Summary

1. 2,2'-Difluoro-6,6'-dicarboxydiphenyl has been prepared from 1-methoxy-2-iodo-3-carboxybenzene by reduction to the amine, diazotization and replacement of the amino group by fluorine, and coupling by means of copper powder.

2. The compound has been resolved into optical isomers through the quinine salt. The active forms of 2,2'-difluoro-6,6'-dicarboxydiphenyl racemize rapidly in hot dilute alkali, fairly readily in hot alcohol, hot acetic anhydride or hot glacial acetic acid, and slowly in cold dilute alkali or in a 40% solution of concentrated hydrochloric acid in absolute alcohol.

3. 2,2'-Dimethoxy-6,6'-dicarboxydiphenyl has been prepared and resolved according to the outlined procedure of Kenner and Turner. The active acids racemized much more slowly than the difluoro compounds.

4. The active 2,2'-dimethoxy-6,6'-dicarbomethoxydiphenyl and the corresponding methyl ester racemized at about the same rate. The active diamide racemized much more slowly.

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Stereochemistry of Diphenyl. XXVIII.[1] Preparation and Properties of 2,2'-Difluoro-3,3'-dicarboxy-5,5'-dimethyl-6,6'-dinitrodiphenyl

BY E. C. KLEIDERER[2] AND ROGER ADAMS

Diphenyls containing fluorine in one or more of the 2,2',6,6'-positions are of especial interest in connection with the stereochemistry of the diphenyls, since fluorine is the smallest substituent which can be introduced in place of a hydrogen. The compounds of this type thus far prepared are the non-resolvable 2,2'-difluoro-3,3'-dicarboxy-6,6'-dimethoxydiphenyl[3] (I), the extremely unstable brucine salt of 2-nitro-6-carboxy-2'-fluorodiphenyl[4] (II), the easily racemized 2,2'-difluoro-3,5,3',5'-tetramethyl-6,6'-diaminodiphenyl[5] (III) and 2,2'-difluoro-6,6'-dicarboxydiphenyl[1] (IV). Although the properties of these compounds agree satisfactorily with those predicted for such structures, nevertheless, it might appear that the mobility of these compounds may be due to some specific property of the fluorine, other than its small size. A compound has, therefore, been

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[1] For paper XXVII see Stanley, McMahon and Adams, THIS JOURNAL, **55**, 706 (1933).

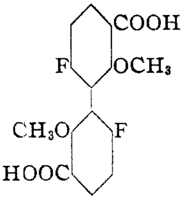
[2] The experimental work was done by E. C. Kleiderer in partial fulfilment of the requirements for the Degree of Doctor of Philosophy in Chemistry at the University of Illinois.

[3] Becker and Adams, THIS JOURNAL, **54**, 2973 (1932).

[4] Stoughton and Adams, *ibid.*, **54**, 4426 (1932).

[5] Kleiderer and Adams, *ibid.*, **54**, 1575 (1932).

synthesized containing 2,2′-difluoro substitution and 6,6′-disubstitution with nitro groups which are relatively large.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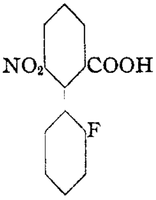
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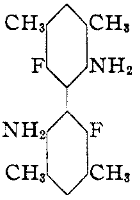
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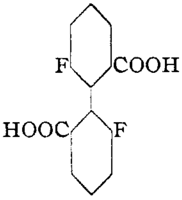
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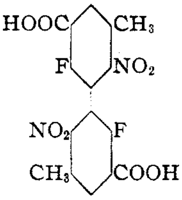
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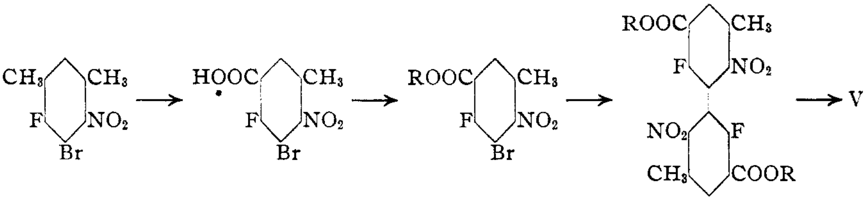
This should be resistant to racemization if the size of the groups is the primary influence, and it, indeed, proved to be so. This is satisfactory evidence that the lability of all the previously studied fluorodiphenyls is due, primarily, to the size rather than to any other specific property of the fluorine atom.

The compound prepared was 2,2′-difluoro-3,3′-dicarboxy-5,5′-dimethyl-6,6′-dinitrodiphenyl (IX). The *l*-form showed no appreciable racemization after several hours of boiling in ethyl alcohol, glacial acetic acid, cyclohexanone and 0.1 *N* sodium hydroxide. The alkaline solution, however, became colored on standing and an extended experiment in this solvent was impossible.

Experimental

The dinitro-difluoro compound was prepared by the following series of reactions


VI VII VIII

1-Bromo-2-fluoro-3-carboxy-5-methyl-6-nitrobenzene (VI).—A mixture of 5 g. of 1-bromo-2-fluoro-3,5-dimethyl-6-nitrobenzene[5] (V) and 20 cc. of concentrated nitric acid (sp. gr. 1.42) diluted with 40 cc. of water, was placed in a sealed tube and heated in a horizontal position for eight hours at 150°. (Longer than eight hours gave considerable decomposition with evolution of carbon dioxide.) Upon cooling, the reaction mixture was made alkaline, filtered and extracted once with ether. Upon acidification with dilute sulfuric acid, the acid precipitated as a light yellow curd. The crude acid was crystallized from dilute alcohol. It formed light yellow needles melting at 249–251° (corr.). In no case was a mixture of acids obtained. The yield was 2 g. (36% of the theoretical).

Anal. Calcd. for $C_8H_5O_4BrFN$: N, 5.04; Br, 28.80; neut. equiv., 278. Found: (micro Dumas) N, 5.34; Br, 28.89; neut. equiv., 275.3.

The evidence that the methyl group adjacent to the fluorine was oxidized and not that adjacent to the nitro was indirect. By the same concentration of nitric acid and under the same conditions used in the oxidation just described, it was found that in 1-

nitro-2,4-dimethylbenzene, the 4-methyl group oxidized exclusively. The methyl ortho to the nitro apparently was unaffected by this reagent.

1-Bromo-2-fluoro-3-carbomethoxy-5-methyl-6-nitrobenzene (VII).—VI was heated with excess of thionyl chloride for five minutes to convert it to the acid chloride. The crude acid chloride was treated with absolute methyl alcohol and refluxed for thirty minutes. The ester was isolated by pouring the methyl alcohol mixture onto ice. It was purified by crystallization from 50% methyl alcohol, from which it crystallized in white needles melting at 88-89° (corr.). The yield was quantitative.

Anal. Calcd. for $C_9H_7O_4BrFN$: N, 4.80. Found: (micro Dumas) N, 4.73.

1-Bromo-2-fluoro-3-carboethoxy-5-methyl-6-nitrobenzene (VII).—The ethyl ester was prepared in the same way as the methyl ester. The ester was purified from 50% ethyl alcohol, from which it crystallized in white needles melting at 65–66° (corr.). The yield was quantitative.

Anal. Calcd. for $C_{10}H_9O_4BrFN$: N, 4.58. Found: (micro Dumas) N, 4.46.

2,2'-Difluoro-3,3'-dicarbomethoxy-5,5'-dimethyl-6,6'-dinitrodiphenyl (VIII).—In a large Pyrex test-tube a mixture of 4.8 g. of (VII) and 5 g. of copper bronze was heated to 225°, when the reaction began as evidenced by the change in color of the copper. The reaction was allowed to continue at 220° for one hour. The melt was extracted with acetone and the solution treated with activated carbon (norite). The essentially colorless acetone was evaporated slowly and absolute methyl alcohol added. After most of the acetone had evaporated the diphenyl compound crystallized in needles, melting upon recrystallization from methyl alcohol at 191–193° (corr.). The yield was 2.26 g. (65%).

Anal. Calcd. for $C_{18}H_{14}O_8F_2N_2$: N, 6.60. Found: (micro Dumas) N, 6.79.

2,2'-Difluoro-3,3'-dicarboxy-5,5'-dimethyl-6,6'-dinitrodiphenyl (V).—A mixture of the ester (VIII), 50% methyl alcohol and a slight excess of sodium hydroxide over that necessary for hydrolysis, was refluxed for thirty minutes, at which time the diester had dissolved and the solution had changed from colorless to light yellow. After cooling, acidifying, evaporating to half volume and again cooling the acid crystallized in short colorless needles These were recrystallized from 50% ethyl alcohol. They melted at 301–304° (uncorr.) on the bloc Maquenne, 318–320° (corr.) with decomposition in a melting-point tube.

Anal. Calcd. for $C_{16}H_{10}O_8F_2N_2$: N, 7.07; neut. equiv., 198. Found: (micro Dumas) N, 7.15; neut. equiv., 196.5.

Resolution of 2,2'-Difluoro-3,3'-dicarboxy-5,5'-dimethyl-6,6'-dinitrodiphenyl (V.) **Strychnine Salt.**—To a solution of 2.1 g. of strychnine dissolved in 300 cc. of absolute methyl alcohol was added 1.23 g. of the acid (V). The solution was evaporated to 210 cc. and allowed to stand overnight in a desiccator. At the end of this time 1.5 g. of salt had crystallized.

The salt for purification was dissolved in 150 cc. of absolute methyl alcohol and allowed to stand overnight. At the end of this time the salt had crystallized out in small cubes. The melting point was 224–228° (corr.), with decomposition.

Rotation. 0.1000 g. made up to 10 cc. with pyridine at 20° gave α_D $-0.75°$, l = 1; $[\alpha]^{20}_D$ $-75°$. Further recrystallization brought no change in rotation.

Anal. Calcd. for $C_{16}H_{10}O_8F_2N_2 \cdot 2C_{21}H_{22}O_2N_2$: N, 7.89. Found: (micro Dumas) N, 7.83.

The mother liquor from the first crop of crystals was evaporated to 150 cc., when 0.35 g. of needle-like crystals came down. These were filtered off and the filtrate was evaporated to 80 cc. and allowed to stand overnight. At the end of this time 1 g. of needle-like crystals had separated. This last fraction was recrystallized from absolute methyl alcohol, m. p. 190–193° (corr.) with decomposition.

Rotation. 0.1000 g. made up to 10 cc. with pyridine at 20° gave α_D -0.50, $l = 1$; $[\alpha]^{20}_{D}$ $-50.0°$. Further recrystallization gave no change in rotation.

Anal. Calcd. for $C_{16}H_{10}O_8F_2N_2 \cdot 2C_{21}H_{22}O_2N_2$: N, 7.89. Found: (micro Dumas) N, 7.56.

As the nitrogen analysis will not distinguish the mono- and distrychnine salts, a portion of salt was decomposed quantitatively and acid and base isolated. The salt proved to be dibasic.

0.2230 g. of salt yielded 0.0830 g. of acid and 0.1350 g. of strychnine. For 0.0830 g. of acid, there is required 0.1400 g. of strychnine for a dibasic salt.

l-2,2′-Difluoro-3,3′-dicarboxy-5,5′-dimethyl-6,6′-dinitrodiphenyl.—The less soluble salt was treated in the cold with 5% aqueous sodium hydroxide for about thirty minutes. At the end of this time the precipitated strychnine was filtered off. The acid was precipitated with dilute hydrochloric acid and purified from 50% alcohol, from which it crystallized in white needles. The melting point (tube) was 298–300° (corr.) with decomposition.

Rotations. 0.1000 g. made up to 10 cc. at 20° with methyl alcohol gave α_D $-0.17°$, $l = 1$; $[\alpha]^{20}_{D}$ $-17.0°$.

Further recrystallization did not change the rotation.

0.0750 g. made up to 10 cc. at 20° with pyridine gave α_D $-0.18°$, $l = 1$; $[\alpha]^{20}_{D}$ $-24.0°$.

0.1000 g. made up to 10 cc. at 25° with cyclohexanol gave α_D $-0.12°$, $l = 1$; $[\alpha]^{20}_{D}$ $-12.0°$.

0.1000 g. made up to 10 cc. at 20° with glacial acetic acid gave α_D $-0.15°$, $l = 1$; $[\alpha]^{20}_{D}$ $-15.0°$.

0.1068 g. made up to 10 cc. at 20° with cyclohexanone gave α_D $-0.154°$, $l = 1$; $[\alpha]^{20}_{D}$ $-14.4°$.

0.1000 g. made up to 10 cc. at 20° with 0.1 *N* sodium hydroxide gave α_D $-0.135°$, $l = 1$; $[\alpha]^{20}_{D}$ $-13.5°$.

Anal. Calcd. for $C_{16}H_{10}O_8F_2N_2$: N, 7.07. Found: (micro Dumas) N, 7.17.

d-2,2′-Difluoro-3,3′-dicarboxy-5,5′-dimethyl-6,6′-dinitrodiphenyl.—The *d*-acid was prepared in the same way as the *l*-isomer. After crystallization from 50% alcohol it melted at 297–301° (corr.) with decomposition.

Rotation. 0.1000 g. made up to 10 cc. at 20° with methyl alcohol gave α_D $+0.15°$, $l = 1$; $[\alpha]^{20}_{D}$ $+15.0°$.

Anal. Calcd. for $C_{16}H_{10}O_8F_2N_2$: N, 7.07. Found: (micro Dumas) N, 7.11.

Racemization Experiments.—Refluxing in 95% ethyl alcohol for five hours; in glacial acetic acid for seven hours; in cyclohexanone for three hours; in 0.1 *N* sodium hydroxide for three hours resulted in no appreciable change in rotation.

Summary

1. 2,2′ - Difluoro - 3,3′ - dicarboxy - 5,5′ - dimethyl - 6,6′ - dinitrodiphenyl has been synthesized and resolved. The probable presence of the two carboxyl groups as 3,3′ and not 5,5′ was determined only by indirect evidence.

2. The active forms are stable to racemization under the conditions used. This is evidence that the mobility of previously prepared fluoro derivatives is due not to any peculiar property of the fluorine atom but probably primarily to its size.

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