144. *The Resolution of Inactive Alcohols by Means of their Esters with Tartranilic Acid.*

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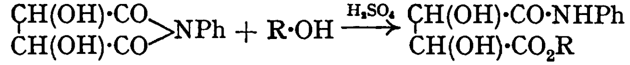
The optical resolution of inactive alcohols has been accomplished by the crystallisation of their (+)-tartranilic esters, which are prepared by the interaction of the alcohols with (+)-tartranil in the presence of sulphuric acid.

Although the possibility of resolving inactive alcohols by the crystallisation of their esters with an optically active acid was suggested over forty years ago by Frankland (Pasteur Memorial Lecture, 1897, 696), the first successful application of the method was not described until Pickard and Littlebury (J., 1906, **89**, 467) resolved α-phenyl-α-4-hydroxyphenylethane and *ac*-tetrahydro-β-naphthol (*ibid.*, p. 1254) by means of the (—)-menthyl carbamates prepared by the direct combination of the alcohols with (—)-menthylcarbimide. The method received no further attention until Read and Grubb (J., 1931, 188) effected a complete resolution of inactive menthol by the crystallisation of its esters with (+)- and (—)-camphor-10-sulphonic acids. A considerable improvement in the method was the introduction of (+)- and (—)-menthoxyacetic acids, the esters of which differ from those of camphor-10-sulphonic acid in being readily hydrolysed by alkali. By means of these acids the complete resolution of inactive menthol (Read and Grubb, *J. Soc. Chem. Ind.*, 1932, **51**, 329T) and *neo*menthol (Read and Grubb, J., 1933, 167) has been effected. More recently, Fujise and Nagasaki (*Ber.*, 1936, **69**, 1893) have employed (—)-menthoxyacetic acid for the resolution of demethoxymatteucinol and 7-hydroxyflavanone. The resolution of inactive menthol has also been accomplished by means of its ester with (—)-menthylglycine (Clark and Read, J., 1934, 1775), the free ester yielding the (+)-alcohol, and the sulphate of the ester, the (—)-alcohol.

Methyl and ethyl (+)-tartranilates, prepared some years ago by one of the authors by Casale's method (*Gazzetta*, 1917, **47**, 373), were well-defined solids which crystallised



$$\begin{matrix}\text{CH(OH)·CO}\\ \text{CH(OH)·CO}\end{matrix}\!\!>\!\text{NPh} + \text{R·OH} \xrightarrow{H_2SO_4} \begin{matrix}\text{CH(OH)·CO·NHPh}\\ \text{CH(OH)·CO}_2\text{R}\end{matrix}$$

readily from the common solvents. The possibility therefore suggested itself of utilising the esters of tartranilic acid for the resolution of inactive alcohols. β-*n*-Octyl alcohol was accordingly converted into its (+)-tartranilate by heating with (+)-tartranil and sulphuric acid : crystallisation of the ester from *iso*propyl alcohol furnished *(—)-β-*n*-octyl (+)-tartranilate* in a pure condition, from which (—)-β-*n*-octyl alcohol, having the full activity, was obtained by hydrolysis.

*(—)-β-*n*-Amyl alcohol, (—)-β-*n*-hexyl alcohol,* and (—)-menthol were isolated in a pure condition by the same method : the dextrorotatory forms of the first two alcohols were prepared by Pickard and Kenyon (J., 1911, **99**, 45). Complete resolution of the tartranilates of *sec.*-butyl and β-methyl-*n*-butyl alcohols failed on account of the formation of mixed crystals of the diastereoisomeric esters; *e.g.*, β-methyl-*n*-butyl alcohol gave a tartranilate which, on crystallisation, had a constant rotation, but the alcohol obtained from it by hydrolysis had $[\alpha]^{18°}_{5893}$ only + 3·6°, whereas the pure lævo-alcohol has $[\alpha]^{20°}_{5893}$ — 5·9°.

Attempts to prepare the tartranilates of α-terpineol and α-phenylethyl alcohol were unsuccessful owing to the readiness with which the alcohols underwent dehydration.

Experimental.

Preparation of (+)-Tartranil.—Aniline (1860 g.) was slowly stirred into an almost saturated, hot aqueous solution of (+)-tartaric acid (3000 g.) : when cold, the aniline hydrogen tartrate was broken up, air-dried, and heated for 8 hours at 140°. Crystallisation from glacial acetic acid furnished 2700 g. of (+)-tartranil in yellowish plates, m. p. 257° (decomp.), having $[\alpha]^{20°}_{5893}$ + 130° (c = 1·580, l = 2) in methyl alcohol (cf. Casale, *loc. cit.*).

*Resolution of β-*n*-Amyl Alcohol.*—(+)-Tartranil (100 g.) was heated with a solution of concentrated sulphuric acid (3 c.c.) in β-*n*-amyl alcohol (200 c.c.) on the steam-bath with mechanical stirring: after 16 hours, the greater part of the tartranil had dissolved. Light petroleum (100 c.c.; b. p. 40—60°) was added to the cooled mixture and after 1 hour the precipitate of unchanged tartranil and a small amount of the tartranilic ester was collected and extracted twice with boiling benzene (100 c.c.), in which the tartranil was insoluble. The benzene extracts and petroleum filtrate were combined and the solvents, together with the excess of the alcohol, were removed by distillation under diminished pressure. The ester was precipitated from the residue by the gradual addition of light petroleum (2 l.), and after three crystallisations from *iso*propyl alcohol gave (—)-β-n-*amyl* (+)-*tartranilate* (11·5 g.) in rosettes of slender needles, m. p. 114°, $[\alpha]_{5461}^{20°}$ + 92·4°, $[\alpha]_{5893}^{20°}$ + 76·9° (c = 2·003, l = 2) in alcohol, this value remaining unchanged on further crystallisation (Found: N, 4·8. $C_{15}H_{21}O_5N$ requires N, 4·9%). The ester was heated on the steam-bath for 1 hour with aqueous potassium hydroxide (35 c.c. of 20%). An ethereal solution of the product, after being washed with dilute hydrochloric acid in order to remove aniline formed in the hydrolysis, and dried over potassium carbonate, furnished, on distillation, (—)-β-n-*amyl alcohol* (2·6 g.), b. p. 119—120°, $d_{4°}^{15°}$ 0·814, $[\alpha]_{5461}^{15°}$ — 15·53°, $[\alpha]_{5893}^{15°}$ — 13·4° ($\alpha_{5461}^{15°}$ 12·64°, $\alpha_{5893}^{15°}$ 10·99°; l = 1). Pickard and Kenyon (*loc. cit.*) give for the (+)-alcohol $[\alpha]_{5893}^{20°}$ + 13·7°.

Resolution of β-n-*Hexyl Alcohol*.—The inactive alcohol (b. p. 135—136°) was obtained in 66% yield by slowly adding acetaldehyde (60 g.) to a mechanically stirred Grignard solution prepared from *n*-butyl bromide (140 g.) and ether (400 c.c.); after being heated for 20 minutes, the solution was decomposed with dilute sulphuric acid. Pickard and Kenyon (*loc. cit.*), using *n*-butyl iodide, record a yield of only 10%, but give no experimental details. The product obtained by heating (+)-tartranil (70 g.) with the alcohol (100 g.) in the presence of concentrated sulphuric acid (1·5 c.c.) for 3 hours at 120° was diluted with light petroleum (200 c.c.; b. p. 40—60°) and, after 30 minutes, the precipitate, consisting mainly of unchanged tartranil, was removed by filtration. The ester was precipitated from the filtrate by the gradual addition of light petroleum (3 l.), combined with that obtained by extracting the tartranil with benzene, and fractionally crystallised first from benzene and finally from *iso*propyl alcohol. The less soluble fractions yielded (—)-β-n-*hexyl* (+)-*tartranilate* (9·5 g.) in pearly plates, m. p. 124°, $[\alpha]_{5461}^{18°}$ + 93·3°, $[\alpha]_{5780}^{18°}$ + 81·6° (c = 2·052, l = 2) in alcohol (Found: N, 4·7. $C_{16}H_{23}O_5N$ requires N, 4·5%). On hydrolysis with aqueous potassium hydroxide, the ester yielded (—)-β-n-*hexyl alcohol*, b. p. 136—137°, $d_{4°}^{18°}$ 0·8178, $\alpha_{5461}^{18°}$ — 11·02°, $\alpha_{5780}^{18°}$ — 9·85°, $[\alpha]_{5461}^{18°}$ — 13·48°, $[\alpha]_{5780}^{18°}$ — 12·04° (l = 1). Pickard and Kenyon (*loc. cit.*) give $[\alpha]_{5893}^{19°}$ + 11·6° for the (+)-alcohol.

Resolution of β-n-*Octyl Alcohol*.—(+)-Tartranil (100 g.), β-*n*-octyl alcohol (200 c.c.), and concentrated sulphuric acid (3 c.c.) were heated on the steam-bath for 24 hours, and the product worked up in the same manner as the β-*n*-amyl ester; the yield of crude ester was 66 g. and 39 g. of tartranil were recovered. After three crystallisations from *iso*propyl alcohol, (—)-β-n-*octyl* (+)-*tartranilate* (15 g.) was obtained in lustrous plates, m. p. 126°, having constant rotations of $[\alpha]_{5461}^{20°}$ + 85·3° and $[\alpha]_{5893}^{20°}$ + 70·9° (c = 2, l = 1) in alcohol (Found: C, 64·0; H, 8·0; N, 4·3. $C_{18}H_{27}O_5N$ requires C, 64·1; H, 8·0; N, 4·2%).

The ester was heated for 30 minutes on the steam-bath with aqueous potassium hydroxide (30 c.c. of 20%); an ethereal extract of the product, after removal of aniline by shaking with dilute hydrochloric acid, furnished (—)-β-*n*-octyl alcohol (3·2 g.), b. p. 95°/25 mm., $d_{4°}^{18°}$ 0·825, $[\alpha]_{5461}^{18°}$ — 11·5°, $[\alpha]_{5893}^{18°}$ — 9·7°.

Resolution of dl-*Menthol*.—A mixture of (+)-tartranil (70 g.), inactive menthol (100 g.), and sulphuric acid (1 c.c.) was heated on the water-bath for 24 hours. The precipitate obtained by the addition of light petroleum gave, on extraction with benzene, 46 g. of unchanged tartranil and 7 g. of the tartranilic ester. The filtrate, on further dilution with light petroleum (3·5 l.), deposited 18 g. of the ester. Fractional crystallisation of the combined crops from *iso*propyl alcohol furnished (—)-*menthyl* (+)-*tartranilate* (7 g.) in needles, m. p. 131°, $[\alpha]_{5461}^{21°}$ + 33·16°, $[\alpha]_{5893}^{21°}$ + 29·85° (c = 1·96, l = 2) in alcohol (Found: N, 4·0. $C_{20}H_{29}O_5N$ requires N, 3·9%). The (—)-menthol isolated from the ester by hydrolysis had b. p. 89°/2 mm., m. p. 43°, $[\alpha]_{5461}^{18°}$ — 58·7°, $[\alpha]_{5893}^{18°}$ — 51·4° (c = 1·976, l = 2) in alcohol.

Experiments with β-*Methyl*-n-*butyl Alcohol*.—The interaction of (+)-tartranil (100 g.) with the alcohol (200 c.c.) and sulphuric acid (6 c.c.) was carried out at 120° for 45 minutes. After removal of unchanged tartranil by the addition of benzene (500 c.c.) the solution was freed from acid by washing with water, dried, and evaporated under diminished pressure. The residue, crystallised twice from benzene containing a little alcohol (5%), furnished β-*methyl*-n-*butyl* (+)-*tartranilate* (45 g.) in long slender needles, m. p. 123—124°, $[\alpha]_{5461}^{17°}$ + 111·2° (c = 2·308, l = 2) in alcohol, the rotation being unchanged by further crystallisation (Found: C, 60·9; H, 7·3. $C_{15}H_{21}O_5N$ requires C, 61·1; H, 7·1%). On hydrolysis, the ester yielded a partially active (+)-β-methyl-*n*-butyl alcohol, b. p. 130°, $d_{4°}^{18°}$ 0·816, $[\alpha]_{5461}^{18°}$ + 3·75°, $[\alpha]_{5780}^{18°}$ + 3·63°; the optically pure (−)-alcohol has $[\alpha]_{5893}^{20°}$ − 5·90° (Marckwald and McKenzie, *Ber.*, 1901, **34**, 485).

Gradual addition of bromine (10 g.) to a well-cooled solution of the original crude ester (20 g.) in glacial acetic acid (100 c.c.), followed by dilution with water, yielded β-*methyl*-n-*butyl* (+)-p-*bromotartranilate*, which, after two crystallisations from *iso*propyl alcohol, formed pearly plates, m. p. 144°, having a constant rotation $[\alpha]_{5461}^{19°}$ + 95·6° (c = 2·06, l = 2) in alcohol (Found : N, 3·9; Br, 21·3. $C_{15}H_{20}O_5NBr$ requires N, 3·8; Br, 21·4%). The ester contained a slight preponderance of the *p*-bromotartranilate of the (−)-alcohol, and, on hydrolysis, gave *p*-bromoaniline (m. p. and mixed m. p. 66°) together with (−)-β-methyl-*n*-butyl alcohol, b. p. 130°, $\alpha_{5461}^{21°}$ − 1·31° (l = 1). The ester isolated from the more soluble fractions had $[\alpha]_{5461}^{19°}$ + 90·4° (c = 2·02, l = 2) in alcohol and gave a dextrorotatory β-methyl-*n*-butyl alcohol, $\alpha_{5461}^{22°}$ + 1·50° (l = 1).

Experiments with β-n-*Butyl Alcohol*.—A mixture of the inactive alcohol (100 c.c.), (+)-tartranil (70 g.), and sulphuric acid (5 c.c.), after being heated for 24 hours on the steam-bath, furnished 62 g. of β-n-*butyl* (+)-*tartranilate*, m. p. 128°, which showed a constant rotation $[\alpha]_{5461}^{18°}$ + 119·7° (c = 2·005, l = 2) in alcohol after two crystallisations from benzene containing a little alcohol (Found : N, 5·2. $C_{14}H_{19}O_5N$ requires N, 5·0%). On hydrolysis, the ester gave a feebly active β-butyl alcohol, $d_{4°}^{22°}$ 0·806, $[\alpha]_{5461}^{22°}$ − 0·27° (l = 1).

(+)-β-*Butyl* (+)-*tartranilate* was prepared in the usual manner from optically pure (+)-β-butyl alcohol, $[\alpha]_{5461}^{22°}$ + 15·82°, $[\alpha]_{5780}^{22°}$ + 14·07°, $d_{4°}^{22°}$ 0·806, obtained by the resolution of the hydrogen phthalate of the inactive alcohol by means of its brucine salt (Pickard and Kenyon, J., 1913, **103**, 1923). It crystallised from benzene in pearly plates, m. p. 128°, and had a much higher rotation, $[\alpha]_{5461}^{20°}$ + 134·3°, $[\alpha]_{5780}^{20°}$ + 117·6° (c = 2·006, l = 2) in alcohol, than any of the fractions obtained in the crystallisation of the tartranilate prepared from the inactive alcohol (Found : N, 5·1. $C_{14}H_{19}O_5N$ requires N, 5·0%).

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[*Received, February* 17*th*, 1939.]