409. *The Complete Optical Resolution of Chloroiodomethanesulphonic Acid.*

By JOHN READ and ANN M. MCMATH.

THE exhibition of optical activity by a substance containing only one carbon atom in its molecule was first demonstrated in 1914 by Pope and Read (J., **105**, 811), who prepared specimens of ammonium *d*- and *l*-chloroiodomethanesulphonate having maximum rotatory powers in dilute aqueous solution of $[M]_{5461}$ + 43·7° and − 29·5°, respectively. The optical resolution was admittedly incomplete, but the work had to be discontinued. It has since been shown that chloroiodomethanesulphonic acid is of unusual interest among simple asymmetric compounds because of its pronounced optical stability (cf. Read and McMath, J., 1925, **127**, 1572; 1926, 2183, 2192; 1927, 537). These later researches included a comparison of the molecular rotatory powers of a series of similarly constituted compounds, and showed the necessity of establishing standard values for the chloroiodomethanesulphonates.

Through the courtesy of Prof. Sir William Pope, who kindly placed some valuable material at our disposal, we were enabled to carry the optical resolution of chloroiodomethanesulphonic acid to completion. The maximum values now recorded, $[M]_{5461}$ + 46·5° and − 46° in dilute aqueous solution, for ammonium *d*- and *l*-chloroiodomethanesulphonate, respectively, are in close correspondence, and the enantiomorphous character of the two salts thereby becomes manifest. The purest specimen of the *d*-salt prepared by Pope and Read contained about 4% of its antimeride. When an equivalent of sulphuric acid was added to a solution of pure ammonium *d*-chloroiodomethanesulphonate, the value fell to + 34°; a similar and more pronounced decline is shown by chloroiodoacetic acid (J., 1927, 543), while chlorosulphoacetic acid shows a reverse change (J., 1926, 2193). These variations are perhaps due to the different rotatory powers of the ionised and un-ionised molecules of the acids.

The diastereoisomeric *strychnine chloroiodomethanesulphonates* give abnormal rotatory powers in dilute aqueous solution, particularly when present together; and neither of them can be purified from large or small admixtures of the other by repeated fractional crystallisation from water. While this base is inapplicable in the optical resolution of the acid, a study of the diastereoisomeric *hydroxyhydrindamine* salts* showed that they have markedly different solubilities and exhibit normal rotatory powers in dilute aqueous solution; the indications obtained by Pope and Read (*loc. cit.*, p. 816) that this base, unlike strychnine, might be used to achieve the complete optical resolution of the acid are thus borne out.

The resolution is effected most conveniently, however, by repeated fractional precipitation of the acid with brucine, as indicated by Pope and Read; it is shown below that both of the antimerides may be obtained in this way with unsuspected ease, four or five series of operations being usually sufficient, even for isolating the second form. The data indicate that throughout the process brucine *d*-chloroiodomethanesulphonate is preferentially deposited from the aqueous reaction mixture, and that the separation of the two salts is remarkably well defined. The two salts crystallise more slowly from glacial acetic acid than from water, and may also be prepared by mixing solutions of the appropriate ammonium salt and brucine acetate in hot glacial acetic acid.

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* The values quoted by us for these salts in a communication dealing with the optical resolution of chlorobromomethanesulphonic acid (J., 1925, **127**, 1578) are now shown to apply to the optically pure substances.

Further experiments on the racemisation of optically active chloroiodomethanesulphonates have confirmed the original statements of Pope and Read concerning their pronounced optical stability. Although it is now shown that considerable racemisation occurs in the presence of a large excess of concentrated ammonia and other alkalis, a very much greater racemising effect is exerted by small proportions of these reagents upon chloroiodoacetic acid (J., 1927, 543). The replacement of the group $^-CO_2H$ by $^-SO_3H$ thus increases the optical stability in this series; at the same time the value of $[M]_D$ for the ammonium salts in dilute aqueous solution declines from $\pm$ 60° to $\pm$ 36°.

EXPERIMENTAL.

Derivatives of d-*Chloroiodomethanesulphonic Acid.*—Optically impure ammonium *d*-chloroiodomethanesulphonate (16·1 g., $[\alpha]_{5461}$ + 9·2°), prepared according to Pope and Read (*loc. cit.*, p. 818), was dissolved in hot H_2O (500 c.c.); 80% of the calc. amount of a hot, conc. aq. solution of brucine sulphate was then added quickly, with stirring. A cryst. separation began in about 2 sec., and after the mixture had cooled the brucine salt was collected and washed with cold H_2O. The brucine was completely eliminated by shaking the salt for a few hrs. at room temp. with a mixture of $CHCl_3$ and the calc. quantity of very dil. aq. NH_3. The aq. solution, when washed with $CHCl_3$ and evaporated to dryness on the water-bath, gave ammonium *d*-chloroiodomethanesulphonate (12·8 g.) having $[\alpha]_{5461}$ + 12·8° ($c = 1$, in H_2O). Three successive repetitions of this process, starting with the salt having $[\alpha]_D$ +12·8°, yielded further specimens of NH_4 salt with $[\alpha]_{5461}$ + 16·1° (10·2 g.), + 16·7° (8·2 g.), and + 16·7° (6·5 g.). When recryst. from the min. amount of hot abs. EtOH, the last fraction gave large colourless plates with $[\alpha]_{5461}$ + 17·0°; a slight insol. residue consisted of $(NH_4)_2SO_4$. Finally, an alc. solution was evaporated almost to crystallising point and then diluted with hot acetone: small glistening plates separated, having $[\alpha]_{5461}$ + 17·0°. Opalescence on addition of acetone denotes the presence of traces of $(NH_4)_2SO_4$. The rotatory power of the salt was unaffected by further crystn.

Pure *ammonium* d-*chloroiodomethanesulphonate* melts at 229—230° (decomp.). It is moderately sol. in boiling glac. AcOH, from which it crystallises in glistening plates (Found: NH_3, 6·2. $CHO_3ClIS{\cdot}NH_4$ requires NH_3, 6·2%). In 1% aq. solution ($l = 2$; room temp., *ca.* 15°) it gave $[\alpha]_{5461}$ + 17·0°, $[M]_{5461}$ + 46·5°; $[\alpha]_D$ + 13·2°, $[M]_D$ + 36°. A 1·25% solution in abs. EtOH gave $[\alpha]_{5461}$ + 20·9°, $[M]_{5461}$ + 57°; $[\alpha]_D$ + 16·9°, $[M]_D$ + 46°. When an equiv. of H_2SO_4 was added to 0·2008 g. of the NH_4 salt, the resulting solution (20·0 c.c.) of free *d*-chloroiodomethanesulphonic acid [in presence of $(NH_4)_2SO_4$] gave α_{5461} + 0·25°, $[\alpha]_{5461}$ + 13·3°, $[M]_{5461}$ + 34°; α_D + 0·19°, $[\alpha]_D$ + 10·1°, $[M]_D$ + 26°.

The Ba salt crystallised from hot H_2O in small glistening leaflets; it underwent no loss of weight at 110°, and in 1% aq. solution had $[\alpha]_{5461}$ + 14·0°, $[\alpha]_D$ + 11·0°.

Strychnine d-*chloroiodomethanesulphonate* was pptd. as an oil upon mixing hot aq. solutions of equiv. wts. of the free acid and base; it formed glistening anhyd. prisms from aq. EtOH or rectified spirit (Found: C, 44·7; H, 4·3.

$C_{22}H_{24}O_5N_2ClIS$ requires C, 44·7; H, 4·1%). A 1·5% aq. solution of the optically pure salt gave $[\alpha]_{5461}$ − 16·6°, $[M]_{5461}$ − 98°; $[\alpha]_D$ − 14·6°, $[M]_D$ − 86°. The crude strychnine salt prep. from a NH_4 salt with $[M]_{5461}$ + 35° gave $[M]_{5461}$ − 97°, the calc. value in dil. aq. solution being − 106°; the rotatory power of this salt remained almost unaltered after 3 recrystns. from aq. EtOH. All the strychnine salts described in this paper melted at about 227° (decomp.).

l-*Hydroxyhydrindamine* d-*Chloroiodomethanesulphonate*.—The cryst. residue obtained by evaporating to dryness an aq. solution containing equiv. amounts of the acid and base was redissolved in warm AcOEt with a little acetone; the *salt* separated on cooling in voluminous feathery needles, m. p. 204° (decomp.) (Found: C, 29·6; H, 3·4. $C_{10}H_{13}O_4NClIS$ requires C, 29·6; H, 3·2%). A 1·6% solution in pure dry acetone gave $[\alpha]_{5461}$ − 12·7°, $[\alpha]_D$ − 10·4°; the salt crystallised in the polarimeter tube after a few hr. A 1·6% solution in pure MeOH (dehydrated with Mg) gave $[\alpha]_D$ − 9·8°, and a 0·6% solution in glac. AcOH gave $[\alpha]_D$ − 6·6°. A 1·3% solution in H_2O gave $[\alpha]_{5461}$ − 6·4°, $[M]_{5461}$ − 26°; $[\alpha]_D$ − 6·0°, $[M]_D$ − 24°. No mutarotation occurred on keeping these solutions for 24 hr.

d-*Hydroxyhydrindamine* d-*chloroiodomethanesulphonate* crystallised from AcOEt in fluffy needles, m. p. 194° (decomp.) (Found: C, 29·5; H, 3·4%). Rotatory powers: in pure dry acetone (1%), $[\alpha]_{5461}$ + 59·0°, $[\alpha]_D$ + 47·1°; in pure dry MeOH (0·9%), $[\alpha]_D$ + 30·0°; in glac. AcOH (0·6%), $[\alpha]_D$ + 29·1°; in H_2O (1·3%), $[\alpha]_{5461}$ + 29·1°, $[M]_{5461}$ + 118°, $[\alpha]_D$ + 23·6°, $[M]_D$ + 96°. The salt crystallised from the acetone after a few hr. No mutarotation was obs. in these solvents.

Derivatives of l-*Chloroiodomethanesulphonic Acid*.—Various fractions of optically impure ammonium *l*-chloroiodomethanesulphonate which had accumulated in the mother-liquors from the prepn. of the *d*-salt (*loc. cit.*, p. 817) were mixed. The hot aq. solution (1100 c.c.) of a resulting specimen of NH_4 salt (41·0 g.) having $[\alpha]_{5461}$ − 4·9° was treated in the usual way with 1/6-equiv. of brucine sulphate dissolved in a little hot H_2O; the ensuing cryst. separation of brucine salt, when decomp. with the calc. amount of dil. aq. NH_3 at room temp., as indicated above, yielded an NH_4 salt (6·6 g.) with $[\alpha]_{5461}$ + 4·6° ($c = 1$ in H_2O). A second 1/6th of the necessary brucine sulphate was then added to the hot filtrate: the ammonium chloroiodomethanesulphonate prepared from the deposit had $[\alpha]_{5461}$ + 2·5°. A third fraction of the NH_4 salt, prepared similarly, had $[\alpha]_{5461}$ − 4·5°, and a fourth had $[\alpha]_{5461}$ − 11·4°. Two successive additions of 1/12th of the calc. amount of brucine sulphate to the last filtrate then yielded fractions of NH_4 salt with $[\alpha]_{5461}$ − 12·3° and − 15·4°, respectively. During all these operations the solution was kept approx. at its original vol. by periodical evaporation. The final mother-liquors contained $(NH_4)_2SO_4$ and other impurities.

In the next stage of the process, ammonium *l*-chloroiodomethanesulphonate (16·8 g.) having $[\alpha]_{5461}$ − 12·2° was dissolved in hot H_2O (350 c.c.) and treated in succession with one portion of 1/4th and 5 portions of 1/8th of the calc. quantity of brucine sulphate, in the usual way. The fractions of ammonium chloroiodomethanesulphonate thus obtained had $[\alpha]_{5461}$ − 7·7° (3·9 g.), − 7·8°, − 10·2°, −12·8°, − 16·0°, and − 16·0°, respectively. A repetition of the process with a mixture of the last 2 fractions yielded *ammonium* l-*chloroiodomethanesulphonate* with a max. rotatory power practically identical with the max. numerical value for the *d*-salt: $[\alpha]_{5461}$ − 16·7°, $[M]_{5461}$ − 46°; $[\alpha]_D$ − 13·0°, $[M]_D$ − 36° ($c = 1$ in H_2O) (Found: NH_3, 6·3%).

Strychnine l-*Chloroiodomethanesulphonate.*—When prep. and purified as indicated above for its diastereoisomeride, this *salt* formed small glistening prisms (Found: C, 44·5; H, 4·3%); $[\alpha]_{5461}$ − 33·0°, $[M]_{5461}$ − 195°; $[\alpha]_D$ − 26·5°, $[M]_D$ − 156° ($c = 1$ in H_2O). No appreciable difference was noticed in the solubilities of strychnine *d*- and *l*-chloroiodomethanesulphonate. The crude strychnine salt prep. from an NH_4 salt with $[M]_{5461}$ − 35·6° gave $[M]_{5461}$ − 166°, the calc. value in dil. aq. solution being − 177°. After 5 recrystns. of this salt from aq. EtOH, the value had changed only to − 163°, and the regenerated NH_4 salt had $[M]_{5461}$ − 36·5°.

l-*Hydroxyhydrindamine* l-*chloroiodomethanesulphonate* crystallises from AcOEt in fluffy needles, m. p. 194° (decomp.), and is more sol. than its diastereoisomeride (Found: C, 29·4; H, 3·4%). A 1·25% solution in pure dry acetone gave $[\alpha]_{5461}$ − 58·9°, $[\alpha]_D$ − 46·9°; the salt is thus truly enantiomorphous with *d*-hydroxyhydrindamine *d*-chloroiodomethanesulphonate, described above.

Brucine d-, l-, *and* dl-*Chloroiodomethanesulphonate.*—The pure salts may be made by mixing hot aq. solutions of equiv. quantities of a sol. brucine salt and the NH_4 salt of the appropriate acid. All 3 salts form small, glistening anhyd. prisms, m. p. 272° (decomp.). They may be recryst. from a large vol. of boiling H_2O, or from hot glac. AcOH; but when the brucine salt of the *dl*-acid is treated in this way the crystals separating always contain an excess of *d*A*l*B. Owing to their slight solubility, their optical rotations could not be measured. When a hot aq. solution of ammonium *dl*-chloroiodomethanesulphonate was inoculated with brucine *l*-chloroiodomethanesulphonate and then treated in the usual way with 1/3rd of the calc. amount of brucine sulphate, the resulting brucine salt yielded ammonium *d*-chloroiodomethanesulphonate (83%) having $[\alpha]_{5461}$ + 6·6°; a similar experiment without inoculation gave an identical result.

Racemisation Experiments.—Ammonium *d*-chloroiodomethanesulphonate with $[\alpha]_{5461}$ + 15·4° suffered no change in rotatory power when its aq. solution was evaporated to dryness 3 times with the addition of dil. aq. NH_3. A 1% aq. solution was left over-night with an equal vol. of conc. aq. NH_3 in an open dish, before evaporation to dryness: the recovered salt was undecomposed and had $[\alpha]_{5461}$ + 8·0°. Distinct partial racemisation was observed also on decomposing brucine *d*- or *l*-chloroiodomethanesulphonate with a large excess of conc. aq. NH_3; a marked excess of NH_3 should thus be avoided in this operation, which can then be safely carried out at room temp.

A 1·7% aq. solution of ammonium *d*-chloroiodomethanesulphonate with $[\alpha]_{5461}$ + 14·9° was mixed with twice its vol. of $N/10$-NaOH and boiled gently for 45 min.; upon exactly neutralising the solution with dil. HNO_3 and making it up to the original vol. with H_2O, the value $[\alpha]_{5461}$ + 11·2° was observed. The resulting solution gave only a slight opalescence with $AgNO_3$ + HNO_3.

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