

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

STEREOCHEMISTRY OF DIPHENYL COMPOUNDS.
THE PREPARATION AND RESOLUTION OF 3,5,3',5'-TETRA-
METHYL-2,2'-DIFLUORO-6,6'-DIAMINODIPHENYL. XIV¹

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The interpretation of the degree of resistance to free rotation of the rings in 2,2',6,6'-substituted diphenyls through x-ray values representing the size of the groups, was discussed in detail in an earlier paper.³ Since that time these values have been applied to various new diphenyl compounds and have fitted in better with the experimental facts than might have been anticipated. However, sufficient data have not as yet been collected so that generalizations might be drawn which would make possible the prediction of the properties of any new derivatives in a quantitative way.

It was pointed out that any diphenyl molecule which showed interference between the 2,2' and 6,6' substituting groups of only a few hundredths of an Å. would probably racemize readily, a property not shown by most of the molecules studied up to this time. It may thus be seen that in 2,2'-difluoro-6,6'-diaminodiphenyl such conditions should exist. On each side of the molecule the interference would be only 0.05 Å.: C-F, 1.39 Å. + C-NH₂, 1.56 Å. = 2.95Å. - 2.90Å. (vertical distance between the 2,2' carbon atoms) = 0.05 Å. In this investigation a homolog of this compound has been described and its ease of racemization determined. The properties are exactly those which were predicted.

The compound synthesized was 3,5,3',5'-tetramethyl-2,2'-difluoro-6,6'-diaminodiphenyl (V). It was readily resolved through the dicamphor-sulfonate salt. The active amines had surprisingly low rotations compared to most of the other optically active diphenyls previously studied, $[\alpha]_D^{20} - 4.1^\circ$ and $[\alpha]_D^{20} + 3.2^\circ$. The former undoubtedly is the maximum rotation for the active compound as it was obtained from the pure, less soluble salt.

The active forms racemized with the greatest ease. By boiling in ethyl alcohol, the *l*-form was half racemized in one hour and completely racemized in two hours; in glacial acetic acid it was entirely racemized in half an hour; even in boiling methyl alcohol the racemization was complete in four hours.

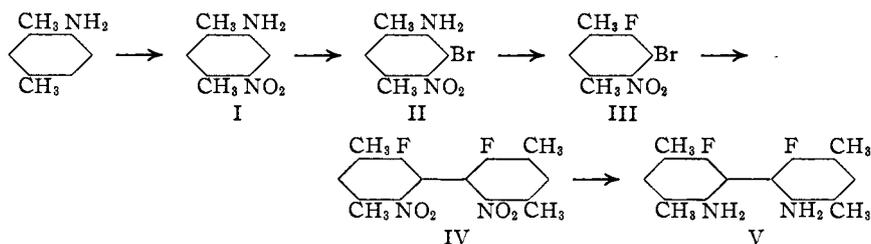
To synthesize this compound the following series of reactions was carried out: 3,5-dimethyl-2-aminobenzene \longrightarrow 3,5-dimethyl-2-amino-6-nitro-

¹ For the preceding papers in this series see Browning and Adams, *THIS JOURNAL*, 52, 4098 (1930); Stanley and Adams, 52, 4471 (1930); Steele and Adams, 52, 4528 (1930); Shildneck and Adams, 53, 343 (1931); Bock and Adams, 53, 374 (1931).

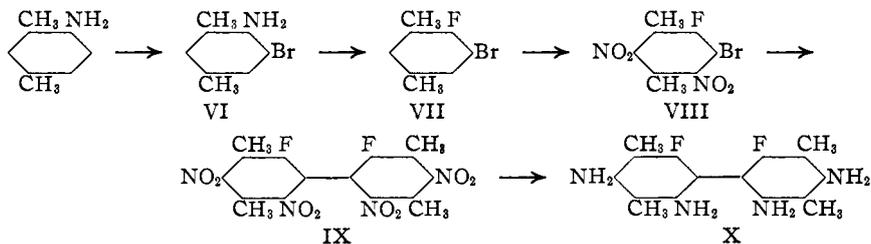
² This communication is a portion of a thesis submitted by E. C. Kleiderer in partial fulfillment of the requirements for the Degree of Doctor of Philosophy in Chemistry at the University of Illinois.

³ Stanley and Adams, *THIS JOURNAL*, 52, 1200 (1930).

benzene (I) \longrightarrow 3,5-dimethyl-2-amino-6-nitro-1-bromobenzene (II) \longrightarrow 3,5-dimethyl-2-fluoro-6-nitro-1-bromobenzene (III) \longrightarrow 3,5,3',5'-tetramethyl-2,2'-difluoro-6,6'-dinitrodiphenyl (IV) \longrightarrow 3,5,3',5'-tetramethyl-2,2'-difluoro-6,6'-diaminodiphenyl (V).



In the experimental part is also described the preparation of 3,5,3',5'-tetramethyl-2,2'-difluoro-4,4',6,6'-tetraaminodiphenyl, as follows: 3,5-dimethyl-2-aminobenzene \longrightarrow 3,5-dimethyl-2-amino-1-bromobenzene (VI) \longrightarrow 3,5-dimethyl-2-fluoro-1-bromobenzene (VII) \longrightarrow 3,5-dimethyl-2-fluoro-4,6-dinitro-1-bromobenzene (VIII) \longrightarrow 3,5,3',5'-tetramethyl-2,2'-difluoro-4,6,4',6'-tetranitrodiphenyl (IX) \longrightarrow 3,5,3',5'-tetramethyl-2,2'-difluoro-4,6,4',6'-tetraaminodiphenyl (X).



This compound was synthesized before the corresponding diamino derivative but, in attempting resolution, crystalline salts could not be isolated using *d*-tartaric acid, *d*-camphorsulfonic acid, or *d*-bromocamphor-sulfonic acid.

Experimental

3,5-Dimethyl-2-amino-6-nitrobenzene (I).⁴—In a 600-cc. beaker, 20 g. of *m*-xylylidine was dissolved in 200 g. of concentrated sulfuric acid. The mixture was then cooled to 5° and not allowed to rise above 15°. To this was slowly added with stirring 16.5 g. of concentrated nitric acid (sp. gr. 1.42). After all of the nitric acid had been added, the mixture was stirred for thirty minutes longer. It was then poured onto ice, when the amine sulfate precipitated. This was filtered off and made alkaline with 10% sodium carbonate solution. The free amine was purified by crystallization from 50% alcohol-water mixture. A small amount of an insoluble by-product always resulted which may have been a dinitro compound. The mononitro compound formed deep orange needles melting at 123–124° and the yield was 23 g. (84%).

⁴ Noelting and Collin, *Ber.*, **17**, 265 (1884).

3,5-Dimethyl-2-amino-6-nitro-1-bromobenzene (II).⁶—In a 1-liter round-bottomed flask, 10 g. of 3,5-dimethyl-2-amino-6-nitrobenzene was dissolved in 100 g. of glacial acetic acid. To this was added, with stirring, 9.5 g. of bromine dissolved in 50 cc. of glacial acetic acid. During the addition, the hydrobromide of the brominated amine crystallized out in white needles. The crystals were filtered off and made alkaline with a 10% sodium carbonate solution and the base thus obtained was used directly for further experimentation.

3,5-Dimethyl-6-nitro-1-bromobenzene-2-diazoniumborofluoride.—In a 300-cc. beaker was placed 25 cc. of concentrated hydrochloric acid. In this was suspended 10 g. of 3,5-dimethyl-2-amino-6-nitro-1-bromobenzene, and the mixture cooled to 0°. A solution of saturated sodium nitrite was added until there remained a slight excess of free nitrous acid as determined by potassium iodide-starch test papers. The solution was filtered from any sodium chloride and to the filtrate was added 27.6 g. of a solution of hydroborofluoric acid, made by mixing 20 g. of 48% hydrofluoric acid and 7.6 g. of boric acid. Upon the addition of the acid, the borofluoride precipitated in white needles. It was filtered off and washed with more hydroborofluoric acid. The yield was 9 g. (67%). The decomposition point of the compound was 195°.

3,5-Dimethyl-2-fluoro-6-nitro-1-bromobenzene (III).—In a small Pyrex test-tube, connected by a wide glass delivery tube to a 500-cc. distilling flask cooled in ice, was placed 3 g. of the 3,5-dimethyl-6-nitro-1-bromobenzene-2-diazoniumborofluoride. The compound was heated with a Méker burner and as soon as it commenced to decompose, the system was placed under reduced pressure and heating continued. The compound became very black and charred but a quantity of the fluorine derivative distilled over. Heating was continued until no more material could be distilled, when the test-tube was emptied of the carbon and refilled with 3 g. more of the borofluoride. It was found that the yield increased when small quantities of the borofluoride were decomposed at a time. Additional fluorine compound could be obtained by reheating the carbon residue obtained from previous decompositions. The fluorine compound was purified by mixing with water and steam distilling and then crystallizing from low-boiling petroleum ether. It formed yellow needles, melting at 49–51°. The yield was 17 g. from 50 g. of borofluoride (45%).

Anal. Calcd. for $C_8H_7O_2BrFN$: Br, 32.22. Found: Br, 31.85.

3,5,3',5'-Tetramethyl-2,2'-difluoro-6,6'-dinitrodiphenyl (IV).—In a 200-cc., round-bottomed, 3-necked flask containing a stirrer and an air-cooled reflux condenser were placed 10 g. of 3,5-dimethyl-2-fluoro-6-nitro-1-bromobenzene and 20 cc. of dry nitrobenzene. The flask was heated in a metal bath for five hours to 200° and vigorously stirred. During this time 20 g. of powdered copper bronze was added in small amounts. The mixture was filtered and the solid was washed with acetone. The filtrates were steam distilled and the diphenyl compound remained as a residue. This was washed with alcohol to remove any remaining nitrobenzene and was crystallized from 50% acetone-water mixture. The compound formed white plates melting at 234–236° (corr.). The yield was 5 g. (75%).

Anal. Calcd. for $C_{16}H_{14}O_2F_2N_2$: N, 8.33. Found: Kjeldahl ($TiCl_3$), N, 8.48.

3,5,3',5'-Tetramethyl-2,2'-difluoro-6,6'-diaminodiphenyl (V).—In a 400-cc. beaker was placed 200 cc. of glacial acetic acid, 20 cc. of concentrated hydrochloric acid and 8 g. of 3,5,3',5'-tetramethyl-2,2'-difluoro-6,6'-dinitrodiphenyl. This mixture was heated to boiling and to it was added 6 g. of zinc dust. The reduction was allowed to proceed at the boiling point for ten minutes. The mixture was then made alkaline by pouring it into an ice-cold solution of 10% sodium hydroxide. The diamine was filtered off

⁶ Noelting, Braun and Thesmar, *Ber.*, **34**, 2257 (1901).

and recrystallized from a 50% alcohol-water mixture. It formed fine white needles, melting at 154–155° (corr.). The yield was 4.5 g. (68%).

Anal. Calcd. for $C_{16}H_{18}F_2N_2$: N, 10.14. Found: N, 9.88.

Resolution of 3,5,3',5'-Tetramethyl-2,2'-difluoro-6,6'-diaminodiphenyl.—To a solution of 8.6 g. of the diamine in 130 cc. of anhydrous ethyl acetate was added 15 g. of *d*-camphorsulfonic acid dissolved in 200 cc. of anhydrous ethyl acetate. The solution was boiled for several minutes, when the salt precipitated out. After cooling and filtering the salt, it was found that all but 2.5 g. of the salt had precipitated. The salt was dissolved in a mixture of 170 cc. of anhydrous ethyl acetate and 28 cc. of absolute ethyl alcohol by heating and the solution was then allowed to stand for six hours. At the end of this time 7 g. of crystals had separated, which were filtered off and washed with anhydrous ethyl acetate and dried. This was shown to be essentially pure *l*-salt by comparison of the rotation with that of recrystallized material, m. p. 171–173°.

Rotation. 0.1500 g. made up to 15 cc. with absolute alcohol at 20° gave $\alpha_D +0.52^\circ$; $l = 2$; $[\alpha]_D^{20} +26.0^\circ$. Recrystallizing from 100 cc. of anhydrous ethyl acetate and 20 cc. of absolute alcohol gave 5 g. of crystals.

Rotation. 0.1500 g. made up to 15 cc. with absolute alcohol at 20° gave $\alpha_D +0.52^\circ$; $l = 2$, $[\alpha]_D^{20} +26.0^\circ$.

Anal. Calcd. for $C_{16}H_{18}F_2N_2 \cdot 2C_{10}H_{16}O(SO_3H)$: S, 8.65. Found: S, 8.40.

The mother liquor from the first crop of crystals was evaporated to 125 cc., 50 cc. more of anhydrous ethyl acetate was added, and the solution allowed to stand overnight at room temperature. A crop of 6.7 g. of crystals came down which consisted of a mixture of the less and more soluble salts. The mother liquor from the second crop of crystals was evaporated to 75 cc. and 75 cc. more of anhydrous ethyl acetate was added. On standing overnight, a crop of 4.5 g. of crystals came down which was filtered off and washed with a small amount of anhydrous ethyl acetate, m. p. 125–130°.

Rotation. 0.1500 g. made up to 15 cc. with absolute alcohol at 20° gave $\alpha_D +0.60^\circ$; $l = 2$, $[\alpha]_D^{20} 30.0^\circ$. The salt was recrystallized from 100 cc. of anhydrous ethyl acetate.

Rotation. 0.1500 g. made up to 15 cc. with absolute alcohol at 20° gave $\alpha_D +0.65^\circ$; $l = 2$, $[\alpha]_D^{20} +32.5^\circ$. The salt was again recrystallized from anhydrous ethyl acetate.

Rotation. 0.1500 g. made up to 15 cc. with absolute ethyl alcohol at 20° gave $\alpha_D +0.65^\circ$; $l = 2$, $[\alpha]_D^{20} +32.5^\circ$.

Anal. Calcd. for $C_{16}H_{18}F_2N_2 \cdot 2C_{10}H_{16}O(SO_3H)$: S, 8.65. Found: S, 8.45.

***l*-3,5,3',5'-Tetramethyl-2,2'-difluoro-6,6'-diaminodiphenyl.**—To the less soluble salt dissolved in water at 0° was added a solution of 10% sodium carbonate. The active amine, which separated in fine white needles, melted at 150–152° (corr.).

Rotation. 0.4352 g. made up to 15 cc. in acetone at 20° gave $\alpha_D -0.24^\circ$; $l = 2$, $[\alpha]_D^{20} -4.1^\circ$.

It was recrystallized from 50% acetone-water mixture by dissolving in cold solvent and evaporating, with stirring, under diminished pressure in the cold until the amine just commenced to crystallize. The melting point was 151–152° (corr.).

Rotation. 0.4000 g. made up to 15 cc. in acetone at 20° gave $\alpha_D -0.22^\circ$; $l = 2$, $[\alpha]_D^{20} -4.1^\circ$.

Anal. Calcd. for $C_{16}H_{18}F_2N_2$: N, 10.14. Found: N, 10.49.

***d*-3,5,3',5'-Tetramethyl-2,2'-difluoro-6,6'-diaminodiphenyl.**—The *d*-form was obtained in a manner similar to the *l*-form and melted as obtained directly from the salt at 150–151° (corr.).

Rotation. 0.4000 g. made up to 15 cc. in acetone at 20° gave $\alpha_D +0.16^\circ$; $l = 2$, $[\alpha]_D^{20} +3.0^\circ$. The active amine was recrystallized using the procedure for the *l*-form and melted at 150–151° (corr.).

Rotation. 0.4000 g. made up to 15 cc. in acetone at 20° gave $\alpha_D +0.17^\circ$; $l = 2$, $[\alpha]_D^{20} + 3.2^\circ$. Another crystallization gave no change in rotation.

Anal. Calcd. for $C_{15}H_{13}F_2N_2$: N, 10.14. Found: N, 10.60.

Racemization Experiments

1. The rotation was taken on the *l*-amine in absolute alcohol.

Rotation. 0.4000 g. made up to 15 cc. with absolute alcohol at 20° gave $\alpha_D -0.21^\circ$; $l = 2$, $[\alpha]_D^{20} -4.0^\circ$. The solution was refluxed for thirty minutes and the rotation taken; it was found to be $[\alpha]_D^{20} -1.5^\circ$; after one hour $[\alpha]_D^{20} -1.4^\circ$ and at the end of two hours $[\alpha]_D^{20} 0^\circ$.

2. The rotation was taken on the *l*-amine in glacial acetic acid.

Rotation. 0.2000 g. made up to 15 cc. with glacial acetic acid at 20° gave $\alpha_D -0.16^\circ$; $l = 2$, $[\alpha]_D^{20} -6.0^\circ$. After refluxing for fifteen minutes, the rotation was $[\alpha]_D^{20} -2.6^\circ$ and in thirty minutes, $[\alpha]_D^{20} 0^\circ$.

3. The rotation was taken on the *l*-amine in methyl alcohol.

Rotation. 0.4000 g. made up to 15 cc. with methyl alcohol at 20° gave $\alpha_D -0.22^\circ$; $l = 2$, $[\alpha]_D^{20} -4.1^\circ$. After refluxing, the following readings were obtained: one hour, $[\alpha]_D^{20} -2.5^\circ$; two hours, $[\alpha]_D^{20} -1.7^\circ$; three hours, $[\alpha]_D^{20} -0.09^\circ$; four hours, $[\alpha]_D^{20} -0.0^\circ$.

3,5-Dimethyl-1-bromobenzene-2-diazoniumborofluoride.—In a 300-cc. beaker was placed 20 cc. of concentrated hydrochloric acid. In this was suspended 5 g. of 3,5-dimethyl-2-amino-1-bromobenzene⁶ and the mixture cooled to 0°. The amine was diazotized by addition of a saturated solution of sodium nitrite in slight excess as shown by potassium iodide starch test papers. The diazonium solution was filtered from any sodium chloride and to the filtrate was added 27.6 g. of a solution of hydroborofluoric acid, made by mixing 20 g. of 48% hydrofluoric acid and 7.6 g. of boric acid. Upon addition of the acid, the borofluoride precipitated in white needles. These were filtered off and washed with more hydroborofluoric acid. The yield was 4.5 g. (60%). The decomposition point was 161°.

3,5-Dimethyl-2-fluoro-1-bromobenzene (VII).—A quantity of diazonium borofluoride was placed in a 500-cc. distilling flask set for distillation. The flask was placed in a metal bath and heated to 170°, when decomposition occurred. The borontrifluoride was run through a dilute solution of sodium hydroxide. Water was added to the heated product and the fluorine derivative steam distilled. The yield was quantitative. The 3,5-dimethyl-2-fluoro-1-bromobenzene was purified by distillation: b. p. 87–89° at 11 mm., n_D^{20} 1.3100, d_{20}^{20} 1.452.

Anal. Calcd. for C_8H_8BrF : Br, 39.40. Found: Br, 39.85.

3,5-Dimethyl-2-fluoro-4,6-dinitro-1-bromobenzene (VIII).—In a cooled 100-cc. beaker was placed 25 cc. of cold fuming nitric acid (sp. gr. 1.60), and the mixture cooled to 0°. To this was added slowly 3.6 g. of 3,5-dimethyl-2-fluoro-1-bromobenzene. The mixture was allowed to stand for three minutes and was then poured onto ice. A very light yellow substance precipitated, which on purification from 70% alcohol–water mixture melted at 86–87°. The yield was 4.6 g. (88%).

Anal. Calcd. for $C_8H_6O_4BrFN_2$: Br, 27.30. Found: Br, 27.27.

3,5,3',5'-Tetramethyl-2,2'-difluoro-4,6,4',6'-tetranitrodiphenyl (IX).—In a 200-cc. 3-necked, round-bottomed flask, containing a stirrer and a reflux air condenser, was placed 30 cc. of dry nitrobenzene. The flask was heated for five hours to 190°, and the contents vigorously stirred. During this time 10 g. of 3,5-dimethyl-2-fluoro-4,6-

⁶ Wheeler and Thomas, THIS JOURNAL, 50, 2286 (1928). See also Schiemann, Ber., 60, 1186 (1927).

dinitro-1-bromobenzene and 10 g. of powdered copper bronze were added in small portions. The mixture was then filtered and the solid washed with acetone. The filtrate was steam distilled and the diphenyl compound was left as a residue. This was washed with alcohol to remove the remaining traces of nitrobenzene and was recrystallized from a 50% acetone-water mixture. It formed long white needles melting at 202-204° (corr.). The yield was 5 g. (69%).

Anal. Calcd. for $C_{16}H_{12}O_8F_2N_4$: N, 13.13. Found: Kjeldahl ($TiCl_3$), N, 12.90.

3,5,3',5'-Tetramethyl-2,2'-difluoro-4,6,4',6'-tetraaminodiphenyl (X).—In a 200-cc. beaker, 3.8 g. of the tetranitro compound was dissolved in 30 cc. of boiling acetic acid and 5 cc. of concentrated hydrochloric acid. To the hot solution 3 g. of powdered zinc was added with stirring and then 2 g. of powdered stannous chloride. The solution was allowed to boil for ten minutes and then cooled. Ammonium hydroxide was added to precipitate the zinc and tin salts and free amine. The solid was filtered and extracted with acetone, which dissolved the amine from the mixture. The amine was purified by crystallization from acetone-water mixture. It formed yellow crystals melting at 250-253°. The yield was 2 g. (74%).

Anal. Calcd. for $C_{16}H_{20}F_2N_4$: N, 18.30. Found: Kjeldahl N, 18.02.

Attempts to Prepare Suitable Salts of 3,5,3',5'-Tetramethyl-2,2'-difluoro-4,6,4',6'-tetraaminodiphenyl.—Attempts were made to prepare salts of the tetraamine with *d*-camphorsulfonic acid, *d*-bromocamphorsulfonic acid and *d*-tartaric acid. The following solvents were tried: water, acetone, chloroform, petroleum ether, alcohol, ethyl acetate, pyridine and methyl alcohol. In no case did a crystalline salt result. The salts were either too soluble or, when thrown out of solution with some solvent, such as petroleum ether, came out as gummy precipitates. Both di- and tetra-salts were tried for the three acids.

Summary

1. The preparation of 3,5,3',5'-tetramethyl-2,2'-difluoro-6,6'-diaminodiphenyl is described. The compound was resolved through the dicamphorsulfonate salt.

2. The active forms racemized readily by heating in a neutral solvent such as ethyl or methyl alcohol or more rapidly in glacial acetic acid.

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