From the appropriate primary benzamides and benzylmagnesium halides benzyl phenyl, benzyl *m*-chlorophenyl, benzyl *p*-methoxyphenyl, *o*-chlorobenzyl *p*-methoxyphenyl and *p*-chlorobenzyl *p*-methoxyphenyl ketones have been obtained in satisfactory yields.

No evidence of rearrangements has been obtained in this type of Grignard reaction.

Six new compounds were prepared and characterized.

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Stereochemistry of Diphenyls. XXVII.[1] Comparison of the Racemization of 2,2′-Difluoro-6,6′-dicarboxydiphenyl and 2,2′-Dimethoxy-6,6′-dicarboxydiphenyl

BY W. M. STANLEY, EDWARD MCMAHON[2] AND ROGER ADAMS

The methoxyl group has been shown in previous researches to have a smaller interference effect when substituted in the 2,2′,6,6′ positions than had at first been predicted. It was found impossible to resolve 2,2′-difluoro-6,6′-dimethoxy-3,3′-dicarboxydiphenyl[3] and the active 2-nitro-6-carboxy-2′-methoxydiphenyl was very readily racemized.[4] The relative interference value of the methoxyl was thus revised from 1.56, as at first estimated, to 1.45. The latter value would conform to all the facts thus far assembled in connection with various hydroxylated and methoxylated diphenyls; the interconversion of the *cis* to the *trans* isomers of di-(3-bromo-2,4,6-trimethylphenyl)2-5-dihydroxybenzoquinone[5] (interference on each side 0.135 Å.), the non-existence of two isomers in di-(2,4-dimethylphenyl)-2,5-dihydroxybenzoquinone[6] (interference on each side, −0.265 Å.) and in 2,2′6,6′-tetramethoxy-3,3′-dicarboxydiphenyl (interference on each side, 0.00 Å.).[7]

A more direct comparison of the methoxyl group and fluorine atom has now been made by the study of 2,2′-difluoro-6,6′-dicarboxydiphenyl (VI) and 2,2′-dimethoxy-6,6′-dicarboxydiphenyl. The two diastereoisomeric salts of each compound were isolated and from these the two active acids of each of the two diphenyls.

The active 2,2′-difluoro-6,6′-dicarboxydiphenyl was completely race-

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(1) For paper XXVI see Yuan and Adams, THIS JOURNAL, **54**, 4434 (1932).

(2) The experimental work on the fluorine derivatives was done by W. M. Stanley; that on the dimethoxy derivatives by Edward McMahon and was presented by him in a thesis 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) Shildneck and Adams, *ibid.*, **53**, 343, 5303 (1931).

(6) Unpublished results of G. C. Finger.

(7) Unpublished results of M. C. Cupery.

mized when heated on a steam cone for eight minutes in 0.1 *N* sodium hydroxide and a marked diminution in rotation occurred when allowed to stand for one week at 25° in 0.1 *N* sodium hydroxide. Complete racemization occurred in boiling alcohol in about two hours and in boiling acetic anhydride in ten minutes, and partial racemization was caused by boiling in glacial acetic acid for five minutes and by standing for one week at 25° in absolute ethyl alcohol containing 40% hydrochloric acid.

On the other hand, the active 2,2'-dimethoxy-6,6'-dicarboxydiphenyl racemized much more slowly, giving the following half-life periods: in boiling 0.1 *N* sodium hydroxide, seven hours and fifty minutes; in boiling sodium ethylate, eleven hours; in boiling glacial acetic acid, seventy-eight minutes; and in boiling alcohol about sixty hours.

The fluorine therefore is a considerably smaller interfering group than the methoxyl. On the basis of calculated values previously used, the interference in the 2,2'-difluoro would be 0.05 Å.; in the 2,2'-dimethoxy, 0.11 Å. on each side of the molecule if the value of 1.45 Å. for the methoxyl is adopted.

The discrepancy between the racemization rates of active 2,2'-dimethoxy-6,6'-dicarboxydiphenyl and of active 2-nitro-6-carboxy-2'-methoxydiphenyl[4] corresponds to the observed fact that for the same interference value, the rate of racemization of a 2,2',6-trisubstituted compound is more rapid than that of a 2,2',6,6'-tetrasubstituted compound.[1,4]

The active esters and amides of 2,2'-dimethoxy-6,6'-dicarboxydiphenyl were prepared and their rates of racemization determined. In glacial acetic acid, the half-life period values of the acid, ester and amide were seventy-eight, eighty-eight, and two hundred and forty minutes, respectively. The atom or group combined to the atom which is attached to the ring thus plays an appreciable part in the interference value of the whole group. A comparison is now being made of various esters and substituted amides of 2,2'-dimethoxy-6,6'-dicarboxydiphenyl to determine the relative effects of these groups.

Experimental

The difluoro acid[8] was prepared from 1-nitro-2-iodo-3-carboxybenzene (III) by a series of reactions of which the stages are shown by the accompanying formulas.

Certain steps in this procedure are of particular interest. Kenner reported that acid reducing agents could not be used on (I) on account of the activity of the iodine atom. Nevertheless, it was found that the reduction could be accomplished by the action of stannous chloride and hydrochloric acid either with or without a little alcohol. The amino group could not be replaced by fluorine using the usual procedure through treatment of the diazonium chloride or diazonium fluoride with hydrofluoric or hydro-

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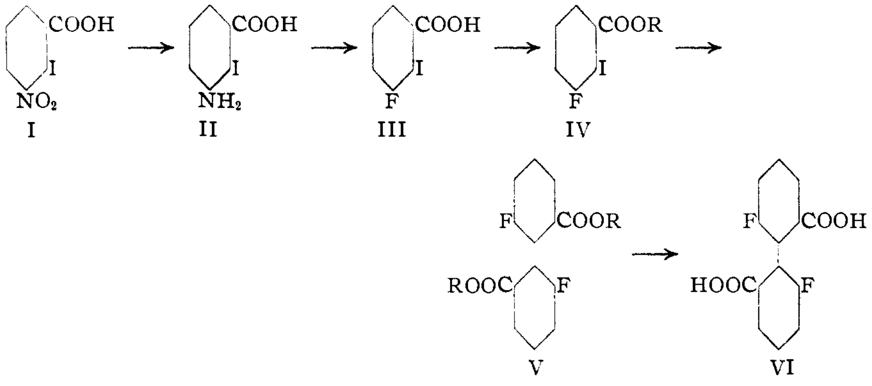
[8] Kenner and Turner [*Chem. & Ind.*, **46**, 218 (1927)] mentioned their intention of preparing 2,2'-difluoro-6,6'-dicarboxydiphenyl but as no description has appeared to date, it has been assumed that this particular research has been abandoned. See also Stanley and Adams, THIS JOURNAL, **52**, 1200 (1930).



borofluoric acid. Only by diazotization of the amino acid in 48% hydrofluoric acid and by then allowing the diazonium fluoride to stand for a considerable time at room temperature was the fluorine introduced.

1-Methoxy-2-nitro-3-carboxybenzene.—In a 3-liter three-necked flask, equipped with a stirrer and a reflux condenser, were placed 50 g. of 1-methyl-2-nitro-3-methoxybenzene[9] and a solution of 160 g. of potassium permanganate in 2 liters of water. The mixture was refluxed, with stirring, for twelve hours. The manganese dioxide was removed by filtration and the filtrate concentrated to about 500 cc. The unoxidized material steam distilled during this process. Upon cooling and acidifying with 10% sulfuric acid 1-methoxy-2-nitro-3-carboxybenzene precipitated and was purified from 400 cc. of 95% alcohol. The yield was 26 g. (58%) of a product melting at 256–257° (corr.). Rieche[10] reports a m. p. of 251°.

1-Methoxy-2-amino-3-carboxybenzene.—A solution of 4 g. of the nitro acid in 100 cc. of hot 95% alcohol was reduced with 0.2 g. of platinum oxide and hydrogen at 2.5 atm. pressure in five minutes. A total of twenty-five such reductions was made, six to a single sample of catalyst. The alcoholic solution of all the 1-methoxy-2-amino-3-carboxybenzene thus obtained was filtered from the platinum and the alcohol distilled until the volume of the residual solution was about 600 cc. Upon cooling, 66 g. of tan-colored amino acid separated. Recrystallization from 95% alcohol raised the melting point to 171–172° (corr.). The mother liquor was evaporated to 300 cc. and cooled and a second crop of crystals obtained. The total yield was 71.5 g. (84%). Pschorr[11] reports m. p. 169–170°.

1-Methoxy-2-iodo-3-carboxybenzene.—To an ice-cold suspension of 60 g. of 1-methoxy-2-amino-3-carboxybenzene in 500 cc. of water containing 51 cc. of concentrated sulfuric acid was added, with stirring, a solution of 24.8 g. of sodium nitrite in 60 cc. of water. Stirring was continued in the cold for thirty minutes and the solution was then added, with stirring, to a boiling solution of 60 g. of potassium iodide in 200 cc. of water in a 3-liter three-necked flask equipped with a reflux condenser and a mechanical stirrer. The mixture was refluxed with stirring for thirty minutes while the evolution of nitrogen was vigorous and then allowed to cool (stirring continued) to room temperature. The product separated and was crystallized from 95% alcohol. The yield was 68 g. (68%) of a product melting at 148–149° (corr.). Kenner and Turner[9] report a melting point of 150–151°.

1-Methoxy-2-iodo-3-carbomethoxybenzene.—The acid was esterified with absolute

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(9) Kenner and Turner, *J. Chem. Soc.*, 2340 (1928).

(10) Rieche, *Ber.*, **22**, 2352 (1889).

(11) Pschorr, *Ann.*, **391**, 27 (1912).

methanol containing a little concentrated sulfuric acid. The yield was 44.5 g. (96%). Upon recrystallization from 95% alcohol, white crystals melting at 56–57° were formed. (Kenner and Turner[9] report a melting point of 57°.) The ester was used without recrystallization for the preparation of 2,2′-dimethoxy-6,6′-dicarbomethoxydiphenyl.

2,2′-Dimethoxy-6,6′-dicarbomethoxydiphenyl.—By heating 5 g. of 1-methoxy-2-iodo-3-carbomethoxybenzene and 10 g. of copper powder in a metal bath at 205–215° for one hour, extracting with boiling benzene and ether and evaporating, the product was obtained; yield, 16 g. from seven runs. It was purified by crystallization from benzene, m. p. 136–137° (corr.).

2,2′-Dimethoxy-6,6′-dicarboxydiphenyl.—The acid was obtained by the action of alcoholic potassium hydroxide on the ester. It was recrystallized from 95% alcohol. The yield was 12.3 g. (90%) of product melting at 293–294°. Kenner and Turner[9] report a melting point of 288–290°.

Resolution of 2,2′-Dimethoxy-6,6′-dicarboxydiphenyl

Monobrucine Salt.—To a hot solution of 1.305 g. of anhydrous brucine in 30 cc. of dry ethyl acetate was added a hot solution of 0.500 g. of 2,2′-dimethoxy-6,6′-dicarboxydiphenyl in 25 cc. of absolute methyl alcohol. Upon cooling for five hours a crop of fine white crystals weighing 0.96 g. separated. After recrystallization from absolute methyl alcohol the salt melted at 198–199° (corr.).

Rotation. 0.2000 g. made up to 20 cc. in chloroform at 20° gave α_D +0.235°; $l = 2$; $[\alpha]_D^{20}$ +11.7°. Recrystallization from absolute methyl alcohol did not raise the melting point or change the rotation.

Kenner and Turner[9] report the preparation of this compound and give a melting point of 268° but do not report its rotation.

Anal. Calcd. for $C_{39}H_{40}O_{10}N_2$: N, 4.02. Found: N, 4 02.

The remaining material which separated upon further evaporation of the solvent was found to be a mixture of the salt with unchanged brucine.

Diquinine Salt.—To a hot solution of 12.88 g. of anhydrous quinine in 80 cc. of absolute methyl alcohol was added a hot solution of 6 g. of 2,2′-dimethoxy-6,6′-dicarboxydiphenyl in 170 cc. of absolute methyl alcohol. Upon evaporation *in vacuo* at room temperature a dry residue was obtained which was heated to boiling with 200 cc. of dry acetone. Upon cooling, 9.79 g. of white crystals separated. After recrystallization from dry acetone, the salt melted at 178–179° (corr.).

Rotation. 0.2045 g. made up to 20 cc. in chloroform at 20° gave α_D +2.27°; $l = 2$; $[\alpha]_D^{20}$ +111.0°. The salt, upon recrystallization from dry acetone, was not changed in melting point or rotation. Kenner and Turner[9] report a melting point of 172–173° and an $[\alpha]_D$ in chloroform of +126°.

Anal. Calcd. for $C_{56}H_{62}O_{10}N_4$: N, 5.90. Found: N, 5.80.

The mother liquor from the first crop of crystals was evaporated to 50 cc. by bubbling nitrogen through the solution. Upon cooling, 0.30 g. of salt separated. This was removed by filtration. The mother liquor was evaporated to dryness. The residue consisted of a resin which, when the last traces of solvent were removed, formed a white powder. The salt could be dissolved in acetone or ethyl acetate and precipitated as a white, flocculent mass by addition of petroleum ether (b. p. 20–40°). Upon filtration, however, this solid turned to a gummy mass which reverted to a white powder when all traces of the solvent were removed. The salt melted at 98–100° (corr.). The weight of salt thus obtained was 8.5 g.

Rotation. 0.1550 g. made up to 20 cc. in chloroform at 20° gave α_D −0.93°; $l = 2$; $[\alpha]_D^{20}$ −60°.

Anal. Calcd. for $C_{56}H_{62}O_{10}N_4$: N, 5.90. Found: N, 5.93.

Kenner and Turner[8] report that the more soluble salt melts at about 60° with decomposition and has an $[\alpha]_D$ in chloroform of $-68°$.

***l*-2,2′-Dimethoxy-6,6′-dicarboxydiphenyl.**—A mixture of 3 g. of the less soluble salt and 40 cc. of 5% sodium hydroxide solution was ground in a mortar. This mixture was extracted with four 15-cc. portions of cold chloroform. The alkaline solution was then acidified with 6 *N* hydrochloric acid. The *l*-acid precipitated as a white spongy mass which was filtered and dried. After drying, the compound was crystalline and melted at 291–292°.

Rotation. 0.0766 g. made up to 20 cc. in dry acetone at 20° gave α_D $-0.88°$; $l = 2$; $[\alpha]^{20}_D$ $-114.9°$.

Kenner and Turner[9] report a melting point of 294–295° and an $[\alpha]_D$ $-115°$.

The active acid was recrystallized from boiling chloroform, but apparently racemized somewhat during the procedure.

Rotation. 0.0785 g. made up to 20 cc. in dry acetone at 20° gave α_D $-0.70°$; $l = 2$; $[\alpha]^{20}_D$ $-89.5°$.

If the *l*-acid was dissolved in dry acetone and excess petroleum ether (b. p. 20–40°) was added, feathery crystals separated after standing in the cold for two hours. The melting point and rotation were unchanged by this treatment.

Anal. Calcd. for $C_{16}H_{14}O_6$: C, 63.6; H, 4.64. Found: C, 63.7; H, 4.57.

***d*-2,2′-Dimethoxy-6,6′-dicarboxydiphenyl.**—Three grams of the more soluble salt was decomposed by the procedure used for the less soluble salt. The *d*-acid obtained in this way melted at 291–292°.

Rotation. 0.0737 g. made up to 20 cc. in dry acetone at 20° gave α_D $+0.80°$; $l = 2$; $[\alpha]^{20}_D$ $+108.5°$.

The *d*-acid was recrystallized from boiling chloroform. Partial racemization took place.

Rotation. 0.0717 g. made up to 20 cc. in dry acetone at 20° gave α_D $+0.62°$; $l = 2$; $[\alpha]^{20}_D$ $+86.5°$.

The *d*-acid was then purified by dissolving in dry acetone and adding excess petroleum ether. The product had the same melting point and rotation.

Anal. Calcd. for $C_{16}H_{14}O_6$: C, 63.6; H, 4.64. Found: C, 63.61; H, 4.77.

Racemization Experiments.—Only a few of the readings taken during the racemization experiments are given. Many more were recorded and from all of them the half-life periods were calculated.

In Sodium Hydroxide

Rotation. 0.0967 g. made up to 20 cc. in 0.1 *N* sodium hydroxide at 20° gave α_D $-2.60°$; $l = 2$; $[\alpha]^{20}_D$ $-269°$. After refluxing for fifty-five minutes the rotation was $-256°$; after eight hours, $-137.5°$; after twenty-three hours, $-16.6°$; after twenty-six hours, $-10.3°$; and after twenty-nine hours the rotation was zero. The half-life period was seven hours and fifty minutes.

In Sodium Ethylate

A solution of sodium ethylate was prepared by dissolving 0.50 g. of sodium in 100 cc. of absolute alcohol.

Rotation. 0.0678 g. of *l*-acid made up to 20 cc. in sodium ethylate solution at 20° gave α_D $-0.83°$; $l = 2$; $[\alpha]^{20}_D$ $-121.8°$. After refluxing for two hours the rotation was $-108°$; after nine hours and thirty minutes, $-67.8°$; after twenty-three hours and thirty minutes, $-36.9°$; and after forty-four hours and thirty minutes, $-3.9°$. The half-life period was eleven hours.

In Ethanol

Rotation. 0.0880 g. made up to 20 cc. in 95% alcohol at 20° gave α_D −1.19°; $l = 2$; $[\alpha]^{20}_D$ −135.5°. After refluxing for forty-five minutes the rotation was −133°; after eight hours and twenty-five minutes, −125°; after twenty-nine hours and thirty minutes, −99°. The half-life period was sixty-one hours and thirty minutes.

In Glacial Acetic Acid

Rotation. 0.0670 g. made up to 20 cc. in glacial acetic acid at 20° gave α_D −1.13°; $l = 2$; $[\alpha]^{20}_D$ −168.5°. After refluxing for two hours and thirty minutes the rotation was −49.2°; after four hours, −20.9°; after five hours and forty-five minutes, −5.5°; and after seven hours and fifteen minutes the rotation was zero. The half-life period was seventy-eight minutes.

Unfortunately racemization tests in chloroform could not be performed since the active acids were soluble only in boiling solvent. The recrystallization of the active acids from chloroform indicated a more rapid racemization than in the other solvents.

***l*-2,2′-Dimethoxy-6,6′-dicarbomethoxydiphenyl.**—In a side-arm test-tube was placed 1 cc. of thionyl chloride and 0.2 g. of *l*-2,2′-dimethoxy-6,6′-dicarboxydiphenyl having a rotation of −114.9°. The tube was stoppered and after standing at room temperature for two and one-half hours, the excess thionyl chloride was removed by suction. The residual acid chloride was treated with 3 cc. of absolute methyl alcohol and allowed to stand for two hours. The methyl alcohol was then evaporated and the crystalline ester was washed with 0.1 *N* sodium hydroxide and then with water. The *l*-ester melted at 101–102°.

Rotation. 0.0560 g. made up to 20 cc. in absolute methyl alcohol at 20° gave α_D −0.78°; $l = 2$; $[\alpha]^{20}_D$ −139°. The solution was evaporated to the appearance of crystals. The material which separated had the same melting point and rotation.

Anal. Calcd. for $C_{18}H_{18}O_6$: C, 65.5; H, 5.45. Found: C, 65.7; H, 5.67.

***d*-2,2′-Dimethoxy-6,6′-dicarbomethoxydiphenyl.**—The *d*-ester was prepared in a similar manner from a sample of *d*-acid having a rotation of +86.5°. The *d*-ester thus obtained melted at 98–99°.

Rotation. 0.0530 g. made up to 20 cc. in absolute methyl alcohol at 20° gave α_D +0.70°; $l = 2$; $[\alpha]^{20}_D$ +132°. The methyl alcohol was evaporated to the appearance of crystals. The material thus obtained had the same melting point and rotation.

Anal. Calcd. for $C_{18}H_{18}O_6$: C, 65.5; H, 5.45. Found: C, 65.64; H, 5.72.

Racemization Experiment

Rotation. 0.0508 g. made up to 20 cc. in glacial acetic acid at 20° gave α_D −0.886°; $l = 2$; $[\alpha]^{20}_D$ −174.5°. After refluxing for forty-five minutes the rotation was −122.5°; after three hours and fifty minutes, −27.6°; after five hours and fifty minutes, −11.8°. Refluxing was then continued overnight to complete the racemization. The acetic acid was then evaporated and the ester thus obtained melted at 135–136° (the m. p. of the racemic ester). The half-life period was eighty-eight minutes.

***l*-2,2′-Dimethoxydiphenyl-6,6′-dicarboxylic Acid Amide.**—The acid chloride prepared as described under the ester was poured slowly into 5 cc. of ice-cold aqueous ammonia (sp. gr. 0.9). Upon standing in the cold for six hours the amide separated as long needles which were filtered and dried. The *l*-amide melted at 230–231° (corr.).

Rotation. 0.0338 g. made up to 20 cc. in absolute methyl alcohol at 20° gave α_D −0.185°; $l = 2$; $[\alpha]^{20}_D$ −54.8°.

The amide was recrystallized from absolute methyl alcohol. The melting point and rotation were unchanged.

Anal. Calcd. for $C_{16}H_{16}O_4N_2$: N, 9.33. Found: N, 9.33.

The *d*-amide obtained by a similar procedure melted at 230–231° (corr.).

Rotation. 0.0190 g. made up to 20 cc. in absolute methyl alcohol at 20° gave α_D +0.102°; $l = 2$; $[\alpha]^{20}_D$ +53.6°. The amide was recrystallized from absolute methyl alcohol. The melting point and rotation were unchanged.

Anal. Calcd. for $C_{16}H_{16}O_4N_2$: N, 9.33. Found: N, 9.31.

Racemization Experiment

Rotation. 0.0582 g. of the *l*-amide made up to 20 cc. in glacial acetic acid at 20° gave α_D −0.38°; $l = 2$; $[\alpha]^{20}_D$ −65.3°. After refluxing for one hour and fifteen minutes the rotation was −51.5°; after four hours and fifteen minutes, −29.2°; after nine hours, −17.2°. Refluxing was then continued overnight, after which time the rotation was zero. The half-life period was four hours. The solvent was evaporated and the racemic amide thus obtained melted at 271–272°. A mixed melting point determination with racemic amide prepared from the racemic acid showed no depression.

2,2′-Dimethoxydiphenyl-6,6′-dicarboxylic Acid Amide.—The racemic amide was prepared from racemic 2,2′-dimethoxy-6,6′-dicarboxydiphenyl as described for the active acids, except that refluxing was necessary to form the acid chloride readily. The amide was recrystallized from 50% alcohol using norite. The melting point was 273–274°.

Anal. Calcd. for $C_{16}H_{16}O_4N_2$: N, 9.33. Found: N, 9.48.

1-Nitro-2-iodo-3-carboxybenzene (I).[12]—This compound was produced by the method of Culhane and Whitmore in 65–75% yields.

1-Amino-2-iodo-3-carboxybenzene (II).—A solution of 320 g. of stannous chloride in 320 cc. of concentrated hydrochloric acid was warmed to 60°, and 40 g. of powdered 1-nitro-2-iodo-3-carboxybenzene was added with stirring. Sufficient ethyl alcohol (about 40 cc.) may be added with stirring if the reduction does not start (much larger amounts of alcohol caused diminution in yield). The mixture was stirred continuously and cooled sufficiently to maintain the temperature between 60 and 75°. After standing for an hour the mixture was cooled and the precipitated tin salt was removed by filtration with suction. The yield of double tin salt was 80 g. The run was repeated twice and the total 240 g. of double tin salt was treated with 750 cc. of water and sufficient aqueous ammonia to obtain an alkaline reaction. The mixture was heated to boiling, cooled and the curdy white precipitate of stannic oxide was removed by filtration with suction. The precipitate was washed with dilute aqueous ammonia and finally with water. The washings were added to the main portion and heated to boiling, cooled and filtered. The filtrate was made barely neutral with concentrated hydrochloric acid. The precipitated amino acid was filtered with suction and dried. The yield was 70.5 g. (68%). The crude product was purified by recrystallizing twice from 20% ethyl alcohol and formed purplish-gray needles, m. p. 133° (corr.). The amino acid was insoluble in cold but soluble in hot concentrated hydrochloric acid. On cooling, the hydrochloride of 1-amino-2-iodo-3-carboxybenzene crystallized out as fine granules which, when pure, start to decompose under 100° and finally melt with decomposition at 263–264°. The hydrochloride was readily soluble in water.

Various attempts to reduce 1-nitro-2-iodo-3-carboxybenzene with ammoniacal ferrous sulfate were unsuccessful. The catalytic reductions with platinum black in hot and cold alcohol, ethyl acetate and glacial acetic acid all resulted in the formation of reddish, insoluble material. Catalytic reduction of the ethyl ester gave negative results. Reductions using zinc dust and acetic acid, and zinc dust and hydrochloric acid, were unsuccessful.

1-Fluoro-2-iodo-3-carboxybenzene (III).—To a solution of 100 cc. of 48% hydrofluoric acid at 25° in a platinum dish was added 42 g. of 1-amino-2-iodo-3-carboxy-

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[12] "Organic Syntheses," Collective Vol. I, 1932, p. 121.

benzene. After solution, the mixture was cooled to 0° by a salt–ice bath. This caused the formation of a gray pasty mass of the amine hydrofluoride. Then 11.5 g. of powdered sodium nitrite was added very slowly with continuous stirring. The precipitate dissolved with the formation of the diazonium fluoride, which was readily soluble. Diazotization was shown to be complete by a positive reaction with starch–potassium iodide paper five minutes after the addition of the last portion of sodium nitrite. The diazotized solution was allowed to come to 30 ± 2° and remain at that temperature for two days. During this period bubbles of nitrogen were continually evolved from the solution and a precipitate slowly formed on the sides and bottom of the platinum vessel. The evolution of bubbles ceased after two days and the precipitate which had formed was removed by filtration with suction and washed with water. The yield was 28 g. (62.5%) of 1-fluoro-2-iodo-3-carboxybenzene which melted at 152–153° (corr.) after two crystallizations from water.

Anal. Calcd. for $C_7H_4O_2IF$: I, 47.76. Found: I, 47.37.

Diazotization of the amine in varying dilutions of hydrochloric acid solution with subsequent treatment with varying amounts of hydrofluoric acid or hydroborofluoric acid, or diazotization in hydrofluoric acid with subsequent addition of hydroborofluoric acid or diazotization in hydrofluoric acid with subsequent boiling with water gave a product soluble in alcohol or water, melting at 144–145° (corr.). This product was readily acetylated with acetic anhydride (whereas the fluoro compound melting at 152–153° was unaffected by similar treatment) to give a product insoluble in alcohol and water and melting at 144°. It is evident that the original compound is 1-hydroxy-2-iodo-3-carboxybenzene and the second the corresponding acetate.

1-Fluoro-2-iodo-3-carbomethoxybenzene (IV).—A mixture of 28 g. of 1-fluoro-2-iodo-3-carboxybenzene and 19 g. of thionyl chloride was refluxed for ten hours. The excess of thionyl chloride was removed by distillation, 50 cc. of absolute methyl alcohol was added slowly and the mixture then refluxed for five hours. The excess alcohol was removed and the ester distilled under reduced pressure. The yield was 25 g. (85%) of a product boiling at 127–128° (4 mm.).

Anal. Calcd. for $C_8H_6O_2IF$: I, 45.33. Found: I, 44.93.

1-Fluoro-2-iodo-3-carboethoxybenzene.—A sample of 7 g. of 1-fluoro-2-iodo-3-carboxybenzene was similarly treated using absolute ethyl alcohol instead of methyl alcohol. The yield of ethyl ester was 6 g.; the boiling point was 148–150° (6 mm.).

Anal. Calcd. for $C_9H_8O_2IF$: I, 43.16. Found: I, 42.85.

2,2'-Difluoro-6,6'-dicarbomethoxydiphenyl (V).—To 28 g. of 1-fluoro-2-iodo-3-carbomethoxybenzene heated to 180° in a 100-cc. three-necked flask fitted with a stirrer and reflux condenser was added slowly with stirring 56 g. of copper powder. A vigorous exothermic reaction occurred after the addition of about half of the copper powder. The reaction mixture was heated at 240° for one hour. It was then cooled and the reaction mixture extracted five times with 50 cc. of ether. The yield was 8.5 g. (57%). The product was crystallized from *p*-cymene and benzene to a constant melting point of 116–117°.

Anal. Calcd. for $C_{16}H_{12}O_4F_2$: C, 62.72; H, 3.95. Found: C, 62.45; H, 3.88.

2,2'-Difluoro-6,6'-dicarboethoxydiphenyl.—The diethyl ester was prepared similarly by the action of copper powder on 1-fluoro-2-iodo-3-carboethoxybenzene. Crystallization of the diethyl ester from *p*-cymene and then from absolute ethyl alcohol gave a product melting at 105–107°.

Anal. Calcd. for $C_{18}H_{14}O_4F_2$: C, 64.64; H, 4.82. Found: C, 64.31; H, 4.64.

2,2'-Difluoro-6,6'-dicarboxydiphenyl (VI).—A mixture of 7.6 g. of dimethyl ester was saponified with an absolute ethyl alcohol solution of potassium hydroxide. Recrystallization from 95% ethyl alcohol raised the melting point to a constant value of 308–311° (corr.). The acid begins to shrink about 50° below the melting point recorded, softens noticeably about 10° below and melts sharply at the point given, forming a meniscus.

Anal. Calcd. for $C_{14}H_8O_4F_2$: C, 60.42; H, 2.90. Found: C, 60.18; H, 2.99. Neut. equiv.: calcd., 278.1. Found: 280.0.

Resolution of 2,2′-Difluoro-6,6′-dicarboxydiphenyl.—To a hot solution of 2.5 g. of 2,2′-difluoro-6,6′-dicarboxydiphenyl in 75 cc. of 95% ethyl alcohol was added with stirring a hot solution of 3.0 g. of anhydrous quinine in 45 cc. of 95% ethyl alcohol. The solution was evaporated to 95 cc. and allowed to cool. A crop of white flaky crystals separated, which was essentially pure salt, as shown by rotation and melting point as compared with recrystallized material. The crystals of pure less soluble salt were removed by filtration with suction, washed with 95% alcohol and dried; weight 2.5 g. Recrystallization from 95% ethyl alcohol gave a pure product of melting point 221–222° (corr.).

Rotation. 0.1695 g. made up to 15 cc. with absolute ethyl alcohol at 20° gave α_D +0.44°; $l = 1$; $[\alpha]^{20}_D$ +38.9°. Recrystallization from 95% ethyl alcohol did not change the melting point or rotation.

Anal. Calcd. for $C_{34}H_{32}O_6F_2N_2$: N, 4.65. Found: N, 4.52.

The mother liquor from the first crop of crystals was further evaporated to 50 cc. Upon cooling, 0.32 g. of salt crystallized out, which was by rotation shown to be impure less soluble salt. The filtrate was evaporated to dryness and the residue of more soluble salt washed once with 25 cc. of a 10% solution of ethyl alcohol in water. After drying, the weight was 2.5 g. and the melting point was 159–160° (corr.).

Rotation. 0.1755 g. made up to 15 cc. with absolute ethyl alcohol at 20° gave α_D −1.18°; $l = 1$; $[\alpha]^{20}_D$ −101°. The more soluble salt was dissolved in ethyl alcohol and precipitated by the addition of water into two fractions. The melting point was unchanged and the rotation of the two fractions identical with that of the original material.

Anal. Calcd. for $C_{34}H_{36}O_6F_2N_2$: N, 4.65. Found: N, 4.32.

***l*-2,2′-Difluoro-6,6′-dicarboxydiphenyl.**—The pure less soluble salt was hydrolyzed by two procedures, both giving practically the same results. The first procedure consisted in digesting 1.0 g. of salt three times for ten minutes each in the cold with 10 cc. of 2 *N* hydrochloric acid. The pasty mass which first formed changed to white flakes on continued stirring. The active *l*-acid so obtained was then washed on a filter with another 10-cc. portion of 2 *N* hydrochloric acid, then with water, and finally crystallized from 95% ethyl alcohol. The melting point was 305–306° (corr.), with a melting behavior similar to that of the racemic acid. A mixed melting point with the racemic acid gave 302–304° (corr.).

Rotation. (a) 0.1535 g. made up to 15 cc. with 95% ethyl alcohol at 20° gave α_D −0.23°; $l = 1$; $[\alpha]^{20}_D$ −22.5°. (b) 0.1008 g. made up to 15 cc. with 0.1 *N* sodium hydroxide at 20° gave α_D −0.835°; $l = 1$; $[\alpha]^{20}_D$ −124°.

The second procedure consisted in digesting 1.2 g. of pure less soluble salt with 10 cc. of cold 2 *N* hydrochloric acid for five minutes. The acid was decanted and the white flakes which were obtained from the pasty mass by stirring were washed with water and dissolved in 2 *N* sodium hydroxide solution. The solution was warmed to 80°, immediately cooled, and extracted three times with 4 cc. each of chloroform. The alkaline solution was then acidified with concentrated hydrochloric acid. The *l*-acid precipitated and was washed with water and dried. After crystallization from 95% ethyl alcohol, the melting point was 305–306° (corr.).

Rotation. 0.0945 g. made up to 15 cc. with 0.1 *N* sodium hydroxide at 20° gave α_D −0.8°; $l = 1$; $[\alpha]^{20}_D$ −127.0°.

Anal. Neut. equiv., calcd., 278.1. Found: 280.

***d*-2,2′-Difluoro-6,6′-dicarboxydiphenyl.**—The *d*-acid was obtained from 2.2 g. of the more soluble salt by the second procedure given above. After recrystallization from 95% ethyl alcohol the melting point was 305–306° (corr.).

Rotation. (a) 0.1387 g. made up to 15 cc. with 0.1 *N* sodium hydroxide at 20° gave α_D +0.94°; $l = 1$; $[\alpha]^{20}_D$ +101.8°. (b) 0.1071 g. made up to 15 cc. with 95% ethyl alcohol at 20° gave α_D +0.12°; $l = 1$; $[\alpha]^{20}_D$ +16.8°.

Synthesis of More Soluble Salt.—An alcohol solution of 0.1071 g. of *d*-acid having a rotation in alcohol of +16.8° was treated with 0.125 g. of quinine. The salt obtained upon evaporation of the alcohol to 2 cc. and precipitation with water was washed with water and dried. The melting point was 163–165° (corr.).

Rotation. 0.0860 g. made up to 15 cc. with absolute ethyl alcohol at 20° gave α_D −0.435°; $l = 1$; $[\alpha]^{20}_D$ −76.0°.

Racemization Experiments

In Sodium Hydroxide—Hot.—The rotation was taken on an alkaline solution of the *l*-acid. *Rotation.* 0.0945 g. made up to 15 cc. with 0.1 *N* sodium hydroxide at 20° gave α_D −0.8°; $l = 1$; $[\alpha]^{20}_D$ −127°. The alkaline solution was heated in a closed container on a steam cone for eight minutes. The rotation was again taken and the acid was found to be completely racemized.

In Sodium Hydroxide—Cold.—The rotation was taken on an alkaline solution of partially active *l*-acid. *Rotation.* 0.0870 g. made up to 15 cc. with 0.1 *N* sodium hydroxide at 20° gave α_D −0.38°; $l = 1$; $[\alpha]^{20}_D$ −66.5°. After standing for one day at room temperature (25°) the rotation was −60°, after two days, −54°, after three days, −45°, after five days, −24°, and after one week the rotation was −18°. A solution of *d*-acid in 0.1 *N* sodium hydroxide racemized from a rotation of +62.3° to +15° after standing at 25° for one week.

In Ethanol.—A solution of *l*-acid was made in 95% ethyl alcohol. *Rotation.* 0.0892 g. made up to 15 cc. with 95% ethyl alcohol at 20° gave α_D −0.12°; $l = 1$; $[\alpha]^{20}_D$ −20.2°. The alcoholic solution was refluxed for one hour and the rotation was then −11.7°. The solution was refluxed an additional hour and a half and the rotation was zero.

In Acetic Anhydride.—A sample of 0.1014 g. of acid having a rotation of −127° in 0.1 *N* sodium hydroxide was dissolved in 15 cc. of acetic anhydride. Warming to 50° for three minutes was required to effect solution. The rotation in acetic anhydride was taken and found to be zero. The solution was boiled for ten minutes and the acetic anhydride removed in a vacuum. The residue was dissolved in 0.1 *N* sodium hydroxide. It was necessary to bring the mixture to boiling to effect solution as the residue went into solution very slowly. The solution was immediately cooled and the rotation in 0.1 *N* alkali was zero.

In Acetic Acid.—A 0.1281-g. portion of acid having a rotation of −66.5° in 0.1 *N* alkali was dissolved in 15 cc. of glacial acetic acid. Solution took place readily in the cold and the rotation was found to be zero. The acetic acid solution was refluxed for five minutes and the acetic acid removed in a vacuum. The residue dissolved readily in cold 0.1 *N* sodium hydroxide. The rotation in 0.1 *N* alkali was found to be −36.6°. Refluxing with glacial acetic acid, therefore, caused partial racemization.

In Alcoholic Hydrochloric Acid.—A solution of *d*-acid was prepared with absolute ethyl alcohol containing 40% concentrated hydrochloric acid. *Rotation.* 0.1181 g. made up to 15 cc. with absolute ethyl alcohol containing 40% of hydrochloric acid at 20° gave α_D +0.09°; $l = 1$; $[\alpha]^{20}_D$ +11.4°. After standing for one week the rotation was +6.6°.

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).