, sept, W 33 Hz |
| **20** | — | — | 4·20, m, $W_{\frac{1}{2}}$ 9 Hz |
| **20** PNB | — | — | 5·60, m, $W_{\frac{1}{2}}$ 8 Hz |
| **21** PNB | — | 5·25, t, spl 9·5 Hz | — |
| **22** | — | — | 4·30, m, $W_{\frac{1}{2}}$ 13·5 Hz |
| **22** PNB | — | 4·20, m, $W_{\frac{1}{2}}$ 7 Hz | 5·47, m, $W_{\frac{1}{2}}$ 9 Hz |

[a] PNB = *p*-nitrobenzoate; Chem shifts in ppm ($\delta$); d = doublet; t = triplet; q = quartet; sept = septuplet; dd = double doublet; qd = quadruple doublet; m = multiplet; spl = splitting.

the actual substrate of the nucleophilic attack is the protonated epoxide, than in those conducted in neutral or basic media, since in the former more positive charge should develop on carbon in the transition state, and this can well explain the higher regioselectivity of the acid-catalyzed opening reactions.[19]

We expected that the epoxidies **1**, **16**, and **17**, with a single O atom in the $\beta$ position, would provide better models for the evaluation of the importance of the inductive effect on the regioselectivity of ring cleavages, than the 2-alkoxy epoxides mentioned above, in which the simultaneous presence of two $\beta$ oxygens would be expected to overshadow most other effects.

The fact that the reaction of epoxide **1** with HCl, HBr and with LAH constantly gives ratios of *ca* 92:8 of products of attack at C(4) and at C(3) indicates a strong preference for attack away from the 6-membered ring O atom, even when only one $\beta$ oxygen is present. Most of this preference should be due to the inductive effect mentioned above, although some other factors could contribute too. The two conformations **1a** and **1b** are expected to be energetically almost equivalent from a purely steric point of view, but it is less easy to assess the value for a possible interaction between the two O atoms, and even to predict if it is attractive or repulsive. Intuitively, the distance between the two atoms appears to be too large, even in **1a**, to make this interaction important. One can therefore reasonably assume that the main products of these reactions are formed by the diaxial opening of conformer **1a**. One additional factor which could destabilize the transition state for the attack at C(3) of conformer **1b**, could be an interaction between the incoming nucleophile, or the forming Y-C bond, and the axial non-bonding electron orbital of O(1). The fact that the reaction of **1** with dimethylamine[15]

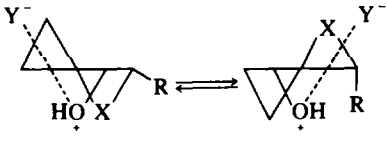



**1a** **1b**

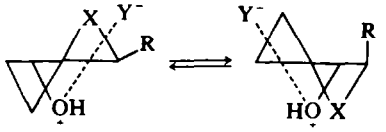
is less regioselective than those with hydrogen halides is, in any case in accordance with a transition state that has a substantial positive charge on carbon in the case of the acid-catalysed reaction, and with the inductive effect being the main cause of the observed regioselectivity.

Conformational factors are more important in the case of the 2-methyl epoxides **16** and **17**. A high preference for attack at C(4) is still observed, but, whereas the regioselectivity is almost complete for the reactions of the *cis* epoxide **17**, it is lower for those of the *trans* isomer **16**. These results agree well with previous ones on the opening of the 3-methylcyclohexene and 3-methoxycyclohexene oxides (Table 1) and can be interpreted in terms of the coexistence of inductive, conformational and stereoelectronic effects.

In the case of the *cis* epoxides diaxial opening of the more stable conformer (**25a**) occurs at position 4, which is also favoured from the point of view of the inductive effect. Therefore the stereoselectivity, which is high (90:10) also in the case of the reaction of *cis*-3-methylcyclohexene oxide (**25a**, X=$CH_2$, R=Me) with HBr, becomes complete in the cases of 3-methoxycyclohexene oxide (**25a**, X=$CH_2$, R=$OCH_3$) and of **17** (**25a**, X=O, R=$CH_3$), when the inductive effect of $\beta$-oxygen further destabilizes the transition state **25b**.




**25a** **25b**

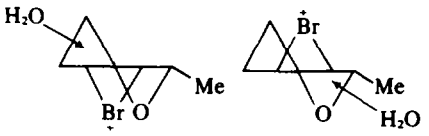



**26a** **26b**

In the *trans* series diaxial opening would involve transition state **26a**, which is disfavoured by the inductive effect, when X=O or R=MeO, and probably also by the repulsive interaction between $Y^-$ and R.[2c] *trans*-3-Methylcyclohexene oxide therefore gives a 64:36 ratio of the products of attack at C(3) and C(4) with HBr, which changes to 10:90 for *trans*-3-methoxycyclohexene oxide and to 20:80 for **16**, indicating a fairly important contribution of the inductive effect in destabilizing transition state **26a** in favour of one involving conformer **26b** with axial R, or a twist conformation, the possibility of which is clearly shown by the fact that also bridged molecules, such as **24** can undergo a considerable amount of diequatorial opening.

Hydride attack in the LAH reductions exhibits a regioselectivity that is remarkably similar to that of attack by halide in the cases of **16**, **17** and of the 3-methylcyclohexene oxides, a fact which is somewhat surprising in view of the rather different natures of the two types of reactions, and particularly of the recent results by Hartman and Rickborn[20] on the LAH reductions of *cis*- and *trans*-3-methoxycyclohexene oxides, where practically no regioselectivity was observed. The latter result that is the only one strongly deviating from the general trend shown by the data of Table 1 is hard to rationalize on the basis of any of the effects we have discussed above.

A final point of interest is provided by the results of the reactions of **4** and **11** with NBA. These reactions are expected to provide bromohydrins of opposite regiochemistry with respect to those obtained in the reactions of the epoxides with HBr, since they should proceed through epibromonium analogues of the protonated epoxides. The nucleophilic opening of these intermediates by water should be subjected to much the same effects as those operating in the opening of epoxonium ions. This is actually substantiated by the 20:80 ratio of bromohydrins **6** and **8** obtained from **4**. The reaction of **11** with NBA, on the other hand, is characterized by an extremely high selectivity, since one of the four diastereoisomeric *trans* bromohydrins (**22**) accounts for about 94% of the bromohydrin mixture. There is an about 96% preference for the formation of the *cis* bromonium ion **28** and for its almost exclusive diaxial opening.




**28** **29**

A similarly high selectivity had been observed in the reaction of 3-methoxycyclohexene with NBS in DMSO-water.[2c] The present result is a further confirmation for the hypothesis that in the reaction of alkenes with N-bromoamides and water the formation of the epibromonium intermediate is reversible and that the rate and product distribution are determined in the subsequent nucleophilic step.[2c] In the present case the high preference for the formation of bromohydrin **22** must therefore be attributed to the more favourable nature of the transition state involving **28**. Should the electrophilic attack by bromine be rate determining, it would be difficult to account for the results, since one would rather expect some preference for the formation of the *trans* ion **29**, if the epoxidation reaction of **11**, which gives an excess of *trans* epoxide, can be taken as a model for the formation of the epibromonium species.

In conclusion, the present results confirm the importance of inductive effects in determing the regioselectivity of epoxide ring opening reactions, but indicate that stereoelectronic and conformational effects cannot be omitted from the picture.

## EXPERIMENTAL

M.ps (Kofler block) are uncorrected. IR spectra, taken on neat liquids or on paraffin oil mulls of solids on a Perkin-Elmer 137, were used for comparison between compounds. NMR spectra were taken on *ca* 10% solns in $CDCl_3$ on a JEOL C-60 HL spectrometer with TMS as the internal standard; 100 MHz spectra of some of the compounds were taken on a JEOL PS-100, double resonance being used to check some of the assignments. GLC analyses were run on a Carlo Erba Fractovap GV and on a Perkin-Elmer F-11, both equipped with 2-m glass columns and flame ionization detectors. The stationary phases were: Column A 1% neopentyl glycol succinate on silanized Chromosorb W, 80–100 mesh; Column B 15% Carbowax 20M on silanized Chromosorb W, 80–100 mesh. Preparative separations were carried out on a Perkin-Elmer F-21 gas chromatograph. Light petroleum, b.p. 40–60°, was used for all chromatographic purifications and crystallizations, except for the crystallizations of the *p*-nitrobenzoates, for which the fraction, b.p. 60–80°, was employed.

*5,6-Dihydro-2H-pyran* (**4**), b.p. 94–95°/760 mm, $n_D^{24}$ 1·4436 (lit.,[21] b.p. 93·5°/760 mm, $n_D^{21}$ 1·4472) was obtained according to Colonge and Boisde.[21]

*3,4-Epoxytetrahydropyran* (**1**). A soln of **4** (8·7 g, 0·104 mole) in $CHCl_3$ (100 ml) was treated at −10° with 0·33 molar peroxybenzoic acid in $CHCl_3$ (315 ml, 0·104 mole), left at −10° for 8 h and at 5° for 16 h, washed with ice-cold 20% NaOH, dried, evaporated and distilled to give 7·5 g (72%) of **1**, b.p. 55–60°/18 mm, $n_D^{25}$ 1·4508; lit.[15] b.p. 152–154°/760 mm, $n_D^{20}$ 1·4537 (Found: C, 59·89; H, 8·11. $C_5H_8O_2$ requires: C, 59·98; H, 8·05%). The product showed a single peak in GLC (column A; temp 60°).

*Tetrahydropyran-3-ol* (**2**). The method of Barker *et al.*,[3a] which gave only very poor yields, was modified as follows. 2,3-Diacetoxytetrahydropyran[3a] (4·6 g) was left at room temp for 24 h with 50 ml of a 40% soln of HBr in AcOH. Evaporation of the solvent, addition of benzene (20 ml), distillation of the benzene, reduction of the residue with LAH (5·5 g) in ether (100 ml) for 4 h under reflux; hydrolysis with water (5·5 ml), 15% NaOH (5·5 ml) and more water (16·5 ml); decantation of the ether soln, evaporation and distillation gave **2** (0·7 g), b.p. 134–140°/80 mm, $n_D^{23}$ 1·4580; lit. [3a] b.p. 92–95° (bath)/15 mm, $n_D^{21}$ 1·4571. The same compound was also prepared in better yield according to Gore and Guigues,[3b] through hydroboration-oxidation of 3,4-dihydro-2*H*-pyran; b.p. 90–94°/20 mm, $n_D^{15}$ 1·4581.

*Tetrahydropyran-4-ol* (**3**) was prepared by the method of Hanschke,[4] except that the reaction was carried out in an open vessel and not in an autoclave. The distilled product was purified by chromatography on alumina (act. I); elution with 95:5 ether/MeOH gave **3**, $n_D^{24}$ 1·4583; lit.[4] $n_D^{20}$ 1·4606. *p*-Nitrobenzoate, m.p. 66–68° (from light petroleum); lit.[4] m.p. 68–69°.

*Reduction of* **1** *with LAH.* The epoxide **1** (500 mg, 5 mmole) in ether (10 ml) was refluxed for 4 h with LAH (122 mg 3·2 mmole). Water (1·2 ml), 15% NaOH (1·2 ml) and water (3·6 ml) were added in succession, the ether was decanted from the ppt, which was extracted with three 5-ml portions of ether. Analysis of the combined organic solutions by GLC (column B; temp 120°) showed that only **2** and **3** were present in a ratio of 93:7; relative retention times, 1·00:1·23. The crude mixture was oxidized with Jones reagent and the product was reacted with 2,4-dinitrophenylhydrazine in EtOH; crystallization of ppt from EtOH yielded the 2,4-dinitrophenylhydrazone of tetrahydropyran-3-one m.p. 170°; lit., m.p. 171°.[3b]

*Reaction of* **1** *with HCl.* A soln of **1** (200 mg) in ether (50 ml) was saturated with dry HCl, left 15 min at room temp, then evaporated *in vacuo* to give an oily crude (230 mg, 80%) which was directly analyzed by GLC (column A; temp 80°). Only **5** and **7** were present in a ratio of 93:7; relative retention times, 1·14:1·00.

*Reaction of* **1** *with* HBr. A soln of **1** (300 mg) in ether (50 ml) was saturated with dry HBr at 0°, the solvent was

evaporated *in vacuo*, the residue taken up in ether, washed with satd $NaHCO_3$ aq, dried and evaporated. GLC (Column A, temp. 80°) showed that only **6** and **8** were present in a ratio of 92:8; relative retention times 1·24:1·00

*Reaction of* **4** *with NBA.* A soln of **4** (0·95 g, 11·3 mmole) in 50:50 dioxane-water (v/v, 20 ml) was treated with NBA (2·23 g, 17·2 mmole) in the same solvent mixture (20 ml), heated on a steam-bath for 10 min, cooled, and extracted with three 30-ml portions of ether. The combined ether extracts were washed ($NaHCO_3$ aq), dried and evaporated. The residue was analyzed by GLC; the ratio of **6** to **8** was 20:80.

*Hydrogenolysis of* **6** *and* **8**. The crude product of the preceding reaction was dissolved in EtOH (25 ml), Raney Ni (9·5 g, washed with EtOH) and Amberlite IRA-400-OH (2 ml) were added and the mixture was stirred in an autoclave under 10 atm of $H_2$ for 48 h. After filtration and concentration to a small volume the product was analyzed by GLC. The peaks for **2** and **3** were present in a ratio of 18;82.

*trans*-2,3-*Dibromotetrahydropyran* (**9**) was prepared from 3,4-dihydro-2*H*-pyran (63 g) according to Lemieux and Fraizer-Reid,[7] and the crude product was immediately converted into trans-2-*methyl*-3-*bromotetrahydropyran* (**10**) with Me MgBr, according to Brandon.[22] The crude product was steam-distilled and then fractionally distilled to give **10**, b.p. 70–80°/22 mm, $n_D^{25}$ 1·4810 (82 g, 62%): lit.[22] b.p. 60–61°/17 mm, $n_D^{20}$ 1·4834. GLC (Column B, temp 125°) and NMR analysis showed that not more than 5% of the *cis* isomer was present.

2-*Methyl*-5,6-*dihydro*-2*H*-*pyran* (**11**). To a mixture of 85% KOH (30 g) and ethylene glycol (70 ml) **10** (17·5 g) was added. After 7-h reflux the product was distilled from the mixture, water was added to the residue and more product was obtained by steam distillation. The dried ($Na_2SO_4$) combined organic layers (6·8 g, 71%) were almost pure **11**, $n_D^{25}$ 1·4360; the strong C=C stretching band at 1680 $cm^{-1}$, characteristic of the vinyl ether **14** was absent. Distillation (b.p. 110°/760 mm) did not change appreciably the refractive index and IR spectrum; lit.[6] b.p. 105°/750 mm, $n_D^{12}$ 1·4430. GLC (column B, temp. 50°) indicated a purity of over 96%.

trans-*and* cis-2-*Methyl*-3,4-*epoxytetrahydropyran* (**16** and **17**). A soln of **11** (9·3 g, 95 mmole) in dry $CHCl_3$ (80 ml) was cooled at −10°, then treated under stirring with 0·43M peroxybenzoic acid in $CHCl_3$ (280 ml, 0·12 mole), while keeping the temp below −5°. The soln was stored at −5° for 40 h, washed with 10% NaOH (300 ml), dried and evaporated *in vacuo*. GLC (Column B, temp 100°) showed that **16** and **17** were present in a ratio of 55:45; relative retention times 1:1·62. The product distilled at 70–75°/30 mm. A part of the crude product was separated into its components by preparative GLC (2 m × 8 mm steel column, 5% Carbowax 20M on Chromosorb B, injection block 150°, column 95°, $N_2$ 200 ml/min). **16**: $n_D^{25}$ 1·4428 (Found: C, 63·00; H, 8·90 $C_6H_{12}O_2$ requires: C, 63·13; H, 8·83%). **17**: $n_D^{25}$ 1·4458 (Found: C, 62·70; H, 8·90 $C_6H_{12}O_2$ requires: C, 63·13; H, 8·83%).

trans-2-*Methyltetrahydropyran*-3-*ol* (**15**). Compound **14** (4·7 g, 0·048 mole), prepared according to Lipp[22], was dissolved in dry THF (50 ml) and treated with 0·85M borane in THF (24 ml, 0·06 equiv), stirred for 4 h at 0° and 3 h at room temp. Excess hydride was destroyed with 3N NaOH (10 ml) and 30% $H_2O_2$ (10 ml) was added. After 2-h stirring and storage overnight the soln was saturated with NaCl and extracted with ether. The dried soln was evaporated *in vacuo* to give an oil which was distilled to yield **15** (2·7 g, 50%), b.p. 100–102°/32 mm; $n_D^{18}$ 1·4530. lit.[3b] b.p. 83–86°/13 mm. The *p*-nitrobenzoate had m.p. 89–91° (from light petroleum). (Found: C, 59·30; H, 5·40; N, 5·60; $C_{13}H_{15}NO_5$ requires: C, 58·86; H, 5·70; N, 5·28.)

cis-2-*Methyltetrahydropyran*-3-*ol* (**13**). The alcohol **15** was oxidized to the ketone **12**, according to Gore and Guigues,[3b] and the ketone (0·200 g, 1·75 mmole), was dissolved in dry THF (5 ml), cooled at −80° and reduced under $N_2$ with 1M Li selectride[14] (4 ml) in THF. After 5 h at −78° the soln was brought to room temp and treated with 3M NaOH (0·5 ml), 36% $H_2O_2$ (0·6 ml), stirred for 30 min and saturated with $Na_2SO_4$. The filtered soln was directly analyzed by GLC, which showed a ratio of **13**:**15** of *ca* 99:1.

The *p*-nitrobenzoate of **13** had m.p. 104–105° (from light petroleum) (Found: C, 59·10; H, 5·70. $C_{13}H_{15}NO_5$ requires; C, 58·86; H, 5·70%).

cis-2-*Methyltetrahydropyran*-4-*ol* (**19**) was prepared by the method of Hanschke,[4] but the reaction was conducted in an open vessel and not in an autoclave. From 3-buten-1-ol (7·2 g) **19** (7·4 g 54%) was obtained, b.p. 103–105°/27 mm, $n_D^{25}$ 1·4512; lit.[4] b.p. 100°/20 mm, $n_D^{20}$ 1·4543. *p*-Nitrobenzoate, m.p. 85–86° (from EtOH–$H_2O$); lit.,[4] m.p. 86·5°. Since the GLC of the distilled alcohol showed the presence of about 10% of a side-product, a pure sample of **19** was obtained by basic hydrolysis of the crystallized *p*-nitrobenzoate.

trans-2-*Methyltetrahydropyran*-4-*ol* (**20**). The alcohol **19** (2·7 g) was converted into the mesylate by treatment with mesyl chloride (6·5 g) in dry pyridine (20 ml), followed by 20-h stirring at room temp, distillation of the solvent *in vacuo*, extraction with ether, washing with 2N HCl and $H_2O$, drying and evaporation. The residue was purified by elution with 1:1 light petroleum/ether from silica gel. The mesylate (1·95 g) was dissolved in dry DMSO (8 ml), treated with anhyd NaOAc (1 g) at 100° for 22 h under stirring. Usual work-up gave a crude acetate which was chromatographed on silica gel. The fraction eluted with 90:10 light petroleum–ether was reduced with LAH in ether to give a not completely pure alcohol **20**, the main component of which had the same retention time as the minor product obtained in the LAH reduction of epoxide **16** and as the hydrogenolysis product of the bromohydrin **22**.

*Hydroboration-oxidation of* **11**. **11** (1 g, 10 mmole) in dry THF (6 ml) was treated with 0·85M borane (5 ml, 12 me quiv) in THF and stirred at room temp for 5 h. Work-up as described above, followed by GLC analysis of the crude product (Column B, temp. 125°) showed that it was composed of 55% **15**, 34·5% **20** + **19** and 10·5% **13**; relative retention times of **13**, **15**, **19** and **20**, 1·00:1·71:2·03:2·03.

*Reduction of the epoxides* **16** *and* **17**. Solns of each of the two epoxides (80 mg, 0·70 mmole) in dry ether (5 ml) were treated with LAH (0·10 g 0·725 mmole) and refluxed for 5 h. The solns were worked up as described for reduction of **1** and analyzed by GLC (Table 1). The crude reduction products of **16** and **17**, on reaction with *p*-nitrobenzoyl chloride in pyridine, followed by recrystallization yielded, respectively, the *p*-nitrobenzoates of **15** and **13**.

*Reactions of* **16** *and* **17** *with* HBr. A soln of the epoxide (100 mg) in dry ether (10 ml) was slowly saturated at 0° with dry HBr, then evaporated *in vacuo*. The residue was taken up twice in dry benzene and evaporated again *in*

*vacuo* to eliminate all the HBr, before the residue was analyzed by GLC (Table 1).

The 8:2 mixture of bromohydrins **21** and **22** obtained from **16** was dissolved in light petroleum and chromatographed on silica gel; 90:10 light petroleum-ether eluted t-4-*bromo*-t-2-*methyltetrahydropyran*-r-3-*ol* (**21**), m.p. 41–43° (from light petroleum) (Found: C, 36·60, H, 5·60 Br, 40·80. $C_6H_{11}BrO_2$ requires: C, 36·94; H, 5·68; Br, 40·97%). *p*-Nitrobenzoate, m.p. 132–133° from light petroleum. Further elution with 80:20 light petroleum-ether gave the bromohydrin **22**.

Epoxide **17** gave t-4-*bromo*-c-2-*methyltetrahydropyran*-r-3-*ol* (**18**) as an oil, containing only a trace (<1%) of the isomer **23**. *p*-Nitrobenzoate of **18** m.p. 120–122° from light petroleum-ether. (Found: C, 45·70; H, 3·90; Br, 24·00. $C_{13}H_{14}BrNO_5$ requires: C, 45·36; H, 4·10; Br, 23·22%).

The mixtures of bromohydrins were analyzed by GLC on column B, (programmed temp, 3°/min, 120–190°); relative retention times of **21**, **18**, **22** and **23**, 1·00:1·07:1·76:1·76.

*Reaction of* **11** *with NBA.* A soln of **11** (2·75 g, 0·028 mole) in 1:1 water-dioxane (20 ml) was treated under stirring at room temp with a soln of NBA (4·30 g, 0·031 mole) in 30 ml of the same solvent mixture, then heated for 10 min on a steam-bath, cooled and extracted with ether. The thoroughly washed and dried ether layer was evaporated to yield 5 g of an oil, the GLC of which exhibited peaks corresponding to **22** + **23**, **18** and **21** in a ratio of 96:1·5; 2·5 some other minor unidentified peaks were also present (*ca* 5% of the total). Elution from silica gel with 90:10 light petroleum–ether gave pure t-3-*bromo*-t-2-*methyltetrahydropyran*-r-4-*ol* (**22**) (60% yield), m.p. 53–55° from light petroleum. (Found: C, 36·60; H, 5·60; Br, 41·3. $C_6H_{11}O_2Br$ requires: C, 36·94; H, 5·68; Br, 40·97%). *p*-Nitrobenzoate, m.p. 127–129° from EtOH.

A soln of **11** (1·0 g, 10·2 mmole) in 1:1 dioxane-water (60 ml) was treated with NBA (2·0 g, 14·5 mmole) and heated 10 min on a steam bath, KOH (15 g) in water (20 ml) was added, the soln was stirred 30 min at room temp, diluted with water (50 ml) and extracted with ether. The washed and dried ether extract was evaporated to a small volume. GLC analysis showed that the epoxides **16** and **17** were present in a ratio of 96:4.

A suspension of the bromohydrin **22** (100 mg 0·512 mmole) in water (20 ml) was treated with 0·1N NaOH (10 ml) and heated on a steam-bath for 20 min. Back-titration with 0·1N HCl showed that the theoretical amount of base had been consumed. Extraction with ether gave pure epoxide **16**: the isolated yield was of only about 60%, owing to the volatility of the epoxide.

*Hydrogenolysis of the bromohydrin* **22**. A soln of **22** (622 mg) in EtOH (40 ml) was treated with 10 ml of a suspension of Raney Ni, which had been washed 3 times with EtOH, and with Amberlite IRA-400 OH (4 ml), and shaken for 24 h at room temp and press. (The original method[5] was thus modified when it was found that it was not necessary to run the reaction under $H_2$ in an autoclave). After filtration and washing of the catalyst with benzene the soln was evaporated on a steam-bath, the residue was taken up in ether, filtered and evaporated to give pure alcohol **20** (342 mg, 92%).

The *p*-nitrobenzoate of **20** had m.p. 67–70° (from light petroleum) (Found: C, 58·80; H, 5·72; N, 5·23, $C_{13}H_{15}NO_5$ requires. C, 58·86; H, 5·70; N, 5·28).

The same reaction, carried out on the crude mixture of bromohydrins obtained in the addition of HBr to a 55:45 mixture of **16** and **17**, gave the alcohols **13**, **15** and **19** + **20** in a ratio of 42:45:13. The calculated ratio is 45:44:11.

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