340. *The Resorcitols. Part II. Resolution of* trans-*Resorcitol.*

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The higher-melting form of resorcitol has been resolved by crystallisation of alkaloidal salts of the bis(hydrogen phthalate) thus proving it to be the *trans*-isomer.

Arguing from the melting points, solubilities, and crystalline forms, and from the mixed melting points of the two dibenzoyl derivatives, Rothstein and co-workers (*Ann. Chim.*, 1930, **14**, 587—591) tentatively assigned the *cis*-configuration to the resorcitol (*cyclo*hexane-1 : 3-diol) isomer of lower melting point, the other being a (±)-*trans*-form. Although the method of proving the structures by resolution of the *trans*-form had been considered (Lindemann and Baumann, *Annalen*, 1929, **477**, 84, 95; Palfray and Rothstein, *Compt. rend.*, 1929, **189**, 188; Rothstein, *Ann. Chim.*, 1930, **14**, 531), no resolution has hitherto been accomplished. Lindemann and Baumann obtained a 55% yield of impure (—)-menthylurethane of the lower-melting isomer and thence inferred that the substance was the *cis*-isomer. This was inconclusive, and further we now find that the *monobrucine* salt of (±)-*trans*-resorcitol bis(hydrogen phthalate) is similarly unchanged in rotation when recrystallised.

That the isomer of higher melting point has the *trans*-configuration has now been proved by resolution by use of alkaloidal salts of the bis(hydrogen phthalate) (cf. Pickard and Kenyon, *J.*, 1911, **99**, 58; Houssa and Kenyon, *J.*, 1930, 2261). An attempt to use the bismenthoxyacetates was abandoned as the esters did not crystallise.

When (±)-trans-*resorcitol bis*(*hydrogen phthalate*) was treated with sufficient brucine to give the dibrucine salt and fractionally crystallised, it gave the *monobrucine* salt of (—)-*trans*-resorcitol bis(hydrogen phthalate) (I), and a second salt (II) which appeared to be the *brucine* salt of a mono(hydrogen phthalate). (I) yielded impure (−)-trans-*resorcitol bis*(*hydrogen phthalate*) and thence (−)-trans-*resorcitol*, m. p. 117·5—118°, $[\alpha]_D^{20^\circ}$ −15·2°. Comparison with the (+)-isomer indicated that this was not quite pure. The *distrychnine* salt of *trans*-(+)-resorcitol bis(hydrogen phthalate) was prepared from the residues from the isolation of (I) and (II), and was similarly converted through the incompletely purified *bis*(*hydrogen phthalate*) into (+)-trans-*resorcitol*, m. p. 117·5—118·5°, $[\alpha]_D^{20^\circ}$ +16·2°. Use of sufficient brucine to form only the monobrucine salt was unsuccessful, rotations ([α] *ca.* −10°) of the crystals deposited in successive crystallisations giving no indication of separation into diastereoisomers.

Similar treatment of cis-*resorcitol bis*(*hydrogen phthalate*) gave a *dibrucine* salt which could not be separated into diastereoisomers.

The bis(hydrogen phthalates) of *cis*- and (±)-*trans*-resorcitol are of interest in that the *cis*-compound has the higher melting point and lower solubility. The solubility of optically active *trans*-resorcitol in acetone at 20° is between 8 and 10%, thus resembling that of the (±)-material which has been recorded as 7·935% in acetone at 17·5° (Rothstein, *loc. cit.*). No depression in melting point was observed when about equal quantities of (+)- and (±)-*trans*-resorcitol were mixed. The specific rotations of the resorcitols are markedly lower than those of the *cyclo*hexane-1 : 2-diols (±46·5°; Wilson and Read, *J.*, 1935, 1269).

EXPERIMENTAL.

[α] was measured in 10% solution in B.P. chloroform unless otherwise indicated.

Resorcitol Bis(*hydrogen Phthalates*).—Phthalic anhydride (160 g.) and *trans*-resorcitol (58 g.) in pyridine (95 g.) were heated for 2 hours in a boiling water-bath. The resulting syrup was diluted with warm water (100 ml.) and then with a mixture of concentrated hydrochloric acid (175 ml.) and warm water (200 ml.), shaken vigorously, and then rapidly cooled by the addition of crushed ice; the slightly turbid liquid was decanted from the ester which was re-extracted similarly by shaking vigorously with a mixture of concentrated hydrochloric acid (85 ml.) and warm water (250 ml.), and then with three 250-ml. portions of warm water. The sticky product was stirred with air and dried as a froth over sulphuric acid and potassium hydroxide in an evacuated desiccator. A solution in acetone soon set to a mass of crystals which, after cooling, was filtered off and washed with a little ice-cold acetone, followed by acetone–*cyclo*hexene (1 : 1) and finally light petroleum. The white crystals had the melting point of the pure substance; yield, 166·5 g. (81%). Recrystallisation from ethyl acetate by addition of *cyclo*hexene gave the pure (±)-trans-*ester* as small, white granular crystals, m. p. 156—157°, soluble in many organic solvents, but sparingly soluble in *cyclo*hexene, and almost insoluble in light petroleum (b. p. 40—60°) and in cold water (Found: C, 64·05; H, 4·64. $C_{22}H_{20}O_8$ requires C, 64·0; H, 4·9%).

The cis-*ester*, similarly prepared, formed white, granular crystals (from ethyl acetate–*cyclo*hexene or from 70% alcohol), rather less soluble than the *trans*-compound; m. p. 186—187° [Found: C, 63·9; H, 4·74; equiv. (direct titration in aqueous alcohol), 207·5. $C_{20}H_{18}O_4(CO_2H)_2$ requires equiv., 206].

Dibrucine Salt of cis-*Resorcitol Bis*(*hydrogen Phthalate*).—*cis*-Recorcitol bis(hydrogen phthalate) (66 g., 1 mol.) and brucine (150 g., 2 mols.) in methyl alcohol (100 ml.), kept overnight, deposited 196 g. of the *dibrucine* salt; repeated crystallisation from ethyl alcohol, chloroform, acetone, and mixtures thereof brought about no separation into diastereoisomers. The salt formed white crystals, sparingly soluble in alcohol or acetone, more soluble in chloroform; $[\alpha]_D^{20^\circ}$ −19·1°. Placed in a bath at 85°, the temperature rising 10° per minute, the salt turned into an opaque froth at 110—115° and melted to a clear liquid at 152—157° (Found: C, 67·8; H, 6·31; N, 4·92; brucine, 65·4. $C_{22}H_{20}O_8,2C_{23}H_{26}O_4N_2$ requires C, 68·0; H, 6·04; N, 4·66; brucine, 65·6%).

Brucine Salts from (±)-trans-*Resorcitol Bis*(*hydrogen Phthalate*).—Acetone (150 ml.) was added to (±)-*trans*-resorcitol bis(hydrogen phthalate) (61 g.) and brucine (anhydrous, 136 g.) dissolved in methyl alcohol (50 g.). After the mixture had been kept overnight, crystals (55 g.), $[\alpha]_D^{20^\circ}$ −31·1°, separated. Recrystallisation, effected by dissolution in acetone and clearing the turbidity with 5—10% of methyl alcohol, gave successive crops, 51 g., $[\alpha]_D^{20^\circ}$ −31·2°, and 39·5 g., $[\alpha]_D^{20^\circ}$ −33·25°. The last crop dissolved in acetone (85 ml.) to give a turbid solution and, when methyl alcohol (20 ml.) was added, crystallisation at once began, to give, in a few hours a compact translucent mass adhering to the bottom of the flask; this was filtered off and washed with acetone before bulky white crystals of another salt appeared. The compact crystals (D) (11 g.) had $[\alpha]_D^{20^\circ}$ −3·25°; the filtrate (F) was reserved. Heating (D) with acetone, in which it did not dissolve, followed by recrystallisation from a (supersaturated) solution in chloroform by addition of acetone gave the *monobrucine* salt (I) of (−)-*trans*-resorcitol bis(hydrogen phthalate) as small, white granular crystals, $[\alpha]_D^{20^\circ}$ −1·25° (constant), retaining a small amount of chloroform when dried at 100°/100 mm. in an air stream. This salt was soluble in about 6 parts of boiling chloroform, but stable supersaturated solutions were readily made by evaporation; it was sparingly soluble in acetone or methyl alcohol and melted at 203·5—205·5° when introduced into a bath at 200° [Found: C, 64·2; H, 5·62; N, 4·1; Cl, 1·38; brucine, 47·9. $9(C_{22}H_{20}O_8,C_{23}H_{26}O_4N_2),CHCl_3$ requires C, 66·0; H, 5·67; N, 3·42; Cl, 1·44; brucine, 48·2%]. Brucine was removed from 0·1500 g. of (I) by extraction with 125 and 100 ml. of benzene in the presence of 10·00 ml. of 0·1N-sodium hydroxide, the residual solution was heated under reflux for 5 hours, and the excess of alkali titrated; this gave a phthalic acid content of 40·0% (required 41·2%); the molar ratio of alkaloid to phthalic acid was 1 : 1·98.

The filtrate (F) became full of bulky white crystals, $[\alpha]_D^{20^\circ}$ −35·25°, which, in two interrupted crystallisations from acetone containing a little methyl alcohol, gave *ca.* 7 g. of the above-mentioned monobrucine salt and 10 g. of another *salt* (II); the latter formed small needles, soluble in warm acetone, and more soluble in methyl or ethyl alcohol and in chloroform, and had $[\alpha]_D^{20^\circ}$ −32·75°; m. p. indefinite (begins to sinter at *ca.* 155°) (Found : C, 65·0; H, 6·36; N, 4·45; brucine, 59·6. $C_{37}H_{42}O_9N_2$ requires C, 67·5; H, 6·43; N, 4·25; brucine, 59·9%. These data agree equally with those for $C_{22}H_{20}O_8,2C_{23}H_{26}O_4N_2,4CH_3OH$).

Strychnine Salt of (+)-trans-*Resorcitol Bis*(*hydrogen Phthalate*).—The filtrates left after isolation of the two brucine salts were evaporated and brucine was removed. This gave a syrup, 25 g. of which were dried, treated in chloroform with strychnine (36 g.), and evaporated until 77 g. of chloroform remained. Crystallisation was induced by addition of acetone (80 g.), and six further crystallisations from 2—4 parts of chloroform with 1 of acetone gave 9·5 g. of the *strychnine* salt, $[\alpha]_D^{20°}$ −14·35°, of the (+)-*trans*-diester. This was sparingly soluble in alcohol or acetone and fairly soluble in boiling chloroform, and readily gave supersaturated solutions in chloroform. It sintered at *ca.* 170° and melted to a slightly brown liquid at 180—182° (Found: C, 64·6; H, 5·2; N, 4·61; Cl, 10·0; strychnine, 55·8. $C_{22}H_{20}O_8,2C_{21}H_{22}O_2N_2,CHCl_3$ requires C, 65·0; H, 5·46; N, 4·67; Cl, 8·87; strychnine, 55·1%).

Bis(*hydrogen Phthalate*) *of* (−)-trans-*Resorcitol*.—Removal of the brucine from (I) (16·5 g.) by adding a slight excess of alkali, acidifying, and extracting with chloroform gave a sticky precipitate which, after washing with water, was converted into a froth and dried in a vacuum over sulphuric acid and potassium hydroxide. The almost colourless, friable product did not crystallise and was impure [Found: equiv., (by direct titration) 228, (by hydrolysis) 115. $C_{22}H_{20}O_8$ requires equiv., 206 and 103, respectively].

Bis(*hydrogen Phthalate*) *of* (+)-trans-*Resorcitol*.—The product (10·5 g.) obtained similarly from 31·5 g. of the strychnine salt described above did not crystallise. It had $[\alpha]_D^{20°}$ +14·6°, falling to +13·2° after one day [Found : equiv., (by direct titration) 242, (on hydrolysis) 123].

(−)-trans-*Resorcitol*.—The crude diester from *ca.* 16 g. of brucine salt was softened with 2—3 ml. of alcohol and heated with 10N-sodium hydroxide in slight excess for 6 hours. The slightly alkaline solution (if neutralised, the solution soon became alkaline when kept) was evaporated on the water-bath under reduced pressure until crystallisation began to spread throughout the mass. Acetone (15 ml.) was added, and the mixture was warmed and filtered, the solid being extracted with four further 10-ml. portions of acetone; evaporation and exposure in a partly evacuated desiccator gave crystalline material (2·69 g.). This was purified by recrystallisation from 30 ml. of hot ethyl acetate–benzene (1 : 4), and treating an acetone solution with charcoal; this afforded (−)-trans-*resorcitol* as fine colourless needles 2·08 g., soluble in water, alcohol, ethyl acetate, or acetone, less soluble in benzene, and almost insoluble in light petroleum; m. p. 117·5—118°; $[\alpha]_D^{20°}$ −15·2° (*c*, 10 in methyl alcohol) (Found : C, 62·5; H, 10·1. $C_6H_{12}O_2$ requires C, 62·0; H, 10·4%).

(+)-trans-*Resorcitol*.—This was similarly prepared. Soxhlet extraction of the products of hydrolysis was less satisfactory, an oil being also produced. The (+)-*isomer* had m. p. 117·5—118·5° and $[\alpha]_D^{20°}$ +16·2° (*c*, 10 in methyl alcohol) (Found : C, 61·7; H, 10·3%).

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