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Brucine as a Reagent for Partially Resolving Bromoalkanes; the Configurations of Some Diastereomeric Dibromoalkanes

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The success in partially resolving *dl*-*threo*-3-chloro-2-butanol by means of brucine¹ suggested the use of this base for establishing the configurations of diastereomeric halogen compounds of which resolvable (*threo* or *dl*) and non-resolvable (*erythro* or *meso*) forms are possible, as for example 2,3-dibromobutane, 3,4-dibromohexane and 4,5-dibromooctane. It has not been possible to prepare optically active 2,3-dibromobutane by the action of hydrobromic acid on optically active 2,3-diacetoxybutane or on the corresponding active bromoacetate or bromohydrin.² Likewise, optically active 4,5-diacetoxyoctane yields inactive 4,5-dibromooctane with hydrobromic acid.³ The failure of these syntheses to yield optically active dibromides necessitates the use of some other method. It is not necessary to resolve completely, but only to show that under identical conditions one isomer becomes optically active and the other does not. We have found that this can be realized by the use of brucine.

The configurations of the inactive forms of the dibromides, which have been assumed previously on the basis of *trans* addition of bromine to the olefins,⁴ and of rates of reaction of the dibromides with potassium iodide^{4,5} are now confirmed. The results are shown in the table. Unfortunately pure compounds were not available in all cases, but the results are none the less certain. It is surprising that the optical activity of the *dl*-4,5-dibromooctane was so low. Rotations were observed with sodium light in 1-dm. tubes.

The partial resolution is due to a difference in the rates with which antipodal dibromoalkanes react with brucine. The products are the corresponding quaternary salts. In the case of propylene bromide and brucine the resulting solid possesses properties decidedly different from those of brucine, or of brucine hydrobromide, and was

shown to consist of equal moles of the two reactants. Because of the addition reaction the recovery of dibromide is low.

Adsorption is a negligible factor, as shown by the figure, where the rotation is plotted against the time of contact between brucine and propylene bromide. If optical activity were the result of asymmetric adsorption, it should develop within a few minutes.

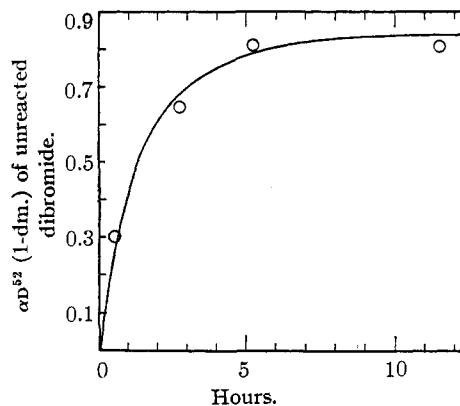


Fig. 1.—Plot of rotation of propylene bromide against time of contact with brucine.

Stereomutation of one dibromoalkane to the diastereomer was negligible, in contrast to the behavior of *threo*-3-chloro-2-butanol.¹ The slight discrepancy in the dielectric constants of the final products is believed to be due to traces of moisture since all values were higher after brucine treatment. It has been pointed out previously that diastereomeric dibromoalkanes are best distinguished by means of dielectric constants.⁶

Although the method is applicable also to monobromides, as shown in the case of 2-bromobutane, it is of little value here because in general such compounds can be prepared from optically active alcohols in a much higher state of optical purity.

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(1) Lucas and Gould, *THIS JOURNAL*, **63**, 2541 (1941).
 (2) Winstein and Lucas, *ibid.*, **61**, 2845 (1939).
 (3) Private communication from Wm. G. Young.
 (4) (a) Dillon, Young and Lucas, *THIS JOURNAL*, **52**, 1953 (1930);
 (b) Wilson and Lucas, *ibid.*, **58**, 2396 (1936); (c) Young, Jasaitis and Levanas, *ibid.*, **59**, 403 (1937).
 (5) Young, Pressman and Coryell, *ibid.*, **61**, 1640 (1939); Wm. G. Young, "Cis-Trans Isomers," Eighth National Organic Symposium, St. Louis, Dec. 28-30, 1939.

(6) (a) Winstein and Lucas, *THIS JOURNAL*, **61**, 1576 (1939); (b) Winstein and Wood, *ibid.*, **62**, 548 (1940); (c) Lucas, Schlatter and Jones, *ibid.*, **63**, 22 (1941).

TABLE I
 EFFECT OF BRUCINE ON SYMMETRICAL DIBROMOALKANES

	Isomer	Purity, %	Before treatment			n_D^{25}	ϵ^{25}	After treatment		
			$^{\circ}\text{C.}$	B. p. mm.	mm.			n_D^{25}	ϵ^{25}	α_D^{25}
1	2,3-Dibromobutane	<i>meso</i>	97	40-45	4-5	1.5091	6.230	1.5091	6.235	-0.07
2	2,3-Dibromobutane	<i>dl</i>	100	77.4-78.0	50	1.5125	5.753	1.5125	5.760	-2.04
3	3,4-Dibromohexane	<i>meso</i>	100	69.7	9	1.5049	4.674	1.5048	4.685	0.00
4	3,4-Dibromohexane	<i>meso</i>	98.5	69.7-70.0	9	1.5048	4.705	1.5048	4.711	+0.07
5	4,5-Dibromooctane	<i>meso</i>	100?			1.4966	4.933	1.4965	4.936	0.00
6	4,5-Dibromooctane	<i>dl</i>	100?			1.4948	5.560	1.4948	5.566	+0.14

Previous dielectric constants^{8b}: (1) 6.245; (2) 5.758; (3) 4.67. The value of 5.753 is preferred for (2), since the m. p. of the starting glycol here was 34.5°, against 34.1° previously.²

Experimental

Propylene Bromide and Brucine.—Eastman Kodak Co. "White-label" propylene bromide was washed with cold 80% (wt.) sulfuric acid until the acid phase did not darken, then washed free of sulfate ion, dried with calcium chloride, and distilled through a 60-cm. column of helices at a reflux ratio of ten; b. p., 49.0-49.5° (30 mm.); n_D^{25} , 1.5188.⁷ To 64.4 g. (0.32 mole) of this bromide in a 125-ml. conical flask was added 42 g. (0.11 mole) of Merck brucine in small portions with vigorous stirring. The resulting thick paste became more viscous and slightly granular after five minutes of stirring. Fifteen minutes later a 12-g. sample of the pasty mixture was subjected to suction filtration and the filtrate was distilled at 1 to 2 mm. during four minutes at room temperature. This yielded a solid residue of about 0.4 g. and a distillate of 0.6 ml. The latter was made up to 1.8 ml. with inactive dibromide. From the observed rotation, α_D^{25} +0.10° (1 dm.), the distillate is calculated to have a rotation of +0.30°. The distillation was finished thirty-five minutes after the brucine and propylene bromide were put together.

Distillation of another sample was finished at one hundred and sixty-five minutes, of a third sample three hundred and ten minutes, and of a fourth sample six hundred and ninety minutes after the start of the experiment. The rotations in each case were +0.65°, +0.81°, and +0.81°, respectively. These data are shown graphically in the figure. The gradual increase in rotation to a maximum indicates that the antipodes react slowly with brucine, one more rapidly than the other.

The rest of the mixture in the flask set to a hard mass after eighteen hours, after which it was placed in an oven at 40° for seventy-two hours to allow the reaction to finish. The resulting hard, translucent gel was ground in a mortar with 50 ml. of propylene bromide to wash out brucine, and the solid dried by pressing it, after filtration, between paper towels under a sodium press. After washing the solid free of propylene bromide with two 50-ml. portions of isopropyl ether, followed by repeated washings with 28-38° ligroin, and drying, a portion of it was recrystallized three times from absolute methanol. The product was colorless needles, soluble about one part in five of boiling water, insoluble in cold chloroform and in boiling isopropyl ether. The aqueous solution gave an immediate precipitate of silver bromide with aqueous silver nitrate.

(7) Later it was found that about 5% of the material was ethylene bromide. Probably this accounts for the high refractive index (+1.0016) compound to the value of 1.51745 at 25.4°, reported by Zawadzki, *Z. physik. Chem.*, **35**, 1471 (1900). dn/dt is approximately -0.0005.

Anal. Calcd. for $\text{C}_{23}\text{H}_{26}\text{N}_2\text{O}_4 \cdot \text{C}_3\text{H}_6\text{Br}_2$: N, 4.69; MeO, 10.4; Br, 26.9. Found: N, 4.61; MeO, 10.56; Br, 27.8.

General Method of Resolution with Brucine.—Four or five ml. of a given dibromide was mixed with 1.3 to 4.0 g. of Merck brucine in a test-tube. After standing at room temperature for ten to fourteen hours, the unreacted bromide was filtered off and distilled away from the dissolved brucine at 0.5 to 2 mm. pressure, with as low a boiling temperature as possible, generally less than 30°. The distillate was cooled by a mixture of "dry-ice" and isopropyl ether. All rotations were observed with sodium light on the pure liquids at 25° in a 1-dm. tube. The experimental conditions were not alike in all cases but for any pair of diastereoisomers the conditions were essentially identical.

***dl*-2-Bromobutane.**—4.0 ml. of purified bromide was mixed with 4.0 g. of brucine and allowed to stand for twelve hours. The rotation was -0.02°.

2,3-Dibromobutanes.—These were prepared from the 2,3-diacetoxybutanes and purified by the method described previously.^{2,4b} The mixture of bromide (4.5 ml.) with brucine (4 g.) was allowed to stand for ten hours. About 2.5 ml. of dibromide was recovered. The properties are given in the table. The rotation of -0.07° observed for the *meso* form was due to the presence of 3% of the *dl*-isomer, as shown by the dielectric constant.⁸

When 8.0 ml. of *dl*-2,3-dibromobutane dissolved in 40 ml. of ligroin (28-38°) was mixed with 13.5 g. of Merck brucine and shaken for ten minutes, the dibromide distillate obtained by rapid filtration and distillation was found to be perfectly inactive. This result shows that asymmetric adsorption is not a factor in causing optical activity because the effect of adsorption should be evident from the start, before the chemical reaction has progressed significantly.

3,4-Dibromohexanes.—Pure *meso*-3,4-dibromohexane and *meso*-dibromohexane containing 1.5% of the *dl* isomer were prepared, respectively, from pure *dl*-3,4-hexanediol and from impure *dl*-3,4-hexanediol containing some of the *meso* isomer^{4,9} by first converting the glycols to the diacetates and allowing these to react with 65% aqueous hydrogen bromide.¹⁰ The pure *meso* dibromide distilled entirely at 69.7° (9 mm.) through a Weston column and

(8) The cell for measuring the dielectric constant is the one used previously.¹ The electrical circuit is the one described by Wood and Dickinson, *THIS JOURNAL*, **61**, 3259 (1939).

(9) These two glycols, and the pure *dl* and *meso*-4,5-octanediols, were generously supplied by Professor Wm. G. Young of the University of California at Los Angeles.

(10) Essentially the procedure of Young, Weiss and Pressman (private communication).

the dibromide mixture at 69.7–70° (9–10 mm.). The value of the dielectric constant is 4.674 for the former and 4.705 for the latter. Winstein and Wood^{6b} approximated the former value remarkably well as 4.67, by extrapolation. Using 4.705 and the values of the pure *meso* and *dl* isomers, viz., 4.674 and 6.732, the composition of the dibromide mixture is 98.5% *meso*, 1.5% *dl*.

A mixture of 4 ml. of each dibromide and 3 g. of brucine was allowed to stand for twelve hours before removal of the dibromide. From the data in the table it is evident that optical activity developed only in the sample which contained some of the *dl* isomer. It is surprising that such a small amount gave such a large value, in comparison to the slight rotation developed with pure *dl*-4,5-dibromooctane.

4,5-Dibromooctanes.—The *meso* and *dl* isomers were prepared from *dl* and *meso*-4,5-octanediol,^{9,11} respectively, through the acetates, by a procedure similar to the one described previously^{4a} but using 7 moles of hydrogen bromide in the form of 65% aqueous solution to one of diacetate, and allowing the mixtures to stand at room temperature in sealed ampoules, the former for one hundred and twenty hours, the latter for sixty hours. Distillation of the oil phase at 1.5 mm. through the Weston column, after having been washed with water and dried with calcium chloride, gave a 65% recovery of each dibromooctane, the *meso* distilling at 65.5 to 68°, the *dl* at 60.2 to 68°. The impurities responsible for the range of boiling point probably were bromohydrins or bromoacetates, for the refractive indices of the middle cuts were 1.4911 and 1.4808, respectively, thus lower than the value for either isomer.

Purification of the dibromooctanes by conversion to the 4-octenes and conversion back to the dibromides was not considered, because of the possibility that stereomutation might take place.¹² Purification by distillation was not practical since the bromides probably form azeotropic mixtures with the bromohydrins. Cold 80% sulfuric acid removed small amounts of impurities, as judged by slight increase in the refractive indices, but the removal was not complete. The use of concentrated sulfuric acid was decided against, in view of the recently described isomerizing action of this acid on 2,2,4-trimethylpentane.¹³

(11) Young, Jasaitis and Levanas, *THIS JOURNAL*, **58**, 2274 (1936).

(12) Lucas, Schlatter and Jones¹⁰ have shown that stereomutation takes place to the extent of 2 or 3% in the interconversion of the 2-pentenes and the 2,3-dibromopentanes.

(13) Whitmore and Johnson, *THIS JOURNAL*, **63**, 1481 (1941).

Purification was accomplished by crystallization from methanol at "dry-ice" temperature, followed by filtration at the same temperature. The *meso* dibromide was crystallized twice from a fourfold volume of methanol. The physical constants did not change between the first and second crystallization. The *dl* isomer, being more soluble, was crystallized twice from a twofold volume of methanol. It separated as a viscous oil, which became crystalline after addition of one drop of water (to 15 ml. of solution) and scratching at "dry-ice" temperature. When crystallized a third time from two volumes of anhydrous methanol it separated in crystalline form after seeding and scratching. Although the properties were not checked between crystallizations, the final product is believed to be essentially pure, as judged by behavior on crystallization.

After removal of methanol and water by pumping off at 5 mm. for one-half hour, the dibromooctanes were distilled at room temperature and 1.5 mm. The *meso* isomer crystallized in the "dry-ice" trap, while the *dl* isomer turned to a glass which crystallized slowly: recovery, *meso* dibromide, 67%; *dl* dibromide, ca. 60%. The physical constants are shown in the table. The dielectric constants have not been reported previously.

A mixture of 4 ml. of dibromide and 1.5 g. of brucine was allowed to stand for thirteen hours. The properties of the recovered dibromides, 2.7 ml., each, are shown in the table.

Summary

A resolvable inactive bromoalkane becomes optically active when allowed to stand for several hours with brucine, as was shown in the case of 2-bromobutane and several dibromoalkanes. The partial resolution is due to a difference in the rates with which the antipodes form quaternary brucinium salts. The effect of adsorption is negligible.

There was no conversion of a *dl* to a *meso* form, or *vice versa* in the case of the 2,3-dibromobutanes, 3,4-dibromohexanes, and 4,5-dibromooctanes. It is possible to differentiate the *dl* from the *meso* isomer, by treatment with brucine, for the former becomes optically active while the latter does not. The configurations previously assumed for these symmetrical dibromoalkanes are confirmed.

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