LXIII.—*Isomeric Salts of the Type $\text{NR}_1\text{R}_2\text{H}_3$. A Correction. Isomeric Forms of d-Bromo- and d-Chloro-camphorsulphonic Acids.*

By FREDERIC STANLEY KIPPING.

THE further investigation of the isomeric α - and β -salts which the author obtained by combining *d*- α -bromo- and *d*- α -chloro-camphorsulphonic acids with *dl*- and with optically active bases such as hydrindamine (Trans., 1900, **77**, 861 *et seq.*; 1903, **83**, 873), benzylhydrindamine (Kipping and Hall, Trans., 1901, **79**, 430), methylhydrindamine (Tattersall and Kipping, Trans., 1903, **83**, 918), and *l*-menthylamine (Tutin and Kipping, Trans., 1904, **85**, 65), has brought to light the fact that the isomerism of these compounds is not determined by a difference in the arrangement in space of the groups united with the quinquivalent nitrogen atom; the suggested explana-

tion of the existence of these isomerides, therefore, is now proved to be incorrect.

In one of the most recent papers on this subject (Trans., 1903, 83, 937), the following statements were made: the β -form of the *l*-hydrindamine salt of the chloro-acid gives, with concentrated hydrochloric acid, crystals of the hydrochloride of the *l*-base, and when, by adding water and evaporating several times to expel hydrochloric acid, this hydrochloride is reconverted into the chlorocamphorsulphonate, the original β -isomeride is recovered unchanged (*loc. cit.*, p. 943). When, however, the hydrochloride obtained from the β -form of the bromo-salt is converted into platinichloride and this salt is separated from the bromo-acid and treated with hydrogen sulphide, the regenerated hydrochloride gives with the ordinary ammonium salt of the bromo-acid the α -form of *l*-hydrindamine bromocamphorsulphonate (*loc. cit.*, p. 944).

In order to account for this transformation of the β - into the α -salt, it was suggested that intramolecular change might occur during the formation and decomposition of the platinichloride and thus the arrangement of the groups around the nitrogen atom might be modified. Even at the time, however, this suggestion did not seem to be a very plausible one, and it was stated that further experiments on this point would be made.

Shortly afterwards, a careful investigation of the *d*-bromocamphorsulphonates of various piperidine derivatives failed to reveal the existence of isomeric salts (Barrowcliff and Kipping, Trans., 1903, 83, 1141), and experiments on the *d*-bromo- and *d*-chloro-camphorsulphonates of *l*-phenylethylamine (*loc. cit.*, p. 1147) also led to negative results; these facts seemed to afford additional and absolutely conclusive evidence that the isomerism of the hydrindamine salts was, in fact, of the nature suggested and in no way determined by the occurrence of isomeric forms of the bromo- and chloro-camphorsulphonic acids.

In spite of this apparently convincing evidence of the homogeneity of the acids in question and also of the further fact that many other workers (Walden, Pope, Wedekind, Lapworth, Jones) had used the *d*-bromo-acid without obtaining the slightest indication of the presence of an isomeride, a fresh investigation of this acid was undertaken.

Some years ago, when the isomeric hydrindamine salts were first discovered, the ammonium salt, prepared from the "pure" acid,* had been repeatedly crystallised and examined polarimetrically, and the aniline salt had also been investigated, but both appeared to be homogeneous; later, in crystallising the *crude* ammonium salt, it is true that a small quantity of a salt not derived from *d*-bromocamphor-

* Acid which had been obtained from the "pure" ammonium salt as originally described by Kipping and Pope.

sulphonic acid was isolated by the author from the last mother liquors, and the same compound was discovered and studied by Harvey and Lapworth (Proc., 1902, **18**, 142), but this substance was easily removed from the main product and could not be contained in the purified salt ordinarily used for the preparation of the acid.

In a much more recent investigation of this ammonium *d*-bromocamphorsulphonate, the results of which have not hitherto been recorded, a large quantity of the salt was first purified by two or three crystallisations, and was then separated into a number of fractions by crystallising it systematically from water; the first and last of these, when examined polarimetrically in 2.5 per cent. aqueous solution, gave $[\alpha]_D 83.6^\circ = [M]_D 275^\circ$ and $[\alpha]_D 83.8^\circ = [M]_D 275.6^\circ$ respectively. The salt was then decomposed with baryta, the ammonia expelled, the acid prepared from the barium salt and again neutralised with ammonia; the whole of this specimen of ammonium salt was then systematically crystallised and separated into eight fractions, each of which had been crystallised several times; the first and last, when examined optically in 2.5 per cent. aqueous solution, gave $[\alpha]_D +84.6^\circ = [M]_D 278^\circ$ (also $[\alpha]_D 85^\circ = [M]_D 279^\circ$) and $[\alpha]_D 84.8^\circ = [M]_D 278.5^\circ$ respectively.

In these experiments, therefore, in which the acid had been submitted to almost exactly the same treatment as in those which were used in the study of the isomeric hydrindamine salts ("Regeneration of the Salts," compare Trans., 1903, **83**, 884 *et seq.*), the greatest observed difference in molecular rotation was 4° , which is well within the limits of experimental error; in the case of the α - and β -hydrindamine salts, the difference was found to be 90° (*loc. cit.*, p. 944).

The study of the *cis*- π -camphanates of *d*- and of *l*-hydrindamine, which had also been in progress in the meantime, only served to confirm the conclusion that the existence of the isomeric salts was independent of any isomerism of the bromo- and chloro-camphorsulphonic acids.

Cis- π -camphanic acid (Trans., 1896, **69**, 943) is a substance so easily identified by its highly characteristic crystalline character that any appreciable quantity of an isomeride or impurity in this substance could hardly escape immediate detection, and yet this acid gave with *dl*-hydrindamine approximately equal quantities of isomeric partially racemic salts (Trans., 1898, **73**, 903), both of which, when decomposed with hydrochloric acid, gave the characteristic crystals of *cis*- π -camphanic acid.

Further, it was found (Proc., 1903, **19**, 286) that the salt obtained by combining *cis*- π -camphanic acid with pure *d*-hydrindamine is a mixture, as is also that obtained from the corresponding *l*-base, and that these compounds are not identical with the salts previously described as partially racemic.

Hence the formation of isomeric compounds, apparently analogous

to those derived from the bromo- and chloro-acids, seemed to be definitely established, and as there is so little relationship between the sulphonic acids on the one hand and *cis*- π -camphanic acid on the other, the fact that isomerides were obtained from both seemed to exclude the possibility of this being due to any peculiarity of the acids themselves.

It will perhaps be admitted that a critical consideration of the whole of the evidence—only part of which has been referred to very briefly—pointed strongly to the conclusion that the isomerism of these salts was caused by a difference in the arrangement of the groups around the nitrogen atom; a great array of experimental data could be quoted in favour of this view,* whereas only one fact of importance could be brought forward against it, namely, that the molecular rotations of the bromo- and chloro-salts (not, however, those of the *cis*- π -camphanates) were abnormal; even this fact seemed to have little bearing on the possible existence of isomeric acids, as the molecular rotations of the β -salts of the bromo-acid were *lower*, those of the β -salts of the chloro-acid *higher*, than the "normal" values obtained for the compounds of the α -series.

The discovery of the true course of the isomerism in the case of the halogensulphonic acids was made during some recent attempts to transform β *l*-hydrindamine bromocamphorsulphonate into the β *l*-chlorocamphorsulphonate. The first named salt was gently warmed with excess of concentrated hydrochloric acid; the solution was then left at the ordinary temperature to crystallise and the precipitated hydrochloride separated. The filtrate from this salt was then repeatedly evaporated with water to expel hydrochloric acid, and the solution, which now contained hydrindamine bromocamphorsulphonate, mixed with excess of the bromo-acid, left to crystallise; the bromo-salt thus obtained, which had doubtless been in part produced from the hydrochloride, had a specific rotation $[\alpha]_D + 38.5^\circ$ in two per cent. aqueous solution, and consisted therefore of the original β *l*-isomeride in a pure condition (*loc. cit.*, p. 897). The crystals of the hydrochloride which had been separated were now repeatedly evaporated with chlorocamphorsulphonic acid, in the expectation of obtaining the β *l*-chloro-salt, but on crystallising the residue from water, the α *l*-chloro-salt was obtained, apparently (not really) free from β *l*-isomeride.

At first, it seemed possible that the β *l*-bromo-salt might correspond with the α *l*-chloro-salt, these being the isomerides having the lower

* Aschan (*Zeit. physikal. Chem.*, 1903, **46**, 293), discussing the author's work, writes as follows: Dagegen haben die von Kipping und seinen Schülern über das Hydrindamin und einige andere, gleich konstituierte Basen ausgeführten bemerkenswerten Untersuchungen entschieden zu dem Schluss geführt, dass Verbindungen des Typus Na_2bc stereoisomer auftreten können.

molecular rotations, in which case the αd -bromo-salt should give the βl -chloro-salt when treated in the manner just indicated; experiment, however, showed that this was not so, and that all the salts of the β -series, as well as those of the α -series, when transformed into the hydrochlorides and then treated with bromo- or chloro-camphorsulphonic acid, or the corresponding ammonium salt, gave invariably the isomeride of the α -series as the main product.

Here then was the clue to the mystery. The hydrochloride prepared from a β -salt gives the α -salt when it is treated with bromocamphorsulphonic acid from a bottle; when, however, it is evaporated with the bromo-acid which the β -salt originally contained, it yields the pure β -salt.

There are, therefore, two isomeric d -bromocamphorsulphonic acids, one of which is contained in the α -salts and in ordinary ammonium d -bromocamphorsulphonate, the other in the hydrindamine salts of the β -series.

That this is so was further established by the following experiment: a sample of pure βl -hydrindamine bromocamphorsulphonate was treated with concentrated hydrochloric acid, the precipitated hydrochloride separated, the filtrate evaporated several times with water, then diluted, and left for some hours; after separating the crystals of the βl -salt which had escaped decomposition, the solution, which contained the liberated bromocamphorsulphonic acid, was treated with $d l$ -hydrindamine hydrochloride. The salt slowly deposited from this solution was free from the α -modification of the partially racemic salt, a fact which proved that the acid could not have been *ordinary* d -bromocamphorsulphonic acid; the salt consisted, in fact, of small, well-defined prisms, indistinguishable by inspection from those of the partially racemic β -salt and doubtless almost identical with those of the *synthetical* partially racemic β -salt recently described (Trans., 1903, 83, 900).

The d -bromo-acid contained in the βl -hydrindamine salt and set free from it by hydrochloric acid is therefore different from the d -bromo-acid obtained from the same salt by first treating with baryta and then decomposing the barium salt with dilute sulphuric acid.

Now the possibility of the existence of isomeric d -bromocamphorsulphonic acids had been under consideration from the very commencement, and in the first paper on these isomeric salts this question was discussed at some length and many experiments were made in order to try and decide it (Trans., 1900, 77, 877—882). The possibility of keto-enolic tautomerism in the group

was considered especially, examined experimentally, and rejected ; that of the existence of stable isomeric acids, represented by the configurations

was also discussed and dismissed, partly from theoretical considerations based on the known behaviour of ordinary *cis*- and *trans*-modifications, but principally, no doubt, because the acid actually obtained from the α -salt was found to be identical with that prepared from the β -isomeride. The new facts just mentioned rendered it necessary, of course, to reconsider these possibilities, and it may now be taken as proved that the existence of structurally isomeric acids, convertible one into the other under particular conditions, but otherwise extremely stable, is the true explanation of the existence of the isomeric α - and β -salts. *d*-Bromocamphorsulphonic acid and the corresponding *d*-chloro-compound exist then in two stable forms ; the acids contained in the β -salts may be named β - or *iso-d*-bromo- and β - or *iso-d*-chloro-camphorsulphonic acids respectively, the components of the α -salts being referred to as the α - or *normal* forms.*

These *iso*-acids and the normal forms are stable in aqueous solution, and in presence of hydrochloric acid even at 100° ; they are also stable in neutral or acid solutions of their salts at 100°. In presence of free base, however, such as caustic potash, baryta, sodium carbonate, hydrindamine, &c., a small proportion of the normal acid is transformed into the *iso*-form, whereas under the same conditions the latter is almost entirely converted into the normal form. The condition of equilibrium seems to be attained when about 90—95 per cent. of the acid is present in the normal form ; if, however, the salt of the β - or *iso*-form is evaporated with a solution of the free base, it is almost entirely transformed into the more sparingly soluble salt of the α - or normal acid.

The question next arises, what is the relationship between these isomeric forms of the sulphonic acids ? In the author's opinion, neither of the isomerides represents the enolic modification, because neither the α - nor the β -hydrindamine salt gives a coloration with ferric chloride or interacts with phenylcarbimide (Trans., 1900, '77, 881). Also because α -bromocamphor, from which the bromo-sulphonic acid is derived, does not give a benzoyl derivative when shaken with benzoic chloride in alkaline solution ; experiments recently made by the author

* The acids here named the β - or *iso*-acids for the sake of clearness should be indexed under the names *da'*-chloro- and *da'*-bromo-camphorsulphonic acid respectively, as they are α' - and not β -derivatives of camphor.

with the object of preparing such derivatives of α -bromocamphor and of camphor gave indubitably negative results. Further, because camphor- π -sulphonic acid and Reychler's camphorsulphonic acid,* both of which contain the group $-\text{CH}_2\cdot\text{CO}-$, and which, therefore, might theoretically exist in an enolic form, but which cannot yield *cis*- and *trans*-isomerides, do not give rise to isomeric hydrindamine salts (Trans., 1901, 79, 370 and 437). It may be concluded, therefore, that the isomeric α - and β - or normal and *iso*-acids are the *cis*- and *trans*-forms, and that the conversion of one into the other in presence of bases takes place as indicated in the following formulæ:

During this transformation, the two compounds become *identical*, that is to say, they both pass through the same unstable enolic form.

A somewhat analogous case which has recently come under the author's observation may be quoted in support of this view. *d*-Methylhydrindone (Proc., 1902, 18, 34) is apparently stable when pure, and is not changed by mineral acids, as is shown by the facts that its specific rotation does not alter appreciably in the course of several weeks, and the optically active ketone is actually prepared in presence of hydrogen chloride; consequently the ketone does not exist in the enolic form under these conditions. When, however, a trace of sodium ethoxide is added to its alcoholic solution, it rapidly and completely racemises, that is to say, it is doubtless converted into equal quantities of the *cis*- and *trans*-isomerides,

* The fact that Reychler's camphorsulphonic acid does not give rise to isomeric hydrindamine salts may be taken as confirming the view that this acid is a β - and not an α -derivative of camphor (compare Armstrong and Lowry, Trans., 1902, 81, 1473).

The discovery of the existence of the isomeric sulphonic acids and the above view as to their relationship account for all the facts observed in the study of the isomeric hydrindamine, benzylhydrindamine, methylhydrindamine, and *l*-menthylamine salts which are derived from them; the free acids, as ordinarily prepared, invariably consist of a mixture of the normal with a small proportion of the *iso*-form.

It may perhaps seem singular that it should have taken so long to arrive at what now appears to be such a simple and obvious explanation of the existence of these isomerides. The reason is, no doubt, that the truth was concealed or obscured by a combination of apparently disconnected facts, of which the following may be mentioned. Firstly, because the explanation originally suggested is, in one sense, so near the truth that it accounted for all the phenomena, excepting the observed values for the molecular rotations of the β -salts, just as well and in an even simpler manner than does the present one; the author's suggestion was that the isomeric salts contained respectively the groupings

the true explanation is that the isomeric forms are *cis*- and *trans*-modifications:

Secondly, because of the production of apparently analogous isomerides from *cis*- π -camphanic acid, in which case the existence of such *cis*- and *trans*-forms seemed, and still seems, to be very improbable; the constitution assigned to this acid (Trans., 1896, 69, 918) is not to be regarded as definitely established, but hitherto no indication of the existence of isomeric forms has been observed, and the nature of the isomeric salts to which it gives rise is still unknown.

Further, it must be borne in mind that no indication of the occurrence of intramolecular change has ever been obtained from an examination of the specific rotations of α -bromo- and α -chloro-camphor or of their sulphonic derivatives, whereas in the case of other α -derivatives of camphor, which are capable of existing in isomeric forms, such evidence is obtained at every turn and the one form passes into the other apparently spontaneously (compare Lowry, Trans., 1899, 75, 211).

Also, it may be again noted, various experiments seemed to prove the non-existence of an enolic form of the bromo-acid (Trans., 1900, 77, 881), and if this were so it seemed obvious that the ordinary acid could not be transformed into an *iso*-form and *vice versa* under the

conditions employed by the author during the study of the isomeric salts; if, on the other hand, such a transformation were possible, then it seemed most probable that on crystallising any salt in the ordinary way only *one* form would be obtained, namely, the more sparingly soluble one, as is usual in such cases.

These and many other reasons, which are recorded in earlier papers, seemed of such weight as to render inadmissible the view that the salts were derived from *cis*- and *trans*-acids; the new facts prove the contrary. Nevertheless, all the old facts remain as recorded, and as regards the experimental part of the work there is, as far as the author knows, nothing to correct and nothing to withdraw.

Salts of the Normal and iso-Forms of Bromo- and Chloro-camphor-sulphonic Acids.

The method invariably used for the preparation of these sulphonic acids is the decomposition of their barium salts with dilute sulphuric acid; the barium salts, which are prepared by boiling the ammonium salts with baryta, are formed in alkaline solution, and will therefore consist of the derivatives of both the normal and *iso*-acids. The acid prepared from this mixture of barium salts is therefore itself a mixture, as is also, doubtless, any salt obtained by neutralising the acid; this is clearly shown by the experiments on the "regeneration" of the salts of hydrindamine, methylhydrindamine, and menthylamine. It seems very probable, therefore, that the only pure salts of the normal acids which have so far been obtained are:

ad-Hydrindamine *d*-bromocamphorsulphonate,

al- " " "

ad-Hydrindamine *d*-chlorocamphorsulphonate,

al- " " "

and possibly the *ad*- and *al*-methylhydrindamine bromocamphorsulphonates and the salt of *l*-menthylamine.

Ordinary ammonium bromocamphorsulphonate certainly appears to be homogeneous, as its optical properties do not change when it is repeatedly crystallised (see above); whether this is due to the impossibility of separating the salt of the normal from that of the *iso*-acid or to the complete transformation of the *iso*- into the normal form during the evaporation of the ammoniacal solution is uncertain; the author inclines to the first view from a practical acquaintance with the extraordinary difficulty met with in separating the normal and *iso*-salts of hydrindamine and other organic bases, such as phenylethylamine (Hunter and Kipping, *Trans.*, 1903, **83**, 1147). When, moreover, it is found that the partially racemic β -modification of hydrind-

amine bromocamphorsulphonate, which behaves like a homogeneous substance, is in reality a mixture of four very different salts,* it is quite credible that ammonium bromocamphorsulphonate and all other salts which have not been specially treated should contain a small proportion of the isomeric salt of the *iso*-acid.

Silver bromocamphorsulphonate, prepared from the acid, is probably also a mixture in spite of the fact that many organic salts, obtained by treating the silver salt with halogen derivatives of bases, were not resolved into appreciably different fractions after repeated crystallisation (Barrowcliff and Kipping, *Trans.*, 1903, **88**, 1141).

As regards the salts of the β - or *iso*-acids, the only compounds hitherto obtained in a pure state are :

βl -	Hydrindamine	<i>d</i> -bromocamphorsulphonate,
βd -	„	<i>d</i> -chlorocamphorsulphonate, and
βl -	„	„

The β -forms of *d*-hydrindamine *d*-bromocamphorsulphonate and of the corresponding salts obtained from *d*-methylhydrindamine, *l*-methylhydrindamine, and *l*-menthylamine were not obtained in a state of purity, as was indeed clearly recognised at the time (Tattersall and Kipping, *Trans.*, 1903, **83**, 924; Tutin and Kipping, *Trans.*, 1904, **85**, 65); that these salts should still contain such a very large proportion of the α -isomeride, as in fact they do (see p. 638), was, however, hardly to be expected.

Molecular Rotations of the Normal and iso-Acids.

Since it seems highly probable that most of the salts of α - or “normal” *d*-bromocamphorsulphonic acid contain a considerable quantity of the isomeric β -salt, it would follow that the value for the molecular rotation of the normal acid ion, as hitherto determined, is too low. The results obtained with the pure *d*- and *l*-hydrindamine salts give, as a mean value, $[M]_D + 269^\circ$, which agrees well with that

* It seems very probable that the bromocamphorsulphonate of dihydro- α -methylindole, melting at 124 – 125° , obtained by Pope and Clarke (*Trans.*, 1904, **85**, 1330) during their experiments on the resolution of the above-named base, is also a mixture of four compounds, namely :

<i>d</i> -	Dihydro- α -methylindole	normal	<i>d</i> -bromocamphorsulphonate,
<i>l</i> -	„	„	„
<i>d</i> -	„	<i>iso</i> -	„
<i>l</i> -	„	„	„

Its molecular rotation, $[M]_D + 242.7^\circ$ shows that it is not a salt of either the pure normal acid or of the pure *iso*-acid (compare p. 638), and the optical inactivity of the base obtained from it proves that its low molecular rotation is not due to excess of the *l*-base.

usually accepted; such a value, however, based on determinations with two bases only can hardly be accepted as final and the true one is probably more nearly $[\text{M}]_{\text{D}} + 280^\circ$.

The only pure salt of the β - or *iso*-bromo-acid which has been examined optically is the *l*-hydrindamine salt, which gives for the *iso*-acid ion the value $[\text{M}]_{\text{D}} + 177^\circ$; the molecular rotations of the "last fractions" of the *d*-methylhydrindamine, *l*-methylhydrindamine, and *l*-menthylamine salts, previously described, approximate to those of the normal rather than to those of the *iso*-acid, and it is obvious therefore that these "last fractions" contained a larger quantity of the normal than of the *iso*-acid.

The molecular rotations of the pure hydrindamine salts of normal chlorocamphorsulphonic acid give the value $[\text{M}]_{\text{D}} + 185.5^\circ$ for the normal acid ion, but the data are insufficient to give a reliable result; in the case of the *iso*-acid, the examination of the same two hydrindamine salts gives $[\text{M}]_{\text{D}} + 233^\circ$ as the mean value for the *iso*-acid ion.

This is one of those cases which shows the extreme difficulty of establishing any definite connection between the constitution of a compound and its specific rotatory power; it can hardly be doubted that the normal forms of the *d*-bromo- and *d*-chloro-acids correspond in configuration, and yet when the former is transformed into the *iso*-modification its molecular rotation falls by about 90° , whereas a corresponding intramolecular change in the chloro-acid increases the molecular rotation by about 48° . This curious fact assisted no doubt in concealing the true nature of the isomerism of the α - and β -salts.

The investigation of the *iso*-forms of *d*-bromo- and *d*-chloro-camphorsulphonic acids will be continued, but, as the only method at present available for their isolation is that of fractionally crystallising their salts with one of the optically active hydrindamines, it is obvious that they cannot be obtained very easily or in large quantities.

The further study of these sulphonic acids and of *d*-methylhydrindone may also help to elucidate the mechanism of tautomeric change, which, according to Lapworth and Hann (*Trans.*, 1902, **81**, 1512), "may be the result of one or both of two superposed reactions, one due to ionisation in the compound itself, accelerated by bases and retarded by acids, and the other due to an additive phenomenon, accelerated by acids and retarded by bases."

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UNIVERSITY COLLEGE,
NOTTINGHAM.