22. *The Rearrangement of* l-*Phenacyl-α-phenylethyldimethylammonium Bromide.*

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The salt named in the title is smoothly converted by sodium hydroxide into the diastereoisomeric forms of ω-dimethylamino-ω-α-phenylethylacetophenone with almost complete retention of optical activity : the reaction therefore most probably involves an *intra*-molecular rearrangement.

One of the stereoisomerides can be quantitatively converted into the other in an almost optically pure condition, thus affording an example of an asymmetric transformation under the influence of a second optically active centre.

In a series of communications Stevens and his collaborators (*J.*, 1928—1932) have observed and investigated a transformation of quaternary ammonium salts which may be formulated as

$$R'\cdot CO\cdot CH_2\cdot \overset{+}{N}RMe_2\}\overset{-}{Br} + NaOH \longrightarrow R'\cdot CO\cdot CHR\cdot NMe_2 + H_2O + NaBr$$

The reaction, which was shown to be unimolecular, occurs only in an alkaline medium, and when a mixture of two salts in which R was different underwent reaction only the rearrangement products of each individual salt could be isolated : the rearrangement was accordingly considered to be intramolecular (Stevens, *J.*, 1930, 2107).

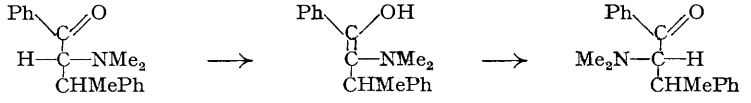
It seemed probable than an examination of the rearrangement products of an optically active quaternary ammonium salt, in which the migrating radical is attached to the rest of the molecule by an asymmetric carbon atom, would afford additional evidence bearing on the mechanism of this type of reaction, and the results of such a study are now presented.

Amongst the salts examined by Stevens was one in which R = CHMePh, prepared by the combination of ω-bromoacetophenone and *dl*-α-phenylethyldimethylamine : since this tertiary base is conveniently prepared from α-phenylethylamine which, in turn, is readily obtainable in an optically pure form, this quaternary ammonium salt was chosen for investigation. This salt reacted readily in sodium hydroxide solution, and since the resulting transformation product, (+)*ω-dimethylamino-ω-α-phenylethylacetophenone*, contains two asymmetric centres it was produced—as was found by Stevens in the case of the corresponding racemic compound—in two diastereoisomeric forms, both of which proved to be optically active.

One of these forms (α-) was converted into its l-*acid malate* which crystallised readily : on decomposition it yielded the α-base almost unchanged in rotatory power. When, however, a partly racemised specimen of the α-form was combined with *l*-malic acid and the salt crystallised, the liberated α-form possessed almost its maximum rotatory power. Furthermore, the second form (β-) on being heated with an alcoholic solution of sodium ethoxide was converted, apparently completely, into the corresponding α-form with $[\alpha]_{5893}^{20°}$ + 40·1° (in methanol). Under similar treatment the rotatory power of the optically pure α-form is reduced from $[\alpha]_{5893}^{20°}$ + 43·2° to + 39·7°—the rotatory powers of both specimens being raised to + 43·0° by crystallisation from methanol.

It therefore seems highly probable that both the α- and the β-form have been produced with almost complete retention of optical activity, and thus experimental evidence of a different character is provided in support of the view that the transformation of quaternary ammonium salts, described by Stevens, involves an intramolecular rearrangement.

Stevens suggested that the conversion of the racemic β-form into the racemic α-form might be effected by the groups arranged round the carbon atom next to the carbonyl group undergoing inversion by enolisation ·



This explanation is rendered more probable by the retention of optical activity during the conversion of the β- into the α-variety. Furthermore, the conversion of the optically active β-form into the α-form in apparently quantitative yield affords an interesting example of an asymmetric transformation under the influence of another optically active centre. Had the enol ⟶ keto change followed its normal course, an equilibrium mixture of the α- and the β-form would have been obtained.

Experimental.

l-α-Phenylethylamine was obtained by applying a procedure briefly outlined by Betti (*Gazzetta*, 1920, **50**, 276) : to a solution of the *dl*-base (48 g., purified by one crystallisation of its acid oxalate) in 96% alcohol (600 c.c.) tartaric acid (59·6 g.) was added, and the mixture was kept at 60° and stirred for 24 hrs., then filtered whilst hot. The undissolved, compact, crystalline residue, recrystallised once from the minimum amount of hot water, yielded the optically pure acid tartrate of *l*-α-phenylethylamine, large rhombs (31 g.) with $[\alpha]_{5893}$ — 13·3°, $[\alpha]_{5780}$ — 13·5°, $[\alpha]_{5461}$ — 14·5°, $[\alpha]_{4358}$ — 16·2° (*l*, 2; *c*, 3·985) in aqueous solution at room temperature. The base was liberated by sodium hydroxide, and steam-distillation and extraction with benzene yielded *l*-α-phenylethylamine, b. p. 73°/14 mm. (14 g.). In the homogeneous state it had, at 17°, α_{5893} — 18·28°, α_{5780} — 19·24°, α_{5461} — 22·90°, α_{4358} — 37·44° (*l*, 0·5).

By fractional crystallisation of the corresponding *d*-bromocamphorsulphonate, Ingold and Wilson (*J.*, 1933, 1503) obtained the value $\alpha_{5461}^{16.5°}$ — 22·92° (*l*, 0·5) for the base, so it is highly probable that optical purity has been reached by both procedures, of which the one described above is clearly more advantageous.

From the more soluble fractions of the acid tartrate salt there was obtained (*d* + *dl*)-α-phenylethylamine with $\alpha_{5461}^{20°}$ + 12·32° (*l*, 0·5). An attempt was made to obtain the optically pure *d*-base by combining this material (24 g.) with racemic acid (29·8 g.) in alcoholic solution at 60° and stirring for 24 hrs. as described above. The crystalline residue on basification yielded, however, α-phenylethylamine (9 g.) with $\alpha_{5461}^{14°}$ + 14·45° (*l*, 0·5). By the use of this highly active material for the preparation of *d*-α-phenylethylamine a considerable saving of *l*-malic acid would result (cf. *Org. Synth.*, II, 506).

l-α-*Phenylethyldimethylamine.*—*l*-α-Phenylethylamine hydrochloride (30 g.), m. p. 160°, $[\alpha]_{5893}$ — 3·7°, $[\alpha]_{5780}$ — 4·2°, $[\alpha]_{5461}$ — 4·5°, $[\alpha]_{4358}$ — 8·8°, (*l*, 2; *c*, 6·865 in aqueous solution), was dissolved in formalin (300 c.c.; 40%) and heated in a pressure bottle to 130° for 3 hrs. The resultant solution, after basification with sodium hydroxide, yielded l-α-*phenylethyldimethylamine* (9 g.), b. p. 81/16 mm., α_{5893} — 32·24°, α_{5780} — 33·92°, α_{5461} — 38·94°, α_{4358} — 70·6° (*l*, 0·5; *t*, 20°), $n_D^{14°}$ 1·5025, $d_4^{16°}$ 0·8986 (Found : N, 9·3. $C_{10}H_5N$ requires N, 9·4%). Its *picrate*, from alcohol, forms plates, m. p. 140—141°, $[\alpha]_{5893}^{19°}$ — 7·4° (*l*, 1; *c*, 1·621 in acetone) (Found : N, 14·6. $C_{16}H_{18}O_7N_4$ requires N, 14·9%).

l-*Phenacyl-α-phenylethyldimethylammonium Bromide.*—A solution of the above tertiary base (8 g.) and ω-bromoacetophenone (10·6 g.) in dry benzene (30 c.c.) after 2 days had deposited a pink crystalline mass; this, after recrystallisation from alcohol–ether (charcoal), yielded the *bromide*, large octagonal plates, m. p. 126°, $[\alpha]_{5893}$ — 71·0°, $[\alpha]_{5780}$ — 73·3°, $[\alpha]_{5461}$ — 85·9°, $[\alpha]_{4358}$ — 155° (*l*, 2 : *c*, 7·104 in ethanol); $[\alpha]_{5893}$ — 74·9°, $[\alpha]_{5780}$ — 78·4°, $[\alpha]_{5461}$ — 90·0°, $[\alpha]_{4358}$ — 156° (*l*, 2; *c*, 1·643 in acetone), both at room temperature (Found : Br, 23·0. $C_{18}H_{22}ONBr$ requires Br, 22·8%).

Conversion of l-*Phenacyl-α-phenylethyldimethylammonium Bromide into the Stereoisomeric* (+)-ω-*Dimethylamino-ω-α-phenylethylacetophenones.*—The *l*-quaternary bromide (11 g.) was warmed on the steam-bath with N-sodium hydroxide (50 c.c.) for 30 mins.; after a few minutes the solution deposited a yellow oil which solidified on cooling (*A*) (7·8 g.), m. p. 90—93°, $[\alpha]_{5893}$ + 25°, $[\alpha]_{5461}$ + 33° (*l*, 2; *c*, 1·66 in methanol).

Separation of the stereoisomerides. (*a*) By following the procedure adopted by Stevens (*J.*, 1930, 2113) this mixture (*A*) of diastereoisomerides was separated by fractional precipitation and fractional crystallisation of their picrates and there were obtained the α-*picrate*, yellow platelets, m. p. 194—196°, $[\alpha]_{5893}^{19°}$ + 7·98° (*l*, 1; *c*, 1·507 in acetone) (Found : N, 11·1. $C_{24}H_{24}O_8N_4$ requires N, 11·3%), and the β-picrate, stout prisms, m. p. 172—174°, $[\alpha]_{5893}^{19°}$ + 58·0° (*l*, 1; *c*, 2·586 in acetone) (for the corresponding racemic compounds, Stevens, *loc. cit.*, gives for the α-form, m. p. 186—187° and for the β-form, m. p. 174—176°).

On decomposition, the α-picrate yielded α-(+)-ω-*dimethylamino-ω-α-phenylethylacetophenone*, very pale yellow needles, m. p. 108°, from methanol (Found : N, 5·4. $C_{18}H_{21}ON$ requires N, 5·2%); $[\alpha]_{5893}$ + 84·2°, $[\alpha]_{5780}$ + 91·2°, α_{5461} + 114°, α_{4358} + 166° (*l*, 0·5; *c*, 1·993 in acetone; *t*, 21°); α_{5893} + 43·2°, α_{5780} + 46·3°, α_{5461} + 54°, α_{4358} + 83° (*l*, 0·5 : *c*, 1·814 in methanol; *t*, 21°).

The β-picrate, on decomposition, yielded the β-(+)-ω-*dimethylamino-ω-phenylethylacetophenone*, deep-yellow platelets, m. p. 108°, from acetone–light petroleum (Found : N, 5·4%); $[\alpha]_{5893}$ + 10·7° (*l*, 2; *c*, 2·017 in acetone), $[\alpha]_{5893}$ + 5·0° (*l*, 2; *c*, 2·258 in methanol). The intensity of the colour of the solutions made it impossible to measure the rotatory powers for other wave-lengths.

(*b*) A solution of the mixed optically active bases (*A*) (4 g.) in warm methanol deposited on cooling the almost pure α-base (1·9 g.); this, on crystallisation, yielded the pure α-base, m. p. 108°, $[\alpha]_{5893}$ + 43·5° in methanol. A second recrystallisation did not alter the rotatory power.

The original mother-liquors, on standing, deposited 0·7 g. of mixed α- and β-bases and, after concentration, the β-base (1·2 g.), which after crystallisation from acetone–light petroleum had m. p. 108°, $[\alpha]_{5893}$ + 5·3° in methanol.

This method of separation proved more effective with the resolved than with the unresolved bases owing to the greater difference in solubility between the α- and the β-form of the resolved diastereoisomerides, which are produced in the approximate ratio 4 : 3.

Determination of the Extent of Retention of Optical Purity of the Bases produced by the Rearrangement.—From a solution of the (+)-α-base (2·2 g.) and *l*-malic acid (0·8 g.) in 50% aqueous acetone the *hydrogen malate* of (+)-ω-dimethylamino-ω-α-phenylethylacetophenone separated in long needles, m. p. 118—119° (Found : N, 3·4. $C_{22}H_{27}O_6N$ requires N, 3·5%). The (+)-α-base regenerated from this salt had $[\alpha]_{5893}^{20°}$ + 43·8° (*l*, 0·5; *c*, 1·869 in methanol), compared with the original value $[\alpha]_{5893}$ + 43·2°.

The (+)-α-base (2 g.) was warmed on the steam-bath for 3 hrs. with a solution of sodium (2 g.) in alcohol (25 c.c.). Dilution with water precipitated the partly racemised α-base, m. p. 106—108°, $[\alpha]_{389}$ + 39·7° (in methanol); crystallisation of this from methanol raised its rotatory power to $[\alpha]_{5893}$ + 43·0° (in methanol).

Some slightly racemised (+)-β-base (2 g.), treated in the same manner, yielded almost optically pure

(+)-α-base, $[\alpha]_{5893}$ + 40·1°; this, after crystallisation from methanol, gave the optically pure (+)-α-base, $[\alpha]^{20°}_{5893}$ + 42·9° (in methanol).

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