for dihydrorotenone is much smaller than that for rotenone, the relative toxicity of the former is nearly half again as great as that of the latter. Yet there is another variable which, if considered, would alter these relative values and bring them closer together, a relationship more credible after an inspection of the curves of the two substances. These curves show that after reaching its maximum the rate of increase of the velocity of fatality with increase in concentration decreases much more rapidly in dihydrorotenone than in rotenone. It is hoped that a formula may be developed which will include this third factor. On the other hand it may not really be significant to express the toxicity of a substance at a single value, but to define it according to the three variables, threshold of toxicity, rate of increase of the velocity of fatality and decrease of this rate.

Conclusions

The toxicity of rotenone begins at a higher concentration than that of dihydrorotenone (about twice, according to Powers' formula) and a lower concentration than that of isorotenone (about one-fourth). The toxicities of rotenone and dihydrorotenone increase with increase in concentration at about the same rate, but this rate is lower in the case of isorotenone (about one-third). At higher concentrations, rotenone is the most toxic and isorotenone the least. According to Powers' formula, which is an expression of relative toxicity based on the first two variables, these substances have the following decreasing order of toxicity: dihydrorotenone, rotenone and isorotenone.

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THE RESOLUTION OF 1-(ALPHA-1-PIPERIDYLBENZYL)-2-NAPHTHOL[1]

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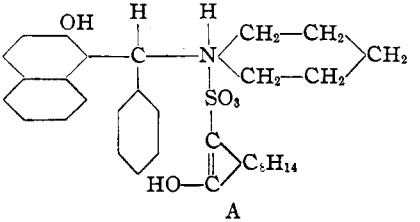
In a previous article on the condensation of secondary amines with naphthols and aldehydes[2] a description was given of the preparation of 1-(α-1-piperidybenzyl)-2-naphthol. This asymmetric amine is one of a series of amines which are being prepared and tested as resolving agents. At the present time only one synthetic amine, namely, α-phenylethylamine, has been used to any great extent for this work, most basic resolving agents being alkaloids, where only one of the two possible active forms is available for use.

[1] An abstract of a portion of a thesis submitted by Joseph B. Littman in partial fulfilment of the requirements for the degree of Doctor of Philosophy at The Ohio State University.

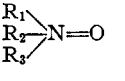
[2] Littman and Brode, THIS JOURNAL, 52, 1655 (1930).

dl-1-(α-1-Piperidylbenzyl)-2-naphthol can be resolved easily by means of *d*-camphorsulfonic acid. It has a high specific rotation, $[\alpha]_D$ −211°. Its use as a resolving agent, however, seems to be limited to strongly acidic compounds. Its solubility properties are poor for an ideal resolving agent but it does have acceptable qualities in its ease of crystallization, stability in the presence of common reagents and resistance to oxidation. In these latter qualities it is a marked improvement over the parent substance from which it is derived, 1-(α-aminobenzyl)-2-naphthol.[3,4]

From a comparison of the structural formula of 1-(α-1-piperidylbenzyl)-2-naphthol-*d*-camphorsulfonate (A) with the general formula of the amine oxides (B) which have been resolved by Meisenheimer,[5] it would appear



A



B

that there was a close relation in their configuration and one might possibly expect an asymmetric nitrogen atom in the first compound. Careful fractionation and a study of the rotation of various fractions failed to show any evidence of more than the two expected fractions in the resolution of a compound containing a single asymmetric atom. In similar attempts Barrowcliff and Kipping[6] did not succeed in resolving benzylmethylpiperidium-*d*-bromocamphorsulfonate and Wedekind[7] found it impossible to resolve quaternary ammonium bases with a double linking between carbon and nitrogen, ($Ph_2C{=}NMePhI$). In the case of the amine oxides, Meisenheimer[8] believes that the double bond between nitrogen and oxygen is semipolar, the oxygen atom figuring both as the fourth positive radical and taking the place of the negative ion of the ammonium salt.

Experimental

Thirty grams of *dl*-1-(α-1-piperidylbenzyl)-2-naphthol[2] was dissolved in 1300 cc. of absolute ethyl acetate on warming to 50°. To this solution, in a 2-liter round-bottomed flask, 22 g. of *d*-camphorsulfonic acid[9] dissolved in 200 cc. of absolute ethyl acetate was added. Soon after the addition of the *d*-camphorsulfonic acid solution, small colorless rosets began to form, which, after sixteen hours' standing, were filtered

[3] Betti, *Gazz. chim. ital.*, **31**, I, 385 (1901).

[4] "Organic Syntheses," John Wiley and Sons, Inc., New York, **1929**, Vol. IX, p. 60.

[5] Meisenheimer, *Ber.*, **41**, 3966 (1908).

[6] Barrowcliff and Kipping, *J. Chem. Soc.*, **83**, 1141 (1900).

[7] Wedekind, *Ann.*, **422**, 119 (1925).

[8] Meisenheimer, *ibid.*, **449**, 188 (1926).

[9] From the Eastman Kodak Co., $[\alpha]_D$ +20.98°.

and washed with hot ethyl acetate; yield, 28.5 g. (Fraction I). After eight more hours the filtrate yielded 7.7 g. of the salt, (Fraction II). The filtrate was evaporated to 850 cc. from which 4 g. of the salt was obtained (Fraction III).

The remaining filtrate was evaporated to dryness under reduced pressure, leaving a residue, somewhat yellow in color, which weighed 9.2 g. (Fraction IV). The total yield in all four fractions was 49.4 g. (theoretical, 51.9 g.).

Fraction I was recrystallized nine times by dissolving in 40 cc. of hot chloroform and then adding twice that volume of ethyl acetate. The degree of resolution and fractionation of the salts was followed by taking the optical rotation of the various fractions. The polarimetric observations were made on a Franz Schmidt and Haensch polarimeter, which was accurate to one hundredth of a degree rotation.

The salt, after the seventh, eighth and ninth recrystallization, had a constant rotation. 0.9385 g. made up to 10 cc. with chloroform at 20° gave $\alpha_D = +0.45°$; $l = 1$; $[\alpha]_D^{28}$ +4.7°. The salt from the ninth recrystallization, levo 1-(α-1-piperidylbenzyl)-2-naphthol-*d*-camphorsulfonate, melted with decomposition at 184–185° (corr.).

Anal. Calcd. for $C_{32}H_{39}O_5NS$: S, 5.82. Found: S, 5.79%.

Fractions II, III and IV were combined and fractionally recrystallized from a mixture of chloroform and ethyl acetate. The final mother liquor on evaporation gave a hard yellow mass which proved to be the dextro 1-(α-1-piperidylbenzyl)-2-naphthol-*d*-camphorsulfonate.

Preparation of the Free Amines.—Five grams of the levo 1-(α-1-piperidylbenzyl)-2-naphthol-*d*-camphorsulfonate was suspended in 50 cc. of water and to this suspension 100 cc. of 10% sodium carbonate solution was added. The mixture was poured into a separatory funnel and extracted thrice with 50-cc. portions of benzene. The benzene extracts were combined and dried with anhydrous sodium sulfate. The dried benzene solution was allowed to evaporate spontaneously in a beaker. The yield was 2.5 g. The levo-(α-1-piperidylbenzyl)-2-naphthol was recrystallized twice from a benzene-ligroin mixture, m. p. 201–202° (corr.).

Rotation. 0.2151 g. made up to 10 cc. with benzene at 20° gave $\alpha_D = -4.55$; $l = 1$; $[\alpha]_D^{27}$ −211°. 0.2036 g. made up to 10 cc. with chloroform at 20° gave $\alpha_D = -3.94$; $l = 1$; $[\alpha]_D^{28}$ −193°.

Three grams of the dextro salt was hydrolyzed with dilute sodium carbonate solution in the same manner as for the levo salt. The *d*-1-(α-1-piperdylbenzyl)-2-naphthol obtained was recrystallized twice from a benzene–ligroin mixture. The yield was 1.4 g., m. p. 199–200° (corr.).

Rotation. 0.2148 g. made up to 10 cc. with benzene at 20° gave $\alpha_D = +4.06$; $l = 1$; $[\alpha]_D^{31}$ +189°.

Summary

1-(α-1-Piperidylbenzyl)-2-naphthol has been resolved into its two active forms by means of *d*-camphorsulfonic acid.

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