

sodium chloride was filtered off. The clear filtrate was fractionated at atmospheric pressure. The lower fractions consisted of unreacted chloroform and alcohol and could be used over again. The higher constant boiling fraction was collected and redistilled three times. The product was considered to be pure; yield, 30%. The simple physical constants were then determined.

Tri-alkyl orthoformates are colorless liquids with a faint characteristic odor, insoluble in water but soluble in all organic solvents. They could be distilled at atmospheric pressure without any decomposition.

### Summary

1. Seven simple tri-alkyl orthoformates have been synthesized from chloroform and sodium alkoxides. Among these, the *i*-propyl and *n*-butyl ortho-esters are new compounds. The rest have been mentioned in the literature, but their simple physical constants are for the first time accurately determined.

PEIPING-WEST, CHINA

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

## STEREOCHEMISTRY OF DIPHENYL. XXIII.<sup>1</sup> OPTICALLY ACTIVE 2,5-DIMETHOXY-2'-NITRO-6'- CARBOXYDIPHENYL AND THE MUTAROTATION OF ITS SALTS

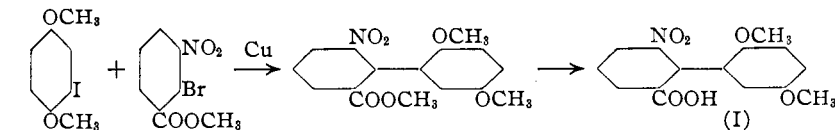
BY H. C. YUAN<sup>2</sup> AND ROGER ADAMS

RECEIVED MARCH 17, 1932

PUBLISHED JULY 6, 1932

On the assumption that the size of the 2,2',6,6' groups is the primary factor in preventing free rotation of the aryl groups in substituted diphenyls, the relative rates of racemization of various derivatives should lead to conclusions concerning the relative size of groups. Since the tetra-substituted derivatives, except in very few instances, present molecules which cannot be racemized at all or only with great difficulty, the 2,2',6-trisubstituted diphenyls offer the most promising field for this study.

In the present investigation a compound was selected containing one group, the methoxyl, which from previously published and unpublished results, was known to be small. The specific compound prepared was 2,5-dimethoxy-2'-nitro-6'-carboxydiphenyl (I).



<sup>1</sup> The last five papers in this series are as follows: (a) Hill and Adams, *THIS JOURNAL*, **53**, 3453 (1931); (b) Bock and Adams, *ibid.*, **53**, 3519 (1931); (c) Woodruff and Adams, *ibid.*, **54**, 1977 (1932); (d) Roll and Adams, *ibid.*, **54**, 2494 (1932); (e) White and Adams, *ibid.*, **54**, 2104 (1932).

<sup>2</sup> This communication is an abstract of a portion of a thesis submitted by H. C. Yuan in partial fulfillment of the requirements for the Degree of Doctor of Philosophy in Chemistry at the University of Illinois.

This acid was converted into a brucine salt in alcohol solution and the solid salt obtained by evaporation. It was then dissolved in hot water and in the course of a few days three-fourths of the total weight of the salt in solution was deposited in the form of a light yellow homogeneous crystalline compound. Upon evaporation of the filtrate, only the same salt could be obtained. It was thus obvious that, if a racemic acid were in hand at the beginning, the second salt during the period of crystallization or of the concentration of the liquors, was gradually converted to the less soluble form which, in turn, precipitated.

The brucine salt thus obtained showed a very interesting phenomenon. When dissolved in an organic solvent such as chloroform, a specific rotation was at first obtained,  $[\alpha]_D^{25} - 167^\circ$ , which, over a period of time, changed gradually to a final value,  $[\alpha]_D^{25} + 3.2^\circ$ , and then remained constant. This obviously presents a new example of mutarotation.<sup>3</sup> The resulting product was presumably an equal mixture of the salts from the *l*-brucine *d*-acid and the *l*-brucine *l*-acid, since the solid salt obtained from such a solution by precipitation with petroleum ether gave an inactive acid on decomposition with cold hydrochloric acid. If the original acid in chloroform or alcohol was mixed with a molecular quantity of brucine in the same solvent and made up to a known volume, rotations identical with the mutarotation values of the solid brucine salt in chloroform or alcohol were obtained. It was noticeable, however, that the final constant rotation did not appear at once but only after some minutes, especially in the case of dry chloroform.

The solid brucine salt was decomposed by ice-cold hydrochloric acid and the active acid thus obtained proved to be the *l*-modification. It racemized with unusual ease. At room temperature the time necessary to reach zero rotation was between sixty and seventy minutes, though at  $0^\circ$  the racemization was much slower. The half-life period was 10.8 min. at  $28^\circ$  and 274 min. at  $0^\circ$ . The *l*-modification showed the same melting point as the racemic acid, due, in all probability, to its conversion to the racemic acid before melting.

The sodium salts of all the previously studied optically active 2,2',6,6'-substituted diphenyls, of which two of the groups were carboxyls, racemized in aqueous solution more readily than the free acid racemized in organic solvents. This was assumed to be due to ionization and the smaller size of the  $\text{COO}^-$  group, though the electrical characteristics of the ion might well be a factor in such experiments. Curiously enough, the sodium salt of 2,5-dimethoxy-2'-nitro-6'-carboxydiphenyl in water racemized less readily

<sup>3</sup> Meisenheimer, who found a somewhat similar phenomenon in 8,8'-dicarboxydinaphthyl, its monoethyl ester and 8-carboxydinaphthyl, prefers to speak of it as racemization. Meisenheimer and Beitswenger, *Ber.*, **65**, 32 (1932). See also Kuhn and Albrecht, *Ann.*, **455**, 272 (1927); **458**, 221 (1927); Kuhn, *Ber.*, **65**, 49 (1932); also Read and McMath, *J. Chem. Soc.*, 1572 (1925).

than the free acid in organic solvents. The sodium salt in absolute alcohol, however, racemized more readily than the free acid in the same solvent.

The cinchonine salt of 2,5 - dimethoxy - 2' - nitro - 6' - carboxydiphenyl showed similar characteristics to the brucine salt. It mutarotated from  $[\alpha]_D^{25} - 135^\circ$  to  $[\alpha]_D^{25} + 57^\circ$ . On the other hand, the strychnine salt showed no change of rotation in solution. This may have been due to a similar solubility of the two diastereoisomeric strychnine salts.

The rates of mutarotation of the salts, racemization of the acids, the half-life periods and the extrapolated maximum rotations are shown in the figures and table.

TABLE I  
ROTATIONS OF BRUCINE *l*-SALT, CINCHONINE *l*-SALT AND *l*-2,5-DIMETHOXY-2'-NITRO-6'-CARBOXYDIPHENYL

Substance, g.	Solvent	Vol., cc.	Temp., °C.	Max. $[\alpha]_D$ by extrap.	Initial $[\alpha]_D$		Final $[\alpha]_D$		Average <i>K</i>	Half-life period in min.	Average deviation of <i>K</i>
					Time, min.	$[\alpha]_D$	Time, min.	$[\alpha]_D$			
$[\alpha]_D: l = 2$											
Brucine salt											
0.0467	Chloroform	10	25	-195°	4	-167°	98	+ 3.2°	0.018	16.8	±0.001
.0597	Abs. alc.	10	25	-165°	4	-119°	70	+ 3.7°	.028	10.8	± .002
.0361	Pyridine	10	25	-166°	4	-124°	60	-69°	.032	9.4	± .002
Cinchonine salt											
0.0480	Chloroform	10	23	-135°	4	-135°	120	+57°	.012	25.0	± .001
<i>l</i> -Acid											
0.1747	Abs. alc.	15	28	- 88°	4	- 74°	70	0.0	.028	10.8	± .002
.0315	Acetone	10	26	-124°	2	-112°	93	.0	.022	13.7	± .002
.0328	Acetic acid	10	26	- 88°	2	- 75°	50	.0	.035	8.6	± .002
.0340	Abs. alc. <sup>a</sup>	10	0	-136°	5	-135°	40	.0	.0011	274.0	.....
Hrs.											
.0395	0.1 <i>N</i> NaOH Solution	10	26	-208°	3.5	-190°	160	.0	.011	27.4	± .001
.0291	Dil. NaOEt <sup>b</sup>	10	27	-289°	2	-195°	20	.0	.082	3.7	± .005

<sup>a</sup> In this experiment  $l = 1$ . <sup>b</sup> A solution of 0.5 g. of metallic sodium in 500 cc. of absolute alcohol was used for this purpose.

From the rotation values at different time intervals, the constant *K* of the rate of mutarotation can be calculated by the formula

$$K = \frac{1}{t} \log \frac{\alpha_0 - \alpha_t}{\alpha_t - \alpha_t}$$

where  $\alpha_t$  is time in minutes,  $\alpha_0$  the initial rotation,  $\alpha_t$  the final rotation,  $\alpha_t$  rotation at time *t*. The half-life period is calculated from the equation  $T = (1/K) \log 2$ .

If the assigned values of the relative size of the groups on the basis of x-ray data are approximately correct, the compound described in this investigation should be more stable than actually found.<sup>4</sup> Neither the 2'-carboxyl nor the 6'-nitro group should collide with the 2-hydrogen atom, but the interference on the other side of the molecule would be (assuming the value of the methoxyl the same as the hydroxyl), NO<sub>2</sub>, 1.92 Å. + OCH<sub>3</sub>, 1.54 Å. = 3.46 Å. - 2.90 Å. = 0.56 Å.; COOH, 1.56 Å. + OCH<sub>3</sub>,

<sup>4</sup> Stanley and Adams, THIS JOURNAL, 52, 1200 (1930).

1.54 Å. = 3.10 Å. - 2.90 Å. = 0.20 Å. Under these conditions the compound should be more stable to racemization if proper conclusions can be drawn from the data on compounds previously studied. It follows, therefore, that the methoxyl has a smaller value than originally assigned to it. A proposed value is 1.45 Å., which would lead to a slight interference between the methoxyl and carboxyl, the latter being the smaller of the nitro and carboxyl groups: COOH, 1.56 Å. + 1.45 Å. = 3.01 Å. - 2.90 Å. = 0.11 Å. This value is slightly larger than that for the fluorine atom which has been directly determined by x-rays and therefore represents probably a fairly correct value.

The 2,5-dimethoxy-2'-nitro-6'-carboxydiphenyl was prepared by condensation with copper of 1-nitro-2-bromo-3-carbomethoxybenzene and 2-iodo-1,4-dimethoxybenzene followed by saponification of the product.

The combination of nitro, carboxyl and hydrogen with another grouping in the 2,2',6,6'-positions is an ideal one for further study since the relative racemization rates can be studied in a reasonably quantitative way. A series of compounds containing the nitro, carboxyl, hydrogen and the halogens, F, Cl and Br and other groups are being prepared and the results will soon be ready for publication. From these compounds conclusions concerning the relative size of the F, Cl, Br, OCH<sub>3</sub>, CH<sub>3</sub>, carboxyl and nitro groups will be possible. The combination of nitro, carboxyl, methoxyl and hydrogen also offers the possibility of determining whether the presence of substituting groups in other positions in the molecule will affect the rate of racemization of molecules in which the 2,2',6,6' groups remain the same.

### Experimental

**2,5-Dimethoxy-2'-nitro-6'-carboxydiphenyl.**—In a 200-cc., three-necked flask fitted with a mechanical stirrer and an air condenser were placed 40 g. of 1-iodo-2,5-dimethoxybenzene<sup>6</sup> and 15 g. of 1-nitro-2-bromo-3-carbomethoxybenzene. Then the flask was gradually heated in a metal bath to 260°, at which temperature the decomposition of the iodo compound to give off iodine vapor was noticed. In small portions, 30 g. of copper bronze was now introduced. Each addition of copper resulted in a rise of temperature sufficient to cause the temporary boiling of the reaction mixture. The addition of all of the copper required about fifty minutes, and during this period the bath temperature was maintained at 260–270°. After all of the copper was added, the bath temperature was raised to 300° to reflux the reaction mixture for twenty minutes. The flask was removed from the bath and cooled. The products were then extracted with 200 cc. of ether. From the ether, by evaporation, a dark oily residue resulted which was transferred to a 500-cc. flask and refluxed with 200 cc. of 5% aqueous sodium hydroxide for four hours. The unsaponifiable oil was separated from the water solution and the water layer was shaken with two 50-cc. portions of ether to remove some tarry substance which was present. The solution was then acidified with dilute hydrochloric acid. An oily substance separated out immediately and solidified upon standing or cooling. It was a mixture of dinitrodiphenic acid and 2,5-dimethoxy-2'-nitro-6'-carboxydiphenyl and weighed 16 g. The crude product was then dissolved in 60 cc. of warm

<sup>6</sup> Kauffmann and Fritz, *Ber.*, **41**, 4413 (1908).

glacial acetic acid and treated with some norite. Upon standing for several hours, 1.5 g. of white crystalline substance was obtained which proved to be 2,2'-dinitro-6,6'-diphenic acid. The mother liquor was diluted with an equal amount of water and decanted from the tarry substance which separated. Another 60 cc. of water was added and the solution was heated to bring all the precipitate to solution. Light yellow long crystals were obtained after standing at room temperature overnight. About half a gram of the same product could be obtained from the tar by extraction with 250 cc. of boiling water. They were combined and recrystallized twice from 20% alcohol. The yield was 5 g.

The 2,5-dimethoxy-2'-nitro-6'-carboxydiphenyl forms lemon-yellow leaflets. It melts at 141–142°. It is very soluble in the common organic solvents except carbon tetrachloride, petroleum ether and slightly soluble in chloroform and hot water.

*Anal.* Calcd. for  $C_{15}H_{13}NO_6$ : Neut. equiv., 303.1; N, 4.62. Found: Neut. equiv., 305.8; N (Micro Dumas), 4.80.

**Alkaloid Salts of 2,5-Dimethoxy-2'-nitro-6'-carboxydiphenyl. (Brucine Salt.)**—A solution of 0.933 g. of 2,5-dimethoxy-2'-nitro-6'-carboxydiphenyl in 10 cc. of alcohol was treated with a solution of 1.292 g. of brucine in 20 cc. of alcohol. No salt was obtained upon cooling, or upon dilution with water or with ethyl acetate. It was then evaporated to dryness and a granular residue was left. The residue was dissolved in 240 cc. of boiling water. Upon standing at room temperature overnight, 1.4 g. of the brucine salt was obtained as slightly yellow short needles. By concentrating the mother liquor to 100 cc., 0.3 g. more of salt was obtained. A third portion of 0.4 g. was obtained by evaporating the mother liquor to dryness at room temperature. Different portions of the salts were identical. Each fraction had the same melting point, 158–160°, the same maximum specific rotation, the same mutarotation. It had one mole of water of crystallization.

*Anal.* Calcd. for  $C_{33}H_{39}N_2O_{10} \cdot H_2O$ :  $H_2O$ , 2.52; N (anhydrous salt), 6.03. Found:  $H_2O$ , 2.26; N, 6.16.

**Mutarotation Experiments.**<sup>6</sup> (See Fig. 1 and Table I.)—Racemic acid was dissolved in chloroform and neutralized with a molecular equivalent of brucine in chloroform. A similar experiment was performed in alcohol. In both instances the constant rotation was, within experimental error, the same as the mutarotation value of the isolated salt dissolved in the same solvent. In these experiments the final reading was not reached immediately.<sup>7</sup> This may have been due to the slowness in salt formation in the organic solvent. It was not due to the fact that the mixture at the equilibrium point consisted of unequal quantities of *l-l* and *l-d* salts because the salt at this point was precipitated completely by addition of petroleum ether and, upon decomposition in the manner found suitable for obtaining active acid from the *l-l* salt, gave only inactive acid.

0.1673 g. of the racemic acid and 0.2130 g. of anhydrous brucine made up to 50 cc. with chloroform gave an initial rotation (four minutes after preparation)  $\alpha_D - 0.13$ ;  $l = 2$ ,  $[\alpha]_D^{25} - 8.6^\circ$ . After eighty minutes  $[\alpha]_D + 0.05^\circ$ ;  $[\alpha]_D^{25} + 3.3^\circ$ . A second experiment required even a longer time for equilibrium to be reached.

0.9330 g. of the racemic acid and 1.2920 g. of anhydrous brucine made up to 45 cc. with absolute alcohol gave an initial rotation (fourteen minutes after preparation)  $\alpha_D + 2.6^\circ$ ,  $[\alpha]_D^{25} 2.6^\circ$ , but it required another hour before  $\alpha_D + 0.30$ ;  $[\alpha]_D^{25} + 3.0^\circ$ .

<sup>6</sup> The numerous intermediate  $\alpha_D$  readings are not recorded but the values found are shown in the curves in the charts.

<sup>7</sup> Mills and Elliot, *J. Chem. Soc.*, 1291 (1928), observed the same phenomenon in *N*-benzenesulfonyl-8-nitro-1-naphthylglycine.

The brucine salt could be dehydrated in the usual way and gave a rotation comparable to that of the hydrated form.

0.0951 g. of salt heated at 100° for five hours made up to 15 cc. with chloroform at 25° (two minutes after preparation) gave  $\alpha_D -2.05^\circ$ ;  $l = 2$ ,  $[\alpha]_D^{25} -162^\circ$ . By extrapolation this corresponds to  $[\alpha]_D^{25} -195^\circ$  for hydrated salt, which is within experimental error of the found value.

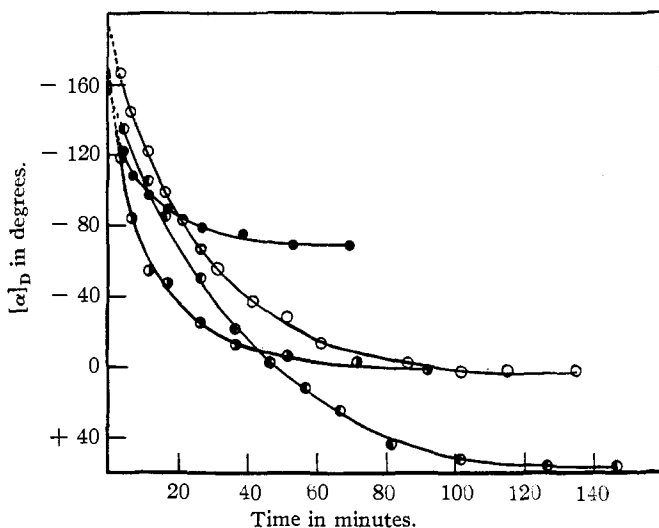


Fig. 1.—Mutarotation curves of brucine and cinchonine salts of 2,5-dimethoxy-2'-nitro-6'-carboxydiphenyl in various solvents. The dotted lines indicate values by extrapolation: ○, brucine salt in chloroform at 25°; ◐, brucine salt in ethanol at 25°; ●, brucine salt in pyridine at 25°; ○, cinchonine salt in chloroform at 23°.

Attempts were made to isolate the other *l*-brucine *d*-acid salt by extracting the filtrate from the *l*-brucine *l*-acid salt which had crystallized out of aqueous solution. The ice-cold filtrate was extracted with ice-cold chloroform and the chloroform solution run immediately into a large volume of petroleum ether. All the brucine salt precipitated but gave a rotation corresponding to the equilibrium rotation value  $[\alpha]_D^{25} +3.0^\circ$  in spite of the fact that the whole operation of extraction and precipitation took less than five minutes.

**Cinchonine Salt.**—A solution of 0.6035 g. of 2,5-dimethoxy-2'-nitro-6'-carboxydiphenyl in 10 cc. of methanol was treated with 0.5864 g. of cinchonine in 30 cc. of boiling methanol. After standing at room temperature overnight, 0.42 g. of the cinchonine salt crystallized out as light yellow small needles. From the mother liquor after two days in the ice box, a second portion of the salt separated which weighed 0.35 g. The filtrate from this material upon evaporation gave a further quantity of salt. The different portions of the salt had the same melting point, 198–204° and mutarotated at the same rate.

*Anal.* Calcd. for  $C_{24}H_{23}N_3O_7$ : N, 7.03. Found: N (micro Dumas), 7.21.

**Strychnine Salt.**—A solution of 0.4819 g. of 2,5-dimethoxy-2'-nitro-6'-carboxydiphenyl in 8 cc. of absolute alcohol was mixed with 0.5314 g. of strychnine in 45 cc. of

boiling alcohol. No crystals were obtained after long standing. The solution was evaporated to dryness and the granular residue was dissolved in 85 cc. of boiling water. Upon standing at room temperature for several hours, 0.38 g. of the strychnine salt crystallized out as compact plates. Two more portions were obtained by further concentration of the solution. They had the same melting point, 220–223° with decomposition, and the same specific rotation. Unlike the other salts, it showed no mutarotation.

A solution of 0.0715 g. made up to 10 cc. with chloroform at 23° gave a rotation  $\alpha_D -0.33^\circ$ ;  $l = 2$ ,  $[\alpha]_D^{23} -23.1$ .

*Anal.* Calcd. for  $C_{33}H_{33}N_3O_8$ : N, 6.59. Found: N (micro Dumas), 6.75.

The acid obtained from the strychnine salt by the procedure described under the brucine salt was inactive.

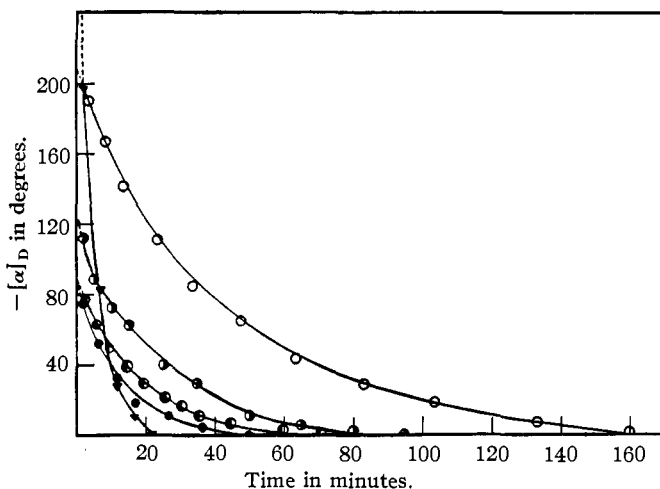


Fig. 2.—Racemization curves of *l*-2,5-dimethoxy-2'-nitro-6'-carboxydiphenyl and its sodium salt. The dotted lines indicate values by extrapolation: ○, *l*-acid in ethanol at 28°; ●, *l*-acid in acetone at 26°; ●, *l*-acid in acetic acid at 26°; ○, sodium salt in water at 26°; ▼, sodium salt in ethanol at 26°.

***l*-2,5-Dimethoxy-2'-nitro-6'-carboxydiphenyl.**—A suspension of 1 g. of the brucine salt in ice-cold 100 cc. 6 *N* hydrochloric acid surrounded with ice-salt mixture was stirred vigorously for a half hour. Then it was left in the ice box overnight. The next morning, finely divided 2,5-dimethoxy-2'-nitro-6'-carboxydiphenyl, which is darker yellow than the salt, had settled to the bottom. The acid was then filtered by suction and washed thoroughly with ice-cold water until the filtrate showed negative tests for both brucine and chloride. The dried acid weighed 0.41 g. It melted at 141–142°.

**Racemization Experiments.**<sup>a</sup>—See Fig. 2 and Table I.

### Summary

1. 2,5-Dimethoxy-2'-nitro-6'-carboxydiphenyl was prepared by condensation of 1-iodo-2,5-dimethoxybenzene and 1-nitro-2-bromo-3-carbomethoxybenzene with copper, and saponification of the product.

2. The acid readily forms brucine and cinchonine salts. Only one salt

with each alkaloid could be isolated. Each of the salts mutarotated to equilibrium values which were equal mixtures of the two diastereoisomeric salts. Strychnine gave a salt which showed no mutarotation and yielded no active acid.

3. By careful decomposition with hydrochloric acid, the *l*-acid was isolated. It racemized rapidly in organic solvents. The sodium salt racemized much more rapidly in absolute alcohol than in water.

URBANA, ILLINOIS

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

**STEREOCHEMISTRY OF DIPHENYL. XXIV.<sup>1</sup>**  
**PREPARATION AND PROPERTIES OF 2,2'-DIFLUORO-3,3'-**  
**DICARBOXY-6,6'-DIMETHOXYDIPHENYL**

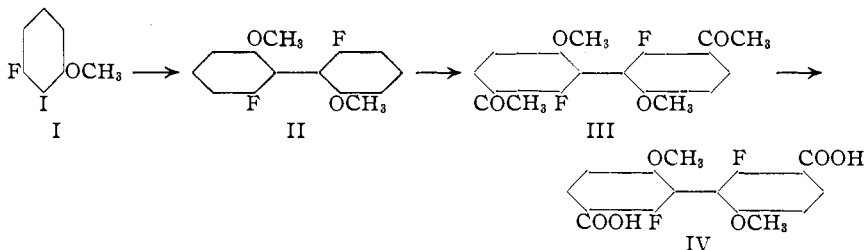
BY B. C. BECKER<sup>2</sup> AND ROGER ADAMS

RECEIVED MARCH 17, 1932

PUBLISHED JULY 6, 1932

The small size of the fluorine atom and, as shown in the previous paper, the similarly small size of the methoxyl group,<sup>1e</sup> made particularly interesting a study of the properties of properly substituted 2,2',6,6'-tetrafluoro-, 2,2',6,6'-tetramethoxy- and 2,6-difluoro-2,6'-dimethoxydiphenyls. On the assumption that the methoxyl is about the same size as the fluorine and calculating the interference possibilities as previously described,<sup>3</sup> none of these three compounds should be capable of resolution.

A representative of the last type has been prepared and is described in this communication. The compound is 2,2'-difluoro-3,3'-dicarboxy-6,6'-dimethoxydiphenyl (IV).



It was prepared (1) by the condensation with copper of 1-fluoro-2-iodo-3-methoxybenzene to 2,2'-difluoro-6,6'-dimethoxydiphenyl (II), (2) by in-

<sup>1</sup> The last five papers in this series are as follows: (a) Hill and Adams, *THIS JOURNAL*, **53**, 3453 (1931); (b) Woodruff and Adams, *ibid.*, **54**, 1977 (1932); (c) White and Adams, *ibid.*, **54**, 2104 (1932); (d) Roll and Adams, *ibid.*, **45**, 2494 (1932); (e) Yuan and Adams, *ibid.*, **54**, 2966 (1932).

<sup>2</sup> This communication is a portion of a thesis submitted by B. C. Becker in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Chemistry at the University of Illinois.

<sup>3</sup> Stanley and Adams, *THIS JOURNAL*, **52**, 1200 (1930).