

123. *Optical Studies of 2,2'-Di-t-butylbiphenylcarboxylic Acids and of 2'-t-Butylbiphenyl-2-carboxylic Acid.*

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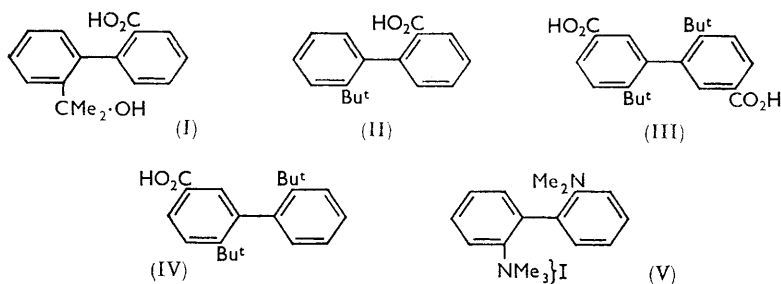
The synthesis of 2'-t-butylbiphenyl-2-carboxylic acid, 2',6-di-t-butylbiphenyl-3-carboxylic acid and of 6,6'-di-t-butylbiphenyl-3,3'-dicarboxylic acid is described. The strychnine and the brucine salts of the mono-t-butylbiphenyl acid undergo second-order asymmetric transformation in ethanol. The di-t-butylbiphenyl acids have been resolved and show high optical stability.

CORBELLINI and ANGELETTI¹ found that the brucine salt of the 2'-(hydroxyalkyl)biphenyl-2-carboxylic acid (I) underwent second-order asymmetric transformation in ethanol and, later, Jamison and Turner² showed that it also underwent first-order transformation in chloroform. We have now prepared 2'-t-butylbiphenyl-2-carboxylic acid (II) and found

¹ Corbellini and Angeletti, *Atti Accad. naz. Lincei, Rend. Classe Sci. fis., mat., nat.*, 1932, **15**, 968.

² Jamison and Turner, *J.*, 1942, 437.

that its strychnine and brucine salts undergo second-order asymmetric transformation; no first-order transformation was observed. On the other hand, 6,6'-di-*t*-butylbiphenyl-3,3'-dicarboxylic acid (III) and 2',6-di-*t*-butylbiphenyl-3-carboxylic acid (IV) were resolved and showed high optical stability.



Scale models based on known atomic radii show that in the di-*t*-butyl acids the two benzene rings cannot become coplanar since, owing to their volume, the two tertiary butyl groups cannot pass the hydrogens in the 2,2'-positions. Interconversion of the (+)- and (-)-forms is therefore inhibited. This is in marked contrast to the asymmetry of 2'-dimethylamino-2-biphenyltrimethylammonium iodide (V) which arises from the "dynamic effect" of the less bulky $\cdot\text{NMe}_3^+$ group:³ the active quaternary iodides whilst optically stable in cold aqueous solution had a half-life of 125 minutes at 99.5°.

Methyl 2'-*t*-butylbiphenyl-2-carboxylate (II) was prepared by heating together equimolecular proportions of methyl *o*-iodobenzoate and *o*-iodo-*t*-butylbenzene in presence of copper bronze. A mixture of 2,2'-di-*t*-butylbiphenyl, dimethyl diphenate, and methyl 2'-*t*-butylbiphenyl-2-carboxylate was obtained. The hydrocarbon was removed by distillation of the mixture under reduced pressure but the esters could not be separated either by distillation or by fractional crystallisation. The mixture of esters was therefore hydrolysed and the acids were eventually separated by tedious and rather wasteful crystallisations from glacial acetic acid (in which the diphenic acid was slightly less soluble) and from aqueous ethanol. *o*-Iodo-*t*-butyl benzene was prepared in greatly improved yield by modifications of Shoemith and Mackie's method.⁴ 2,4-Dinitro-*t*-butylbenzene was reduced in aqueous solution with sodium disulphide and the nitro-amine was deaminated through the diazonium fluoroborate or with hypophosphorous acid. The above authors found that during the diazotisation of *o*-amino-*t*-butylbenzene decomposition of the diazonium sulphate set in at -8° and we therefore performed the diazotisation at -35° and allowed the reaction mixture to warm to -13° , then added it to aqueous potassium iodide solution. This procedure resulted in greatly enhanced yields of the iodo-compound.

The dimethyl ester of the acid (III) was obtained by heating methyl 3-iodo-4-*t*-butylbenzoate with copper bronze. The preparation of the iodo-ester from methyl 3-amino-4-*t*-butylbenzoate hydrochloride (or sulphate) presented unexpected difficulty because of the instability of the diazonium salt. The crude iodo-ester was a green viscous oil; it was distilled under reduced pressure and appeared to be homogeneous. Addition of light petroleum produced a wax-like solid; this crystallised from light petroleum and was found to be a 1:1 molecular compound of the iodo-ester and methyl 3-hydroxy-4-*t*-butylbenzoate. The iodo-ester is a liquid at room temperature and was obtained from the mother-liquors after all the molecular compound had been removed. It is surprising that the molecular compound distils under reduced pressure as if it were an individual substance,

³ Shaw and Turner, *J.*, 1933, 135.

⁴ Shoemith and Mackie, *J.*, 1928, 2334.

and in ethereal solution it did not yield the phenolic component when extracted with cold alkali. On the other hand, when the solid compound was stirred with cold 30% aqueous sodium hydroxide or warmed with a 10% solution of sodium hydroxide a mixture of the iodo-ester and sodium 3-hydroxy-*t*-butylbenzoate was obtained. By this means the iodo-ester was recovered from the molecular compound. In later preparations the solid compound was not isolated, but the oil obtained after vacuum-distillation was stirred with successive amounts of cold concentrated sodium hydroxide solution and the sodium salt of the hydroxy-acid was removed by repeated washing with water. The iodo-ester thus obtained was hydrolysed, and the iodo-acid was purified by crystallisation from methanol and from light petroleum, then converted into its methyl ester.

When heated with copper bronze the molecular compound gave 5,5'-dimethoxy-carbonyl-2,2'-di-*t*-butylbiphenyl ether.

Ethyl 3-amino-4-*t*-butylbenzoate hydrochloride was also prepared. The diazonium chloride derived from it was very unstable but there was no evidence of compound formation between the iodo- and the hydroxy-ester. Washing with alkali failed again to remove the hydroxy-ester from the ethereal solution but on removal of the solvent a mixture of the two solid esters was obtained. These were easily separated by crystallisation from ethanol in which the hydroxy-ester was very soluble.

The methyl ester of the monocarboxylic acid (IV) was prepared by heating equimolecular amounts of methyl 3-iodo-4-*t*-butylbenzoate and *o*-iodo-*t*-butylbenzene. The products were partially separated by distillation under reduced pressure, the main fraction consisting of a mixture of 2,2'-di-*t*-butylbiphenyl and the required unsymmetrical ester. This was hydrolysed with ethanolic potassium ethoxide, and the hydrocarbon removed by extraction with ether. The unsymmetrical acid was then obtained on acidification of the alkaline solution.

The strychnine salt of the monocarboxylic acid (II) was prepared in ethanol, and a series of crops was obtained whose rotations in chloroform solution were approximately the same ($[\alpha]_{5791} -46.0^\circ \pm 0.4^\circ$). The acid regenerated from these salts was laevorotatory and it was thus apparent that the strychnine salt had undergone second-order asymmetric transformation. Recrystallisation of the salts from methanol was more satisfactory than from ethanol since considerable dissociation into free acid and base occurred in the latter solvent. (When prepared in methanol the strychnine salt also underwent asymmetric transformation.) The purest salt had $[\alpha]_{5791} -49.9^\circ$ in chloroform and racemised slowly during several days at room temperature. In boiling ethanol it racemised quickly. The highest rotation obtained for the acid was $[\alpha]_{5791} -24.3^\circ$ and $[\alpha]_{5461} -29.8^\circ$ in ethanol. Racemisation of the (–)-acid in ethanol was studied at 57°, 67°, and 79° (half-life 35, 14.1, and 5.6 minutes respectively). The activation energy was 24 kcal. mole⁻¹. The brucine salt was also prepared in ethanol and it, too, underwent second-order asymmetric transformation but to a smaller extent. The maximum rotation obtained for the recovered acid was $[\alpha]_{5791} +7.7^\circ$ in ethanol.

6,6'-Di-*t*-butylbiphenyl-3,3'-dicarboxylic acid (III) was resolved through its brucine salt. The (+)-acid salt, which was the more soluble in ethanol, was a gel but it was possible to separate the two salts since their solubilities in ethanol differed considerably.

The free acids were obtained having $[\alpha]_{5791} \pm 18.6^\circ (\pm 0.3^\circ)$ in acetone. The acids showed high optical stability and were not racemised in aqueous alkali or in pyridine at the boiling point.

2',6-Di-*t*-butylbiphenyl-3-carboxylic acid (IV) was converted into its strychnine salt, and the two diastereoisomers were separated by crystallisation from ethanol. The (+)-acid salt was crystalline and was readily obtained optically pure whereas the (–)-acid salt was an oil. The (±)-acid, however, was more sparingly soluble than the active acids, and the crude (–)-acid obtained from the oil was isolated optically pure by crystallisation from methanol. The acids had $[\alpha]_{5791} \pm 25.5^\circ$ and $[\alpha]_{5461} \pm 28.4^\circ (\pm 0.5^\circ)$ in chloroform. The active acid retained its activity after sublimation at 130°/1 mm. and even after melting.

EXPERIMENTAL

2,4-Dinitro-t-butylbenzene.—*t*-Butylbenzene (100 g.) was added, with stirring, within $\frac{1}{2}$ hr., to nitric acid (500 c.c.; *d* 1.51) at 0°. Then the solution was left at 60–65° for 15 min. and poured on crushed ice. The crude dinitro-compound was filtered off and was melted under boiling water (3 l.), then cooled quickly with vigorous stirring. After crystallisation from ethanol the dinitro-*t*-butylbenzene was obtained as white prisms which became yellow on exposure to light and had m. p. 63–64° (yield 85%).

3-Nitro-4-t-butylaniline.—A hot solution of sodium disulphide (2 mol.) in water (200 c.c.) was added within a few minutes to a vigorously stirred suspension of 2,4-dinitro-*t*-butylbenzene (45 g.) in boiling water (500 c.c.). After 1 hour's boiling, with stirring (the volume of water being maintained), the mixture was cooled and the crude nitro-amine was filtered off. After purification through its hydrochloride the base was crystallised from ethanol and from light petroleum (b. p. 40–60°). It melted at 55–56° (yield 75%).

o-Nitro-t-butylbenzene.—(a) *3-Nitro-4-t-butylaniline* (60 g.) was diazotised in hydrochloric acid and the diazonium solution kept at 0–10° for 1 hr. (this was essential, otherwise much base was recovered). To the filtered solution hydrogen fluoroborate was added, and the precipitated diazonium fluoroborate was filtered off, washed with ether, and dried *in vacuo* over sulphuric acid (85 g.). It was decomposed by adding it gradually to a boiling mixture of ethanol (3 parts) and concentrated sulphuric acid ($\frac{1}{2}$ part). The nitro-*t*-butylbenzene was obtained with b. p. 102–104°/6 mm. (40 g., 72%).

(b) The aniline (60 g.) was diazotised as above and the filtered diazonium solution was added with stirring to hypophosphorous acid (600 c.c.) at 0°. By this method the nitro-*t*-butylbenzene was obtained in 75% yield.

o-t-Butylaniline.—The above nitro-compound (70 g.) was reduced with iron filings and water containing a little acetic acid. The base obtained (88%) had b. p. 93°/5 mm.

o-Iodo-t-butylbenzene.—*o-t*-Butylaniline (22 g.) was dissolved in dilute sulphuric acid (*d* 1.2; 120 c.c.) and cooled to –35°. A concentrated aqueous solution of sodium nitrite (10.5 g.) was added within 5 min. and the mixture allowed to warm in the freezing solution (carbon dioxide and ethanol) to –13° during 2 hr. The resultant brown gelatinous suspension was added to an aqueous solution of potassium iodide (75 g.). The diazonium iodide which separated decomposed readily. The mixture was made alkaline and the crude iodo-hydrocarbon from two similar experiments was steam-distilled. The distillate was extracted with ether, and the ethereal extract was washed successively with acid, sodium metabisulphite solution, acid, and water, then dried (CaCl₂). After removal of the solvent the residue was distilled and *o*-iodo-*t*-butylbenzene, b. p. 94–96°/3 mm. (68–78%), was obtained.

2,2'-Di-t-butylbiphenyl.—The above iodo-hydrocarbon (20 g.) reacted with copper bronze (20 g.) at 225° (bath). The reaction was complete after $\frac{1}{2}$ hr. and the product was extracted with chlorobenzene. The solvent was removed and the residue distilled under reduced pressure. *2,2'-Di-t-butylbiphenyl*, b. p. 140°/2 mm., was obtained. Light petroleum (b. p. 60–80°; 2 c.c.) was added to the oil, and the hydrocarbon, which crystallised, separated from ethanol as stout plates, m. p. 63–64° (Found: C, 90.2; H, 9.9. C₂₀H₂₆ requires C, 90.2; H, 9.8%).

2'-t-Butylbiphenyl-2-carboxylic Acid.—A mixture of *o*-iodo-*t*-butylbenzene (20 g.) and methyl *o*-iodobenzoate (20 g.) reacted with copper bronze at 210° (bath) for $\frac{1}{2}$ hr. The product was extracted with chlorobenzene and after removal of the solvent the residue was distilled under reduced pressure. The lower fractions collected were liquids; the main fraction, b. p. 160–180°/5 mm. (13 g.), crystallised on addition of light petroleum (b. p. 40–60°) and was recrystallised three times from light petroleum (b. p. 40–60°). It was found to be an inseparable mixture of dimethyl diphenate and methyl 2'-*t*-butylbiphenyl-2-carboxylate and it was therefore hydrolysed with ethanolic potassium ethoxide. The resultant mixture of acids was separated by fractional crystallisation from glacial acetic acid followed by crystallisation from aqueous ethanol. 2'-*t*-Butylbiphenyl-2-carboxylic acid crystallised from aqueous ethanol in needles, m. p. 182–183° (Found: C, 80.1; H, 7.2. C₁₇H₁₈O₂ requires C, 80.3; H, 7.1%).

3-Nitro-4-t-butylbenzoic Acid.—*p-t*-Butylbenzoic acid (50 g.) was added gradually to ice-cold nitric acid (500 c.c., *d* 1.51). Then the solution was kept at 60° for 15 min. and poured on ice. The acid crystallised from dilute acetic acid in small prisms, m. p. 162–163° (65%). Decarboxylation of the acid, followed by nitration of the resulting nitro-hydrocarbon, to give

2,4-dinitro-*t*-butylbenzene, m. p. 63—64° (Shoemith and Mackie⁴), confirmed that the acid was the 3-nitro-isomer.

Methyl 3-Nitro-4-t-butylbenzoate.—3-Nitro-4-*t*-butylbenzoic acid (150 g.) was converted into its methyl ester, b. p. 162°/6 mm., plates, m. p. 45—46° (from methanol) (Found: C, 60·8; H, 6·5. Calc. for C₁₂H₁₅NO₄: C, 60·7; H, 6·4%). It was described as an oil by Kelbe and Pfeiffer.⁵

The *ethyl ester* had b. p. 162—165°/5 mm., m. p. 22—24° (Found: C, 62·1; H, 6·7. C₁₃H₁₇NO₄ requires C, 62·1; H, 6·8%).

Methyl 3-Amino-4-t-butylbenzoate Hydrochloride.—The above methyl nitro-ester (146 g.) was reduced with iron filings, water, and a little acetic acid at 100°. The mixture was extracted with hot methanol, and the filtered extract freed from the bulk of solvent by distillation. The residue was poured into an excess of concentrated hydrochloric acid at 0°. The resulting paste was filtered off and dried at 100° (121 g., 80%). The *hydrochloride* crystallised from alcohol in thin plates, m. p. 198—200° (Found: Cl, 15·0. C₁₂H₁₆ClNO₂ requires Cl, 14·6%).

The corresponding ethyl ester hydrochloride was similarly prepared from ethyl 3-nitro-4-*t*-butylbenzoate. A pure specimen was not obtained since it was too soluble in all the usual solvents. The free *base* was a viscous oil, b. p. 160°/4 mm. (Found: C, 70·6; H, 9·3. C₁₃H₁₉NO₂ requires C, 70·6; H, 8·7%). In attempts to crystallise this hydrochloride from dilute hydrochloric acid it was hydrolysed to 3-*amino-4-t-butylbenzoic acid hydrochloride* which crystallised in prisms, m. p. 238—239° (Found: C, 57·5; H, 6·8. C₁₁H₁₆ClNO₂ requires C, 57·5; H, 6·9%).

3-Iodo-4-t-butylbenzoic Acid.—To the above methyl ester hydrochloride (44 g.) in concentrated hydrochloric acid at -25° the requisite amount of sodium nitrite in aqueous solution was added quickly. The mixture was left for 90 min., initially at -15°, and allowed to warm to -5°, then quickly added to aqueous potassium iodide solution (46 g.). The resultant oil which contained some low-melting solid was extracted with ether, and the ethereal solution was washed repeatedly with alkali, then successively with sodium metabisulphite solution, acid, and water, and dried. After removal of the ether the residue was distilled. The distillate was a green viscous oil, b. p. 164—168°/10 mm., which on addition of light petroleum (b. p. 40—60°) gave a wax-like solid (25·5 g.). It was recrystallised several times from light petroleum and separated as hair-like needles, m. p. 58—59° (Found: C, 54·8; H, 6·1; I, 24·1. C₁₂H₁₅IO₂, C₁₂H₁₆O₃ requires C, 54·8; H, 5·9; I, 24·1%).

On several occasions when the pure molecular compound was allowed to crystallise very slowly from light petroleum small rod-shaped crystals were deposited. The supernatant solution was then carefully decanted and immediately the hair-like needles of the molecular compound crystallised. The rods were identified as methyl 3-hydroxy-4-*t*-butylbenzoate.

The diazotisation of the base hydrochloride was repeated many times, the temperature conditions being varied and also the time allowed for the reaction to proceed. From all experiments the molecular compound was obtained in good yield; if the temperature was maintained too low or insufficient time allowed for complete diazotisation then unchanged base was recovered. The diazonium sulphate appeared to be even more unstable than the chloride and when it was added to aqueous potassium iodide the molecular compound was again the main product. The mother-liquors from the crystallisation of the molecular compound were repeatedly concentrated and cooled to -35° until no more solid compound separated. The crude liquid iodo-ester was then obtained on removal of the solvent. The iodo-ester was recovered from the molecular compound by addition of cold 30% aqueous sodium hydroxide solution. After being stirred for a few minutes the hydroxy-ester underwent hydrolysis and was easily removed as the sodium salt of the hydroxy-acid. Under these conditions no hydrolysis of the iodo-ester occurred. Alternatively, the green oil obtained from the vacuum-distillation of the crude "iodo"-product was similarly treated with cold alkali, and the iodo-ester was thus obtained free from the hydroxy-ester. The iodo-ester was hydrolysed with ethanolic potassium ethoxide to 3-*iodo-4-t-butylbenzoic acid*, needles, m. p. 202—203° (from ethanol) (Found: C, 43·5; H, 4·4. C₁₁H₁₃IO₂ requires C, 43·4; H, 4·3%).

The pure iodo-acid was converted into its *methyl ester*, b. p. 156—158°/4 mm., m. p. ~12° (Found: C, 45·6; H, 4·8. C₁₂H₁₅IO₂ requires C, 45·3; H, 4·8%).

The *ethyl ester* crystallised from ethanol in cubes, m. p. 58—59° (Found: C, 47·1; H, 4·9. C₁₃H₁₇IO₂ requires C, 47·0; H, 5·2%).

⁵ Kelbe and Pfeiffer, *Ber.*, 1886, **19**, 1723.

Ethyl 3-amino-4-*t*-butylbenzoate hydrochloride was diazotised under the conditions employed for the methyl ester base. The product was a mixture of the iodo- and hydroxy-esters, each of which was a solid. They were readily separated by crystallisation from ethanol and the less soluble iodo-ester was obtained pure.

Methyl 3-Hydroxy-4-t-butylbenzoate.—Methyl 3-amino-4-*t*-butylbenzoate hydrochloride (12 g.) was diazotised at -15° and allowed to warm to $+10^{\circ}$ during which time decomposition with evolution of nitrogen was apparent. When the reaction was complete the solid *ester* which had separated (4.8 g.) was filtered off, dried and crystallised from light petroleum (b. p. $40-60^{\circ}$), forming needles, m. p. $108-109^{\circ}$ (Found: C, 69.3; H, 7.7. $C_{12}H_{16}O_3$ requires C, 69.2; H, 7.7%). Hydrolysis was readily effected by stirring the ester with cold 10% aqueous sodium hydroxide. The sodium salt separated and dissolved to a clear solution when water was added. Acidification gave 3-*hydroxy-4-t-butylbenzoic acid*, rectangular needles (from aqueous ethanol), m. p. $187-188^{\circ}$ (Found: C, 68.0; H, 7.25. $C_{11}H_{14}O_3$ requires C, 68.0; H, 7.25%).

5,5'-Dimethoxycarbonyl-2,2'-di-t-butylbiphenyl Ether.—The molecular compound (methyl 3-iodo-4-*t*-butylbenzoate, plus methyl 3-hydroxy-4-*t*-butylbenzoate) (45 g.) reacted with copper bronze at 240° (bath). The product was extracted with chlorobenzene and after removal of the solvent a crystalline *ether* was obtained (4.2 g.) that recrystallised from methanol as rhombohedra, m. p. $173-174^{\circ}$ (Found: C, 72.3; H, 7.7; O, 19.3. $C_{24}H_{30}O_5$ requires C, 72.4; H, 7.6; O, 20.1%).

6,6'-Di-t-butylbiphenyl-3,3'-dicarboxylic Acid.—The above iodo-ester (18 g.) reacted vigorously with copper bronze at 235° (bath). The product was extracted with chlorobenzene and after removal of the solvent the crude ester crystallised and was washed with light petroleum (b. p. $40-60^{\circ}$). Two crystallisations from methanol gave *dimethyl 6,6'-di-t-butylbiphenyl-3,3'-dicarboxylate* as needles, m. p. $201-202^{\circ}$ (5.5 g., 62%) (Found: C, 75.2; H, 8.0. $C_{24}H_{30}O_4$ requires C, 75.3; H, 7.9%). Ethyl 3-iodo-4-*t*-butylbenzoate with copper bronze at 245° similarly gave *diethyl 6,6'-di-t-butylbiphenyl-3,3'-dicarboxylate*, needles (from ethanol), m. p. $144-145^{\circ}$ (Found: C, 76.0; H, 8.4. $C_{26}H_{34}O_4$ requires C, 76.1; H, 8.4%). Hydrolysis with ethanolic potassium ethoxide of each ester gave 6,6'-*di-t-butylbiphenyl-3,3'-dicarboxylic acid*, hexagonal prisms (from acetic acid), m. p. 345° (Kofler block) (Found: C, 74.4; H, 7.5. $C_{22}H_{26}O_4$ requires C, 74.5; H, 7.4%).

2',6-Di-t-butylbiphenyl-3-carboxylic Acid.—A mixture of methyl 3-iodo-4-*t*-butylbenzoate (32 g.) and *o*-iodo-*t*-butylbenzene (26 g.) was heated with copper bronze in a bath at 220° . Then the mixture was extracted with chlorobenzene and after removal of the solvent an oil was obtained. On addition of methanol the symmetrical ester crystallised and was filtered off. The residue was distilled under reduced pressure and the main fraction (7 g.) was collected at $156-180/2$ mm. It was hydrolysed with ethanolic potassium ethoxide and 2,2'-*di-t-butylbiphenyl* was removed from the alkaline solution by extraction with ether. The acid was then precipitated on acidification of the alkaline solution. 2',6-*Di-t-butylbiphenyl-3-carboxylic acid* crystallised from methanol in slender prisms, m. p. 233° with slight previous softening (Found: C, 81.1; H, 8.5. $C_{21}H_{26}O_2$ requires C, 81.2; H, 8.4%).

Alkaloid Salts of 2'-t-Butylbiphenyl-2-carboxylic Acid.—Rotations of salts were measured at room temperature for "AnalaR" chloroform solutions ($c \sim 1$) and of acid for ethanol solutions ($c \sim 1$) in 2 dm. tubes.

Strychnine salt. To a boiling solution of (\pm)-acid (5 g.) in ethanol (100 c.c.) strychnine (6.6 g.) was added. The salt which separated overnight at room temperature (8.0 g.) had $[\alpha]_{5791} -45.6^{\circ}$. Evaporation of the mother-liquor gave successive crops whose specific rotations were approximately the same as above. A portion of salt on decomposition gave an acid, $[\alpha]_{5791} -19.9^{\circ}$. When prepared in more concentrated solutions of ethanol the specific rotations of the salts were lower and acids were recovered whose specific rotations varied from $[\alpha]_{5791} -13.5^{\circ}$ to -18.2° . Recrystallising the salt from ethanol gave erratic results because of dissociation into free acid and base; methanol was therefore preferred and recrystallisation from this solvent was continued until the specific rotation of the salt remained constant.

Strychnine (-)-2'-t-butylbiphenyl-2-carboxylate crystallised from methanol in sheaves of rectangular prisms, m. p. $208-212^{\circ}$, $[\alpha]_{5791} -49.9^{\circ}$, $[\alpha]_{5461} -58.6^{\circ}$ (Found: C, 77.3; H, 6.8. $C_{17}H_{18}O_2 \cdot C_{21}H_{22}N_2O_2$ requires C, 77.5; H, 6.8%). When it was boiled under reflux in chloroform solution for 15 min. its specific rotation fell to $[\alpha]_{5791} -38.2^{\circ}$ and $[\alpha]_{5461} -44.8^{\circ}$. This salt, the "partial racemate," was always recovered from rotation solutions when the chloroform

was removed by heat or by slow evaporation. When the methanol mother-liquor from recrystallisations was allowed to evaporate slowly to dryness at room temperature the residual salt yielded acid of low rotation ($[\alpha]_{5791} - 6.3^\circ$). All salts were decomposed in the usual manner with ice-cold sodium hydroxide solution. Addition of ice-cold acid to the alkaline solution (after extraction with chloroform) gave the free acid. The purest strychnine salt gave acid, m. p. 185–187°, $[\alpha]_{5791} - 24.3^\circ$, $[\alpha]_{5461} - 29.8^\circ$. Crystallisation from ethanol caused complete racemisation of the acid.

Brucine salt. The (\pm)-acid (1 g.) and brucine (1.44 g.) were dissolved in boiling ethanol (14 c.c.). After 2 days at 4° the first crop of salt separated (1.2 g.), having $[\alpha]_{5791} - 23.9^\circ$ and $[\alpha]_{5461} - 29.7^\circ$. From the reduced mother-liquor a second crop separated with the same rotation. After recrystallisation from ethanol the rotation was unchanged. The acid recovered from the salt had $[\alpha]_{5791} + 7.7^\circ$. The preparation of brucine salt was repeated twice, the rotation of the recovered acids being $+3.3^\circ$ and $+5.1^\circ$.

Racemisation of (-)-acid. The rate of racemisation in boiling ethanol was measured for a solution (20 c.c.) containing 0.2268 g. of (-)-acid. The temperature was rapidly raised to the b. p. (79°) and after a suitable interval the solution was rapidly cooled to room temperature. Polarimetric readings were taken at 20°. The heating and cooling processes were repeated until racemisation was complete; α_{5791} ($l = 2$) fell from -0.39° to 0° . From a logarithmic plot, k was found to be $0.00207 \text{ sec.}^{-1}$ and the half-life 5.6 min. The racemisation of the (-)-acid in ethanol was also followed at 57° and 67° in a well-lagged water-jacketed polarimeter tube ($l = 2$) thermostatically controlled. The rate constants were found to be 0.00033 and 0.00082 sec.^{-1} , and the half-life periods 35 and 14.1 min. respectively. From these data the activation energy was found to be 24 kcal. mole $^{-1}$.

*Resolution of 6,6'-Di-*t*-butylbiphenyl-3,3'-dicarboxylic Acid.*—All rotations were measured in "AnalaR" acetone at room temperature ($c \sim 0.5$) in 2 dm. tubes. The acid (6.5 g.) and brucine (14.4 g.) were dissolved in ethanol (450 c.c.), and the solution kept overnight at +4°. The first fraction of salt (6.1 g.) separated as rosettes of thin rectangular plates and had $[\alpha]_{5791} - 41.8^\circ$, $[\alpha]_{5461} - 46.8^\circ$. The second fraction (1.4 g.) which separated after concentration of the mother-liquor had $[\alpha]_{5791} - 42.4^\circ$, $[\alpha]_{5461} - 50.2^\circ$. Further concentration of the mother-liquor yielded a gel which contained a small amount of crystalline salt and since the gel was very soluble in ethanol it was possible to separate them. The crystalline salt was recrystallised four times from ethanol and was then optically pure.

*Brucine (+)-6,6'-di-*t*-butylbiphenyl-3,3'-dicarboxylate* crystallised from ethanol as a hydrate in rosettes of long, thin rectangular plates, m. p. 210° with previous softening, $[\alpha]_{5791} - 37.8^\circ$, $[\alpha]_{5461} - 43.9^\circ$ (Found: C, 65.3; H, 7.4. $\text{C}_{22}\text{H}_{26}\text{O}_4 \cdot 2\text{C}_{23}\text{H}_{26}\text{N}_2\text{O}_4 \cdot 6\text{H}_2\text{O}$ requires C, 65.3; H, 7.3%). On being heated *in vacuo* at 70° for several hours the salt lost its water of crystallisation and the loss in weight corresponded to $6\text{H}_2\text{O}$. On exposure to air the anhydrous salt very quickly reverted to the hydrated form. Decomposition of the above salt yielded (+)-acid, and from the gel the (-)-acid was obtained.

(+)-6,6'-Di-*t*-butylbiphenyl-3,3'-dicarboxylic acid crystallised from ethanol in glistening plates, from glacial acetic acid in sheaves of rectangular rods, and from aqueous acetic acid in plates. From these solvents it always had solvent of crystallisation which was completely removed only by heating the products *in vacuo* at 130° for several hours. From aqueous acetic acid the (+)-acid crystallised with 1 mol. of water of crystallisation, and had m. p. 345° with loss of solvent at 200° (Kofler block), $[\alpha]_{5791} + 18.1^\circ$, $[\alpha]_{5461} + 23.6^\circ$ (Found: C, 70.9; H, 7.2. $\text{C}_{22}\text{H}_{26}\text{O}_4 \cdot \text{H}_2\text{O}$ requires C, 70.9; H, 7.6%).

The *anhydrous acid*, m. p. 345°, had $[\alpha]_{5791} + 18.6^\circ$, $[\alpha]_{5461} + 24.1^\circ$ (Found: C, 74.7; H, 7.6. $\text{C}_{22}\text{H}_{26}\text{O}_4$ requires C, 74.5; H, 7.4%).

The (-)-acid crystallised from glacial acetic acid with 1 mol. of acetic acid of crystallisation; it had m. p. 345° with loss of solvent at 240° (Kofler block), $[\alpha]_{5791} - 17.7^\circ$, $[\alpha]_{5461} - 22.8^\circ$ (Found: C, 69.7; H, 7.2. $\text{C}_{22}\text{H}_{26}\text{O}_4 \cdot \text{C}_2\text{H}_4\text{O}_2$ requires C, 69.6; H, 7.3%). Heating *in vacuo* at 130° for several hours gave the unsolvated acid, $[\alpha]_{5791} - 18.9^\circ$, $[\alpha]_{5461} - 24.2^\circ$.

After being boiled in sodium hydroxide or in pyridine solution for 3 hr. the active acid was recovered unchanged.

*Resolution of 2',6-Di-*t*-butylbiphenyl-3-carboxylic Acid.*—Rotations of salts and acids were measured at room temperature in "AnalaR" chloroform ($c \sim 1$) in 2 dm. tubes unless otherwise stated.

The above acid (3.1 g.) and strychnine (3.4 g.) were dissolved in ethanol (120 c.c.) and kept

at room temperature overnight. The first crop of salt (1.4 g.) separated as fine needles, $[\alpha]_{5791} - 8.9^\circ$, $[\alpha]_{5461} - 11.0^\circ$. After concentration of the mother-liquor more salt was obtained (1.2 g.) with approximately the same rotation. On further concentration an oil was obtained that did not crystallise. This was decomposed and gave the crude (–)-acid. The crystalline (+)-acid salt was purified by recrystallisation from ethanol.

Strychnine (+)-2',6-di-*t*-butylbiphenyl-3-carboxylate crystallised from ethanol in slender needles, m. p. 160–161°, $[\alpha]_{5791} - 9.5^\circ$, $[\alpha]_{5461} - 12.6^\circ$ (Found: C, 74.2; H, 7.8). $C_{21}H_{26}O_2, C_{21}H_{22}N_2O_2, 2H_2O$ requires C, 74.1; H, 7.7%). When heated *in vacuo* at 80° the salt lost 2 mols. of water of crystallisation. The free acids were obtained from the strychnine salts by decomposition with formic acid. (+)-2',6-Di-*t*-butylbiphenyl-3-carboxylic acid crystallised from methanol in needles, m. p. 181–185°, $[\alpha]_{5791} + 25.5^\circ$, $[\alpha]_{5461} + 28.4^\circ$ (Found: C, 80.8; H, 8.3). $C_{21}H_{26}O_2$ requires C, 81.2; H, 8.4%). In toluene its rotation was $[\alpha]_{5791} + 45.4^\circ$, $[\alpha]_{5461} + 51.8^\circ$.

The crude (–)-acid was crystallised from methanol, and a small amount of (±)-acid separated. This was filtered off and the mother-liquor was concentrated: the (–)-acid crystallised. Recrystallisation from methanol gave the pure (–)-acid, m. p. 181–185°, $[\alpha]_{5791} - 25.8^\circ$ and $[\alpha]_{5461} - 28.3^\circ$.

The active acids melted rather indefinitely and it was suspected that they contained solvent of crystallisation since erratic analytical figures for the same sample were obtained on several occasions. The (–)-acid was therefore heated at 130°/1 mm. and sublimed under these conditions. The *acid* so obtained melted at 192–193° and had $[\alpha]_{5791} - 65.5^\circ$ and $[\alpha]_{5461} - 72.4^\circ$ in toluene (Found: C, 80.9; H, 8.6%). A portion of the pure (–)-acid was melted and allowed to solidify: its specific rotation in toluene was unchanged.

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