

CCLXXXIX.—*A New Method of Diagnosing Potential Optical Activity. Part II. The Optical Activity of Chlorobromoacetic Acid.*

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CHLOROBROMOACETIC acid was first isolated in 1923 by Vanderstichele (J., **123**, 1225), and no attempts to resolve it into optically active components have been recorded. Vanderstichele's method consists in adding water to chlorobromoacetyl chloride, prepared by the elegant method of Crompton and Triffitt (*ibid.*, 1921, **119**, 1874) from $\alpha\beta$ -dichlorovinyl ethyl ether. Since the acid is stated to undergo some decomposition during the subsequent distillation, it appeared desirable to devise an alternative process which would lead directly to the pure anhydrous acid, starting preferably from chlorobromomalonic acid. Although the diethyl ester of the latter acid has been described (*Ber.*, 1891, **24**, 2995), its saponification would be impracticable owing to the reactivity of the associated halogen elements. By the successive action of bromine and sulphuryl chloride upon a solution of malonic acid in dry ether, it was found possible, however, to prepare chlorobromomalonic acid in practically quantitative yield. When maintained at 130°, chlorobromomalonic acid is converted quantitatively into chlorobromoacetic acid, melting at 38°, this being 15° higher than the value recorded by Vanderstichele (*loc. cit.*). A new and expeditious method of proceeding from malonic acid to chlorobromomalonic and chlorobromoacetic acids is thus rendered available, and we propose in due course to undertake a detailed study of these interesting substances and certain of their derivatives.

All attempts to resolve chlorobromoacetic acid into optically active components by the use of brucine, in accordance with the customary methods, were unsuccessful. Similarly, upon fractionally crystallising the *l*-hydroxyhydrindamine salt from ethyl acetate, a homogeneous separation, consisting of transparent plates, was obtained.

Slow deposition of the salt from a dilute solution in cold chloroform containing a small proportion of dry methyl alcohol also yielded a homogeneous separation of transparent plates, identical with the salt deposited from ethyl acetate.

Rapid crystallisation during the cooling of a hot supersaturated solution in chloroform led, however, to a remarkably different result, an initial separation of soft, silky needles, equivalent in weight to the bulk of the original material, being succeeded by the slow formation of a relatively small amount of the transparent plates

mentioned above. The two kinds of crystals were isomeric and interconvertible; they showed little difference in melting point, and possessed practically the same optical rotatory power when dissolved in dry methyl alcohol or acetone.

A solution of the plates in chloroform containing dry methyl alcohol gave $[M]_D -50^\circ$, whilst the corresponding value in glacial acetic acid was -62° ; no change in the optical rotation was noticed in either instance upon keeping or warming the solutions. The needles, however, behaved in a widely different manner when dissolved in these two solvents. In the first solvent no appreciable optical rotation was exhibited by a freshly-prepared solution, but on heating and keeping the solution, the rotation rose gradually to the value, $[M]_D -50^\circ$, given by the plates. In glacial acetic acid, the solution gave an initial value of $[M]_D -32^\circ$, which rose upon heating to -58° , this value also being identical with the rotatory power of the plates in the same solvent.

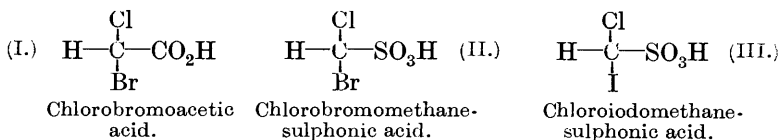
These relationships may be explained on the assumption that the plates and needles consist, respectively, of *l*-hydroxyhydrindamine *dl*-chlorobromoacetate (*lBdlA*) and *l*-hydroxyhydrindamine *d*-chlorobromoacetate (*lBdA*). The identical values of $[M]_D$ given by the two salts when dissolved in methyl alcohol or acetone must then be regarded as characteristic of the partly racemic salt, *lBdlA*; this conclusion is supported by the approximate coincidence of the values in question with those determined for *l*-hydroxyhydrindamine dichloroacetate under similar conditions. It appears, therefore, that the salt *lBdA* undergoes a rapid partial racemisation to *lBdlA* when dissolved in acetone or methyl alcohol. In the case of chlorobromomethanesulphonic acid (J., 1925, **127**, 1572), a similar change occurs slowly in methyl alcohol, whilst in acetone a disturbed equilibrium is attained between the diastereoisomeric salts *lBdA* (19%) and *lBlA* (81%).

The racemising action of methyl alcohol is suppressed to some extent by dilution with chloroform, so that when dissolved at the ordinary temperature in chloroform containing a little dry methyl alcohol, the salt *lBdA* appears to be optically stable. Owing to the opposed optical rotatory effects of the basic and acidic components, the salt has no measurable optical activity in this solvent. Upon heating, the racemising action of the methyl alcohol contained in the solution is enhanced, with the result that the optical rotation characteristic of the salt *lBdlA* is slowly attained. A closely similar effect is produced in glacial acetic acid.

It is only in chloroform containing not more than a trace of methyl alcohol that the existence of a disturbed equilibrium of the type $lBdA \rightleftharpoons lBlA$ can be presumed from the observations recorded below.

In a hot concentrated solution of this kind, the tabular salt *lBdlA* passes into such an equilibrium mixture, in which the salt *lBdA* obviously predominates, since the first crystalline deposit, formed to the extent of 75% or more on cooling, consists of needles of this salt. The diastereoisomeric salt *lBIA* cannot be isolated, the only other substance deposited by the mother-liquor being the partly racemic salt *lBdlA*. The total optical rotatory effect of the material receives a substantial increment in the positive sense as a result of the conversion of the salt *lBdlA* to *lBdA*. The reverse conversion of *lBdA* to *lBdlA* occurs at once on dissolving the first of these salts in methyl alcohol; the resulting partly racemic salt then remains practically unaffected by the subsequent addition of chloroform and crystallisation at the ordinary temperature.

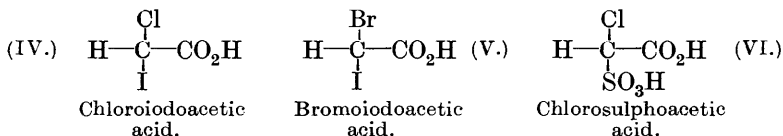
Comparing the above observations with those recently recorded for chlorobromomethanesulphonic acid (*loc. cit.*), it may be concluded that the mobility of the atoms H, Cl, Br, and the group CO_2H , associated with the asymmetric carbon atom of configuration (I), is markedly greater than that of the same three atoms and the group SO_3H attached to the sole carbon atom of configuration (II) :



Moreover, it has already been demonstrated (*loc. cit.*) that configuration (II) is exceedingly more mobile in this respect than configuration (III). In the three systems indicated, the mobility is thus lessened by the substitution of (a) SO_3H for CO_2H , and (b) I for Br. The anticipation (*loc. cit.*, p. 1583) that certain asymmetric compounds containing two carbon atoms in the molecule would prove capable of giving rise in suitable solvents to a dynamic equilibrium between diastereoisomeric salts is thus justified, and it is shown that an asymmetric two-carbon atom molecule may, indeed, possess a more pronounced optical mobility than an appropriate closely related one-carbon atom molecule. The great mobility of configuration (I) is emphasised further by the fact that when the optically active acid was brought into combination with *dl*-hydroxyhydrindamine, by mixing equal weights of the salts *dBIA* and *lBdlA* in chloroform solution, the initial optical activity disappeared in a few minutes, whereas with configuration (II) the acid retained its activity for about 30 hours in similar circumstances (*loc. cit.*, p. 1581).

From the results just reviewed it may now be anticipated that chloriodoacetic acid (IV) and bromiodoacetic acid (V) will probably exhibit an optical stability less than that of (III) above, and

possibly of the same order as chlorosulphoacetic acid (VI), which, according to Backer and Burgers (J., 1925, **127**, 233), racemises only slowly in cold aqueous solution. This aspect of the research is receiving attention.



It is noteworthy that in the present instance the lævorotatory base favours a dextrorotatory orientation of the acid, and thus it appears that no general statement is possible in cases of this kind concerning the sense of the optical rotation imposed by the resolving agent upon the mobile asymmetric system with which it is associated (compare *loc. cit.*, p. 1583).

The data brought forward above afford an indication that the values of $[M]_D$ observed for the needles in cold chloroform and glacial acetic acid are to be attributed to the pure salt *lBdA*, rather than to an equilibrium mixture. By subtracting the corresponding values for the tabular salt *lBdlA*, an approximate expression is obtained for the molecular rotation exerted by the acid part of the first molecule in the solvent concerned (*loc. cit.*, p. 1577). The values are thus $+50^\circ$ in chloroform and $+30^\circ$ in glacial acetic acid; the corresponding values for configurations (II) and (III) in the latter solvent are $+125^\circ$ and $+46^\circ$, respectively, but no data can be determined for chloroform in these instances, owing to the insolubility of the salts concerned.

In general, the investigation of the optical activity of chlorobromoacetic acid is rendered difficult owing to the very limited number of suitable solvents, the sparing solubility and darkening of the optically active salts in these solvents, the small polarimetric readings, and the exceeding sensitiveness of the mobile asymmetric system.

An attempted partial asymmetric synthesis of an optically active chlorobromoacetic acid by heating the acid brucine salt of chlorobromomalonic acid to 130° yielded brucine *dl*-chlorobromoacetate (compare Marckwald, *Ber.*, 1904, **37**, 349); this result is in keeping with the last of the factors mentioned in the preceding paragraph.

In our first communication (*loc. cit.*, p. 1584), it was indicated that the salts of chlorobromomethanesulphonic acid with the optically active hydroxyhydrindamines provided a new and highly-refined means of testing certain aspects of the problem of complete asymmetric synthesis. In accordance with this conception, experiments have been devised to ascertain the possibility of disturbing the

delicate optical equilibrium $lBIA \rightleftharpoons lBdA$ existing in acetone solution by submitting the solution to certain external agencies which have been deemed to possess an asymmetric directive influence on chemical processes (compare van 't Hoff, "Die Lagerung der Atome im Raume," 1894, p. 30; Cotton, *Ann. Chim.*, 1896, **8**, 373; Byk, *Z. physikal. Chem.*, 1904, **49**, 641; McKenzie and Walker, *J.*, 1922, **121**, 349). The equilibrium, however, remained unaffected when the solution was exposed to a beam of plane or circularly polarised (mercury green) monochromatic light in a magnetic field (367 *C.G.S.* units), and a similar result attended the use of a solution of the salt $lBdIA$ in dry methyl alcohol. These experiments, although fruitless, appear worthy of record, as affording a stronger indication than has hitherto been forthcoming of the impracticability of achieving a complete asymmetric synthesis by means of the agencies in question. We propose, in due course, to carry out a number of still more refined experiments, with the aim of investigating the conceivable exertion by such agencies of an accelerative or delaying influence upon the attainment of optical equilibria in instances of the kind under notice.

EXPERIMENTAL.

Preparation of Chlorobromomalonic Acid and Chlorobromoacetic Acid.—An ice-cooled solution of malonic acid (52 g.) in dry ether (200 c.c.) was treated gradually with bromine (27 c.c.; 1 mol.); at the end of the reaction sulphuryl chloride (46 c.c.; somewhat more than 1 mol.) was added slowly. The product, after drying for 6 days over calcium chloride and sodium hydroxide in a slow current of dry air, crystallised in long, transparent prisms. Crystallisation was inhibited by admitting moist air or by diminishing the pressure within the desiccator. The crude material was purified by cautiously adding light petroleum to a strong solution in dry ether: the resulting hard, glittering needles gave analytical results corresponding to anhydrous chlorobromomalonic acid, and melted at 138° when heated rapidly.

Chlorobromomalonic acid, which is very deliquescent, dissolves readily in water, alcohol, or ether. It decomposes with evolution of carbon dioxide at temperatures much exceeding 100°; in aqueous solution, a corresponding effervescence sets in well below 100°, and in a vacuum a similar change appears to take place slowly at the ordinary temperature, particularly with impure specimens of the substance.

The normal *brucine* salt was very sparingly soluble in water and in the ordinary organic solvents. The acid *brucine* salt was sparingly soluble in water or ethyl acetate; it dissolved readily in alcohol,

acetone, or chloroform, and was insoluble in ether. A solution in chloroform ($c = 0.70$) had $[\alpha]_D -15.2^\circ$, and showed no mutarotation.

Chlorobromoacetic acid, $\text{CHClBr}\cdot\text{CO}_2\text{H}$, was obtained by heating chlorobromomalonic acid at 130° until the evolution of carbon dioxide was complete. The resulting colourless liquid crystallised on cooling, forming fine needles, which, drained on porous plate, melted at 38° . The substance is extremely deliquescent and it dissolves readily in water, alcohol, acetone, or ether (Found: M , by titration, 177. $\text{C}_2\text{H}_2\text{O}_2\text{ClBr}$ requires M , 173.5). When heated under reflux for an hour with an excess of $N/10$ -sodium hydroxide, the acid suffered hydrolysis of the halogen elements to the extent of 66%. It is thus far less stable in this respect than chlorobromomethanesulphonic acid (J., 1925, 127, 1585).

Experiments on the Optical Resolution of Chlorobromoacetic Acid.—

1. *Brucine chlorobromoacetate*, prepared from its components by fractional precipitation from acetone, forms minute needles. It is very sparingly soluble in water and in most of the usual organic solvents, with the exception of chloroform, in which it is appreciably soluble in the cold. An almost saturated solution in chloroform, containing 0.2528 g. in 20.0 c.c., gave $\alpha_D -0.43^\circ$ in a 2-dm. tube, whence $[\alpha]_D -17.0^\circ$. No mutarotation was observed, and the successive fractions of the salt gave practically identical values. An elaborate series of fractional precipitations from methyl alcohol led to a similar result. The brucine salt was also fractionally precipitated by adding successive quantities of a warm aqueous solution of brucine hydrochloride to a similar solution of ammonium chlorobromoacetate, but no appreciable difference was observed in the rotatory powers of the various fractions, which resembled in every respect the fractions prepared from the organic solvents mentioned above. The brucine salt also appeared to be homogeneous after repeated recrystallisation from boiling methyl alcohol.

An unsuccessful attempt to effect a partial asymmetric synthesis was made by heating the acid brucine salt of chlorobromomalonic acid to 130° with a little nitrobenzene, until the evolution of carbon dioxide was complete. The resulting clear solution deposited crystals of brucine chlorobromoacetate on cooling, and a further amount of this salt was precipitated from the mother-liquor on the addition of ether. In its optical rotatory power and other characteristics, the product was identical with the salt prepared in the other ways just described.

2. *l-Hydroxyhydrindamine dl-chlorobromoacetate*. Chlorobromoacetic acid was mixed in acetone solution with an equivalent weight of *l*-hydroxyhydrindamine, the resulting salt being isolated by evaporating the solution to dryness and washing the crystalline

residue with dry ether. Owing to the ready solubility of the salt in acetone and methyl alcohol, it was recrystallised from warm ethyl acetate. The transparent plates prepared in this way melted with decomposition at 165° . Further purification was effected by redissolving the salt in a small quantity of warm, dry methyl alcohol and adding about 25 times the volume of chloroform. Crystallisation began in about 2 hours and was complete in 24 hours. The product consisted of well-developed plates of rectangular appearance, the average length of side being 3 or 4 mm., and the thickness about 1 mm. M. p. 165° . The salt is almost insoluble in pure chloroform (Found: C, 40.2; H, 4.0. $C_{11}H_{13}O_3NClBr$ requires C, 40.6; H, 4.0%).

A solution of 0.2518 g. of the salt in pure dry methyl alcohol made up to 20 c.c. gave the constant value $\alpha_D -0.50^{\circ}$ in a 2-dcm. tube, whence $[\alpha]_D -20.0^{\circ}$ and $[M]_D -65^{\circ}$. The corresponding initial values in pure dry acetone were $[\alpha]_D -56^{\circ}$ and $[M]_D -182^{\circ}$. A slow downward mutarotation similar to that exhibited by *d*-hydroxyhydrindamine acetate, etc., occurred when this solution was kept (compare J., 1912, **101**, 759, 777; 1925, **127**, 1575). *l*-Hydroxyhydrindamine dichloroacetate, which crystallised from warm acetone containing methyl alcohol in small, glittering prisms, m. p. 139° , gave $[M]_D -195^{\circ}$ in acetone, and showed a closely similar mutarotation. This salt gave the constant value $[\alpha]_D -24.6^{\circ}$, $[M]_D -68^{\circ}$, in pure dry methyl alcohol (Found: C, 47.2; H, 4.3. $C_{11}H_{13}O_3NCl_2$ requires C, 47.5; H, 4.7%). Repeated attempts to obtain a second form of crystalline separation of *l*-hydroxyhydrindamine dichloroacetate by varying the conditions of crystallisation were unavailing.

l-Hydroxyhydrindamine *d*-chlorobromoacetate. *l*-Hydroxyhydrindamine *dl*-chlorobromoacetate was dissolved with the aid of heat in the minimum amount of dry methyl alcohol, to which was then added about 20 times the volume of chloroform. The solution was concentrated to approximately half bulk on a boiling water-bath, so as to remove practically all the methyl alcohol. Rapid crystallisation set in upon then allowing the resulting supersaturated solution in chloroform to cool, and the liquid became permeated with radiating aggregates of soft, silky needles, averaging about 1 cm. in length. After the lapse of an hour or so, crystalline plates characteristic of *l*-hydroxyhydrindamine *dl*-chlorobromoacetate began to separate; accordingly in most of the subsequent operations the needles were separated from the mother-liquor about 20 minutes after crystallisation had begun. When washed with chloroform and dried, the needles melted with decomposition at about 157° . The yield amounted to 75% or more of the weight of the original salt,

depending upon the precise conditions adopted. The salt is almost insoluble in pure chloroform. It was found possible to transform the needles of the *d*-chlorobromoacetate to the tabular *dl*-chlorobromoacetate, and *vice versâ*, at will, by observing the conditions of crystallisation described above. The two substances gave practically identical results when analysed by combustion.

When dissolved in pure dry acetone, by warming, and examined under the conditions indicated above, *l*-hydroxyhydrindamine *d*-chlorobromoacetate gave an initial value of $[M]_D -178^\circ$, declining to -129° after 36 hours, with darkening of the solution. In pure dry methyl alcohol a constant value of $[M]_D -64^\circ$ was observed. In these respects, the salt was practically indistinguishable from *l*-hydroxyhydrindamine *dl*-chlorobromoacetate.

Polarimetric Discrimination between l-Hydroxyhydrindamine dl-Chlorobromoacetate and l-Hydroxyhydrindamine d-Chlorobromoacetate.—1. Upon dissolving 0.1032 g. of *l*-hydroxyhydrindamine *dl*-chlorobromoacetate (plates) at the ordinary temperature in a mixture of chloroform with about one-twentieth of its volume of dry methyl alcohol, and making the solution up to 20.0 c.c., the value $\alpha_D -0.16^\circ$ was observed in a 2-dcm. tube, whence $[\alpha]_D -15.5^\circ$ and $[M]_D -50^\circ$. No change in rotation was observed on keeping or heating this solution.

A similar determination made with *l*-hydroxyhydrindamine *d*-chlorobromoacetate (needles) revealed the absence of any measurable optical rotation under the conditions noted. After heating the solution for 20 minutes on the water-bath, the value $[M]_D -38^\circ$ was observed, and upon keeping the solution at the ordinary temperature for a further 12 hours the value rose to -50° . As in (2) below, precise measurements of mutarotation were rendered difficult through the darkening of the solution.

2. A solution in glacial acetic acid containing 0.2024 g. of *l*-hydroxyhydrindamine *dl*-chlorobromoacetate (plates) made up to 20.0 c.c. at the ordinary temperature, gave $\alpha_D -0.40^\circ$ in a 2-dcm. tube, whence $[\alpha]_D -19.7^\circ$ and $[M]_D -62^\circ$. The reading remained unaltered after keeping the solution or heating it on the water-bath.

A similar solution of *l*-hydroxyhydrindamine *d*-chlorobromoacetate (needles), which had been purified by four successive recrystallisations, gave an original value $[M]_D -32^\circ$, which rose to -50° after heating for 20 minutes on the water-bath and to -58° after heating for a further 2 minutes over a small flame. The weight of salt used in this experiment was 0.2001 g., the actual successive readings of α_D observed in the polarimeter being -0.20° , -0.31° , and -0.36° . All the operations described under (1) and (2) were carried out in duplicate without any sensible difference being noticed in the

results. The concentrations adopted were practically the highest attainable at the ordinary temperature.

3. For purposes of control, similar observations were made upon solutions of *l*-hydroxyhydrindamine dichloroacetate. The values in chloroform containing dry methyl alcohol were $[\alpha]_D -16.6^\circ$, $[M]_D -46^\circ$, and in glacial acetic acid $[\alpha]_D -24.7^\circ$, $[M]_D -68^\circ$. In both instances, the optical rotation remained constant on heating or keeping the solutions.

Exhibition of Optical Activity by Chlorobromoacetic Acid in Combination with an Optically Inactive Base.—1. A solution of β -naphthylamine acetate in glacial acetic acid failed to give a precipitate or separation when added to solutions of the *d*- or *dl*-chlorobromoacetate of *l*-hydroxyhydrindamine in the same solvent, and the replacement of acetic acid by chloroform led to no more satisfactory result. Similar experiments with other symmetric bases demonstrated the impracticability of transferring the chlorobromoacetic acid to combination with such a base, so as to produce a salt possessing the requisite range of solubility.

2. Upon using *d*-hydroxyhydrindamine in place of the *l*-base, it was found possible to prepare specimens of *d*-hydroxyhydrindamine *dl*-chlorobromoacetate (plates) and *d*-hydroxyhydrindamine *l*-chlorobromoacetate (needles), by applying the methods described above. These salts behaved in every way as the respective enantiomers of the salts already discussed, and showed the corresponding optical rotatory powers, mutarotation, etc. In order to bring *l*-chlorobromoacetic acid into combination with *dl*-hydroxyhydrindamine, a mixture of 0.2014 g. of *d*-hydroxyhydrindamine *l*-chlorobromoacetate and 0.2014 g. of *l*-hydroxyhydrindamine *dl*-chlorobromoacetate was dissolved rapidly to 20.0 c.c. in chloroform containing a little dry methyl alcohol. The value of α_D observed 1.5 minutes after the first contact of the solid with the solvent was about -0.1° , and within the course of a further minute or so the solution became completely inactive. In the absence of racemisation, the calculated value of α_D for the conditions adopted is about -0.3° . Two similar experiments were carried out with glacial acetic acid as a solvent; in these instances, 4 to 5 minutes elapsed before a polarimetric reading could be taken, and no optical activity could be established.

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