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BROMINATION OF 3-CYCLOHEXENE-1-CARBOXYLIC ACID, EPOXYDATION OF METHYL 3-CYCLOHEXENE-1-CARBOXYLATE AND OPENING OF METHYL *cis*- AND *trans*-3,4-EPOXYCYCLOHEXANE-1-CARBOXYLATE: STEREOCHEMICAL RESULTS

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Abstract—Bromination of 3-cyclohexene-1-carboxylic acid (**1**) gives mixtures of the *trans*-dibromo-derivatives **3** and **4** and *cis*-3-hydroxy-*trans*-4-bromocyclohexane-1-carboxylic acid lactone (**5**). Lactone **5** is obtained by brominating **1** in the presence of triethylamine, showing that halogen preferentially attacks the double bond *anti* with respect to the carboxyl group. Epoxydation of the methyl ester of **1** also takes place prevalently *anti* to the methoxycarbonyl group. Ring opening of methyl *cis*-3,4-epoxycyclohexane-1-carboxylate (**7**) with hydrogen bromide gives methyl *trans*-3-bromo-*cis*-4-hydroxy- (**13**) and *cis*-3-hydroxy-*trans*-4-bromocyclohexane-1-carboxylate (**6**). Similar opening of methyl *trans*-3,4-epoxycyclohexane-1-carboxylate (**11**) affords methyl *trans*-3-hydroxy-*cis*-4-bromocyclohexane-1-carboxylate (**14**). The steric course of these reactions is ascribed to the effect of the electron-withdrawing substituent.

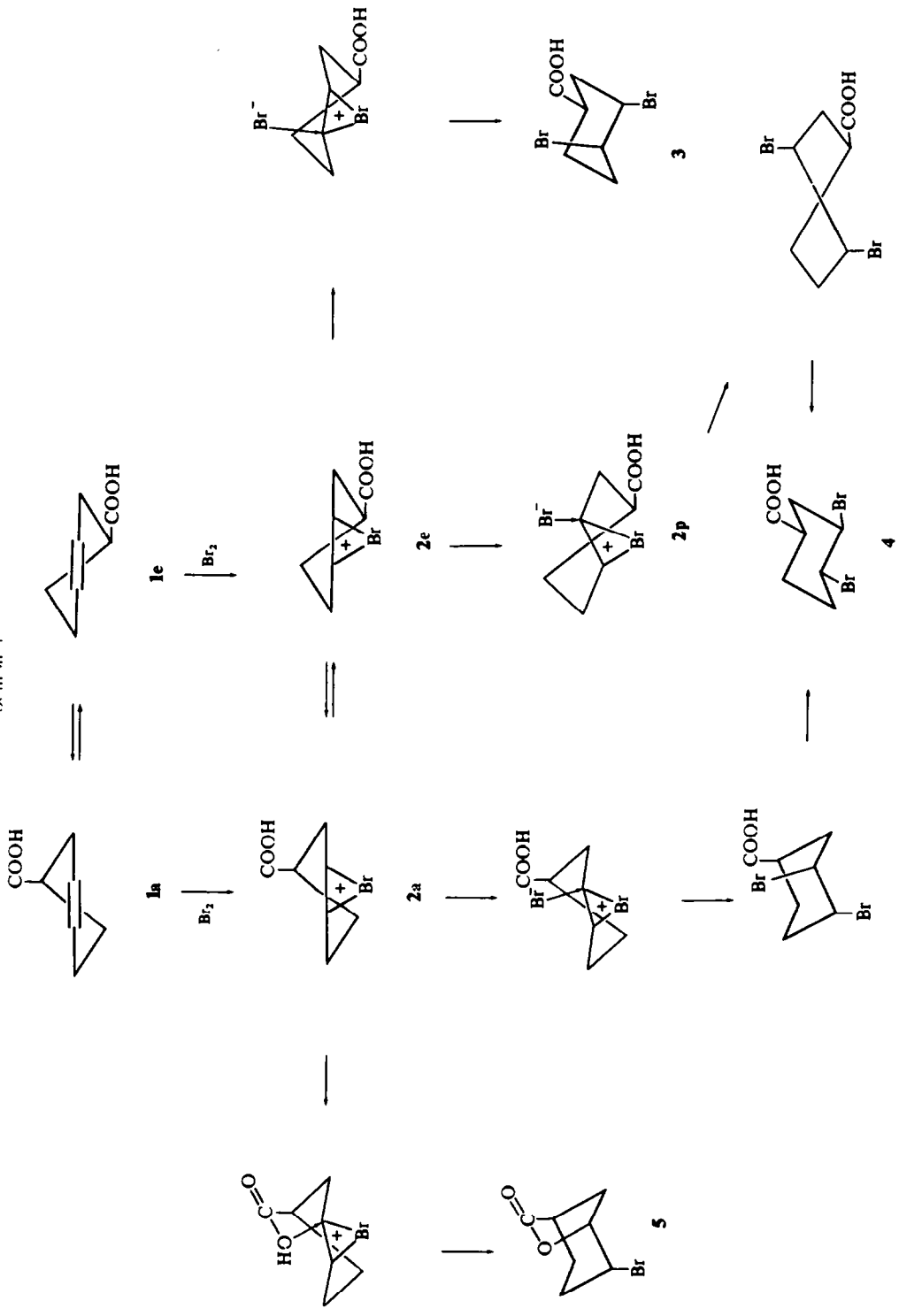
THE SYNTHESIS of several bromocyclohexanols bearing a third ring substituent was undertaken as a continuation of previous studies on the stereochemistry of the substitution of hydroxyl groups in vicinal bromohydrins.[1-3] Since literature results[4,5] on electrophilic additions to 3-cyclohexene-1-carboxylic acid (**1**) and its methyl ester (**10**) indicated these reactions could exhibit high stereoselectivity, it was decided to re-examine these transformations, in view of their possible utilization for the stereospecific synthesis of bromohydrins.

RESULTS AND DISCUSSION

Bromination of unsaturated acid **1** in $CHCl_3$ solution gave a mixture containing the two dibromoacids **3** and **4** in a 90:10 ratio and 7% of the bromolactone **5**.

Bromonium ions are generally assumed to be intermediates in the addition of bromine to olefins.[6] Dibromide **3** could be formed by antiparallel attack[7] of bromide ion on C-4 of the *trans*-bromonium ion (**2e**), with the carboxyl group equatorially oriented (Scheme 1). Dibromide **4** could be formed either by parallel attack on C-3 of **2e**, through a pre-boat transition state (**2p**), or by antiparallel attack on C-3 of a conformer with axial carboxyl group (**2a**). It is known[8] that in **1** conformation **1a** contributes by 15%; it can therefore be reasonably assumed that **2a** gives a similar contribution to the conformational equilibrium of the bromonium ion **2**. Dibromides **3** and **4** could analogously be formed also from the *cis*-bromonium ion. In addition, bromonium ion **2a** may undergo an intramolecular attack by the carboxyl group, thus affording the *trans*-bromolactone **5**, the main product when bromination is carried

SCHEME 1

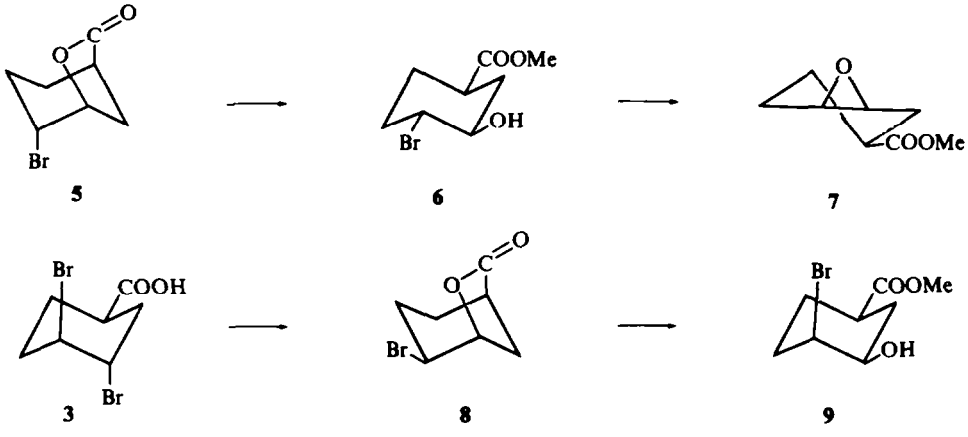


out in the presence of Et_3N. In this case, the carboxylate ion becomes the favoured nucleophile, and there is a preference for intramolecular attack. Since the bromo lactone (**5**) can originate only from the *trans* bromonium ion **2**, its formation in 66% yield demonstrates that bromine preferentially attacks the double bond *anti* with respect to the carboxyl group.*

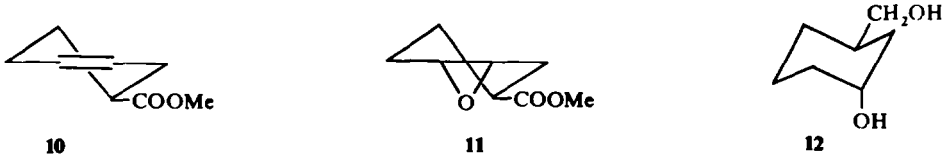
Also the ratio between the dibromides **3** and **4** is changed by the presence of Et_3N (95:5 instead of 90:10). An analogous effect of the presence of amines has been previously observed in the bromination of some 3- and 4-substituted cyclohexenes.[9] This fact was explained by the intervention of amine-bromine complexes as brominating agents. In the present case, however, since the amine is protonated by acid (**1**), it seems more likely that the change is due to competition of the intramolecular attack by the carboxylate ion on C-3 of the *trans* bromonium ion (**2a**), with respect to attack of an external bromide ion, more hindered also because it must approach the reaction center in an orientation parallel to the axial carboxylate group.

When heated in MeOH in the presence of H_2SO_4, the *trans*-bromolactone (**5**) is converted into the bromohydroxyester (**6**);[4] isomer **9** can easily be obtained by similar treatment of the *cis*-bromolactone **8** (Scheme 2). The *cis*-epoxide **7** is formed from the bromohydrin (**6**) by mild alkali treatment.

SCHEME 2



It has been reported that epoxidation of ester **10** affords exclusively *trans*-epoxide **11**, since only the diol **12** was obtained by subsequent LAH reduction.[5] This *anti* stereoselectivity was ascribed to a steric effect by the substituent at C-1. However Rickborn

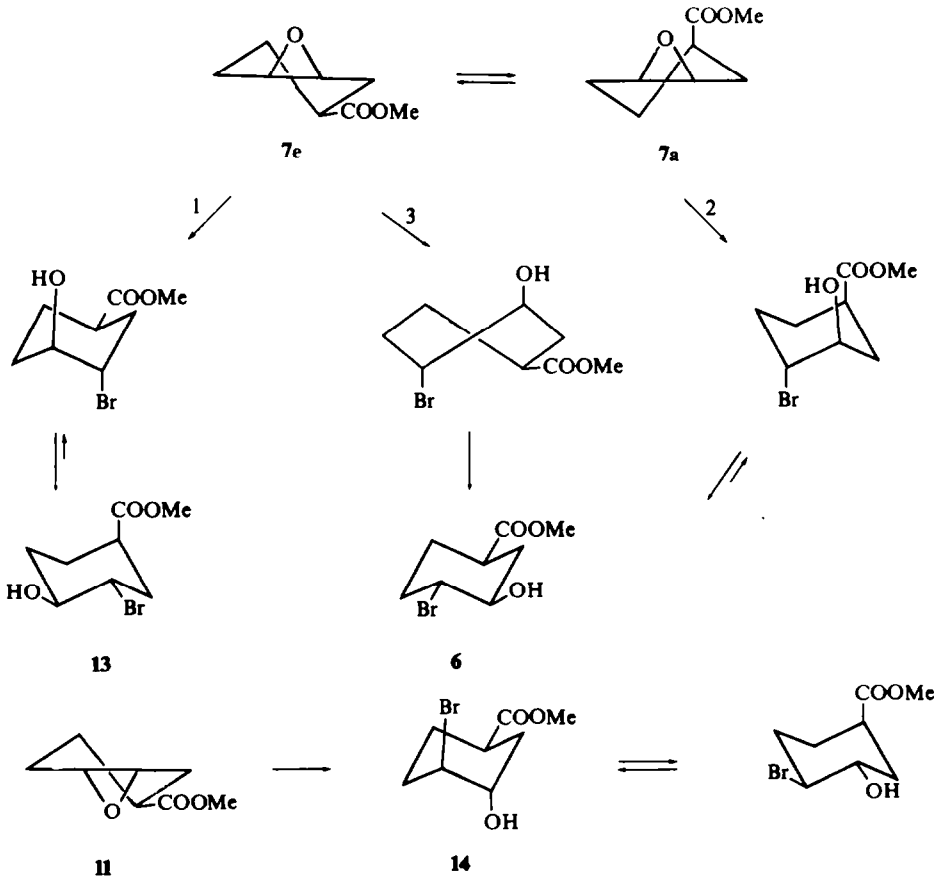


* It is assumed here that bromonium ions are formed irreversibly, as is generally accepted.[6] D. J. Pasto and J. A. Gontarz [*J. Am. Chem. Soc.* **93**, 6902 (1971)] assume, on the basis of results obtained from brominations carried out in MeOH, that bromonium ions should form reversibly. However, the conditions employed by the above authors are very different from those of the present work and the bromination mechanism is not necessarily the same in both cases.

and Lwo[10] have shown that the steric effects of 4-alkyl substituents decrease the reaction rate, but have only a minor influence on the stereochemistry of the epoxydation of cyclohexenes. In our hands, treatment of **10** either with *p*-nitroperoxybenzoic acid in $CHCl_3$ or with peroxybenzoic acid in ether, gave a mixture of two epoxides (**11** and **7**) in the ratio 66:34. An interesting similarity exists between bromination of the triethylammonium salt of the acid **1** and epoxidation of the ester **10**: in both cases the electrophilic reagent exhibits a certain preference for attack *anti* to the substituent at C-1. Such a preference is higher in the epoxidation of **10** than in that of 4-methylcyclohexene, which affords only 53·6% of *trans*-epoxide,[10] even if the two cyclohexene derivatives should have very similar conformational equilibria.[8,10] This seems to indicate that the effect of the COOMe group is polar rather than steric in nature. Analogous directive effects have been proposed to explain similar results obtained from 4-cyanocyclopentene[11] and 4-cyanocyclohexene.[12]

An inductive effect also appears to be operative in the reaction of epoxide **7** with HBr: two products (**13** and **6**) are formed in the ratio 80:20. The bromohydroxyester **13** is the normal reaction product resulting from a diaxial opening of **7**, which should react in the more stable half-chair conformation **7e**, with equatorial COOMe (Scheme 3, reaction 1). Two mechanisms, similar to those proposed for the formation of **4**

SCHEME 3



from **1**, could also be valid for the transformation **7** → **6**: (a) diaxial opening of **7** in a conformation with axial COOMe (**7a**) (reaction 2); (b) opening of **7e** through a pre-boat transition state (reaction 3). However, in the absence of particular steric and polar factors, the latter mechanism appears to be very unlikely. It is known that the two epoxides derived from 4-*t*-butylcyclohexene, in which the alkyl group is in a fixed equatorial position, give only *trans* diaxial halohydrins by treatment with hydrogen halides.[1,13] Moreover, only axial attack was observed[14] in the hydride reduction of the same epoxides. Only very small amounts (2%) of equatorial alcohols were detected[15] in the hydride reduction of 4-methylcyclohexene oxides, although an appreciable population of conformers with axial Me groups may be present in these compounds. This should also indicate that a small substituent such as a Me group at C-4 exhibits greater conformational control over the ring opening than anticipated from its conformational preference in the ground-state of the epoxides. It has been shown[8] that in the unsaturated ester **10** in $CHCl_3$ solution the equatorial conformer is preferred over the axial by 0·8–0·9 Kcal/mole (corresponding to 80% equatorial). This value is very near to that (approximately 1 Kcal/mole) evaluated for 4-methyl-cyclohexene.[10,15] Moreover the interaction between the COOMe and the epoxidic oxygen should reduce the preference for the axial conformation of the *cis*-epoxide (**7a**), which should therefore be less than 20%.

It is generally dangerous to make attempts at quantitatively relating reaction product distribution to ground-state conformational population.[16,17] However, the COOMe at C-1 can hardly disfavour path 1 over paths 2 and 3 by a steric effect. Therefore it seems more probable that the formation of 20% of **6** in the HBr opening of the *cis*-epoxide **7** is at least in part due to the polar effect of the COOMe group. The electron-withdrawing effect of this substituent may induce some preference for nucleophilic attack on C-4 by exerting a greater inhibitory influence on the development of a cationic character on C-3 in the transition state of the "borderline S_N2" mechanism[18] involved in the ring opening of **7**. Therefore paths 2 or 3, otherwise unfavourable, could partially be followed. A demonstration of the correctness of this interpretation was obtained by the HBr-opening of the *trans*-epoxide **11**: since in this case both the conformational and the inductive effect of the COOMe group direct nucleophilic attack on C-4, practically pure bromohydrin **14** was formed.

The influence of inductive effects of remote polar substituents has been demonstrated[19] in the addition of 2,4-dinitrobenzenesulphenyl chloride to 4-substituted cyclohexenes. Furthermore, a polar effect of a methoxycarbonyl group, analogous to that discussed above, also seems to operate in the hydroboration of the unsaturated ester **10**.[20] A strong inductive effect of the OMe group was also claimed[21] for the preferential attack on C-1 of *trans*-3-methoxycyclohexene oxide by both acidic and basic reagents, although in this case the substituent, adjacent to the oxirane ring, may also exert a steric effect.[22]

EXPERIMENTAL

M.ps (Kofler block) are uncorrected. NMR-Jeol C-60 HL spectrometer, TMS as internal standard. Analytical GLC-Fractovap C. Erba, mod. G.V.; columns: 3% OV 17 on gas chrom Q 80–100 mesh for epoxides **7** and **11**; 1% neopentyl glycol succinate (NPGS) on chromosorb W 80–100 mesh for methyl esters of dibromoacids **3** and **4** and for bromohydroxyesters **6** and **13**; carrier gas N_2. Preparative GLC–Perkin–Elmer, mod. F 21; column: 5% cyclohexane dimethanol succinate on chromosorb G 60–80 mesh.

Brominations of 3-*cyclohexene*-1-*carboxylic acid.* (a) *In the absence of base.* A 20% excess of a 2M soln of Br in $CHCl_3$ was added dropwise to a stirred soln of **1** (5·0 g, 0·04 mole) in $CHCl_3$ (250 ml). Extraction with $NaHCO_3$ aq followed by acidification gave, after extraction with ether and evaporation of the extract, a mixture of **3** and **4** (6·7 g). Evaporation of the $CHCl_3$ layer afforded bromolactone **5** (0·59 g), m.p. 104–105° (lit.[4] m.p. 106°). A sample of the crude mixture of **3** and **4** was esterified with CH_2N_2; ratio of esters of **3** and **4**[23] (GLC), 90:10, retention times (injection block temp 160°, column temp 130°, flow rate 50 ml/min) 7 min 50 sec and 16 min 30 sec.

(b) *In the presence of* Et_3N. The unsaturated acid **1** (10·0 g, 0·08 mole) dissolved in $CHCl_3$ (450 ml) was treated with a 20% excess Br in the presence of an equimolar amount of Et_3N (8·1 g). After extraction of the amine with 2N HCl, the mixture was worked-up as in (a), affording **5** (10·7 g) and a mixture of **3** and **4** (6·6 g). This mixture with CH_2N_2 gave the methyl esters of **3** and **4** in the ratio (GLC) 95:5.

Methyl cis-3-*hydroxy*-trans-4-*bromocyclohexane*-1-*carboxylate* (**6**). Ester **6**, m.p. 98–99°, was prepared by refluxing a soln of bromolactone **5** in MeOH in the presence of 0·5% (v/v) H_2SO_4. (lit.[4] m.p. 96°).

cis-3-*Hydroxy*-cis-4-*bromocyclohexane*-1-*carboxylic acid lactone* (**8**). Lactone **8** was obtained, in much higher yield than described,[4] as follows: the dibromoacid **3** (7·1 g, 0·025 mole) in 40 ml of water was exactly neutralized with 1N NaOH and the soln heated at 50–60° for 30 min. After cooling to room temp the bromolactone **8** (2·5 g), m.p. 101–102°, crystallized. Further heating of mother liquors for 1 hr, followed by cooling, afforded a second crop (1·3 g), m.p. 101–102° (lit.[4] m.p. 101°).

Methyl cis-3-*hydroxy*-cis-4-*bromocyclohexane*-1-*carboxylate* (**9**). A soln of **8** (2·5 g) in MeOH (60 ml) containing 0·5% (v/v) H_2SO_4 was refluxed for 5 hr. Most of the solvent was evaporated and the residue diluted with water and extrated with Et_2O. The organic layer afforded on evaporation crude **9** (2·8 g), which crystallized from AcOEt-pet ether as pure **9**, m.p. 65–66°. (Found: C, 40·83; H, 5·43; Br, 33·90. $C_8H_{13}BrO_3$ requires C, 40·50; H, 5·48; Br, 33·75%).

The same product was obtained by esterification of the corresponding acid[4] with CH_2N_2.

Methyl cis-3,4-*epoxycyclohexane*-1-*carboxylate* (**7**). A soln of **6** (4·0 g) in 2-propanol (60 ml) was titrated with 1N NaOH aq at room temp, with phenolphthalein as indicator: 17 ml (theoretical 16·9 ml) were consumed in about 4 hr. Dilution with water, extraction with Et_2O and evaporation of the extract gave the epoxide **7** (2·1 g), b.p. 89–90°/3·5 mm, n_D^{25} 1·4638. (Found: C, 61·30; H, 7·89. $C_8H_{12}O_3$ requires C, 61·54; H, 7·69%). The NMR spectrum showed an unresolved multiplet at δ 3·07 ppm (oxirane protons) and a sharp singlet at δ 3·59 ppm (carboxylate Me). The product was GLC pure.

Epoxidation of methyl 3-*cyclohexene*-1-*carboxylate* (**10**). (a) *With* p-*nitroperoxybenzoic acid in* $CHCl_3$. Pure (99%, Prolabo) *p*-nitroperoxybenzoic acid (4·0 g, 0·022 mole) was slowly added to a stirred soln of **10** (2·0 g, 0·014 mole) in $CHCl_3$ (20 ml) at 0°. After standing for 20 hr at 0° the *p*-nitrobenzoic acid was filtered and the soln, washed with 10% Na_2CO_3 aq and dried ($MgSO_4$), was evaporated under red. press. Distillation of the residue afforded a mixture of the two epoxides **7** and **11** (1·8 g), b.p. 68°/1·3 mm. n_D^{25} 1·4618 (lit.[5] b.p. 50–51°/0·5 mm; n_D^{21} 1·4630). In the NMR spectrum the oxirane protons of both **7** and **11** appear as an unresolved multiplet at δ 3·07 ppm; however the carboxylate Me's give two distinct singlets at 215·6 and 216·5 Hz (at 60 MHz). Furthermore GLC analysis showed that **11** and **7** were present in the ratio 66:34; retention times (injection block temp 150°, column temp 95°, flow rate 25 ml/min) 35 min 20 sec and 44 min. The two components were separated by prep. GLC. Epoxide **11** had n_D^{25} 1·4610.

(b) *With peroxybenzoic acid in* Et_2O. A 0·37 M soln of peroxybenzoic acid in ether (130 ml, 0·048 mole) was added dropwise to a stirred soln of **10** (5·0 g, 0·036 mole) in ether (30 ml) cooled at 0°. After standing for 20 hr at 0° the soln was treated in the usual way. Distillation of the residue gave unreacted **10** (2·5 g) b.p. 35°/1 mm and a mixture of the epoxides **7** and **11** (1·7 g), b.p. 63–65°/0·9 mm, n_D^{25} 1·4620. Ratio of **11** and **7** (GLC), 66:34.

Opening of **7** *with* HBr. A soln of **7** (2·0 g) in $CHCl_3$ (70 ml) was shaken for 15 min with 48% HBr aq (40 ml). The organic layer was washed with water, 10% $NaHCO_3$ aq, dried ($MgSO_4$) and evaporated under red. press. Distillation of the residue afforded a mixture of **6** and **13** (3·0 g), b.p. 108–110°/0·6 mm. (Found: C, 40·80; H, 5·38; Br, 33·95. $C_8H_{13}BrO_3$ requires: C, 40·51; H, 5·52; Br, 33·72%). GLC analysis before and after distillation showed the two peaks of **6** and **13** in the ratio 20:80; retention times (injection block temp 130°, column temp 120°, flow rate 50 ml/min) **6**, 25 min 10 sec; **13**, 28 min 20 sec.

A sample (1·10 g) of this mixture dissolved in 2-propanol (10 ml) was titrated with 1N NaOH aq at room temp in presence of phenolphthalein. The consumption of base amounted to 4·55 ml (theoretical 4·6 ml), first 3·7 ml being consumed much more quickly than the remainder. After the usual work-up pure **7** (0·56 g) was obtained.

Opening of **11** *with* HBr. Treatment of **11** (0·5 g) with HBr as described for **7** afforded bromohydrin **14**,

b.p. 118–120°/1·5 mm. (Found: C, 40·75; H, 5·48. $C_8H_{13}BrO_3$ requires: C, 40·51; H, 5·52%). GLC analysis before distillation showed that the product (retention time 34 min) was over 96% pure.

A sample (0·22 g) was dissolved in 2-propanol (3·0 ml) and titrated at room temp with 1N NaOH aq in the presence of phenolphthalein. The comsumption of base (0·90 ml, theoretical 0·93 ml) was much more rapid than in the case of **6**. Epoxide **11** was recovered from the solution.

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