

Hydrolysis of 2,2,4-Trimethoxybutane.—One mole (148 g.) of 2,2,4-trimethoxybutane was mixed with 20 ml. of water containing 1 ml. of concentrated hydrochloric acid. Hydrolysis was apparently extremely rapid as evidenced by the fact that the temperature of the mixture dropped from 23 to -15° in a few minutes. The mixture was warmed for a few minutes under a reflux condenser, the acid neutralized with solid carbonate, and the liquid product fractionated at atmospheric pressure through a short column. The yield of 4-methoxybutanone-2 was 76 g. (75% of the theoretical). The following constants were determined for this compound: b. p. $139-140^{\circ}$ at 745 mm.; n_D^{27} 1.4025, n_D^{12} 1.4091; d_{27} 0.9182; MR_D' , calcd. 26.95, MR_D' , found, 27.10.

Anal. Calcd. for $C_5H_{10}O_2$: methoxy, 30.4; mol. wt., 102.1. Found: methoxy, 30.4; mol. wt., cryoscopic in benzene, 101.

Proof of the Structure of 2,2,4-Trimethoxybutane.—From the evidence thus far presented the trimethoxybutane obtained from monovinylacetylene might be formulated either as 2,2,3-trimethoxybutane or 2,2,4-trimethoxybutane. Hydrolysis of the first compound would have yielded 3-methoxybutanone-2, which has been previously described by Gauthier,⁶ and for which a boiling point of $113-114^{\circ}$ at 759 mm. has been reported.

(6) Gauthier, *Ann. chim.*, [8] **16**, 322 (1909).

The ketone prepared from our trimethoxybutane reacted with phenylhydrazine to form a phenylhydrazone. It oxidized readily with alkaline permanganate to form acetic acid in small yield as the only identified product, thus showing the presence of a CH_3-CO- group. It is evident that the methoxy group must be in the 4 position in the ketone (II) and therefore also in the trimethoxybutane (I).

Acknowledgment.—The authors gratefully acknowledge the assistance of E. I. du Pont de Nemours and Co. in supplying us with the monovinylacetylene used in this work.

Summary

1. Monovinylacetylene reacts with methyl alcohol in the presence of boron fluoride, mercuric oxide and trichloroacetic acid to yield 2,2,4-trimethoxybutane in good yield.
2. A new ketone, 4-methoxybutanone-2, prepared by the hydrolysis of 2,2,4-trimethoxybutane has been described.
3. This work is being continued with other oxy compounds.

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

Stereochemistry of Diphenyls. XXXV.¹ The Effect of 3' Substituents on the Rate of Racemization of 2-Nitro-6-carboxy-2'-methoxydiphenyl

BY S. L. CHIEN² AND ROGER ADAMS

Although it is fair to assume from the experimental evidence already available that in a diphenyl molecule the effect of the 2,2',6,6'-substituted groups is the principal factor governing the rate of racemization of the active forms, nevertheless it has been demonstrated that substituents in other positions contribute to the stability of racemization of the active diphenyls. Kuhn and Albrecht³ found that the half-life period of active 2,4'-dinitro-6,6'-dicarboxydiphenyl was only one-third of that of the 2,4,4'-trinitro-6,6'-dicarboxydiphenyl, when observed under similar conditions.

Yuan and Adams⁴ studied a series of substituted 2-nitro-6-carboxy-2'-methoxydiphenyls in

(1) For the previous paper in this field see Knauf and Adams, *THIS JOURNAL*, **55**, 4704 (1933). See also Adams and Yuan, *Chem. Rev.*, **12**, 261 (1933).

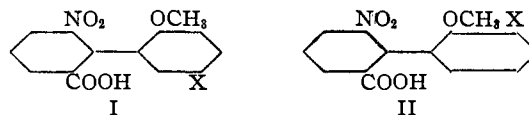
(2) Submitted as a thesis for the Degree of Doctor of Philosophy in Chemistry at the University of Illinois. Research Fellow of the China Foundation for the Promotion of Education and Culture, 1933-34.

(3) Kuhn and Albrecht, *Ann.*, **458**, 221 (1927).

(4) Yuan and Adams, *THIS JOURNAL*, **54**, 2966, 4434 (1932).

which the groups methoxyl, methyl, chloro, bromo and nitro were in the 5'-position. By a comparison of the half-life periods of the active forms of these compounds with that of the unsubstituted diphenyl⁵ it was demonstrated that a group in the 5'-position increased the antipodal stability of the molecule. The order of the stability to racemization is represented as follows: unsubstituted $< OCH_3 < CH_3 < Cl < Br < NO_2$. Four possible effects on the molecule due to the 5' substituents were discussed by Yuan and Adams.

The present investigation was undertaken to produce the analogous active 3' substituted 2-nitro-6-carboxy-2'-methoxydiphenyl (II) in order to compare the relative effects of groups in 3' and



(5) Stoughton and Adams, *ibid.*, **54**, 4426 (1932).

5' positions (I). The half-life periods of the free active 3' and 5' substituted compounds were determined at room temperatures and are given in Table I. The specific rotations and the rates of racemization of the 3' compounds are given in Table II.

TABLE I
HALF-LIFE PERIODS^a IN MINUTES OF ACTIVE 3' AND 5' SUBSTITUTED 2-NITRO-6-CARBOXY-2'-METHOXYDIPHENYLS AND THEIR SODIUM SALTS

Substituent group	Acids in alcohol		Acids in acetone		Sodium salts in water		Sodium salts in alcohol	
	3'	5'	3'	5'	3'	5'	3'	5'
-OCH ₃	98.1	10.8	92.7	13.7	135.0	27.4	32.1	3.7
-CH ₃	331.9	11.5	253.0	..	321.3	30.1	105.6	3.8
-Cl	711.3	31.0	646.0	..	458.1	40.2	163.6	9.7
-Br	827.0	32.0	996.8	..	628.5	43.6	250.9	11.5
-NO ₂	1905.2	35.4	1482.9	..	794.8	35.0	418.1	16.7

^a The 3' derivatives at 25°. The 5' derivatives at 26° [Yuan and Adams, THIS JOURNAL, 54, 4435 (1932)]. The average deviation of the individual velocity constants was less than 7%. The values could readily be duplicated within that value.

The following general conclusions may be drawn from the data here presented: (1) the same order of stability for the various substituents exists in both the 3' and the 5' series; (2) the 3'-substituted compounds are in each case much more stable than the corresponding 5' isomers; (3) the sodium salts of the 3'-substituted compounds, with the exception of the 3'-methoxy and the 3'-methyl derivatives, racemize in water more readily than the corresponding acids racemize in organic solvents (similar tests on the 5' derivatives showed the opposite effect); (4) the sodium salts of the compounds of both series racemize in alcohol more readily than either the free acids in organic solvents or the sodium salts in aqueous solution.

It is obvious that the weight of the group is not a factor in slowing down the semi-circular oscillations, and thus in rendering the molecule

TABLE II
ROTATIONS^k OF FIVE SUBSTITUTED 2-NITRO-6-CARBOXY-2'-METHOXYDIPHENYLS AND THEIR SODIUM SALTS

Compound group at 3'	Wt. ^a in g.	Temp. ^b °C.	Max. [α] _D calcd.	Time ^c min.	Rotations in degrees ^d		Time, min.	Final		Average K	Av. dev. K	Half-life period in min.
					Initial α _D	[α] _D		α _D	[α] _D			
Free acids in absolute alcohol ^e												
-OCH ₃	0.0555	24.7	-70.5	8	-0.74	-66.7	673	0	0	0.00307	±0.00005	98.1
-CH ₃	.0611 ^b	25	-102.4	10	-.49	-100.2	2930	0	0	.000907	±.000015	331.9
-Cl	.0862	24	-41.9	10	-.715	-41.5	4710	0	0	.000426	±.000009	711.3
-Br	.0618	25	-38.3	7	-.47	-38.0	6143	0	0	.000364	±.000010	827.0
-NO ₂	.1005	25	-13.5	13	-.27	-13.4	12180	0	0	.000158	±.000009	1905.2
Free acid in acetone												
-OCH ₃	0.0671	25	-71.4	4	-0.93	-69.3		Ref. ^f		0.00327	±0.00020	92.7
-CH ₃	.0304	25	-115.7	7	-.69	-113.5		Ref. ^f		.00119	±.000011	253.0
-Cl	.0656	25	-47.5	5	-.62	-47.3		Ref. ^f		.000466	±.000012	646.0
-Br	.0588	25	-45.3	8	-.53	-45.1		Ref. ^f		.000302	±.000008	996.8
-NO ₂	.0761	25	-27.2	17	-.41	-26.9		Ref. ^f		.000203	±.000009	1482.9
Sodium salts in water ^g												
-OCH ₃	0.0317	25.4	-179.1	8	-1.09	-171.9		Ref. ^f		0.00223	±0.00014	135.0
-CH ₃	.0222	25.3	-257.1	13	-1.11	-254.5		Ref. ^f		.000937	±.000027	321.3
-Cl	.0342	25	-172.8	7	-1.17	-171.1		Ref. ^f		.000655	±.000006	458.1
-Br	.0492	24.8	-173.7	10	-1.69	-171.8		Ref. ^f		.000479	±.000015	628.5
-NO ₂	.0299	24.5	-164.1	25	-0.96	-160.5		Ref. ^f		.000379	±.000017	794.8
-OCH ₃ ^h	.0479	25.5	-176.9	9	-1.62	-169.1		Ref. ^f		.00209	±.00006	144.0
Sodium salt in absolute alcohol ⁱ												
-OCH ₃	0.0610 ^c	25.6	-194.4	4	-1.45	-178.3	401	0	0	0.00939	±0.00014	32.1
-CH ₃	.0378	25.3	-317.8	4	-2.34	-309.5		Ref. ^f		.00285	±.00005	105.6
-Cl	.0370	25.3	-201.5	5	-1.46	-197.3		Ref. ^f		.00184	±.00003	163.6
-Br	.0427	25.2	-197.6	6	-1.66	-194.4		Ref. ^f		.00120	±.00004	250.9
-NO ₂	.0295	25.4	-325.2	9	-1.89	-320.3		Ref. ^f		.000720	±.000026	418.1

^a Made up to 10 cc. ^b Made up to 25 cc. ^c Made up to 15 cc. ^d $l = 2$. ^e All have been duplicated. Error less than 10%. ^f Not carried to completion. Eight to twelve readings were taken during the period of partial racemization and from these half-life periods were calculated. ^g 0.1 N NaOH solution was used. ^h 0.056 N NaOH solution was used. ⁱ Solution of 0.15 g. of sodium in 150 cc. of absolute alcohol was used. ^j Represents the time necessary for preparing the solution for readings. ^k The rotations were taken on the acids directly obtained from decomposition. The acids were not recrystallized so as to avoid possible racemization.

more stable to racemization, since the chlorine and bromine derivatives differ only very slightly in effect from each other and both are less effective than the lighter nitro group. This result is in accord with the results on the 5' derivatives.

Although no new light has been thrown on the mechanism of the effect of the 3' or 5' groups on the whole molecule, one possible explanation for the additional effectiveness of the 3' groups lies in the close proximity of the 3' group to the methoxyl. The slight repulsion of the methoxyl toward the other ring would increase the interference with the nitro or carboxyl group, and thus slow down the racemization rate. It is noticeable that the effect is the greater, the more polar the 3' group.

The two alkaloidal diastereoisomeric salts of the 3'-chloro and the 3'-nitro derivatives were both isolated, as well as the two pairs of active acids. The two salts of the 3'-bromo derivative were not isolated due, probably, to the fact that the salts were very soluble and that during the slow evaporation of the solvent, entire conversion of the more soluble to the less soluble salt occurred. No modification of the experimental conditions in order to obtain both salts was attempted, as only one was necessary for results described in this investigation. With the methoxyl and methyl derivatives, one salt only was isolated. All the alkaloidal salts were relatively stable as compared with the 5' analogous salts, since none showed signs of mutarotation at room temperature for four hours and only by long standing, overnight to several days, was a change in the rotation observed.

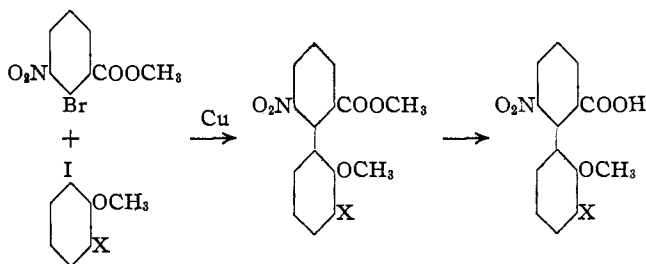
Turner⁶ has recently called attention to the tendency for some salts of certain diphenyls to show what he believes to be anomalous rotations. Thus, he points out that the alkaloidal salts of diphenic acid showed a rotation opposite to that of the alkaloid. This phenomenon also occurs in some members of this series of compounds. The strychnine salt of *l*-2-nitro-6-carboxy-2'-methoxy-3'-chlorodiphenyl is dextrorotatory (+42.8°), while that of the *d* acid is levorotatory (-51.7°). The brucine salts of 2,3'-dinitro-6-carboxy-2'-methoxydiphenyl showed the same behavior (*l* acid salt, +100°; *d* acid salt, -116.4°).

The active acids showed the same phenomenon peculiar to those previously described diphenyls

which are resolvable but racemizable at room temperature, in that the active forms melt at the same point as the racemic modification. This is due, undoubtedly, to complete racemization of the active acids before the observed melting point is reached.

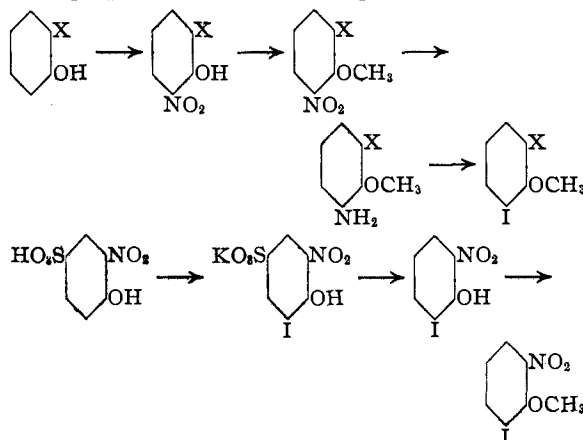
Experimental

The compounds studied in this investigation were prepared by condensing 1-nitro-2-bromo-3-carbomethoxybenzene with the properly substituted *o*-iodoanisoles, 2-methoxy-6-iodoanisole, 2-methyl-6-iodoanisole, 2-chloro-6-iodoanisole, 2-bromo-6-iodoanisole and 2-nitro-6-iodoanisole, in the presence of copper bronze, saponification of the reaction mixture and isolation of the desired diphenyls from the products



where X = OCH₃, CH₃, Cl, Br and NO₂.

The half molecules used in the condensation were prepared by the following series of reactions



2-Nitro-6-iodoanisole could also be made by the nitration of *o*-iodophenol followed by methylation, but the yield was smaller than in the preparation indicated.

2-Bromo- and 2-chloro-6-nitroanisole were also prepared by the nitration of *o*-bromo- and *o*-chloroanisole according to the method of Ingold and Smith⁷ with the slight modification that

(6) Lesslie and Turner, *J. Chem. Soc.*, 347 (1934).

(7) Ingold and Smith, *J. Chem. Soc.*, 1690 (1927).

one mole equivalent of nitric acid was used and the two isomeric 4- and 6-nitro compounds were separated by steam distillation. The 2-bromo- and 2-chloro-6-nitroanisoles were the more volatile and were purified by a second steam distillation. The yields were 35–40% of the theoretical.

2-Methoxy-6-iodoanisole.—2-Methoxy-6-nitroanisole was prepared by the methylation of 3-nitroguaiacol⁸ with dimethyl sulfate and anhydrous potassium carbonate in xylene solution containing 1 cc. of diethylamine. The nitro compound was reduced in the usual way with iron powder and water in the presence of a little hydrochloric acid. From 57 g. of nitro compound a yield of 39.5 g. (83%) of the crude amine, which is a pale-yellow liquid, b. p. 129–136° (7 mm.), was obtained. Without further purification it was diazotized in a solution of 35 cc. of concentrated sulfuric acid in 50 cc. of water with a solution of 18 g. of sodium nitrite in 40 cc. of water at –2°. After the diazotized solution had stood for twenty minutes in the cold, it was slowly added to a previously cooled solution of 72 g. of potassium iodide in 120 cc. of 10% sulfuric acid. The product was extracted with chloroform and a yield of 48 g. (77.3%) of a heavy yellow liquid was obtained; b. p. 124–125° at 4 mm., d_{20}^{20} 1.7831, n_D^{20} 1.6127.

Anal. Calcd. for $C_8H_9O_2I$: I, 48.07. Found: (micro) I, 48.11.

2-Methyl-6-iodoanisole.—The method of G. M. Robinson⁹ was followed. Diazotization of 41.1 g. of 2-methyl-6-aminoanisole¹⁰ b. p. 222–223° and treatment with potassium iodide in the usual manner gave a yield of 56 g. (75.3%) of 2-methyl-6-iodoanisole, a pale yellow liquid boiling at 124–126° (22 mm.). Although the boiling point of the product obtained in this investigation is far different from that reported by Robinson (200° at 19 mm.) there can be no doubt that it is 2-methyl-6-iodoanisole as shown by its analysis, method of preparation and subsequent reactions.

Anal. Calcd. for C_8H_9OI : I, 51.18. Found (micro): I, 51.55.

2-Chloro-6-aminoanisole.—2-Chloro-6-nitrophenol was obtained in a 31.7% yield by the nitration of *o*-chlorophenol according to the method of Meldola and Streatfield¹¹ for the preparation of the corresponding bromo compound. The phenol was methylated in the usual manner with dimethyl sulfate and anhydrous potassium carbonate in xylene solution and an 83% yield of 2-chloro-6-nitroanisole melting at 55–57° (reported as 56° by Holleman)¹² was obtained. A solution of 20 g. of the pure 2-chloro-6-nitroanisole in 250 cc. of warm 95% alcohol was reduced catalytically with hydrogen in the presence of 0.3 g. of platinum oxide.¹³ After reduction (about three hours) the mixture was heated to boiling and filtered. The filtrate was evaporated to a small volume and 15 g. (90%) of fine, pale-yellow needles separated. When pure after

recrystallization from 95% alcohol, the melting point was 179–180° (with decomposition).

Anal. Calcd. for C_7H_7ONCl : N, 8.89. Found (micro Dumas): N, 8.98.

2-Chloro-6-iodoanisole.—A suspension of 30 g. of 2-chloro-6-aminoanisole in 300 cc. of 10% sulfuric acid was converted by diazotization and treatment with potassium iodide in the usual manner into 42 g. of 2-chloro-6-iodoanisole (82%). The product boiling at 98–101° (3.5 mm.) was collected. On cooling, the liquid solidified to colorless flakes. After purification by recrystallization from 95% alcohol it had a melting point of 94–95°.

Anal. Calcd. for C_7H_6OClI : Cl + I, 60.49. Found (micro): Cl + I, 59.7.

2-Bromo-6-nitroanisole.—It was reported by Ingold and Smith¹⁴ that 2-bromo-6-nitrophenol could not be methylated conveniently with dimethyl sulfate. In this investigation, however, it was found that in xylene the methylation with dimethyl sulfate takes place very smoothly.

In a 2-liter 3-necked flask, fitted with a mechanical stirrer, a separatory funnel and a reflux condenser, was placed a mixture of 50 g. of 2-bromo-6-nitrophenol,¹¹ 320 cc. of dry xylene and 55 g. of anhydrous potassium carbonate. The mixture was heated to boiling on a hot-plate and 100 g. of dimethyl sulfate was added slowly. The end of the reaction was marked by the disappearance of the red potassium salt of the phenol, which took about two to three hours. After cooling, 30 cc. of 5% sodium hydroxide solution was added and the mixture was heated for one hour to destroy the excess of dimethyl sulfate. The mixture was then subjected to steam distillation and the xylene passing over first was separated. The anisole followed and was recrystallized from 70% alcohol; pale yellow needles, m. p. 66–66.5° (reported as 66° by Ingold and Smith). The yield was 48.5 g. (91%).

2-Bromo-6-aminoanisole.—Upon reduction of 60 g. of 2-bromo-6-nitroanisole with iron powder and water in the presence of a little hydrochloric acid, a yield of 47 g. (90%) of pure amine was obtained. It is a colorless liquid, b. p. 157–159° (30 mm.), d_{20}^{20} 1.5548, n_D^{20} 1.6550.

Anal. Calcd. for C_7H_7ONBr : N, 6.94. Found (micro Dumas): N, 7.22.

2-Bromo-6-iodoanisole.—A suspension of 60 g. of 2-bromo-6-aminoanisole in 160 cc. of 38% sulfuric acid was converted by diazotization and treatment with potassium iodide into 2-bromo-6-iodoanisole. The product boiling at 155–157° (37 mm.) was collected. On cooling, the liquid solidified. After recrystallization from 95% alcohol, 76.3 g. (85%) of colorless flakes, m. p. 92–93°, was obtained.

Anal. Calcd. for C_7H_6OBrI : Br + I, 66.11. Found (micro): Br + I, 66.07.

2-Nitro-6-iodophenol.—In a 5-liter round-bottomed flask was placed a mixture of 150 g. of potassium 2-nitro-6-iodophenol-4-sulfonate.¹⁵ 300 cc. of concentrated sulfuric acid and 100 cc. of water. The mixture was heated to a clear solution and distilled with superheated steam. Con-

(8) Klemenc, *Monatsh.*, **33**, 701 (1912).

(9) G. M. Robinson, *J. Chem. Soc.*, **109**, 1084 (1916).

(10) Hofmann and von Miller, *Ber.*, **14**, 570 (1881).

(11) Meldola and Streatfield, *J. Chem. Soc.*, **73**, 685 (1898).

(12) Holleman, *Rec. trav. chim.*, **35**, 14 (1915).

(13) "Organic Syntheses," Collective Vol. I, 1932, p. 452.

(14) Ingold and Smith, *J. Chem. Soc.*, 1694 (1927).

(15) Armstrong and Brown, *ibid.*, [2] **10**, 869 (1872).

siderable decomposition took place at the beginning and a large amount of iodine was liberated. After the steam had been passed for about ten minutes, however, the decomposition ceased (this was marked by the disappearance of iodine vapor in the flask) and the hydrolysis then proceeded smoothly. The reservoir was changed at this point and the 2-iodo-6-nitrophenol which distilled over slowly was collected. After recrystallization from 95% alcohol, 30 g. (29%) of yellow needles, m. p. 109–110° (reported as 110–111° by Brenans¹⁶) was obtained.

2-Nitro-6-iodoanisole.—A solution of 30 g. of 2-nitro-6-iodophenol in 100 cc. of xylene was methylated with dimethyl sulfate and anhydrous potassium carbonate. The product was purified by steam distillation. After recrystallization from 50% alcohol, 29.5 g. (93%) of pale yellow needles, m. p. 60–61°, was obtained.

This product has been made previously by Brenans¹⁶ from the methylation of 2-nitro-6-iodoanisole but he did not mention the reagent used. He reported the same melting point 60–61°.

Condensation of 1-Nitro-2-bromo-3-carbomethoxybenzene with Substituted *o*-Iodoanisoles to Form Substituted 2-Nitro-6-carboxy-2'-methoxydiphenyls.—In a 200-cc. 3-necked flask fitted with a mechanical stirrer and air condenser, was placed a mixture of 10 g. of 1-nitro-2-bromo-3-carbomethoxybenzene,¹⁷ and 15–20 g. of the substituted *o*-iodoanisole. The flask was heated in a Wood's metal bath and as soon as the bath temperature reached 220° (240° in the case of 2-methyl-6-iodoanisole), 20 g. of activated copper bronze¹⁸ was added in small portions through one neck of the flask. During the addition, which took about half to three-quarters of an hour, the temperature of the bath was kept at 220–230° (240–250° for 2-methyl-6-iodoanisole). When all the copper had been added, the bath temperature was raised to 240–250° (270–280° for 2-methyl-6-iodoanisole) and the stirring continued for one and one-half hours. After cooling, the thick mass was transferred into a Soxhlet extraction shell and thoroughly extracted for twenty-four hours with 250 cc. of boiling 95% alcohol. The alcoholic extract was evaporated to about 75 cc. and then saponified by refluxing for four hours with 200 cc. of 10% sodium carbonate solution.

The mixture was distilled on a water-bath until all of the alcohol had been removed. After cooling, the aqueous solution was decanted from the unsaponified oily residue, which consisted of a mixture of unreacted iodo compound and any diphenyl formed from its symmetrical coupling, and acidified with diluted hydrochloric acid. The precipitate was filtered and redissolved in 10% sodium bicarbonate solution. The solution was then filtered to remove any insoluble material and the filtrate acidified. Brown crystals separated. The precipitate in every case was a mixture of 2,2'-dinitro-6,6'-dicarboxydiphenyl and the substituted 2-nitro-6-carboxy-2'-methoxydiphenyl. The mixture was extracted four times with 25-cc. portions of boiling benzene, in which the 2,2'-dinitro-6,6'-dicarboxydiphenyl was practically insoluble. After filtration, the benzene solution was evaporated to dryness and the residue recrystallized from acetone-petroleum ether (low

boiling) mixture as follows. The crude product was dissolved in the minimum amount of acetone. Low boiling petroleum ether was then added until the solution became cloudy. As soon as a layer of tar was formed on the bottom of the beaker, the supernatant liquid was poured into another beaker and the process repeated until no more tar appeared. The solution was then allowed to stand for about six to ten hours and filtered. The pure substituted 2-nitro-6-carboxy-2'-methoxydiphenyl was thus obtained.

All five substituted 2-nitro-6-carboxy-2'-methoxydiphenyls are soluble in alcohol, ether, acetone, and hot benzene but insoluble in petroleum ether and water.

TABLE III
PROPERTIES OF DIPHENYLS

No.	Acid	Substituted <i>o</i> -iodoanisole condensed with 1-nitro-2-bromo-3-carbomethoxybenzene	Yield, % pure.
1	2-Nitro-6-carboxy-2',3'-dimethoxydiphenyl	2-Methoxy-6-iodoanisole	17.2
2	2-Nitro-6-carboxy-2'-methoxy-3'-methyl-diphenyl	2-Methyl-6-iodoanisole	18.7
3	2-Nitro-6-carboxy-2'-methoxy-3'-chloro-diphenyl	2-Chloro-6-iodoanisole	7.9
4	2-Nitro-6-carboxy-2'-methoxy-3'-bromo-diphenyl	2-Bromo-6-iodoanisole	3.7
5	2,3'-Dinitro-6-carboxy-2'-methoxydiphenyl	2-Nitro-6-iodoanisole	15.5

No.	Form and color	M. p. (corr.), °C.	Analyses, % N Calcd.	Found
1	Colorless flakes	199–200	4.62	4.71
2	Colorless flakes	189–193	4.88	4.94
3	Ivory flakes	172–173	4.55	4.50
4	Pale yellow needles	182–183	4.00	4.08
5	Pale yellow needles	173–173.5	8.81	8.82

^a The yield was calculated on the basis of the amount of 1-nitro-2-bromo-3-carbomethoxybenzene employed.

Resolution of the Substituted 2-Nitro-6-carboxy-2'-methoxydiphenyls.—A solution of the alkaloid in warm absolute alcohol was treated with a solution of the substituted 2-nitro-6-carboxy-2'-methoxydiphenyl in the same solvent, heated to boiling and filtered. The filtrate was allowed to stand in the ice-box for a certain period of time until the first fraction separated.

During concentration of the mother liquor to dryness *in vacuo* at room temperature, several fractions were separated. In the cases where the group at 3' position was nitro or chloro two diastereoisomeric salts were obtained. For the other three diphenyls, however, all the fractions had similar crystalline form, melting point and specific rotation. In those cases where only one salt was obtained the fractions were mixed. These salts and the two less soluble salts from the nitro and chloro compounds were recrystallized to constant rotation from chloroform-absolute alcohol mixture; all gave *l* acids on decomposition.

The more soluble salt of the nitro compound was obtained by treating the last fraction (0.72 g.) with 20 cc. of chloroform, in which the less soluble salt is extremely

(16) Brenans, *Bull. soc. chim.*, [3] **27**, 401 (1902).

(17) Stoughton and Adams, *THIS JOURNAL*, **54**, 4426 (1932).

(18) Kleiderer and Adams, *ibid.*, **55**, 4219 (1933).

soluble, and filtering. The crystals were washed three times with 10-cc. portions of chloroform and dried. On decomposition, the salt gave a *d* acid.

The more soluble salt of the chloro compound was obtained from a solution of the last fraction (1 g.) in 15 cc. of chloroform and 15 cc. of absolute alcohol. On evaporating slowly to dryness, two different kinds of crystals were formed. One was the same as the less soluble salt as obtained by the concentration of the initial solution of the salt, and the other, large transparent cubical crystals with an orange color. The latter could be picked out easily from the mixture. By decomposition it proved to be the slightly impure salt of the *d* acid.

The analytical samples were dried at 100° over phosphorus pentoxide *in vacuo* for twenty-four hours.

Decomposition of the Alkaloidal Salts to Form the Active Substituted 2-Nitro-6-carboxy-2'-methoxydiphenyls.—The active acids were obtained by the following method. A chloroform solution of the alkaloidal salt was extracted twice with 20-cc. portions of 10% sodium hydroxide solution. The aqueous layer was thoroughly washed with chloroform and filtered. The temperature of the solution was kept below 5° by adding ice from time to time to avoid racemization. The filtrate was acidified with cold dilute hydrochloric acid and allowed to stand in the ice-box overnight. The next morning the active acid 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 the alkaloid and chloride. It was dried in a vacuum desiccator over calcium chloride.

TABLE IV
CONSTANTS OF SALTS

Compound group at 3'	Substituted 2-nitro-6-carboxy-2'-methoxydiphenyl salt	Form and color	M. p. (corr.), °C.	Wt. in g.	Temp., °C.	Rotation ^g in α _D	[α] _D	Analyses, N Calcd. Found
—OCH ₃	Strychnine, <i>l</i> -acid ^a	Colorless needles	208–210					6.78 6.82
—CH ₃	Cinchonine, <i>l</i> -acid ^a	Colorless needles	226–229 ^c	0.0191	24.5	+0.68	+178.0	7.46 7.29
—Cl	Strychnine, <i>l</i> -acid ^a	Colorless needles	150.5–153.5 ^d	.0245	25	+ .21	+ 42.8	6.74 6.83
—Br	Cinchonine, <i>l</i> -acid ^a	Colorless needles	201–206	.0170	24	+1.04	+305.9	6.69 6.81
—NO ₂	Brucine, <i>l</i> -acid ^a	Orange needles	149.5–156.5					8.07 8.11
—Cl	Strychnine, <i>d</i> -acid ^a	Orange cubes	149.5–162	.0271	25	–0.28	– 51.7	6.74 6.39
—NO ₂	Brucine, <i>d</i> -acid ^a	Orange cubes	197–199 ^c					8.07 7.66
—OCH ₃	Strychnine, <i>l</i> -acid ^b	Colorless needles	143.5–147.5	.2700 ^f	25	– .56	– 25.9	Ref. <i>h</i>
—NO ₂	Brucine, <i>l</i> -acid ^b	Yellow plates	140–147.5 ^e	.0175	25	+ .35	+100.0	Ref. <i>i</i>
—NO ₂	Brucine, <i>d</i> -acid ^b	Yellow cubes	192–195.5	.0073	24.5	– .17	–116.4	Ref. <i>j</i>

^a Anhydrous form. ^b Hydrated form. ^c Melted with decomposition. ^d Melted with evolution of gas. ^e Made up to 10 cc. with anhydrous chloroform. ^f Made up to 25 cc. ^g *l* = 2. ^h Calcd. for C₂₈H₃₄O₇N₂·1.5H₂O: H₂O, 4.18; C, 66.84; H, 5.61. Found: H₂O, 4.04; C, 67.05; H, 5.97. ⁱ Calcd. for C₂₇H₃₄O₁₀N₄·2.5H₂O: H₂O, 6.09. Found: H₂O 6.18. ^j Calcd. for C₂₇H₃₄O₁₀N₄·2H₂O: H₂O, 4.93. Found: H₂O, 4.87. All the salts showed no mutarotation at room temperature in four hours.

TABLE V
CONSTANTS OF ACTIVE ACIDS

Compound group at 3'	Acid	Form and color	M. p., ^d (corr.), °C.
—OCH ₃	<i>l</i> -acid ^a	White microcrystals	199–201
—CH ₃	<i>l</i> -acid ^a	Yellowish microcrystals	191–193
—Cl	<i>l</i> -acid ^a	Yellowish needles	171.5–173
—Cl	<i>d</i> -acid ^b	Yellowish needles	170.5–172
—Br	<i>l</i> -acid ^a	White microcrystals	180.5–182.5
—NO ₂	<i>l</i> -acid ^a	Yellowish microcrystals	170.5–172.5
—NO ₂	<i>d</i> -acid ^c	Yellowish microcrystals	169.5–171.5

^a See Table II for rotations. ^b Rotation. 0.0352 g. made up to 10 cc. with absolute alcohol at 25° gave α_D +0.10; *l* = 2, [α]_D²⁵ +14.2°. This acid was slightly impure. ^c Rotation. 0.0735 g. made up to 10 cc. with absolute alcohol at 25° gave α_D +0.19; *l* = 2, [α]_D²⁵ +12.9°. This acid was the pure *d*-acid. ^d The active acids melted at practically the same temperature as the corresponding racemic form. This was probably due to racemization of the active forms before melting.

Summary

1. A series of 3'-substituted 2-nitro-6-carboxy-2'-methoxydiphenyls has been prepared. These compounds are all more stable to racemization than the unsubstituted compounds or the corresponding 5' derivatives. The order of the stability is as follows: unsubstituted < OCH₃ < CH₃ < Cl < Br < NO₂.

2. The increased stability of the 3' over the 5' derivatives may be due in part to the repulsion of the 2'-methoxyl group toward the other ring because of the presence of the adjacent 3' substituent.

3. The salts of two of the acids showed a dextro rotation for the *l*-alkaloid-*l*-acid and a levo rotation for the *l*-alkaloid-*d*-acid.

URBANA, ILLINOIS

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