53. *The Optical Stability of* 1 : 2 : 3 : 4-*Tetrahydro*-2-*naphthylamine.*

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Pope and Harvey's report[1] that 1 : 2 : 3 : 4-tetrahydro-2-naphthylamine racemises during liberation from its salts, or during the preparation of its derivatives, has been examined. The base has been resolved as its hydrogen (+)-tartrate, and it is shown that the (+)- and the (−)-bromocamphor-sulphonate of the amine used by the above-mentioned authors contain some two-thirds of the amine in its racemic form; it was probably this racemic material initially present that led to the isolation of partially racemised crystalline derivatives. In the present work no evidence of optical instability was obtained.

Many examples are recorded in the literature of the racemisation of alcohols, esters, and other alkyl–oxygen compounds in which the oxygen atom is attached to the asymmetric centre of the molecule. This has been interpreted in terms of unimolecular alkyl–oxygen heterolysis, and has contributed much to our understanding of this subject.[2]

Relatively few examples of the analogous racemisation of amines are known. Although the optical instability of derivatives of α-amino-acids can clearly be ascribed to the ionisation of the α-hydrogen atom, a few examples remain where the reason for it is not obvious. At the outset of the present work the best authenticated case appeared to be in the report by

[1] Pope and Harvey, *J.*, 1901, **79**, 74.

[2] Davies and Kenyon, *Quart. Rev.*, 1955, **9**, 203.

Pope and Harvey,[1] reiterated by Cloetta and Waser,[3] that 1 : 2 : 3 : 4-tetrahydro-2-naphthylamine is extensively racemised during its liberation from its salts and during reaction at the nitrogen atom. To determine the mechanism of the process which causes optical instability in the amine, and its chemical consequences, we have examined this report.*

By treating the amine (2 mols.) with ammonium (+)- or (−)-3-bromocamphor-8-sulphonate (1 mol.), Pope and Harvey obtained the (+)-amine (+)-bromocamphorsulphonate, $[\alpha]_D$ +86·5° (in EtOH), and the (−)-amine (−)-bromocamphorsulphonate, $[\alpha]_D$ −86·2° (in EtOH); the resolution was therefore assumed to be complete. Treatment of the salt of the (+)-amine with alkali gave, in separate experiments, the (+)-amine, α_D +30·5° and +37·24°. The active bromocamphorsulphonates were then converted, usually *via* the free base, into a number of solid derivatives, which, in every case, could be separated by fractional crystallisation into racemic and optically active fractions. The maximum rotatory powers of particular active fractions were : hydrochloride, $[\alpha]_D$ +71·9° and −69·7° (in H_2O); (+)-amine (+)-camphor-10-sulphonate, +47·7°, and (−)-amine (−)-camphor-10-sulphonate, −47·4° (in H_2O); by use of the principle of the additivity of the molecular rotations of the anion and cation of a salt, these compounds were shown probably to be optically pure. Pope and Harvey concluded that partial racemisation occurred during liberation of the base from its salts, and that more extensive racemisation accompanied the preparation of the derivatives. They ascribed this behaviour to the ionisation of the α-hydrogen atom. Cloetta and Waser [3] found difficulty in crystallising the (+)-bromocamphorsulphonate of the amine, and so resolved the base by the use of ½ mol. of (+)-tartaric acid. The resulting salt had $[\alpha]_D$ +57·8° (in H_2O) and gave the hydrochloride, $[\alpha]_D$ +43·64° (in H_2O). These authors stated that the formation of the hydrochloride is accompanied by partial inversion.

We have resolved 1 : 2 : 3 : 4-tetrahydro-2-naphthylamine as its hydrogen tartrate formed from equimolecular amounts of the base and of (+)-tartaric acid. After recrystallisation from water the most active salt had $[\alpha]_D$ +86° (in H_2O) and gave successively the amine α_D +95·83° (undiluted), and (without its isolation) the amine hydrochloride, $[\alpha]_D$ +67·5° (in H_2O) raised to +71·9° by recrystallisation from water. This corresponds well with Pope and Harvey's maximum values of +71·9° and −69·7°; it is therefore probably safe to assume, as these authors do, that this amine hydrochloride is optically pure. The rotatory power of the optically pure amine may therefore be calculated to be about 102°.

No loss of optical activity was observed when the amine was recovered after prolonged treatment in solution with sodium ethoxide, sodium hydroxide, or excess of hydrochloric acid. Similarly when the amine was dissolved in acid and liberated with alkali successively four times, it was recovered with undiminished optical activity. Again, the use of sodium carbonate or of sodium ethoxide in the decomposition of the hydrogen tartrate did not alter the rotatory power of the amine obtained.

We therefore prepared the (+)-bromocamphorsulphonate from our active hydrochloride and hydrogen tartrate in order to repeat Pope and Harvey's original experiments, and obtained products with $[\alpha]_D$ +101° and +102° (in EtOH). In aqueous solution the corresponding values are $[\alpha]_D$ +86° and +87°, respectively. Assuming the additivity of the molecular rotations of the anion ($[M]_D$ +277°) [1] and cation ($[M]_D$ +132°)[1, 5] of the salt in dilute aqueous solution, we derive $[M]_D$ +409° for optically pure (+)-1 : 2 : 3 : 4-tetrahydro-2-naphthylammonium (+)-bromocamphorsulphonate, whence $[\alpha]_D$ = +89° (in H_2O). This confirms the substantial optical purity of our specimens, as would be expected if no racemisation occurred during their preparation.

The above (+)-bromocamphorsulphonate, $[\alpha]_D$ +101 to +102° (in EtOH), is to be

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* Pickard and Kenyon[4] found that the corresponding 1 : 2 : 3 : 4-tetrahydro-2-naphthol is optically stable and does not undergo unimolecular alkyl-oxygen heterolysis. These results have been confirmed and extended by Barratt (unpublished work).

[3] Cloetta and Waser, *Arch. exp. Pathol. Pharmakol.*, 1913, **73**, 398.
[4] Pickard and Kenyon, *J.*, 1912, **101**, 1427.
[5] See p. 253.

compared with that of $[\alpha]_D$ +86·5° and −86·2° which Pope and Harvey assumed to be optically pure, and upon which they performed their experiments. The probability therefore immediately arises that the inactive compounds which they isolated by fractional crystallisation of derivatives of the amine were not formed by racemisation during reaction, but were derived from racemic base present in the incompletely resolved bromocamphorsulphonate. This has been confirmed by performing the cycle of operations

amine → hydrochloride → bromocamphorsulphonate → amine

avoiding fractional crystallisation of any of the intermediate salts, whereupon the amine was recovered with undiminished optical activity.

Pope and Harvey considered this possibility that their original bromocamphorsulphonates might be partially racemic, but claimed to have disproved it by finding racemisation in the cycle of reactions camphorsulphonate → amine → camphorsulphonate. Unfortunately no details of this experiment are given and we have not detected any racemisation during these reactions. To confirm that fractionation had not occurred during the final isolation of our camphorsulphonate the cycle amine → camphorsulphonate → amine was performed, isolation of the salt being avoided. No racemisation was observed. The camphorsulphonate from our most active (+)-amine had $[\alpha]_D$ +46·3° (in H_2O) which compares well with Pope and Harvey's maximum values, and therefore, as these authors assumed, probably represents optical purity.

Why Pope and Harvey, in separate experiments, obtained amine of varying rotatory power from the same specimen of bromocamphorsulphonate, which forms part of their evidence for the occurrence of racemisation, is not clear. The rotatory power of the amine varies with temperature but not sufficiently to account for this large difference, and, although the amine rapidly forms a carbonate in the air, we have shown that this exerts only a small effect on the rotatory power of the amine.

We conclude therefore that, whereas Pope and Harvey probably obtained the amine hydrochlorides and camphorsulphonates optically pure, the bromocamphorsulphonates, upon whose reactions they based their conclusions of optical instability, were only about one-third resolved. In all probability the racemic solid, which they isolated from the active derivatives by recrystallisation, was derived from the two-thirds of inactive amine initially present and was not formed during reaction. It is unfortunate that they did not investigate similarly the reactions of their hydrochlorides or camphorsulphonates, or isolate the liquid amine rather than its solid derivatives, or measure the optical rotatory power of their bromocamphorsulphonates in aqueous solution rather than in ethanol; any of these experiments would have indicated the source of their racemic product.

We have obtained no evidence of optical instability.

EXPERIMENTAL

(+)-1 : 2 : 3 : 4-*Tetrahydro*-2-*naphthylammonium Hydrogen* (+)-*Tartrate*.—The (±)-amine (80 g., 1 mol.) in acetone (*ca.* 125 c.c.) was added to a solution of (+)-tartaric acid (80 g., 1 mol.) in water (125 c.c.). Next day the thick mass of crystals was separated, washed with 50% aqueous acetone (50 c.c.) and with acetone (50 c.c.) and dried *in vacuo* (yield, 126 g.). Nine recrystallisations from water gave the salt, m. p. 217°, $[\alpha]_D^{18}$ +86° ((*l*, 1; *c*, 0·4360 in H_2O).

(+)- *and* (−)-1 : 2 : 3 : 4-*Tetrahydro*-2-*naphthylamine*.—(i) The above hydrogen (+)-tartrate (5 g.) was shaken for a few min. with 50% aqueous potassium hydroxide (10 c.c.). The liberated base was extracted with ether, and the extract washed and dried ($MgSO_4$), yielding the (+)-amine (2·2 g.), b. p. 115°/*ca.* 12 mm., α_D^{20} +96·0° (*l*, 1; undild.), α_{5463}^{19} +115·40°, α_{5893}^{19} +95·83°, α_{6563}^{19} +75·88° (*l*, 1; undild.).

(ii) A sample of the (−)-amine hydrogen (+)-tartrate (5 g.) $[\alpha]_D^{20}$ −12° (*l*, 1; *c*, 2·632 in water), which was recovered from the mother-liquors of the resolution, was warmed for 20 min. (steam bath) with a solution of sodium carbonate (5 g.) in water (100 c.c.). More sodium carbonate (15 g.) was added and the free base extracted by the usual procedure; it had α_D^{24} −33·73° (*l*, 0·5; undild.).

(iii) A further sample of the same hydrogen tartrate as in (ii) was suspended in ethanol (40 c.c.) containing sodium ethoxide (from 4 g. of sodium). After the mixture had refluxed for 0·5 hr., water (20 c.c.) was added, and most of the ethanol distilled off. Extraction of the residue with ether gave the amine, α_D^{24} −35·20° (*l*, 0·5; undild.). The difference in rotatory power between these two samples is probably not significant.

From the amine, α_D +81·20° (*l*, 1; undild.), were prepared the *N*-(1 : 2 : 3 : 4-tetrahydro-2-naphthyl)dithiocarbamate, m. p. 142°, $[\alpha]_D^{22}$ +62° (*l*, 1; *c*, 0·466 in EtOH) [Bamberger and Müller[6] report m. p. 142° for the (±)-compound], and *N*-(1 : 2 : 3 : 4-tetrahydro-2-naphthyl)-thiourea, m. p. 195°, $[\alpha]_D^{22}$ +84° (*l*, 1; *c*, 0·557 in EtOH) (Found : C, 64·5; H, 7·25; N, 13·5; S, 15·55. Calc. for $C_{11}H_{14}N_2S$: C, 64·0; H, 6·85; N, 13·6; S, 15·55%).

(+)-1 : 2 : 3 : 4-*Tetrahydro-2-naphthylammonium Carbonate.*—In contact with air the amine forms a crust of the carbonate in a few minutes,[6] and much more slowly becomes coloured through oxidation. (It may be inferred that this difficulty influenced Pope and Harvey's choice in basing their evidence for racemisation on the rotatory power of the amine's solid derivatives, rather than that of the amine itself.) Before the optical rotations of specimens of the amine were measured the polarimeter tubes (capillary, end-filling), capillary-teat pipette, and rubber teat were always flushed with nitrogen; similarly, specimens of the amine were always sealed under nitrogen. With rapid work and these precautions, no formation of carbonate was apparent. The effect of a small amount of carbonate on the rotatory power of the amine was determined as follows :

Solid carbon dioxide was added to a solution of a few drops of the amine, α_D^{18} +81·20° (*l*, 1·0; undild.), in ether. The thick white precipitate of carbonate was separated and dried *in vacuo* at room temperature; it had $[\alpha]_D^{21}$ +92° (*l*, 1; *c*, 0·4570 in EtOH), +78° (*l*, 1; *c*, 0·922 in CH_2Cl_2), α_D^{20} +80·42° (*l*, 1; *c*, 0·844 in the amine of α_D^{18} +81·20°). The presence of a small amount of the carbonate therefore has little effect on the rotatory power of the amine.

(+)-1 : 2 : 3 : 4-*Tetrahydro-2-naphthylammonium Chloride.*—The amine (0·2894 g.), α_D^{19} +95·83 (*l*, 1; undild.), was dissolved in 0·231N-hydrochloric acid (8·52 c.c., 1·00 equiv.), and the solution diluted to 10 c.c.; it then had $[\alpha]_D^{20}$ +67·5° (*l*, 1), whence the ratio of [α] for the amine hydrochloride to α for the amine is +0·704. This value was duplicated in a second experiment. The presence of a few drops of concentrated hydrochloric acid did not change this rotation. By recrystallisation from water a less soluble fraction of the hydrochloride was obtained, having $[\alpha]_D^{17}$ +72° (*l*, 1; *c*, 1·293 in H_2O).

Optical Stability of the Amine to Acid and Base.—(i) *Hydrochloric acid.* A solution of the optically impure (+)-amine hydrochloride (0·2502 g.) in water (25 c.c.) containing concentrated hydrochloric acid (1·0 c.c.) had α_D +0·46° (*l*, 1). This value was unchanged after the sample had been kept for 3 days in the dark.

(ii) *Sodium ethoxide.* The amine (5 g.), α_D +52·10° (*l*, 1; undild.), was dissolved in a solution of sodium (0·05 g.) in ethanol (10 c.c.). Next day water was added and the amine was recovered, b. p. 120°/15 mm., α_D +51·70° (*l*, 1; undild.).

(iii) *Sodium hydroxide.* The amine (3 g.) which was isolated from (ii) was dissolved in a solution of sodium hydroxide (2 g.) in *ca.* 95% ethanol. After 2 weeks the amine was recovered, α_D +51·92° (*l*, 1; undild.).

Optical Stability during Repeated Formation and Decomposition of the Amine Hydrochloride.—The amine (4 g.), α_D −68·93° (*l*, 1; undild.), was dissolved in 50% hydrochloric acid (10 c.c.), and the solution then made alkaline with 50% aqueous potassium hydroxide to liberate the amine. Acid and alkali were added in turn till the salt had been formed three times and decomposed three times. At each stage the pH of the solution was checked with Universal indicator. The amine finally recovered (*ca.* 2 g.) had b. p. 120°/15 mm., α_D −68·90° (*l*, 1; undild.).

(+)-1 : 2 : 3 : 4-*Tetrahydro-2-naphthylammonium* (+)-*Bromocamphorsulphonate.*—(i) *From the hydrochloride.* A saturated aqueous solution of ammonium (+)-3-bromocamphor-8-sulphonate (0·35 g.) was added to a solution of the amine hydrochloride (0·2 g.), $[\alpha]_D$ +72° (*l*, 1; *c*, 1·293 in H_2O), in water (10 c.c.). The amine (+)-bromocamphorsulphonate soon separated as needles, which were washed with water and dried *in vacuo*; they had $[\alpha]_D^{14}$ +86° (*l*, 1; *c*, 0·895 in H_2O), $[\alpha]_D^{17}$ +101° (*l*, 1; *c*, 1·071 in EtOH).

(ii) *From the hydrogen* (+)-*tartrate.* On mixing hot saturated aqueous solutions of the hydrogen (+)-tartrate, $[\alpha]_D^{18}$ +82° (*l*, 1; *c*, 0·4360 in H_2O), and of ammonium (+)-bromocamphorsulphonate (1·1 g.), the (+)-bromocamphorsulphonate of the amine separated after about 30 sec.; it was isolated as described above; it (0·86 g.) then showed m. p. 188·5—190°, $[\alpha]_D^{20}$ +87° (*l*, 1; *c*, 0·3676 in H_2O).

(iii) *From the amine.* Ethereal solutions of (+)-bromocamphorsulphonic acid and of the

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[6] Bamberger and Müller, *Ber.*, 1888, **21**, 847.

amine, α_D +84·8° (l, 1; undild.), were mixed; the salt which separated had $[\alpha]_D^{20}$ +81° (l, 1; c, 1·142 in H_2O).

The Cycle Amine ⟶ Hydrochloride ⟶ Bromocamphorsulphonate ⟶ Amine.—The amine (2·2 g.), α_D^{14} +84·8° (l, 1; undild.), in ether (10 c.c.) was treated with an excess of ethereal hydrogen chloride whereupon the amine hydrochloride was quantitatively precipitated. When aqueous solutions of this hydrochloride and of ammonium (+)-bromocamphorsulphonate were mixed, the (+)-bromocamphorsulphonate of the amine immediately separated. After 1 hr. the solid and supernatant liquid were jointly treated with an excess of 50% potassium hydroxide solution, and the amine was recovered; it had α_D^{13} +83·64° (l, 1; undild.).

(+)-1 : 2 : 3 : 4-*Tetrahydro-2-naphthylammonium* (+)-*Camphorsulphonate.*—The amine (0·5 g.), α_D^{20} +96·8° (l, 1; undild.), in ethanol (5 c.c.) was mixed with (+)-camphor-10-sulphonic acid (0·8 g.) in ethanol (2 c.c.). The camphorsulphonate separated on being kept; it was washed with alcohol and with ether and dried at 100°/16 mm.; it had m. p. 219·5—220·5°, $[\alpha]_D^{20}$ +46·3° (l, 1; c, 2·243 in H_2O), $[\alpha]_D^{20}$ +70·5° (l, 1; c, 0·921 in EtOH).

The Cycle Camphorsulphonate ⟶ Amine ⟶ Camphorsulphonate.—A mixture of the above-mentioned (+)-amine (+)-camphorsulphonate (0·6 g.), $[\alpha]_D^{20}$ +46·3° (in H_2O), and an excess of 20% sodium carbonate solution was kept at 60° for a few minutes. The liberated amine was collected in ether and treated with a solution of (+)-camphorsulphonic acid (0·36 g.) in ethanol. After 2 hr. the (+)-amine (+)-camphorsulphonate was filtered off, washed with ether, and dried at 100° *in vacuo*; it (0·4 g.) had $[\alpha]_D^{22}$ +46·8° (l, 1; c, 2·820 in H_2O).

The Cycle Amine ⟶ Camphorsulphonate ⟶ Amine.—The amine (1·0 g.), α_D^{22} +81·2° (l, 1; undild.), in ether was shaken with (+)-camphorsulphonic acid (1·6 g.) in water. The ether was boiled off, leaving a homogeneous solution from which the (+)-amine (+)-camphorsulphonate separated on cooling. After 4 days the crystals and supernatant liquid were jointly treated with an excess of 2N-sodium hydroxide, yielding the amine, α_D^{20} +80·58° (l, 1; undild.).

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