662. *Methods of Resolution. Part II.** N-(−)-*Menthyl*-p-*sulphamylbenzoic Acid.*

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As a representative of a new class of optically active acids, *N*-(−)-menthyl-*p*-sulphamylbenzoic acid has been prepared by an easy synthesis. With its aid, a complete resolution of (±)-menthol has been effected, but an attempt to resolve (±)-*trans*-2-methyl*cyclo*hexanol failed.

In a programme designed to find new or improved methods of optical resolution, the resolution of alcohols has been chosen for investigation. This field has recently been surveyed by Ingersoll ("Organic Reactions," Vol. II, Chap. 9, Wiley, New York, 1944), and his review show that very few new procedures have been introduced since 1939.

The most common procedure, separation of the diastereoisomeric salts formed from an active base and an acid ester of the racemic alcohol, has several inherent defects. The salts often tend to dissociate during recrystallisation, and it may be difficult to follow the progress of a resolution, because the salts have indefinite melting points and may also be of variable composition, so that decomposition of a fraction to liberate the acid ester may be necessary in assessing its optical purity. Neutral esters formed from an active acid and the racemic alcohol are more attractive from the point of view of manipulation, because they have fixed compositions and usually sharp melting points when optical purity is attained. The introduction of menthoxyacetic acid (*J. Soc. Chem. Ind.*, 1932, **51**, 329T) and menthylglycine (*J.*, 1934, 1775) by Read and his associates, and of tartranilic acid by Barrow and Atkinson (*J.*, 1939, 638), represented important advances in this respect, and our object has been to carry out exploratory work on further types of active acids.

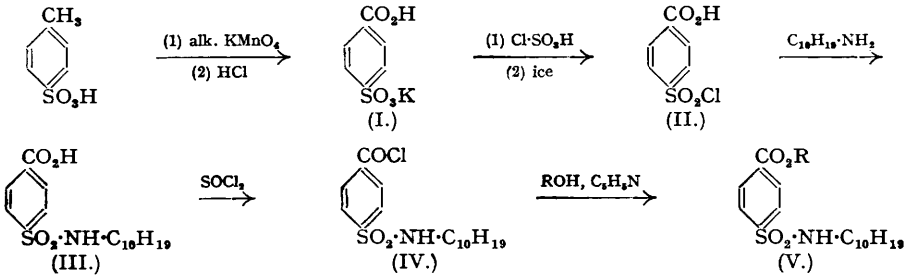
The acids mentioned above have a feature in common, in being built up from a unit carrying the carboxyl function, and an additional simple unit, an alcohol or amine, which may be varied to provide a series of reagents of the same type. This type of flexibility is a very desirable feature in a resolving agent, and other requirements for an active acid of the type sought are that it should (*a*) be easy to prepare, (*b*) preferably be available in both active forms to facilitate complete resolution, (*c*) be stable enough to be converted into esters in good yield through the acid chloride, and to be recovered for use again after hydrolysis of the esters, and (*d*) yet be susceptible to further degradation to recover the active component used in its synthesis, if this is valuable and required for other purposes. Menthoxyacetic acid and menthylglycine do not meet condition (*d*), as menthol or menthylamine cannot be recovered from them, and tartranilic acid does not meet any except (*a*). The requirement (*b*) in general will only be met if the active component is a simple synthetic compound which is available by an easy resolution; most natural products will be excluded as components.

A logical choice if the above conditions are to be fulfilled is an amido-acid, which may be built up from an active amine and an inactive dicarboxylic acid, and *N*-menthylphthalamic acid (*J.*, 1949, 577) has been used in several successful resolutions (*ibid.*; Macbeth, Mills, and Simmonds, *J.*, 1949, 1011; L. H. Darling, unpublished work), although the separation of the diastereo-mixtures has usually proved to be tedious. Menthylamine is not an ideal choice for the active component, as it is not readily available in the (+)-form, but it has been adopted as a convenient unit from which to build model resolving agents, and is so used in the present research. Most reagents derived from menthylamine will not meet requirement (*d*) (although *N*-menthylphthalamic acid does), because it is usually very difficult to liberate menthylamine from its acyl derivatives. 2-Phenylethylamine and 2-*p*-tolylethylamine are available in both active forms (Ingersoll and Burns, *J. Amer. Chem. Soc.*, 1932, **54**, 4712; Ingersoll, *Org. Synth.*, Coll. Vol. II, 1943, 506), and their use may lead more readily to reagents meeting this requirement.

Attention has now been turned to the possibility of using a sulphamyl-acid for optical

* "Esters of *N*-Substituted Phthalamic Acids" by Human and Mills (*J.*, 1949, S77) is regarded as Part I.

resolution of alcohols, and it has been found that *N*-(−)-menthyl-*p*-sulphamylbenzoic acid (III) is a suitable type of reagent, and is easily prepared and esterified as follows:



Good overall yields may be realised, and the several esters (V) prepared were solids with desirable physical properties.

An attempt was made to prepare the acid chloride (II) by direct oxidation of toluene-*p*-sulphonyl chloride by the method of de Jong (*Verslag Akad. Wetensch. Amsterdam*, 1923, **32**, 14), but only poor yields were obtained of a product difficult to handle. The oxidation of *N*-(−)-menthyltoluene-*p*-sulphonamide (VI; R = $C_{10}H_{19}$) was also tried as a route to (III), but oxidation with potassium permanganate caused simultaneous destruction of the menthyl radical, and the only identifiable product was *p*-sulphamylbenzoic acid (VII). The same

$$\underset{\text{(VI.)}}{(p)\text{-R·NH·SO}_2\text{·C}_6\text{H}_4\text{·CH}_3} \longrightarrow \underset{\text{(VII.)}}{(p)\text{-NH}_2\text{·SO}_2\text{·C}_6\text{H}_4\text{·CO}_2\text{H}}$$

product (VII) was obtained by the oxidation of *N-cyclo*hexyltoluene-*p*-sulphonamide (VI; R = C_6H_{11}) with chromic acid.

The experiments had to be terminated after two resolutions had been tried. One was very successful, in that the diastereo-mixture obtained by esterifying (III) with (±)-menthol could easily be separated to give two optically pure esters, from which (+)- and (−)-menthol could be obtained. An attempt to resolve (±)-*trans*-2-methyl*cyclo*hexanol failed because of the very slow separation of the diastereo-mixture.

Experimental.

(All rotations were observed with 2% solutions in B.P. chloroform.)

p-*Carboxybenzenesulphonyl Chloride* (II).—*p*-Carboxybenzenesulphonic acid, prepared by oxidation of toluene-*p*-sulphonic acid with alkaline permanganate, was conveniently isolated as its rather sparingly soluble acid potassium salt (I) (cf. Maarse, *Rec. Trav. chim.*, 1914, **33**, 207, who used the barium salt). Anhydrous toluene-*p*-sulphonic acid (34·5 g.) and potassium hydroxide (13·5 g.) were dissolved in water (300 ml.), and the solution was heated to 80°, stirred mechanically, and treated gradually during 1·5 hours with a slight excess of potassium permanganate (63 g.) dissolved in hot water (250 ml.). Excess of permanganate was destroyed with alcohol, manganese dioxide was filtered off, and the solution was acidified to Congo-red with hydrochloric acid, and evaporated to dryness. The residue was recrystallised from a minimum of water (150 ml.), and the crystalline product dried at 140°. The average yield of the anhydrous salt (I) was 92% (44 g.).

For conversion of the salt (I) into the acid chloride (II), the use of carefully distilled chlorosulphonic acid was necessary to get good yields. The finely powdered salt (24 g.) was stirred slowly into chlorosulphonic acid (80 ml., five-fold excess), the temperature being kept below 30°, and the mixture was left overnight. The clear solution was stirred into chipped ice, and the granular precipitate was collected, washed well with cold water, and dried *in vacuo* over sulphuric acid. The product (21 g., 95% yield) had m. p. 230—235°; for the acid chloride (II), de Jong (*loc. cit.*) reported m. p. 235—236° (decomp.). Recrystallisations from ether or *o*-dichlorobenzene did not effect an improvement in m. p.

Attempts were made to oxidise toluene-*p*-sulphonyl chloride, dissolved in a mixture of glacial acetic acid and acetic anhydride, with chromium trioxide following de Jong (*loc. cit.*) but from the original method and several modifications only poor results were obtained, and the product was invariably greenish, and very difficult to filter and wash.

N-(−)-*Menthyl*-p-*sulphamylbenzoic Acid* (III).—Preliminary experiments showed that reaction of the acid chloride (II) with (−)-menthylamine in anhydrous pyridine gave only poor yields (≪30%) of (III). Reaction under Schotten–Baumann conditions, the acid chloride being added to menthylamine in chloroform solution, shaken with aqueous alkali, also gave indifferent yields (50%), possibly because the acid chloride is readily soluble in aqueous alkali and quickly hydrolysed in it.

Better results followed the use of an excess of menthylamine (3 mols.) as condensing agent. The acid chloride (22 g.) was added with thorough shaking to a solution of (−)-menthylamine (46·5 g.) which had been purified through its formyl derivative (Human and Mills, *J.*, 1948, 1457), in dry ether (500 ml.), and

the mixture was left overnight. The ethereal solution was shaken with two portions of dilute aqueous sodium hydroxide, and the combined aqueous solution was warmed above 60°, stirred vigorously, and gradually acidified with hydrochloric acid. The precipitated fine needles, m. p. 198° (23 g., 70%), were practically pure N-(−)-*menthyl*-p-*sulphamylbenzoic acid*, and recrystallisation from dilute alcohol raised the m. p. to 201—202° (Found: C, 60·3; H, 7·2. $C_{17}H_{25}O_4NS$ requires C, 60·2; H, 7·4%). From the ethereal solution menthylamine (31 g.) was recovered.

N-(−)-*Menthyltoluene*-p-*sulphonamide* was prepared by allowing toluene-*p*-sulphonyl chloride to react with (−)-menthylamine in solution in anhydrous pyridine; it formed fine needles from aqueous alcohol, m. p. 160—161° (Found: C, 65·7; H, 8·6; N, 4·5. $C_{17}H_{27}O_2NS$ requires C, 66·0; H, 8·8; N, 4·5%). When it was oxidised with a slight excess of potassium permanganate in alkaline solution under the conditions used for oxidising toluene-*p*-sulphonic acid, the oxidation was slow (*N*-menthyltoluene-*p*-sulphonamide is practically insoluble in aqueous alkali), but the permanganate was eventually decolorised. About half of the toluene-*p*-sulphonyl compound was recovered unchanged, and the only acidic product which could be isolated was *p*-sulphamylbenzoic acid, m. p. 280° (decomp.) (Kelly, Robson, and Short, *J.*, 1945, 240). When *N-cyclo*hexyltoluene-*p*-sulphonamide (Hall and Turner, *J.*, 1945, 694) was oxidised with the calculated amount of chromic acid in hot dilute sulphuric acid, unchanged starting material and *p*-sulphamylbenzoic acid were the only products identified.

Esterification of N-(−)-*Menthyl*-p-*sulphamylbenzoic Acid.*—The acid (III) was warmed on the steam-bath for one hour with pure thionyl chloride (6 mols.), giving a clear brownish solution which was then evaporated to dryness under reduced pressure. Addition and evaporation of two successive lots of dry benzene removed traces of thionyl chloride and left a residue of the acid chloride (IV) in quantitative yield, as a porous mass, m. p. 100—110°. The chloride was very susceptible to hydrolysis, and attempts to obtain an analytically pure sample by recrystallisation from benzene–light petroleum were unsuccessful; the best samples, fine needles, m. p. 110—114°, still contained traces of the free acid (III).

The crude acid chloride was suitable for ester formation, and by dissolving small quantities of it in dry benzene, adding a slight excess of dry methanol or (−)-menthol, then excess of dry pyridine, and allowing the mixtures to stand for one hour, the respective esters were obtained in good yield; the *methyl* ester (V; R = CH_3) separated from aqueous methanol as fine needles, m. p. 112—112·5° (Found: N, 3·9. $C_{18}H_{27}O_4NS$ requires N, 4·0%), and the (−)-*menthyl* ester (V; R = $C_{10}H_{19}$) as fine needles, m. p. 150—151°, $[\alpha]_D^{20}$ −79·6° (Found: N, 2·9. $C_{27}H_{43}O_4NS$ requires N, 2·9%).

The presence of the menthylsulphamyl-group does not confer solubility in aqueous alkali, and alcoholic alkali is needed for the successful hydrolysis of all esters (V).

Resolution of (±)-*Menthol.*—*N*-(−)-Menthyl-*p*-sulphamylbenzoic acid (45 g.) was converted into the acid chloride, which was dissolved in dry benzene (80 ml.) and stirred into a solution of (±)-menthol (21 g.) and dry pyridine (15 ml.) in dry benzene (70 ml.); the exothermic reaction was not checked, and the solution was set aside for 3 hours. Pyridine and a little unesterified acid were removed in the usual way, and the crude mixture of (+)- and (−)-menthyl esters was obtained as a brownish syrup (64 g.). When this syrup was dissolved in light petroleum (b. p. 60—140°, 3 ml./g.) and the solution was cooled in the refrigerator, two types of crystal were obtained—coarse granules with $[\alpha]_D$ −50° approx., and a fine powder with $[\alpha]_D$ 0° approx.—which were readily separated by stirring and decantation. The mother-liquor still contained over 60% of the original esters with $[\alpha]_D$ −35°, and on successive concentrations, coolings, and seedings with both of the above types of solid, it yielded several further crops of each, separating simultaneously as before.

The powdery material with $[\alpha]_D$ −10° to 0° (20·3 g.) was best recrystallised from *iso*propanol containing 10% of water; it then formed large shining scales, and two such recrystallisations gave material (16·3 g.) with m. p. 142—143°, $[\alpha]_D^{20}$ +9·5°, not altered by further recrystallisation. This was (+)-*menthyl* N-(−)-*menthyl*-p-*sulphamylbenzoate* (Found: N, 3·0. $C_{27}H_{43}O_4NS$ requires N, 2·9%). This ester (16 g.) was dissolved in a warm solution of potassium hydroxide in methanol (50 ml. of 1M.), and refluxed for 1 hour. Separation of a solid potassium salt caused much bumping. The solution was cooled and diluted somewhat, and then slowly steam-distilled through a 30-cm. column of Fenske helices. Methanol was separated first, then (+)-menthol distilled over; it was collected when it had solidified, drained well, crushed, and dried (KOH) *in vacuo*, and then had m. p. 42—44°, $[\alpha]_D^{20}$ +48·6°.

The course, granular material with $[\alpha]_D$ −50° to −60° (26 g.) could be purified by recrystallisation from light petroleum (b. p. 100—140°) and seeding with the authentic (−)-menthyl ester. Four recrystallisations (100 ml. of solvent each) gave an ester, rectangular plates, m. p. 150—151°, $[\alpha]_D^{20}$ −79·5°, identical with the authentic (−)-menthyl ester (9·5 g.). Hydrolysis by the method used for the (+)-menthyl ester yielded (−)-menthol with m. p. 42—44°, $[\alpha]_D^{20}$ −48·4° (lit. values: m. p. 44—45°, $[\alpha]_D^{20}$ −48·8°).

The alkaline mother-liquors from the hydrolyses were heated nearly to boiling and acidified with hydrochloric acid, with recovery of pure *N*-(−)-menthyl-*p*-sulphamylbenzoic acid (acidification in the cold causes its separation as a gum). Menthylamine was not liberated when the acid was boiled with concentrated hydrochloric acid or concentrated aqueous sodium hydroxide.

Attempted Resolution of (±)-trans-2-*Methyl*cyclo*hexanol.*—This alcohol (Jackman, Macbeth, and Mills, *J.*, 1949, 1717) (15 g.) was esterified with the acid chloride from *N*-(−)-menthyl-*p*-sulphamylbenzoic acid (48 g.), and the crude mixture of esters was obtained as a brown solid (61 g.), m. p. 119—129°, $[\alpha]_D$ −40° approx. Two recrystallisations from methanol (200 ml.) gave large needles, m. p. 139—141°, $[\alpha]_D^{16}$ −42·0°, but the rotation only changed slowly during four more recrystallisations from methanol (then 16 g., $[\alpha]_D^{18}$ −43·5°), and a further four from light petroleum (b. p. 90—110°) (then 6 g., $[\alpha]_D^{18}$ −46°), and the m. p. remained at 139—141° (Found: N, 3·2. $C_{24}H_{37}O_4NS$ requires N, 3·2%).

Hydrolysis of this *ester* yielded a sample of (−)-*trans*-2-methyl *cyclo*hexanol with α_D^{19} −2·5° (homogeneous) instead of $\alpha_D^{20.5}$ −35·6° (Gough, Hunter, and Kenyon, *J.*, 1926, 2052).

We express our thanks for financial assistance from the Commonwealth Research Fund, and to Messrs. Howards Ltd. for providing (±)-menthol.

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