179. *The Replacement of "Obstacle" Groups in Optically Active Diphenyls.*

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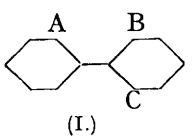
A DIPHENYL derivative of type (I) is optically active because the group A acts as an obstacle to the free rotation of the nucleus containing B and C. It appeared of interest to determine whether activity would be preserved when the group A was *completely* replaced by some other group D. Suitable reactions are the replacement of the amino-group by hydroxyl or halogen by diazotisation and of carboxyl by the amino-group by the reactions of Hofmann and Curtius. It has not yet proved possible to prepare an amine of this simple type. 6-Nitrodiphenic acid on reduction gave a product which did not possess the properties of a simple amino-acid, and the Ullmann reaction, which appeared to offer a simple route, did not lead to the isolation of the desired compounds when applied to 2-iodonitrobenzene with either 2-iodo-*m*-toluidine or 2-iodo-*m*-acetotoluidide or to 2-iodo-3-nitrotoluene with 2-bromoaceto-*p*-toluidide, or 2-iodoacetanilide or 1-iodonaphthalene. 6 : 6′-Diamino-2 : 2′-ditolyl was therefore used. The *d*-base after diazotisation is readily converted by the action of potassium iodide into 6 : 6′-di-iodo-2 : 2′-ditolyl, which shows a strong dextrorotation. Consequently the activity must be preserved at every stage of the reaction. This may happen through the rate of introduction of the iodo-groups being high compared with the rate of racemisation of the 2 : 2′-dimethyl compound (especially if the 6 : 6′ carbon atoms are left in a charged condition)



(I.)

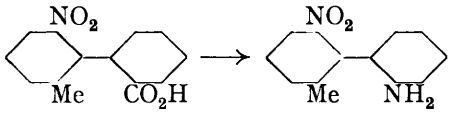
or through the elimination of the diazo-nitrogen and the introduction of the iodo-group being coupled reactions, so that, in effect, the 6 : 6′-positions are never left free from substituents. However, since the mechanism of this reaction is by no means clear, the *l*-base was converted into the solid diazoborofluoride (Balz and Schiemann, *Ber.*, 1927, **60**, 1186). The conversion of a dried diazoborofluoride into the corresponding fluoride by heating would seem necessarily to involve the production of a free radical or ion (II):

$$R{\cdot}N_2BF_4 \longrightarrow \overset{+}{R} + N_2 + BF_3 + F' \longrightarrow RF \quad \text{(II.)}$$

On decomposing the borofluoride a product of slight activity was obtained, but the result was not regarded as unambiguous.

Attempts to convert optically active 6 : 6′-dimethyldiphenic acid into 6 : 6′-diamino-ditolyl by means of the Hofmann or Curtius reaction were unsuccessful.

Next, optically active 6-nitro-2-methyldiphenyl-2′-carboxylic acid (III) was converted into the corresponding amine by both the Hofmann and the Curtius reaction. The amine

(III.) 

was in each case active. Whilst this work was in progress, Wallis and Moyer (*J. Amer. Chem. Soc.*, 1933, **55**, 2598) described the preparation of optically active 3 : 4-dinitro-2-α-naphthylaniline from 3 : 4-dinitro-2-α-naphthylbenzoic acid by means of the Hofmann reaction. They have discussed the significance of this observation.

Since (III) is so stable optically, it was hoped to simplify the reaction still further by employing optically active *2-nitrodiphenyl-2′-carboxylic acid*. This acid, however, furnished uniform alkaloidal salts.

Experimental.

6 : 6′-*Di-iodo*-2 : 2′-*ditolyl*.—*d*-6 : 6′-Diamino-2 : 2′-ditolyl (6·7 g.) (Meisenheimer and Horing, *Ber.*, 1927, **60**, 1425) was converted into the di-iodo-compound by the method of Angeletti (*Gazzetta*, 1933, **63**, 145). The product (1·4 g.) had $[\alpha]_D$ + 19° in chloroform (c = 5·8; l = 2) and formed needles, m. p. 84°, $[\alpha]_D$ + 24° in chloroform (c = 1·35; l = 2), after recrystallisation from alcohol.

6 : 6′-*Difluoro*-2 : 2′-*ditolyl*.—*l*-6 : 6′-Diamino-2 : 2′-ditolyl (10 g.), dissolved in hydrochloric acid (40 c.c.) and water (100 c.c.), was diazotised with sodium nitrite (7·7 g. in 15 c.c. of water), the filtered solution added to a solution of borofluoric acid (from 12 g. of boric acid and 30 c.c. of 40% hydrofluoric acid), the precipitated diazoborofluoride washed with hydrofluoric acid, alcohol, and ether, dried (14 g.), and decomposed by being introduced slowly into a flask heated on a steam-bath. The product that distilled in steam was a colourless oil of characteristic odour, which rapidly solidified. 1·8 G. of this solid in 15 c.c. of chloroform showed α_D − 0·14° (l = 2); the activity persisted unchanged for 2 days. The solid was recrystallised from methyl alcohol and gave 6 : 6′-*difluoro*-2 : 2′-*ditolyl* as stout prisms, m. p. 45° (Found: C, 76·8; H, 5·5. $C_{14}H_{12}F_2$ requires C, 77·1; H, 5·5%); the product still showed slight lævorotation.

6 : 6′-*Dimethyldiphenic Acid*.—The following route provides an alternative to that of Meyer (*Ber.*, 1911, **44**, 2203): *m*-Xylene $\xrightarrow{(1)}$ 2-nitro-*m*-xylene $\xrightarrow{(2)}$ 2-nitro-*m*-toluic acid $\xrightarrow{(3)}$ 2-amino-*m*-toluic acid $\xrightarrow{(4)}$ 2-iodo-*m*-toluic acid $\xrightarrow{(5)}$ methyl 2-iodo-*m*-toluate $\xrightarrow{(6)}$ 6 : 6′-dimethyldiphenic acid. Stages 4—6, which do not appear to have been previously described, were carried out by the usual methods, *viz.*, the Sandmeyer reaction, methyl-alcoholic hydrogen chloride, and heating with copper bronze, respectively. The yields were 70% in stage 4 and 84% in stage 5.

In stage 6, copper bronze (22 g.) was added slowly to methyl 2-iodo-*m*-toluate (30 g.), heated so that the temperature did not exceed 270°. The product was extracted in acetone, recovered, and boiled with 3*N*-sodium hydroxide until solution occurred (about 3 hours). It was then filtered into hydrochloric acid, 13·2 g. of precipitate (m. p. *ca.* 220°) being obtained. This product was best purified by extraction of impurities with hot benzene. 6 : 6′-Dimethyldiphenic acid was obtained as a white powder, m. p. 231—233°, which crystallised from aqueous alcohol in iridescent plates (Meyer states that the yield is very poor and the acid melts at 230° with previous sintering).

Resolution.—The quinidine salt was not obtained crystalline and the brucine salt gave no indication of separation, but both the quinine and the morphine salt proved suitable, the latter appearing the better of the two. Morphine (5·6 g.) was added to 6 : 6′-dimethyldiphenic acid (5·0 g.) in alcohol (75 c.c.). On cooling, 4·8 g. of salt, m. p. 196°, $[\alpha]_{5461}$ − 65·5° in acetic acid (c = 2), were obtained and the properties were little altered after thorough extraction with alcohol, $[\alpha]_{5461}$ changing only to 64·7° (c = 2 in acetic acid). On decomposition this salt gave the *d*-acid, $[\alpha]_D$ + 15° in methyl alcohol (c = 2). The alcoholic mother-liquor would not give a further crop of the morphine salt and therefore the whole was decomposed. The *l* + *dl* acid so obtained had $[\alpha]_D$ − 11·5° in methyl alcohol (c = 2).

Curtius Reaction.—The *l* + *dl* acid when treated by the process outlined below gave a benzene layer which showed lævorotation, but on removal of the benzene the residual product proved to be insoluble in hydrochloric acid. It was not examined further.

Hofmann Reaction.—The *d*-acid amide dissolved rapidly in the aqueous hypobromite (details as below). The filtrate was acidified with hydrochloric acid, and the resultant precipitate dissolved in aqueous ammonia and reprecipitated by hydrochloric acid. The product after boiling with benzene formed a brown powder, m. p. 257° (decomp.), $[\alpha]_D$ − 33° in methyl alcohol (c = 2) (Found : C, 71·1; H, 5·2; N, 10·2%). No 6 : 6′-diamino-2 : 2′-ditolyl was isolated.

Experiments with 6-Nitro-2-methyldiphenyl-2′-carboxylic Acid.—This acid was resolved by Stoughton and Adams (*J. Amer. Chem. Soc.*, 1930, **52**, 5264) by crystallisation of the brucine salt from a very large volume of water, but the following method is advantageously employed. Quinidine (28 g.) in hot alcohol (240 c.c.) was added to a boiling solution of the acid (20 g.) in alcohol (160 c.c.). The less soluble quinidine salt was deposited immediately and on extraction with boiling alcohol soon attained constant rotatory power, $[\alpha]_D$ + 212° in acetic acid (c = 1). No further crop could be obtained from the alcoholic mother-liquor and therefore the acid was recovered ($[\alpha]_D$ − 55° in methyl alcohol, c = 1) and converted into the brucine salt in acetone solution. This was extracted with hot acetone until of constant rotatory power. The quinidine salt on decomposition gave the *d*-acid, $[\alpha]_D$ + 69°, and the brucine salt gave the *l*-acid, $[\alpha]_D$ − 69° (c = 1 in methyl alcohol).

Hofmann Reaction with the d-*Acid.*—The acid was evaporated with thionyl chloride, and the residue dissolved in benzene and shaken with aqueous ammonia (*d* 0·88). 2 G. of the resultant amide were added to 25 c.c. of sodium hypobromite solution (prepared from sodium hydroxide 7 g., water 50 c.c., and bromine 1 c.c.), and the mixture gently warmed on the steam-bath. The product was extracted with benzene, the benzene evaporated, and the amine extracted from the residual oil by warm dilute hydrochloric acid. After decoloration with norit, this extract was filtered into a 1 dm. polarimeter tube and proved to be dextrorotatory, α_D + 0·79°.

Curtius Reaction with the l-*Acid.*—2·5 G. were evaporated with thionyl chloride, and the residue was taken up in benzene and boiled for 5 hours after addition of sodium azide (1·5 g.). Sodium hydroxide (7 c.c. of 3*N*) was then added, and the heating continued for a further 2 hours. A small amount of solid material A (0·6 g.) was filtered off, the benzene layer separated and evaporated, and the amine extracted from resinous matter (0·8 g.) by means of dilute hydrochloric acid. The hydrochloric acid extract was shaken with norit and filtered into a 1 dm. polarimeter tube and proved to be lævorotatory, α_D − 3·37°. The base was precipitated with aqueous ammonia and extracted with benzene, and the benzene evaporated. The viscous residue solidified after some weeks and was then readily purified by precipitation from hydrochloric acid by aqueous ammonia or from benzene by petroleum. *6-Nitro-2′-amino-2-methyldiphenyl* formed a yellow powder, m. p. 50—53°, $[\alpha]_D$ − 48° in 6*N*-hydrochloric acid (c = 5·8; l = 0·5) (Found : C, 68·1; H, 5·2. $C_{13}H_{12}O_2N_2$ requires C, 68·4; H, 5·3%). The base was acetylated with acetic anhydride containing a drop of sulphuric acid. *6-Nitro-2′-acetamido-2-methyldiphenyl* crystallised from methyl alcohol in rosettes, m. p. 93—95° (Found : N, 10·4. $C_{15}H_{14}O_3N_2$ requires N, 10·4%). The product was slightly dextrorotatory, α_D + 0·10° (c = 2·9 in methyl alcohol; l = 1).

The solid A (above) was insoluble in aqueous ammonia or hydrochloric acid, and sparingly soluble in ethyl alcohol, but crystallised from acetic acid in prisms, m. p. 210° (Found : N, 11·3%), α_D − 0·57° in chloroform (c = 2; l = 1).

The experiment was repeated with the *d*-acid with strictly comparable results at each stage.

Reduction of 6-Nitrodiphenic Acid.—Schmidt and Kampf's method (*Ber.*, 1903, **36**, 3738) was followed. The product was insoluble in the usual solvents, although easily soluble in dilute aqueous ammonia. The properties, but not the analytical data, favour a lactam structure (Found : C, 65·6, 65·6; H, 3·6, 3·6. $C_{14}H_{11}O_4N$ requires C, 65·4; H, 4·3%. $C_{14}H_9O_3N$

requires C, 70·4; H, 3·7%). In view of previously reported analytical difficulties with lactams (Kenner and Stubbings, J., 1921, **119**, 593) a different sample was submitted to Dr. A. Schoeller, who found C, 65·2; H, 3·6%. By solution in aqueous sodium hydroxide and back-titration with hydrochloric acid the equivalent was found to be 127, 129 (phenolphthalein), 243, 243 (methyl-red), and 262, 265 (incipient precipitation).

The reduction was repeated with *d*-6-nitrodiphenic acid, a blank experiment showing that hot hydrochloric acid has little racemising action on the nitro-acid. The products were filtered off, dissolved in aqueous ammonia, and filtered into polarimeter tubes. (A) Nitro-acid with hydrochloric acid only, α_D — 22·1°. (B) Nitro-acid with hydrochloric acid and tin, α_D 0·0°.

An attempt was made to characterise the reduction product by suitable derivatives. No definite product could be isolated after interaction with *p*-toluenesulphonyl chloride in alkaline solution; with hot acetic anhydride and subsequent decomposition with water, prisms, m. p. 251° (decomp.), were obtained [Found: C, 64·2; H, 3·8. Schoeller with a new sample found C, 64·0; H, 3·8. $C_{16}H_{13}O_5N$ (6-acetamidodiphenic acid) requires C, 64·2; H, 4·3%].

2'-Nitrodiphenyl-2-carboxylic Acid.—A mixture of methyl 2-iodobenzoate (30 g.) and 2-iodonitrobenzene (30 g.), heated in an oil-bath at 230°, was treated gradually with copper bronze (30 g.) so that the temperature did not exceed 270°. The product was extracted in acetone, recovered, and boiled for 3 hours with 3*N*-sodium hydroxide. After dilution the solution was filtered from 2 : 2'-dinitrodiphenyl and poured into hydrochloric acid. The gummy precipitate was dissolved in aqueous ammonia and reprecipitated. Recrystallised from chloroform, *2'-nitrodiphenyl-2-carboxylic acid* formed almost colourless needles, m. p. 168° (Found: equiv., 243. $C_{13}H_9O_4N$ requires equiv., 243).

The acid gave morphine and quinine salts which were not obtained crystalline. The quinidine salt, m. p. 196—198°, $[\alpha]_D$ + 136° in chloroform (c = 1), showed no change in crystalline form (rosettes of needles) or rotatory power when recrystallised from alcohol. The brucine salt crystallised from acetone in nodules, m. p. 218° (decomp.), and three successive crops gave $[\alpha]_D$ — 25·9°, — 20·4°, — 20·7° (c = 1 in chloroform). No mutarotation was observed during 4 days and no significance is attached to these slight differences. The strychnine salt was a sparingly soluble substance which crystallised from alcohol in needles, m. p. 216°. It gave $[\alpha]$ — 25° (c = 1 in chloroform), unchanged after recrystallisation from acetone.

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