

CCXXX.—*The Optical Resolution of 2:4-Dinitro-2'-methyldiphenyl-6-carboxylic Acid.*

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THE resolution of 2-phenylnaphthylene-1:3-diamine into optically active forms (J., 1929, 1512) was attempted in order to justify the constitution assigned to it. Its achievement therefore appears to have only the one explanation. Any alternative explanation must be stereochemical in nature and would involve the assumption that

as a result of the different effects of the two amino-groups the phenyl nucleus is displaced towards one or other of these groups, as shown in (I). Were this the case to any marked extent, free rotation of the phenyl nucleus might become impossible. Nevertheless, such a structure would not be dissymmetrical unless, *in addition*, the bond joining the phenyl to the naphthalene ring were no longer in a straight line with the 1 and 4 positions of the phenyl nucleus (II)



We regard this alternative explanation as exceedingly unlikely, particularly as the original view accorded so well with the purely chemical behaviour of the base and of its derivatives. Yet it seemed desirable to attempt the resolution of some diphenyl derivatives heavily substituted in one nucleus but not in the other. Few such compounds were known, but we found that they may be prepared by what appears to be a general type of reaction, only two examples of which have previously been recorded (Gull and Turner, J., 1929, 491). When equimolecular quantities of ethyl 2-chloro-3 : 5-dinitrobenzoate and an aromatic iodo-compound are heated together in presence of copper-bronze, ethyl 2 : 4-dinitrodiphenyl-6-carboxylates alone are formed. For present purposes we have prepared by this process *ethyl 2 : 4-dinitrodiphenyl-*, *2 : 4-dinitro-2'-methyl-diphenyl-*, and *2 : 4-dinitro-3'-methyl-diphenyl-6-carboxylate*, and from these the corresponding acids. The first and the last of these acids could not be resolved by any of the methods employed, but systematic resolution of the *brucine* salt of 2 : 4-dinitro-2'-methyl-diphenyl-6-carboxylic acid led to both the *d*- and the *l*-form in the optically pure condition. The successful resolution of the 2'-methyl acid, and the non-resolution of the other two acids mentioned above, are satisfactorily explained by the accepted theories (Turner and Le Fèvre, *Chem. and Ind.*, 1926, 831; Bell and Kenyon, *ibid.*, p. 864; Mills, *ibid.*, pp. 883, 905), and the total evidence now put forward suggests that until contradictory results are forthcoming it is unnecessary to replace our theory of the optical activity of the phenylnaphthylenediamine by a purely stereochemical one, although it is admitted that the analogy between the two sets of compounds is not complete.

The resolution of the 3'-methyl acid was attempted because, if it had been successful, the dissymmetry of the molecule could only be explained by assuming that the 2-nitro- and the 6-carboxy-group caused the molecule to take up a form in which the two nuclei were

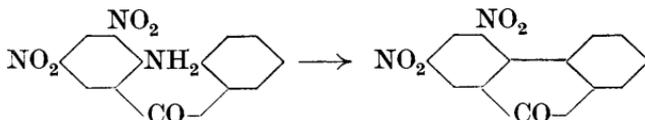
not co-axial. The methyl group would then provide the necessary extra feature for dissymmetry.

We have also succeeded in effecting the incomplete resolution of the 2'-methyl acid by partial esterification with *l*-menthol. The *l*-acid underwent esterification more rapidly than the *d*-acid, and the unesterified acid was markedly dextrorotatory. It was thought possible that, if a mixture of *l*-menthyl 2-chloro-3:5-dinitrobenzoate and *o*-iodotoluene was heated with copper-bronze, asymmetric synthesis might result. This was actually found to occur, for the 2:4-dinitro-2'-methyldiphenyl-6-carboxylic acid finally obtained had a definite dextrorotation. This is the first example of an asymmetric synthesis of this type or in this series.

An interesting point arose in connexion with the optical activity of the 2:4-dinitro-2'-methyldiphenyl-6-carboxylic acids. These have $[\alpha]_{5791} \pm 18.7^\circ$ in ethyl-alcoholic solution, but when they are crystallised from benzene they form compounds, $C_{14}H_{10}O_6N_2 \cdot 0.5C_6H_6$, which in alcoholic solution have $[\alpha]_{5791} \pm 7.8^\circ$. The benzene of crystallisation is not removed by repeated evaporation of the alcoholic solution of the compound, although boiling alkali readily removes it, and prolonged boiling of the alkaline solution does not cause any racemisation.

The large effect on the rotation produced by the benzene of crystallisation is noteworthy, and considerable interest attaches to the observation in view of the theory put forward by Bennett and Willis (J., 1929, 256) as to the structure of organic "molecular" compounds. The racemic acid shows no tendency to combine with benzene.

2:4-Dinitrodiphenyl-6-carboxylic acid is readily converted by warm concentrated sulphuric acid into 2:4-dinitrofluorenone, identical with the product obtained by Ullmann and Broido (*Ber.*, 1906, 39, 356) from 3:5-dinitro-2-aminobenzophenone.



The *l*-2'-methyl acid similarly gave the methyl derivative of this fluorenone. This was inactive, as might have been expected (compare Bell and Robinson, J., 1927, 2234).

EXPERIMENTAL.

Ethyl 2:4-Dinitrodiphenyl-6-carboxylate.—A mixture of 20 g. of ethyl 2-chloro-3:5-dinitrobenzoate and 20 g. of iodobenzene was heated at 220° , 17 g. of copper-bronze being gradually added. The

reaction proceeded at 240°, and when it was complete the mixture was extracted with chloroform. The 12 g. of crude *ester* obtained crystallised from alcohol in rosettes of pale yellow, rectangular needles, m. p. 84—85° (Found : C, 56·9; H, 3·7. $C_{15}H_{12}O_6N_2$ requires C, 57·0; H, 3·8%).

2 : 4-Dinitrodiphenyl-6-carboxylic Acid.—It was found impossible to hydrolyse the above ester by the usual processes, including that described by Ullmann (*Annalen*, 1909, **366**, 89). The following method, however, gave excellent results : A mixture of 20 g. of the ester, 100 c.c. of water, 202 c.c. of concentrated sulphuric acid, and 400 c.c. of glacial acetic acid was boiled for 4 hours. The dark green solution was diluted with water, and the dark green, crystalline precipitate (14 g.) was dissolved in dilute sodium hydrogen carbonate solution and so freed from a trace of tarry matter. Precipitation of the solution with hydrochloric acid gave *2 : 4-dinitrodiphenyl-6-carboxylic acid*, which crystallised from light petroleum-benzene in pale yellow prisms (12 g.), m. p. 193—194° (Found : C, 54·0; H, 2·8. $C_{13}H_8O_6N_2$ requires C, 54·2; H, 2·8%).

2 : 4-Dinitrofluorenone.—A solution of the last-named acid in 20 parts of concentrated sulphuric acid was heated at 100° for 10 minutes, water added, and the yellow precipitate collected, extracted with sodium carbonate solution, washed, and dried. It had m. p. 193—194°.

Attempted Resolution of 2 : 4-Dinitrodiphenyl-6-carboxylic Acid.—Many attempts were made to obtain salts with various alkaloids in a number of solvents. All were unsuccessful except in the case of brucine. The acid (1 g.) in alcoholic solution was treated with brucine (1·6 g.). An immediate crystalline precipitate of the brucine salt was obtained. This was recrystallised from alcohol (170 c.c.) and gave 1·9 g. with $[\alpha]_{5791} -16·8^\circ$ for $c = 1·243$ in acetone. After recrystallisation from alcohol the salt had $[\alpha]_{5791} -15·1^\circ$ for $c = 1·252$ in acetone. A solution of equivalent quantities of the acid and brucine had $[\alpha]_{5791} -15·4^\circ$ for $c = 2·016$ in acetone. The salt having $[\alpha]_{5791} -15·1^\circ$ gave rise to an inactive acid.

Resolution was also attempted by the fractional precipitation method of Pope and Read (*J.*, 1914, **105**, 817) : an alcoholic solution of the acid (1 g.) was treated with successive quantities of brucine (0·5 g.) and three crops of salt were obtained having respectively $[\alpha]_{5791} -15·4^\circ$, $-14·8^\circ$, and $-15·5^\circ$ in acetone solution. When these were decomposed, inactive acids were obtained.

Attempt to effect the Asymmetric Synthesis of 2 : 4-Dinitrodiphenyl-6-carboxylic Acid.—*Preparation of l-menthyl 2-chloro-3 : 5-dinitrobenzoate.* A mixture of 10 g. of 2-chloro-3 : 5-dinitrobenzoic acid and 20 g. of *l*-menthol was heated under reflux at 150° for 10 hours,

dry hydrogen chloride being passed in from time to time. The cooled mixture was dissolved in ether, the solution extracted with sodium carbonate solution and washed with water, the excess of ether removed, and the resulting product steam-distilled. The residue solidified on cooling (10 g.). The *ester* crystallised from alcohol in slender, pale yellow needles, m. p. 113—114°, and had $[\alpha]_{D_{791}} -53.6^\circ$ for $c = 2.385$ in acetone (Found : Cl, 9.4. $C_{17}H_{21}O_6N_2Cl$ requires Cl, 9.2%).

When the ester was heated with copper-bronze and iodobenzene, only a very small quantity of product was obtained. It was not further examined.

Incomplete Esterification with Menthol of 2 : 4-Dinitrodiphenyl-6-carboxylic Acid.—A mixture of 7 g. of the acid with 14 g. of *l*-menthol was heated under reflux at 150° for 12 hours. The reaction product was dissolved in ether, and the extract shaken with sodium hydrogen carbonate solution. The aqueous solution was repeatedly extracted with ether until free from menthol, and the acid then precipitated. It proved to be optically inactive.

Ethyl 2 : 4-Dinitro-2'-methylidiphenyl-6-carboxylate.—A mixture of 50 g. of ethyl 2-chloro-3 : 5-dinitrobenzoate and 50 g. of *o*-iodotoluene was heated at 220° and 50 g. of copper-bronze were gradually added. The cooled product was extracted three times with *o*-dichlorobenzene. After removal of the solvent, 32 g. of crude ester were obtained. The *ester* crystallised from alcohol in hexagonal laminae, m. p. 95—96° (Found : C, 58.2; H, 4.3. $C_{16}H_{14}O_6N_2$ requires C, 58.2; H, 4.3%).

Hydrolysis of Ethyl 2 : 4-Dinitro-2'-methylidiphenyl-6-carboxylate.—A mixture of 20 g. of the ester, 200 c.c. of concentrated sulphuric acid, 400 c.c. of glacial acetic acid, and 100 c.c. of water was boiled under reflux for 4 hours. The diluted solution obtained deposited crystals on cooling, and these were recrystallised from benzene. 2 : 4-Dinitro-2'-methylidiphenyl-6-carboxylic acid forms small, pale yellow, rectangular plates, m. p. 156—157°, and is readily soluble in alcohol, acetone and chloroform, but sparingly soluble in benzene and light petroleum (Found : C, 55.7; H, 3.5. $C_{14}H_{10}O_6N_2$ requires C, 55.6; H, 3.3%).

Resolution of 2 : 4-Dinitro-2'-methylidiphenyl-6-carboxylic Acid.—When a mixture of equivalent quantities of brucine and the acid was caused to crystallise from alcoholic solution, no resolution occurred. Repeated crystallisation of the salt from acetone failed to effect any change in rotation.

A similar result was obtained when the brucine salt was prepared by treating an aqueous solution of the ammonium salt with brucine

hydrochloride. Resolution was, however, effected by the following process.

A solution of 12 g. of the acid in acetone was treated with a half-equivalent of brucine (7.8 g.) and the resulting solution (400 c.c.) was allowed to crystallise. Clusters of rectangular needles separated (8 g.), having $[\alpha]_{5791} -7.2^\circ$ in chloroform ($l = 2, c = 2.002$). To the mother-liquor were added a further 7.8 g. of brucine, and 9 g. of salt were obtained, consisting mainly of rectangular plates and having $[\alpha]_{5791} -5.8^\circ$ in chloroform ($l = 2, c = 2.052$). On removal of some of the acetone from the mother-liquor, a further 5 g. of salt separated in rectangular needles, having $[\alpha]_{5791} -2.4^\circ$ in chloroform ($l = 2, c = 2.04$).

After five crystallisations of the three salts from acetone, these had respectively $[\alpha]_{5791} -11.7^\circ, -7.3^\circ$, and -2.2° in chloroform, and when decomposed gave three fractions of acid having respectively $[\alpha]_{5791} -17.5^\circ, 0.0^\circ$, and $+16.8^\circ$ in alcoholic solution. Decomposition of the salts was effected as follows: A chloroform solution of the salt was shaken with approximately the calculated amount of aqueous ammonia, and the alkaline solution then extracted thrice with chloroform. Acidification of the solution, followed by extraction with ether, afforded the free acid.

By employing the fractional crystallisation method, using brucine hydrochloride and the ammonium salt of the acid in aqueous solution, the same salts were obtained, and they crystallised from the aqueous solution in the same order.

1-2 : 4-Dinitro-2'-methylidiphenyl-6-carboxylic acid crystallised from aqueous solution in pale yellow, hexagonal prisms, m. p. 158—159°, and had $[\alpha]_{5791} -18.6^\circ$ in ethyl-alcoholic solution (Found: C, 55.5; H, 3.2. $C_{14}H_{10}O_6N_2$ requires C, 55.6; H, 3.3%). It is sparingly soluble in water or light petroleum, readily soluble in acetone and in alcohol, but less so in benzene. It crystallises from benzene in clumps of hexagonal plates, m. p. 158—159° (with previous softening at 140°), and then has $[\alpha]_{5791} -7.8^\circ$ in ethyl-alcoholic solution. From an equivalent-weight determination it was found that 0.5 mol. of benzene of crystallisation was present. After being heated for 2 days at 100°, the compound still had the same composition and rotation. An alcoholic solution of the compound was evaporated and the process was twice repeated. The compound remained unchanged. It was dissolved in aqueous sodium hydroxide and the solution was boiled until free from benzene. The acid recovered by acidification, etc., had $[\alpha]_{5791} -18.6^\circ$ in ethyl-alcoholic solution.

The benzene-free acid had $[\alpha]_{5791} -19.5^\circ$ in acetone ($c, 1.382$) and -11.2° in benzene ($c, 1.318$).

d-2 : 4-Dinitro-2'-methyldiphenyl-6-carboxylic acid has properties similar to those of its *l*-isomeride. It has $[\alpha]_{5791} -18.8^\circ$ in ethyl alcohol (*c*, 1.462), and after crystallisation from benzene contains 0.5 mol. of benzene, then having $[\alpha]_{5791} +7.8^\circ$ in ethyl alcohol (*c*, 1.772) (Found : C, 55.6; H, 3.5. $C_{14}H_{10}O_6N_2$ requires C, 55.6; H, 3.3%).

Asymmetric Synthesis of 2 : 4-Dinitro-2'-methyldiphenyl-6-carboxylic Acid.—A mixture of 15 g. of *l*-menthyl 2-chloro-3 : 5-dinitrobenzoate ($[\alpha]_{5791} -53.6^\circ$ in acetone) and 15 g. of *o*-iodotoluene was heated at 200° and 15 g. of copper-bronze were gradually added. A vigorous reaction ensued. The product was extracted with *o*-dichlorobenzene and gave 5 g. of crude ester. The latter was boiled under reflux for 4 hours with a mixture of 50 c.c. of concentrated sulphuric acid, 100 c.c. of glacial acetic acid, and 25 c.c. of water. The resulting solution was diluted, made alkaline, and extracted with ether until free from menthol. Acidification of the alkaline solution, followed by ether extraction, gave 0.5 g. of acid having $[\alpha]_{5791} +4.4^\circ$ in acetone.

Incomplete Esterification of 2 : 4-Dinitro-2'-methyldiphenyl-6-carboxylic Acid.—A mixture of 5 g. of the acid with 10 g. of *l*-menthol was heated at 140° for 6 hours. The reaction product was extracted with ether, and the ethereal solution shaken with sodium hydrogen carbonate solution. The alkaline solution was extracted with ether until free from menthol, and the free acid precipitated with hydrochloric acid. In this way were obtained 2 g. of acid, having $[\alpha]_{5791} +2.8^\circ$ in acetone (*l* = 2, *c* = 2.5).

Preparation of 2 : 4-Dinitro-3'-methyldiphenyl-6-carboxylic Acid.—A mixture of 10 g. of ethyl 2-chloro-3 : 5-dinitrobenzoate and 10 g. of *m*-iodotoluene was heated at 220° and 10 g. of copper-bronze were gradually added. Vigorous reaction occurred at 230° . The reaction mixture was extracted with *o*-dichlorobenzene and 8 g. of crude ester were obtained. It crystallised from alcohol in pale yellow, hexagonal plates, m. p. $120-121^\circ$ (Found : C, 58.3; H, 4.1. $C_{16}H_{14}O_6N_2$ requires C, 58.2; H, 4.3%).

The ester was hydrolysed by the method already described, 25 g. giving 21 g. of crude acid. The latter crystallised from benzene-light petroleum in pale yellow, cubic crystals, m. p. $118-119^\circ$ (Found : C, 55.8; H, 3.5. $C_{14}H_{10}O_6N_2$ requires C, 55.6; H, 3.3%).

A mixture of the acid with twice its weight of menthol was heated at 140° for 6 hours. The unesterified acid was optically inactive.

The acid readily formed a brucine salt, but repeated crystallisation of the latter was unaccompanied by change in its rotatory power. When the ammonium salt and brucine hydrochloride were used in

aqueous solution, a similar result was obtained. The method of Pope and Read (*loc. cit.*) also failed to effect resolution.

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