LXXX.—*The Optical Resolution of Chloroiodoacetic Acid.*

By Ann Mortimer McMath and John Read.

As a result of a study of certain simple compounds with asymmetric molecules containing one and two carbon atoms, we recently came to the conclusion that the optical stability of such molecules was increased in the series under consideration by the substitution of (*a*) SO_3H for CO_2H, and (*b*) I for Br (J., 1926, 2185). We were thus led to anticipate that chloroiodoacetic acid and bromoiodoacetic acid would exhibit a tendency towards racemisation greater than that of chloroiodomethanesulphonic acid, and possibly of the same general order as that shown by chlorosulphoacetic acid. This anticipation has now been substantiated by the preparation and examination of the two optically active modifications of chloroiodoacetic acid, and it is hoped ultimately to secure corresponding evidence for bromoiodoacetic acid.

Chloroiodoacetic acid, which has been rendered readily available through the introduction of the valuable method of Crompton and Carter (J., 1923, **123**, 576), may be resolved with ease into its optically active components, either by fractional crystallisation of the hydroxyhydrindamine salts or by fractional precipitation from aqueous solution with brucine.* With both of these bases the less soluble salt is of the type *lBlA*, and in practice the use of *d*-hydroxyhydrindamine would be necessary in preparing the optically pure *d*-acid in quantity through the intermediary of this base. Exceptionally, it has proved possible with the aid of brucine alone to prepare, not only the pure *l*-acid, but also the *d*-acid of practically the same rotatory power, by fractional precipitation from aqueous solutions of different concentrations. The highest optical rotatory powers observed in dilute aqueous solution for ammonium *l*- and *d*-chloroiodoacetate are $[M]_D - 60°$ and $+ 56°$, respectively.

The optical stability of ammonium *d*- and *l*-chloroiodoacetate in aqueous solution appears to be somewhat more pronounced than that of the corresponding derivatives of chlorosulphoacetic acid; a further indication is thus afforded of the stabilising influence of the iodine atom, to which we have drawn attention in preceding communications. The decline in optical rotatory power upon heating such solutions is distinct but not rapid; it is accelerated considerably by the addition of free alkali, and the presence of an equivalent of sodium hydroxide produces complete racemisation at the ordinary temperature in a few hours.

In a recent brief paper, Backer and Mook (*Verslag Akad. Wetenschappen Amsterdam*, 1926, **35**, 737) claim to have obtained aqueous solutions of ammonium *d*- and *l*-chlorobromoacetate displaying a feeble optical activity, the maximum value of $[M]_D$ being ± 8°. We have been unable to establish any such optical activity after repeated fractional separation of the brucine salt from cold water or from alcohol (compare also J., 1926, 2183); moreover, since it is reported that an aqueous solution of the slightly active ammonium chlorobromoacetate containing an equivalent of sodium hydroxide failed to racemise in 24 hours, the optical stability of chlorobromoacetic acid would appear to be even greater than that of chloroiodoacetic acid, a conclusion which is opposed to our current views.

EXPERIMENTAL.

Preparation of Chloroiodoacetic Acid.—The acid was made by the method of Crompton and Carter (J., 1923, **123**, 576), with the following modifications. Upon keeping the mixture of iodine

---

* In presenting these results for publication we acknowledge our indebtedness to Professor Holland Crompton, through whose courtesy we were enabled to inaugurate the experiments concerned, subsequent to the preparation by him of optically active specimens of ammonium chloroiodoacetate.

monochloride and αβ-dichlorovinyl ethyl ether for 3 weeks (*loc. cit.*), iodine was often liberated to such an extent that very little chloroiodoacetyl chloride remained. Excellent yields were obtained, however, on warming the reaction mixture to 50° after keeping it for 30 minutes only. Upon then removing the solid iodine by filtration and treating the crude chloroiodoacetyl chloride with the calculated amount of water, hydrolysis was found to be complete within about 4 hours, as indicated by solidification. The yield of the acid was finally enhanced by washing the crude product forthwith with light petroleum, prior to recrystallising the almost colourless residue from this solvent.

Following the preparation of chlorobromoacetic acid from chlorobromomalonic acid (J., 1926, 2183), several unsuccessful attempts were made to prepare chloroiodoacetic acid from halogenated malonic or acetic acids, or their esters, by treatment with sodium or potassium iodide in presence of alcohol, ether, or acetone (compare *Ber.*, 1893, **26**, 596; 1910, **43**, 1528). Direct iodination in aqueous or alcoholic solution also proved to be impracticable. Attempts to chlorinate or brominate iodoacetic acid, using sulphuryl chloride and bromine, respectively, in presence of dry ether, likewise resulted in the liberation of iodine. Incidentally, it was not found possible to prepare iodoacetic acid satisfactorily in accordance with the accepted method of heating monochloroacetic acid with potassium iodide in presence of absolute alcohol (compare Sudborough and James, "Practical Organic Chemistry," 1915, p. 118). The yield of the purified acid was increased sevenfold by using acetone in place of alcohol; moreover, the irritating vapour produced in the first method appears to consist mainly of ethyl iodoacetate.

Resolution of Chloroiodoacetic Acid with l-*Hydroxyhydrindamine*.—Hot methyl-alcoholic solutions of the acid (10 g. in 200 c.c.) and base (6·7 g. in 200 c.c.) were mixed in a shallow dish and evaporated to dryness at once, whilst cooling, in a brisk current of air. The residual mass of almost colourless, silky needles was redissolved in the minimum quantity of hot methyl alcohol, diluted considerably with ethyl acetate, and rapidly concentrated on the water-bath until crystallisation occurred readily when the solution was cooled and stirred. Two successive fractions had $[\alpha]_D - 32{\cdot}4°$ in aqueous solution ($c = 1{\cdot}00$). Upon recrystallisation from the same solvent, separation occurred more readily than from the original solution, and a constant value of $[\alpha]_D - 34{\cdot}0°$, $[M]_D - 126°$, was readily attained for pure l-*hydroxyhydrindamine* l-*chloroiodoacetate* in dilute aqueous solution ($c = 1{\cdot}00$). The salt forms brittle transparent prisms, m. p. 149° (decomp.); it dissolves readily in water or in warm methyl alcohol, sparingly in acetone, and is practically insoluble in ethyl acetate or chloroform (Found : Cl + I, 43·6. $C_{11}H_{13}O_3NClI$ requires Cl + I, 44·0%). The solutions in organic solvents darken when kept. Aqueous solutions exhibited no mutarotation, and only a very slight decrease in rotatory power was observed after evaporating such solutions to dryness. A distinct downward mutarotation occurred in methyl-alcoholic solution ($c = 1·20$), the value of $[M]_D$ declining from − 135° to − 103° in 5 days; at the same time, the solution gradually developed a brown colour, indicative of decomposition. A solution in glacial acetic acid decomposed much more rapidly, with liberation of iodine. In chloroform containing a little methyl alcohol, the salt gave $[\alpha]_D$ − 32·0°, $[M]_D$ − 118° ($c = 0·67$). Upon treatment with the requisite quantity of brucine acetate in hot methyl alcohol, it yielded brucine *l*-chloroiodoacetate, having $[\alpha]_D$ − 22·0° in methyl alcohol ($c = 0·60$); when this salt was decomposed in the cold with ammonia, the resulting ammonium *l*-chloroiodoacetate had $[\alpha]_D$ − 24·4°, $[M]_D$ − 58° in aqueous solution ($c = 2·75$).

The mother-liquor from the original separation of *l*-hydroxyhydrindamine *l*-chloroiodoacetate became very dark; after most of the solvent had evaporated, the residual oily mass was induced to crystallise by treatment with light petroleum. Further treatment with ether yielded two fractions, having $[\alpha]_D$ − 5·9° and − 2·0°, and $[M]_D$ − 22° and − 7°, respectively, in aqueous solution ($c = 1·00$). The second fraction, composed of minute, feathery needles, appeared to consist of almost pure l-*hydroxyhydrindamine* d-*chloroiodoacetate*, the calculated value for the molecular rotation of the corresponding acid ion in dilute aqueous solution being + 53·5°. The brucine salt precipitated from the mixed fractions was fractionally recrystallised from hot water, and the final fraction, having $[\alpha]_D$ + 14·0° in methyl alcohol ($c = 0·60$), when decomposed in the usual way with dilute ammonia yielded an optically impure ammonium *d*-chloroiodoacetate having $[\alpha]_D$ + 16·0°, $[M]_D$ + 38° in aqueous solution ($c = 2·00$).

Resolution of dl-*Chloroiodoacetic Acid with Brucine.*—1. The crude brucine salt, obtained by mixing the components in warm methyl alcohol, had $[\alpha]_D$ − 9·7° in methyl alcohol ($c = 0·60$). Recrystallisation from warm methyl alcohol gave two successive fractions yielding specimens of ammonium chloroiodoacetate with $[\alpha]_D$ − 2° and + 1°, respectively, in dilute aqueous solution.

2. Following preliminary experiments on fractional precipitation with brucine in accordance with the method of Pope and Read (J., 1914, **105**, 817), a warm aqueous solution of ammonium *dl*-chloroiodoacetate (4·4 g. of acid in 300 c.c.) was treated with a

similar solution of one-quarter the calculated weight of brucine hydrochloride (2·3 g. of base in 75 c.c.). After the crystalline brucine salt had been separated from the cold liquid, the filtrate was treated thrice in succession in an exactly similar way with fresh quantities of brucine, the volume of the solution being kept practically constant by evaporation on the water-bath after each filtration. The four fractions of brucine salt had roughly the same weight (2·75 g.), and the respective values of $[\alpha]_D$ in methyl alcohol ($c = 0{\cdot}60$) were − 22°, − 8°, + 6°, and + 8°. After two recrystallisations from water containing a little methyl alcohol, the first fraction gave, upon decomposition with ammonia, a specimen of ammonium *l*-chloroiodoacetate having $[\alpha]_D$ − 25·1°, $[M]_D$ − 60°, in water ($c = 2{\cdot}11$). Further observations indicated that this specimen of ammonium *l*-chloroiodoacetate was optically pure. An aqueous solution of ammonium *l*-chloroiodoacetate (6·53 g. in 250 c.c.) having $[M]_D$ − 32°, prepared from a number of intermediate fractions of the brucine salt which had accumulated in several series of operations, was treated in the usual way with two successive quantities of one-quarter the calculated amount of brucine hydrochloride. The two specimens of ammonium *l*-chloroiodoacetate obtained by decomposing the ensuing fractions of brucine *l*-chloroiodoacetate had the respective values $[\alpha]_D$ − 25·0°, $[M]_D$ − 59°, and $[\alpha]_D$ − 24·4°, $[M]_D$ − 58° in 3% aqueous solution. The two specimens were then mixed and treated once again with one-quarter the calculated amount of brucine hydrochloride under the usual conditions: the resulting brucine salt, when decomposed in the cold with dilute ammonia, yielded ammonium *l*-chloroiodoacetate having $[\alpha]_D$ − 25·0°, $[M]_D$ − 59°. The corresponding pure, air-dried *brucine* l-*chloroiodoacetate* had $[\alpha]_D$ − 22·0° in methyl alcohol ($c = 0{\cdot}60$); this salt forms small, glistening prisms, m. p. 158—160° (decomp.), which dissolve very sparingly in hot water and readily in warm methyl alcohol.

After the addition of one-half the calculated amount of brucine hydrochloride to a hot aqueous solution of ammonium *dl*-chloroiodoacetate, the succeeding fractions of the brucine salt usually exhibit a low dextrorotation in methyl alcohol; the fractions are also more readily soluble and consist of large, glistening prisms. A fraction of the brucine salt having $[\alpha]_D$ + 6° in methyl alcohol yielded ammonium *d*-chloroiodoacetate having $[\alpha]_D$ + 17·5°, $[M]_D$ + 42°, in 4% aqueous solution. After the original brucine salt had been recrystallised three times from hot water, the corresponding ammonium *d*-chloroiodoacetate had $[\alpha]_D$ + 15·0°, $[M]_D$ + 36°. Fractional precipitation of this salt with one-half the calculated quantity of brucine gave an ammonium salt having

$[\alpha]_D + 15{\cdot}8°$, $[M]_D + 38°$. Prolonged evaporation of aqueous solutions of brucine *d*-chloroiodoacetate on the water-bath appears to bring about partial racemisation of the acid component of the salt.

3. The preparation of optically pure brucine *d*-chloroiodoacetate by the normal methods of fractional crystallisation or fractional precipitation is thus difficult; success was achieved, however, by conducting the second of these operations from a solution having about 3·5 times the concentration noted in paragraph (2) above. Two aqueous solutions were prepared, each of 500 c.c.; these contained, respectively, 22·0 g. of *dl*-chloroiodoacetic acid as ammonium salt and 46·6 g. of brucine in the form of hydrochloride. Upon rapidly adding a portion (150 c.c.) of the hot brucine solution to the whole of the first solution on the water-bath, crystallisation began about one minute after mixing and continued rapidly. The fraction (19·8 g.) collected by filtering the cold mixture consisted of practically pure *brucine* d-*chloroiodoacetate*. This had $[\alpha]_D + 21{\cdot}0°$ in methyl alcohol ($c = 0{\cdot}60$); 0·7647 g. of the corresponding ammonium *d*-chloroiodoacetate contained in 20·0 c.c. of aqueous solution gave $\alpha_D + 1{\cdot}80°$ in a 2-dcm. tube, whence $[\alpha]_D + 23{\cdot}5°$ and $[M]_D + 56°$. A second fraction of brucine salt, yielded similarly by the filtrate from the first fraction, gave a specimen of ammonium *l*-chloroiodoacetate having $[M]_D - 32°$. Both these fractions of brucine salt were allowed to separate spontaneously without inoculation. Further experiments indicated that the character of the crystalline separation may be controlled to some extent by seeding the supersaturated solution in such instances with specimens of brucine *l*- or *d*-chloroiodoacetate; it is proposed to submit this interesting aspect of the investigation to fuller inquiry.

Ammonium l- *and* d-*Chloroiodoacetate*.—The ammonium salts were prepared by shaking cold aqueous suspensions of the corresponding brucine salts with the calculated amounts of a standard solution of ammonia in presence of chloroform, the ammonia being added in small portions. Traces of brucine were finally removed from the aqueous layer by two further extractions with chloroform. After the value of α_D in a 2-dcm. tube had been observed for the resulting aqueous solution of the ammonium salt, an aliquot portion of the solution was evaporated to dryness on the water-bath in order to determine the concentration. The highest values observed for ammonium *l*- and *d*-chloroiodoacetate were $[\alpha]_D - 25{\cdot}1°$, $[M]_D - 60°$, and $[\alpha]_D + 23{\cdot}5°$, $[M]_D + 56°$, respectively, in dilute aqueous solution as recorded above. The salts form colourless, glistening needles (decomp. 149—150°), which usually become yellow and then brown when kept for a few days in a desiccator (Found : NH_3, 7·2.

$C_2H_5O_2NClI$ requires NH_3, 7·2%). It is thus advisable to keep the active acids in the form of their brucine salts. Crystalline ammonium *l*-chloroiodoacetate having $[\alpha]_D$ — 25·1°, $[M]_D$ — 60°, after being kept for 10 days in a desiccator, gave $[\alpha]_D$ — 24·6°, $[M]_D$ — 58° in aqueous solution ($c = 0{\cdot}50$) and $[\alpha]_D$ — 24·4°, $[M]_D$ — 57° in methyl alcohol ($c = 0{\cdot}75$).

No appreciable racemisation was noticed upon evaporating 5 c.c. of a 3·76% aqueous solution of ammonium *d*-chloroiodoacetate, having $[\alpha]_D$ + 19·0°, to dryness on the water-bath. Sustained evaporation of larger volumes, however, produced a noticeable decline in the rotatory power; a slow decline occurred also on keeping aqueous solutions at the ordinary temperature for long periods.

Upon dissolving 0·2116 g. of ammonium salt having $[M]_D$ — 58° in 20·0 c.c. of water containing 2 c.c. of 2*N*-ammonia and evaporating the solution to dryness on the water-bath, the recovered salt had $[\alpha]_D$ — 10·4°, $[M]_D$ — 25°. Further, 0·2200 g. of ammonium salt having $[\alpha]_D$ — 24·1° was dissolved in water containing an equivalent of sodium hydroxide and made up to 20·0 c.c.; the value of α_D in a 2-dcm. tube after 30 minutes was — 0·50°, and when kept for 24 hours at the ordinary temperature the solution had become optically inactive. No appreciable removal of halogen by hydrolysis was detected at the end of this time. In a similar experiment the value of α_D declined over-night from — 0·68° to zero.

An aqueous solution of 0·1882 g. of ammonium salt having $[\alpha]_D$ + 19·0°, $[M]_D$ + 44°, was made up to 20·0 c.c. with water containing one equivalent of hydrochloric acid. The resulting value of α_D in a 2-dcm. tube was + 0·15°, whence the free acid under these conditions has $[\alpha]_D$ + 0·9°, $[M]_D$ + 2°.

The authors are indebted to the Department of Scientific and Industrial Research for a maintenance grant and to the Carnegie Trust for a Fellowship which enabled one of them (A. M. M.) to take part in this work. The investigations are being continued.

United College of St. Salvator and St. Leonard,
University of St. Andrews. [*Received, January 7th,* 1927.]