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# THE STERIC COURSE OF THE CONVERSION OF SOME BROMOHYDRINS INTO DIBROMIDES WITH PHOSPHORUS TRIBROMIDE AND THIONYL BROMIDE

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**Abstract**—The conversion of (*S*)-(−)-2-bromo-1-butanol into 1,2-dibromobutane with $SOBr_2$, $SOBr_2$-pyridine, and $PBr_3$ was investigated. While the reactions with $SOBr_2$ produced dibromides with low specific rotations (positive in the absence and negative in the presence of pyridine), $PBr_3$ gave a levorotatory product with much higher optical activity. Equilibrated mixtures of *trans*-dibromides were obtained in the reactions of the 4-t-butylcyclohexene *trans*-diaxial bromohydrins with $SOBr_2$ and $SOBr_2$-pyridine, whereas with $PBr_3$ the dibromide was more than 90% diaxial. It can be deduced from the data that (−)-1,2-dibromobutane almost certainly has the (*S*) configuration. Asymmetric bromination of 1-butene in the presence of dihydrocinchonine afforded dextrorotatory 1,2-dibromobutane.

IT WAS reported[1] that certain cyclic and acyclic olefins afford optically active dibromides on bromination in the presence of *Cinchona* alkaloids. It was also deduced that the rotations of the dibromides depend mainly on the chirality at C-9 of the alkaloid molecule and, in the case of bromination in the presence of cinchonine or dihydrocinchonine, the dibromides very probably contain an excess of the (*R*) of (*R:R*) enantiomers. Whereas this deduction proved valid in the cases of the dibromides derived from cyclohexene and 4-methylcyclohexene, the configurations of these products being known,[2,3] the lack of definite data on absolute configurations of acyclic dibromides prevented an analogous verification of the hypothesis concerning such compounds.

This point was clarified by determining the absolute configuration of an acyclic 1,2-dibromide. We chose 1,2-dibromobutane (**3**) and used as the starting material for its preparation 2-bromobutyric acid (**1**), the configuration of which is known.[4,5] This acid was reduced to the bromohydrin **2**, which was successively converted into the desired dibromide **3**.

$$\underset{\mathbf{1}}{Et{-}CHBr{-}COOH} \rightarrow \underset{\mathbf{2}}{Et{-}CHBr{-}CH_2OH} \rightarrow \underset{\mathbf{3}}{Et{-}CHBr{-}CH_2Br}$$

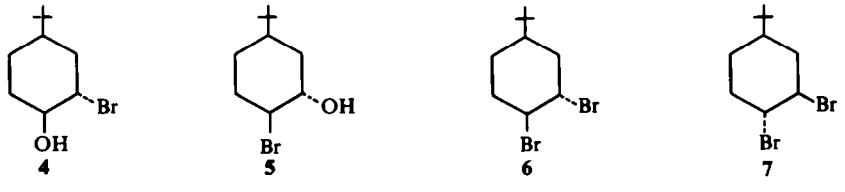
2-Bromobutyric acid was partially resolved by crystallization of its dehydroabiethylamine salt, to obtain the (*S*)-(−)-enantiomer. Among the various reagents employed for the reduction of (*S*)-**1** or its methyl ester to (*S*)-**2** (LAH,[6] aluminum hydride and diborane) the latter gave the best results. The levorotatory acid gave a levorotatory bromohydrin, the configuration and optical purity of which can be assumed to be the same as that of the starting acid. The steric course of the subsequent conversion of **2** into **3** was more difficult to foresee because of the well known tendency of vicinal bromine to participate in displacement reactions.[7] Fickett *et al.*[8]

based their configuration of 1,2-dichloropropane on a similar sequence, and found that the reaction of (*S*)-(+)-2-chloropropanol with thionyl chloride and pyridine gave (*S*)-(−)-1,2-dichloropropane, for which they assumed an optical purity of about 95%. However bromine is much more efficient than chlorine in anchimeric assistance.

When the conversion of (*S*)-**2** ($[\alpha]_D$ −7·34°) into the dibromide was carried out with thionyl bromide in the presence and in the absence of pyridine the 1,2-dibromobutane which was obtained had a specific rotation of −0·73° and +0·60° respectively. On the other hand $PBr_3$ gave a dibromide with $[\alpha]_D$ −7·38°, indicating that with this reagent racemization is much less important than with thionyl bromide.

Winstein explained the retention of configuration observed in the conversion of the diastereoisomeric 3-bromo-2-butanols[9] and of *trans*-2-bromocyclohexanol[10] into the corresponding dibromides with $PBr_3$, as occurring either with no inversion or with an inversion on each of the two asymmetric centres, through the attack of bromide on an intermediate bromonium ion. There are no data on the stereochemical behaviour of primary 2-bromo alcohols in displacements by bromine; however one would expect that they should show less tendency than secondary ones to give intermediate bromonium ions. Even if such an intermediate should form in the conversion of **2** into **3** by $PBr_3$, one would probably observe a strong racemization, possibly accompanied by retention of configuration. The behaviour of a bromonium ion formed from **2** should probably not be very different from that of the conjugate acid of 1,2-epoxybutane, which affords, on treatment with hydrobromic acid, mixtures of variable composition (depending upon reaction conditions) containing in any case an excess of 1-bromo-2-butanol.[11] Therefore the bromide ion should attack preferentially the primary C atom of the bromonium ion formed from **2** to give **3** with an excess of retention.

To obtain more information about the extent of anchimeric assistance by neighbouring bromine in displacement reactions on bromohydrins, we also studied the action of $PBr_3$ and thionyl bromide on rigid *trans*-2-bromocyclohexanols, where neighbouring group effects should be particularly prominent. For this purpose a mixture of the diaxial bromohydrins **4** and **5**[12] was prepared by treating the mixed 4-t-butyl-1,2-epoxycyclohexanes,[13] obtained by epoxydation of 4-t-butylcyclohexene, with hydrobromic acid. This mixture was used without separation into its components, because both **4** and **5** should behave similarly and give the same *trans* products. Whereas reaction of **4** and **5** (mixture) with thionyl bromide alone or in the presence of




**4** **5** **6** **7**

pyridine at 70° afforded the *trans* dibromides **6** and **7** in the ratio of about 7:3, the same treatment of the bromohydrins with $PBr_3$ gave the dibromide **6** and only a small amount (less than 10% relative to **6***) of the diequatorial isomers.† Heating the pure

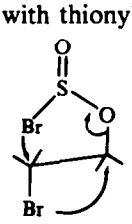
* In this reaction monobromoderivatives are also obtained.[14]

† Retention of configuration was also observed by Barton *et al.* [D. H. R. Barton, E. Miller and H. T. Young, *J. Chem. Soc.* 2598 (1951)] in the reaction of 5α-bromocholestan-3β, 6β-diol-3-benzoate with $PBr_3$ at room temperature.

diaxial dibromide **6** with thionyl bromide in the presence of a small amount of water, in order to better simulate the conditions employed for the transformation of the bromohydrins into the dibromides, caused isomerization of the product to **7** to the extent of about 15%; in the analogous treatment with thionyl bromide-pyridine-water the dibromide **6** was recovered almost unchanged. This indicates that hydrogen bromide acts as an isomerizing agent only in the absence of pyridine. The ratio of the dibromides formed from the bromohydrins **4** and **5** with thionyl bromide is almost the same as that present in the equilibrium mixture obtainable by thermal isomerization of **6** to **7** (65:35).[3] This fact seems to suggest that the transition state of the transformation of **4** and **5** into **6** and **7** by thionyl bromide could be the same as that proposed for the isomerization of diaxial into diequatorial dibromides, represented as a bromide-bromonium ion pair.[15] Since the relative quantities of **6** and **7** are the same both in the absence and in the presence of pyridine, it may be safely assumed that the role of hydrogen bromide, which is formed in the reaction, is also in the former case of secondary importance in determining the ratio of the two dibromides. The high retention observed in the reaction of **4** and **5** with phosphorus tribromide seems to exclude a mechanism analogous to that discussed above. Moreover, preliminary results[14] have shown that optically active *trans*-2-bromocyclohexanol[16] affords optically active 1,2-dibromocyclohexane on reaction with $PBr_3$.

It therefore appears that phosphorus tribromide should be less prone than thionyl bromide to give reactions involving bromonium intermediates, and it seems extremely likely that the absolute configuration of the acyclic dibromide **3** obtained with $PBr_3$ is the same as that of the starting acid, even if some racemization cannot be ruled out. Since the reported maximum rotation for (*R*)-**1** is $[\alpha]_D$ +39·5°,[17] it may be deduced that the specific rotation of (*S*)-**3** should be not less than −23·5°.

The above results show that the conversion of **2** into **3** with thionyl bromide and thionyl bromide-pyridine causes, respectively, inversion and retention accompanied by strong racemization. No racemization was observed when optically active 1,2-dibromobutane was heated with thionyl bromide and with $PBr_3$-methanol under the conditions employed for the conversion of **2** into **3**. The strong racemization observed in the reaction of **2** with thionyl bromide-pyridine could be explained by the intervention of a mechanism involving a bromonium ion or a bromide-bromonium ion pair as intermediates, but other mechanisms cannot be excluded, particularly in the absence of pyridine. For instance, a cyclic transition state of the type **8** could explain the slight excess of inversion observed in the latter case; such an intermediate ($S_Ni'$ mechanism) is analogous to that proposed to explain the formation of rearranged chloro derivatives in the treatment of certain alcohols with thionyl chloride.[18,19]




**8**

Lucas and Gould[20] observed that *threo*-3-chloro-2-butanol afforded *d,l*-2,3-dichlorobutane showing a little but measurable optical activity. They stated that this was due

to contamination of the dichloro derivative by traces of bis-(2-chloro-1-butyl) sulphite. In the case of the conversion of **2** into **3**, the optical activity was surely due to formation of an excess of inverted product, since no sulphite was present in 1,2-dibromobutane, as shown by qualitative and elemental analysis; moreover, the sulphite of **2** has a rotation of the same sign as that of the bromohydrin.

Asymmetric bromination of 1-butene in the presence of dihydrocinchonine afforded 1,2-dibromobutane with $[\alpha]_D$ +0·32°. On the basis of the data reported above it may be deduced that the maximum optical yield of the asymmetric reaction is about 1·4%, and that the product very probably contains an excess of the (*R*) enantiomer. This is in accordance with the previously expressed hypothesis about the steric course of asymmetric brominations, and with rough calculations made after the method of Brewster.[5,21]

## EXPERIMENTAL

M.ps (Kofler block) are uncorrected. Optical rotations (Perkin–Elmer photoelectric polarimeter, mod. 141) are accurate within ±0·01°. IR spectra (Perkin–Elmer mod. 257 grating spectrophotometer on liquid films, thickness 0·1 mm. GLC (Fractovap G. V. C. Erba), column NPGS, carrier gas $N_2$, flame-ionization detector; retention times of **6** and **7** were respectively 3 min 45 sec and 11 min (injection block temp 160°, column temp 135°, flow rate 46 ml/min).

(S)-(−)-2-*Bromobutyric acid*

Racemic 2-bromobutyric acid[22] (50 g, 0·3 mole) was dissolved in 20 ml $Me_2CO$ and added to a soln of dehydroabiethylamine[23] (84·5 g, 0·3 mole) in 150 ml of the same solvent. After standing overnight at room temp, the salt (122 g) was collected and washed with $Me_2CO$; it had m.p. 153–156°, $[\alpha]_D^{25}$ +19·28° (*c* 1·6, $CHCl_3$). 50 g of this material was dissolved in 400 ml EtOH by gently warming and allowed to cool at room temp. After 12 hr 18 g of salt separated out, m.p. 159–161°, $[\alpha]_D^{25}$ +16·79° (*c* 1·5, $CHCl_3$). A similar crystallization of another 50 g of the same salt afforded 18 g of product, m.p. 156–159°, $[\alpha]_D$ +16·93° (*c* 1·6, $CHCl_3$). The two fractions were combined and again crystallized from EtOH (250 ml) to obtain 15 g of salt m.p. 158–161°, $[\alpha]_D^{25}$ +16·31° (*c* 1·5, $CHCl_3$). After treatment of all of this salt with 10% NaOH aq, the base was eliminated by extraction with $Et_2O$, the aqueous layer was acidified with 10% HCl aq, extracted with $Et_2O$, and the dried ($MgSO_4$) extract was evaporated. Distillation of the residue afforded 3·88 g of the (*S*)-(−)-acid, b.p. 105–107°/15 mm, $[\alpha]_D^{25}$ −14·70° (*c* 5·0, $Et_2O$). Lit.[17] b.p. 66–69°/0·04 mm, $[\alpha]_D$ +39·5° for *R*-(+)-1.

(S)-(−)-2-*Bromo*-1-*butanol*

$NaBH_4$ (1·5 g, 39·6 mmole) was suspended in anhyd THF (35 ml) and 2-bromobutyric acid (5·0 g, 30 mmole), $[\alpha]_D^{25}$ −12·38° (*c* 3·87, $Et_2O$), was slowly added with stirring. To the stirred mixture $BF_3$·$Et_2O$ (5·0 g, 35 mmole), dissolved in 30 ml of anhyd THF, was added dropwise during 1 hr. After standing overnight the reaction mixture was hydrolyzed by adding 30 ml $H_2O$ and the organic layer was washed with sat $NaHCO_3$ aq, dried ($MgSO_4$) and evaporated. The residue (4·25 g) was distilled to give 3·0 g of (*S*)-(−)-2-bromo-1-butanol b.p. 69–71°/15 mm; $n_D^{20}$ 1·4790; $d_{20}^{20}$ 1·4617; $[\alpha]_D^{25}$ −7·34° (neat). Lit.[24] b.p. 65–66°/13 mm; $n_D^{20}$ 1·4802 (racemic product).

*Reactions of* (S)-(−)-2-*bromo*-1-*butanol with* $SOBr_2$ and with $PBr_3$

(a) *With* $SOBr_2$. A mixture of (*S*)-(−)-2-bromo-1-butanol (2·0 g, 13 mmole), $[\alpha]_D^{25}$ −7·34° (neat) and $SOBr_2$ (13·4 g, 64·4 mmole) was heated at 70° for 5 hr, then poured onto ice and extracted with $Et_2O$. The extract was washed with sat $NaHCO_3$ aq, dried ($MgSO_4$) and evaporated. The residue (2·36 g) afforded on distillation 1·53 g of 1,2-dibromobutane, b.p. 66–68°/15 mm; $n_D^{25}$ 1·5128, $[\alpha]_D^{25}$ +0·60° (neat). (Found: C, 22·52; H, 3·55; Br, 73·53. Calc. for $C_4H_8Br_2$: C, 22·24; H, 3·75; Br, 74·02%). Lit.[25] b.p. 80·5–80·7°/50 mm; $n_D^{25}$ 1·5125; $d_4^{25}$ 1·7870.

(b) *With* $SOBr_2$ *in the presence of pyridine*. A mixture of (*S*)-(−)-2-bromo-1-butanol (2·0 g, 13 mmole), $[\alpha]_D^{25}$ −7·34° (neat), $SOBr_2$ (7·5 g, 36 mmole) and anhyd pyridine (0·8 g, 10 mmole) was heated at 70° for

5 hr. After treatment with ice, extraction with $Et_2O$, washing of the extract with 5% $NaHCO_3$ aq and evaporation, the 1,2-dibromobutane, purified as described above, had $[\alpha]_D^{25}$ −0·73° (neat); $n_D^{25}$ 1·5128.

(c) *With* $PBr_3$. (*S*)-(−)-2-bromo-1-butanol (2·0 g, 13 mmole), $[\alpha]_D^{25}$ −7·34° (neat) was mixed at −10° with $PB_3$ (2·2 g, 8·1 mmole). The mixture was left at room temp for 9 days in a sealed tube. The 1,2-dibromobutane (0·8 g) was isolated and purified in the usual way: it had $[\alpha]_D^{25}$ −7·38° (neat); $n_D^{24}$ 1·5130.

This reaction was repeated by using a bromohydrin with $[\alpha]_D^{25}$ −3·42° (3·53 g) and $PBr_3$ (4·12 g). In the distillation of the crude dibromide, condenser and collecting flask were cooled at −20°. The pure 1,2-dibromobutane (1·94 g) had $[\alpha]_D^{25}$ −3·46°.

*Bis (2-bromo-1-butyl) sulphite*

The sulphite of **2** ($[\alpha]_D^{25}$ −1·23°), was prepared by reacting the bromohydrin (2·4 g, 15·7 mmole) with $SOCl_2$ (1·13 g, 9·5 mmole) in the presence of pyridine (1·4 g, 17·7 mmole) following the method described by Price and Berti.[26] The crude product (1·9 g) had $\alpha_D^{25}$ −1·47°; $n_D^{25}$ 1·5002. The IR spectrum of the product shows a strong S=O band at 8·30 μ; no OH stretching band was present. (Found: C, 27·35; H, 4·47; Br, 45·69; S, 8·82. $C_8H_{16}Br_2O_3S$ requires: C, 27·28; H, 4·58; Br, 45·39; S, 9·10%).

*Treatment of optically active 1,2-dibromobutane with the brominating agents*

(a) *With* $SOBr_2$. A mixture of 2·5 g (11·6 mmole) of **2** ($[\alpha]_D^{25}$ +0·32° (neat)) and 15·0 g (72·1 mmole) $SOBr_2$ was heated for 5 hr at 70°. The recovered dibromide had $[\alpha]_D^{25}$ +0·32° (neat).

(b) *With* $PBr_3$-MeOH. The same dibromide (2·16 g, 10 mmole) was mixed at −10° with anhyd MeOH (0·32 g, 10 mmole) and $PBr_3$ (1·7 g, 6·3 mmole). After 15 days (room temp) the 1,2-dibromobutane was recovered: $[\alpha]_D^{25}$ +0·32° (neat).

cis-4-*t*-*Butyl*-trans-2-*bromocyclohexanol* (**4**) *and* trans-5-*t*-*butyl*-trans-2-*bromocyclohexanol* (**5**)

A soln of *cis*- and *trans*-4-t-butyl-1,2-epoxycyclohexane[13] (2·0 g, 13 mmole) in $CHCl_3$ (100 ml) was shaken for 10 min with 48% HBr aq (50 ml). The organic layer was washed with $H_2O$, dried ($MgSO_4$) and evaporated. Distillation of the residue afforded 2·8 g of a mixture of **4** and **5**, b.p. 96–98°/1 mm, which solidified on standing. The solid was crystallized from pet ether to give prisms, m.p. 65–70°. (Lit.[12] **4** m.p. 66–67°, **5** m.p. 78°). A sample (63 mg), dissolved in 10 ml of 2-propanol, was titrated with aqueous 0·1N NaOH at room temp, with phenolphthalein as indicator. The consumption of base amounted to 2·65 ml (theoretical 2·68 ml). The IR spectrum of the epoxide recovered from this treatment showed bands at 1255, 875 (*cis*-epoxide),[12] 1235 and 850 (*trans*-epoxide)[12] $cm^{-1}$. The relative intensities of these bands were almost identical to those present in the IR spectrum of the original mixture from which **4** and **5** were prepared.

*Treatment of* **4** *and* **5** *with the brominating agents*

(a) *With* $PBr_3$. A mixture of **4** and **5** (1·0 g, 4·2 mmole) was treated at −10° with $PBr_3$ (0·85 g, 3·1 mmole). After standing in a sealed tube for 3 days at room temp the reaction mixture was decomposed with ice. The crude product, isolated in the usual way, weighed 1·1 g. GLC analysis revealed, as the main components, monobromo derivatives[14] and the diaxial dibromide **6**;[3] small amounts (5–10%) of the dibromide **7**[3] and perhaps the *cis*-dibromides, were also present. The ratio of **6** to **7** was about 90:10.

(b) *With* $SOBr_2$. The mixture of **4** and **5** (2·85 g, 12·1 mmole) and $SOBr_2$ (13·4 g, 64·4 mmole) was heated at 70° for 5 hr. After standing overnight at room temp the mixture was poured onto ice. The dibromides, isolated and purified in the usual way, amounted to 2·5 g after distillation (b.p. 90–94°/0·6 mm). GLC analysis showed that the ratio of **6** to **7** was 70:30.

(c) *With* $SOBr_2$ *in the presence of pyridine*. The mixture of **4** and **5** (2·35 g, 10 mmole), $SOBr_2$ (5·4 g, 26·0 mmole) and pyridine (0·8 g, 10 mmole) was worked up as described under (b). The relative amounts of the dibromides **6** and **7** so obtained were 68 and 32%.

*Treatment of* **6** *with the brominating agents*

(a) A mixture of **6** (1·5 g, 5 mmole), $SOBr_2$ (5·4 g, 26·0 mmole) and $H_2O$ (90 mg, 5 mmole) was heated at 70° for 5 hr. After the usual treatment a mixture of **6** and **7** in the ratio 85·5:14·5 was obtained.

(b) After a similar treatment of **6** (1·5 g, 5 mmole), $SOBr_2$ (2·7 g, 13 mmole), $H_2O$ (90 mg, 5 mmole) and pyridine (0·32 g, 4 mmole), the dibromide obtained was contaminated by only 3% of **7**.

*Asymmetric bromination of* 1-*butene*

A soln of Br (16·0 g, 100 mmole) in $CHCl_3$ (10 ml) was added slowly to a stirred soln of 1-butene (5·0 g, 89·1 mmole) and dihydrocinchonine (5·0 g, 16·9 mmole), cooled at 0°. The mixture was then washed with 10% $H_2SO_4$ aq, $NaHCO_3$ aq and $H_2O$. After drying ($MgSO_4$) and evaporation of the solvent, the residue was distilled to give 1,2-dibromobutane (13·4 g), b.p. 65–68°/15 mm, $n_D^{23}$ 1·5132, $[\alpha]_D^{25}$ +0·32° (neat).

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