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

Stereochemistry of Diphenyls. XLI.[1] The Effect of 4'-Substitution on the Rate of Racemization of 2-Nitro-6-carboxy-2'-methoxydiphenyl

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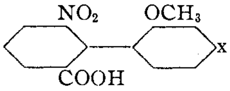
The stability to racemization of diphenyls has been shown to depend partly on the character of the groups in the 2,2',6,6' positions, and partly, though to a less extent, on the nature of the substituents in the 3,4,5 or 3',4',5' position.[3,4,5,6] A systematic study has been undertaken to determine the nature and extent of this latter effect by observing the rate of racemization, under similar conditions, of 2-nitro-6-carboxy-2'-methoxydiphenyl with the same series of groups substituted in the 3', 4' and 5' positions. In the preceding papers[4,5] of this series it has been shown that the order of stability in the 3' and 5' substituted 2-nitro-6-carboxy-2'-methoxydiphenyls is as follows: unsubstituted $< OCH_3 < CH_3 < Cl < Br < NO_2$. The 3' derivatives were found to be much more stable than the 5' in that the half-life periods of the former were much longer. The greater stability[5] of the 3' series may, perhaps, be related to the proximity of the 3' substituents to the methoxyl group in the 2' position.

In the present investigation the rate of mutarotation of the cinchonine salts and the rate of racemization of the free active acids and sodium salts of the 4' substituted 2-nitro-6-carboxy-2'-methoxydiphenyls have been determined (I).



where $x = CH_3, OCH_3, Cl, Br, NO_2$

A comparison of the 3', 4' and 5' substituted acids is given in Table I.

TABLE I

HALF-LIFE PERIODS OF VARIOUS DIPHENYLS

Position of the substituent in 2-nitro-6-carboxy-2'-methoxydiphenyl	Temperature 25°: Half-life period in minutes Group substituted Nitro	Bromo	Chloro	Methyl	Methoxy
$3'^{b,5}$	1905	827	711	331	98
$4'^{a}$	115	25.0	12.0	2.6	3.6
$5'^{b,4}$	35.4	32.0	31.0	11.5	10.8

[a] Acetone as solvent. [b] Ethyl alcohol as solvent.

From these data it may be deduced that (1) the stability to racemization of the 4' substituted compound in acetone is in the order: $CH_3 < OCH_3 < Cl < Br < NO_2$, and (2) the stability to racemization of the 4' substituted compounds is somewhat less than is found for the 5' substituted diphenyls and much less than for the 3' derivatives. One exception appears in that the 4'-nitro compound is more stable than the corresponding 5'-nitro derivative.

The mutarotations of the cinchonine salts and the racemization of the sodium salts are given in Table II. The sodium salts racemize faster in absolute alcohol than either the free acid in an organic solvent or the sodium salt in water. This is exactly comparable to the 3' and 5' series. The rate of racemization of the 4'-methoxyl and methyl derivatives as free acids is $OCH_3 > CH_3$, but this order is reversed in the racemization of the sodium salts in alcohol or water, or in the mutarotation of the cinchonine salt.

Although the mechanism for the change in antipodal stability of the diphenyls with the introduction of substituents into the 3,4,5 or 3',4',5' position is still obscure, it may be noted that the order of increase in stability in the 3', 4' or 5' series is the same as that of the dipole moments of the individual groups introduced into the positions indicated, the more negative the group the greater the stability.

Experimental

The diphenyls described in this investigation were prepared by condensing 1-nitro-2-bromo-3-carbomethoxybenzene with *o*-iodoanisole, 2-iodo-5-methylanisole, 1,3-dimethoxy-4-iodobenzene, 2-iodo-5-bromoanisole, 2-iodo-5-chloroanisole and 2-iodo-5-nitroanisole, in the presence of copper bronze, saponification of the products, and the isolation of the desired diphenyls from the mixtures. The diphenyls were resolved with cinchonine and the active acids obtained by the method given by Yuan and Adams.[4] The active acid and the corresponding racemic mixture in each case had the same melting point, which is in agreement with previous results for easily racemized diphenyls.

The values for the rates of racemization and mutarotation as given in Table II were calculated from the equation of a first order reaction. It should be pointed out that the true rate of reaction should be calculated from the equation for a reversible first order reaction, but the results

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[1] For the last paper in this series see Li and Adams, THIS JOURNAL, **57**, 1565 (1935). Also Yuan and Adams, *Chem. Rev.*, **12**, 261 (1933).

[2] Part of thesis submitted in partial fulfilment for the Degree of Doctor of Philosophy in Chemistry at the University of Illinois.

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

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

[5] Chien and Adams, *ibid.*, **56**, 1787 (1934).

[6] Searle and Adams, *ibid.*, **56**, 2112 (1934).

TABLE II

ROTATIONS OF 4′ SUBSTITUTED 2-NITRO-6-CARBOXY-2′-METHOXYDIPHENYLS AND THEIR SALTS

4′ group	Wt. made up to 10 cc., g.	T, °C.	Min. before initial reading	Initial α_D $l = 2$	Final α_D	Av. K	Av. dev. of K	Half-life period, min.
Cinchonine Salt in Chloroform								
OCH_3	0.0432	27.5–28.5	4	+0.15	+0.62	0.087	±0.008	3.5
CH_3	.0417	24.5–26	3	− .27	+ .94	.0290	± .002	10.4
Cl	.0443	25.5–26.5	3	− .26	+1.35	.0140	± .001	21.5
Br	.0473	24.5–25.5	2	− .43	+1.34	.0112	± .001	26.9
NO_2	.0512	24 –25	8	+2.41	+1.00	.0034	± .0004	88.5
Free Acid in Acetone								
OCH_3	0.1108	25.3	2	−0.38	0	0.084	±0.008	3.6
CH_3	.1025	25	5	− .15	0	.117	± .008	2.6
Cl	.0732	24 –25.5	4	− .17	0	.0249	± .0028	12.0
Br	.0640	25 –26	6	− .19	0	.0120	± .0012	25.0
NO_2	.0898	25.5–26.5	6	+ .57	0	.0262	± .0049	115.0
Free Acid in Absolute Ethyl Alcohol[a]								
CH_3	0.1198	25.8–26.2	2	−0.14	0	0.095	±0.001	3.2
Cl	.0819	24.5–25.5	5	− .20	0	.037	± .002	8.1
Br	.0507	23 –24.5	4	− .08	0	.017	± .002	17.7
Sodium Salt in Water								
OCH_3	0.0971	26.5–27.5	6	−0.87	0	0.045	±0.003	6.7
CH_3	.0841	24.5–25	..	− .18	0	.0228	± .0006	13.3
Cl	.0787	24.5–25	9	− .47	0	.0099	± .004	30.4
Br	.0632	23.5–25	16	− .28	0	.0083	± .0001	36.2
NO_2	.0901	25	10	+2.07	0	.0361	± .0025	83.4
Sodium Salt in Absolute Ethyl Alcohol								
OCH_3	0.0994	26.5	5	−0.08	0	0.602	......	0.5
CH_3	.0934	24 –25	5	− .17	0	.025	±0.003	1.2
Cl	.0806	24.5–25	3	− .97	0	.0578	± .0041	5.1
Br	.0557	24.0–25	9	− .22	0	.043	± .002	7.0
NO_2	.0772	25 –26	5	+3.75	0	.0138	± .0014	28.4

[a] The methoxyl and nitro compounds were not sufficiently soluble in ethyl alcohol to obtain accurate values.

have been calculated on the basis of a first order reaction in order that they may be directly compared to the results previously reported. In order to transform these results into the true value for a reversible first order reaction it is merely necessary to multiply the K value given by 1.151.

1-Nitro-2-bromo-3-carbomethoxybenzene.—This compound was prepared by the method of Stoughton and Adams.[7]

4 - Iodo - 1,3 - dimethoxybenzene.—1,3 - Dimethoxybenzene[8] was treated with iodine and mercuric oxide according to the method of Kauffmann and Kieser.[9]

2-Iodo-5-nitroanisole.—A mixture of 38 g. of 4-amino-5-nitroanisole in a solution of 100 cc. of concentrated sulfuric acid and 400 cc. of water was cooled to 0°. To this, with constant stirring, was slowly added 16 g. of sodium nitrite dissolved in 50 cc. of water. The cold solution was filtered and to the cold filtrate 40 g. of potassium iodide dissolved in 50 cc. of water was slowly added. The solution was allowed to stand for one-half hour at room temperature and then heated for one hour on a steam-bath. On cooling, the product separated as brown crystals, which were crystallized from alcohol. The yield was 55 g. (85%) m. p. 127–128°; reported[10] melting point, 127–128°.

2-Bromo-5-nitroanisole.—A mixture of 12.6 g. of copper sulfate, 4 g. of copper turnings, 30.8 g. of sodium bromide, 3 cc. of concentrated sulfuric acid, and 200 cc. of water was placed in a 2-liter 3-necked flask equipped with a mercury-sealed stirrer, a reflux condenser and a long-stem separatory funnel. The material was refluxed until the solution had only a yellowish color.

The diazonium salt was prepared as given for the 2-iodo-5-nitroanisole, using 33.6 g. of 2-amino-5-nitroanisole and 14 g. of sodium nitrite. After filtering the solution, it was slowly added to the boiling cuprous bromide solution. The material was steam-distilled and finally recrystallized from alcohol. Very light cream-colored crystals were obtained, m. p. 104°.

Anal. Calcd. for $C_7H_6O_3NBr$: Br, 34.4; N, 6.04. Found: Br, 34.0; N, 6.26.

2 - Nitro - 5 - methylanisole.—2 - Nitro - 5 - methylphenol[11] was methylated according to the method of Haworth and Lapworth.[12,13]

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[7] Stoughton and Adams, THIS JOURNAL, **54**, 4428 (1932).

[8] Ullmann, *Ann.*, **327**, 115 (1903).

[9] Kauffmann and Kieser, *Ber.*, **45**, 2334 (1912).

[10] Meldola and Eyre, *Proc. Chem. Soc.*, **17**, 134 (1901).

[11] Staedel, *Ann.*, **259**, 210 (1890).

[12] Haworth and Lapworth, *J. Chem. Soc.*, **123**, 2986 (1923).

[13] Hodgson and Nixon, *ibid.*, 2166 (1930).

2-Iodo-5-methylanisole.—A solution of 10 g. of 2-nitro-5-methylanisole in 150 cc. of ethyl alcohol was reduced by platinum oxide catalyst and hydrogen.[14] The resulting amino compound was used in the preparation of the 2-iodo-5-methylanisole without further purification.

The 2-amino-5-methylanisole[15] was suspended in 100 cc. of 10% sulfuric acid and cooled to 0°. A solution of 5 g. of sodium nitrite in 25 cc. of water was slowly added with constant stirring. To this cold solution was added 15 g. of potassium iodide dissolved in 50 cc. of water. The resulting solution was allowed to come to room temperature and heated on a steam-bath until no more nitrogen was evolved. The oil was separated, the water layer extracted with ether, the combined ether solution and oil shaken with 2% sodium hydroxide and finally dried over potassium hydroxide; colorless liquid, b. p. 109.5–110° (3 mm.). The yield was 11.6 g. (76%); d^{20}_{20}, 1.6912; n^{20}_{D} 1.6103; *M* (calcd.), 50.51; found, 50.91.

Anal. Calcd. for C_8H_9OI: I, 51.21. Found: I, 51.34.

2-Acetylamino-5-nitroanisole.—A mixture of 100 g. of 2-amino-5-nitroanisole and 150 cc. of acetic anhydride was heated for four hours and then poured into water. The resulting product was purified by recrystallization from alcohol, m. p. 156–157°. The melting point has previously been reported as 153–154°.[16]

2-Acetylamino-5-aminoanisole.—This compound was prepared by the reduction of 2-acetylamino-5-nitroanisole with iron and water in the usual manner. The product was recrystallized from benzene, m. p. 119–120°. It is colorless when pure but is very readily oxidized by the air to a deep red solution, hence the crude product was used directly for preparing 2-amino-5-bromo or 2-amino-5-chloroanisole. The literature[17] gives the melting point of this compound as 72°.

Anal. Calcd. for $C_9H_{12}O_2N_2$: N, 15.50. Found: N, 15.55.

2-Amino-5-bromoanisole.—After reduction of 82 g. of 2-acetylamino-5-nitroanisole with iron and water, extraction of the product with alcohol and the removal of the alcohol by distillation, the product was poured into 500 cc. of cold 10% sulfuric acid and diazotized in the usual manner with 28 g. of sodium nitrite in 100 cc. of water. The diazonium solution was then added to a boiling solution of cuprous bromide which had previously been prepared from 50 g. of copper sulfate, 16 g. of copper turnings, 120 g. of sodium bromide, 10 cc. of concentrated sulfuric acid, and 600 cc. of water. The solution was refluxed for one and one-half hours, cooled, made slightly alkaline with 10% sodium hydroxide, and the product steam distilled. The white needles obtained were recrystallized from high-boiling petroleum ether, m. p. 61–62°; reported melting point, 60–61°;[18] yield, 41 g. (50%).

2-Iodo-5-bromoanisole.—To a solution of 50 g. of 2-amino-5-bromoanisole in 400 cc. of water and 50 cc. of concentrated sulfuric acid cooled in an ice-bath, 17 g. of sodium nitrite dissolved in 100 cc. of water was slowly added. After standing in the cold for one hour, the diazonium solution was filtered on a cold Büchner funnel. The filtrate was then added to a solution containing 100 g. of potassium iodide in a solution of 20 cc. of concentrated sulfuric acid in 200 cc. of water, which had been previously cooled to 10°. A little benzene was added to prevent the diazonium iodide complex from exploding as it does upon contact with air. When all the diazonium solution had been added, the solution was allowed to come to room temperature and finally heated on a steam-bath until no more nitrogen was evolved. Sodium bisulfite was added to remove the free iodine, the solution extracted with carbon tetrachloride and shaken with mercury to remove all traces of free iodine. The solvent was removed by distillation and the residual oil distilled; b. p. 161–162° (8 mm.). The resulting light yellow oil solidified on cooling and colorless needles melting at 37° were obtained by recrystallization from alcohol. The yield was 38.5 g. (50%).

Anal. Calcd. for C_7H_6OBrI: total halogen, 66.13. Found: total halogen, 66.3.

2-Amino-5-chloroanisole.—This was prepared according to the directions given for the 2-amino-5-bromoanisole. From 82 g. of 2-acetylamino-5-nitroanisole, 28 g. of 2-amino-5-chloroanisole (44%) was obtained which melted at 51°; reported melting point, 52°.[19]

2-Iodo-5-chloroanisole.—This compound has been reported by Jannasch and Hinterskirch[20] but Ingold, Smith and Voss[21] have shown their compound to be 2-chloro-4-iodoanisole. The 2-iodo-5-chloroanisole was prepared from 23 g. of 2-amino-5-chloroanisole by the method given for the 2-iodo-5-bromoanisole; b. p. 150° (20 mm.); 135° (10 mm.); yield, 32.5 g. (85%). The product has a melting point of about 20°.

Anal. Calcd. for C_7H_6OClI: total halogen, 58.8. Found: total halogen, 58.7.

2-Nitro-6-carboxy-2′,4′-dimethoxydiphenyl.—In a 200-cc., 3-necked flask equipped with a mechanical stirrer and a reflux condenser was placed 30 g. of 4-iodo-1,3-dimethoxybenzene and 15 g. of 1-nitro-2-bromo-3-carbomethoxybenzene. The mixture was heated in a Wood's metal bath to 240–250° and 35 g. of activated copper bronze[22] was added in small quantities. The addition required about forty-five minutes. The bath temperature was then raised to 290° and heated for one hour. After cooling, the material was transferred to a Soxhlet extractor and extracted overnight with ethyl alcohol. To the alcohol solution 100 cc. of 5% sodium hydroxide was added, the solution diluted to 400 cc. and refluxed overnight. It was then cooled and filtered. The clear filtrate was acidified and the crude acids filtered and dissolved in sodium bicarbonate solution. This solution was filtered and the acids precipitated by the addition of hydrochloric acid. The crude acids were filtered and then dissolved in glacial acetic acid. The product which crystallized out was 2-nitro-6-carboxy-2′,4′-dimethoxydiphenyl. No 2,2′-dinitro-6,6′-dicarboxydiphenyl was obtained. The 2-nitro-6-carboxy-2′,4′-dimethoxydiphenyl was recrystallized from dilute alcohol, m. p. 213–214°; yield, about 2 g.

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[14] "Organic Syntheses," Coll. Vol. I, p. 235.

[15] H. Fritzsche, *Chem. Zentr.*, **92**, IV, 267 (1921).

[16] Ingold and Ingold, *J. Chem. Soc.*, 1317 (1926).

[17] Farbwerke vorm. Meister Lucius and Bruning, German Patent 294,159; *Chem. Zentr.*, **87**, II, 707 (1916).

[18] W. Fritzky, U. S. Patent 1,792,156; *C. A.*, **25**, 1844 (1931).

[19] Herold, *Ber.*, **15**, 1685 (1882).

[20] Jannasch and Hinterskirch, *ibid.*, **31**, 1711 (1898).

[21] Ingold, Smith and Voss, *J. Chem. Soc.*, 1248 (1927).

[22] Kleiderer and Adams, THIS JOURNAL, **55**, 4219 (1933).

Anal. Calcd. for $C_{15}H_{13}O_6N$: N, 4.62. Found: N, 4.64.

2,4'-Dinitro-6-carboxy-2'-methoxydiphenyl.—The procedure was similar to that used in the preparation of 2-nitro-6-carboxy-2',4'-dimethoxydiphenyl with the following variation. The temperature employed was 230–240° throughout the entire coupling reaction. The mixture of crude esters was saponified by diluting the alcohol (1:1) with water, adding 20 g. of sodium carbonate and refluxing for four and one-half hours. The alcohol was removed by distillation and the aqueous solution was then treated as given for the 2-nitro-6-carboxy-2',4'-dimethoxydiphenyl. The crude acids were dissolved in glacial acetic acid, treated with a little norite and filtered. On cooling the first crystals which separated were 2,2'-dinitro-6,6'-dicarboxydiphenyl, m. p. 255–260°. The second crop of crystals was of pale yellow color and after recrystallizing from alcohol small yellow platelets of 2,4'-dinitro-6-carboxy-2'-methoxydiphenyl were obtained, m. p. 203.5–206°; yield, 1.3 g.

Anal. Calcd. for $C_{14}H_{10}O_7N_2$: neut. equiv., 318; N, 8.81. Found: neut. equiv., 308; N, 8.95.

2-Nitro-6-carboxy-2'-methoxy-4'-methyldiphenyl.—For this preparation 20 g. of 2-iodo-5-methylanisole and 10 g. of 1-nitro-2-bromo-3-carbomethoxybenzene was treated as given for the 2,4'-dinitro-6-carboxy-2'-methoxydiphenyl. The temperature employed was 205–215° and heating was continued for three hours. The temperature must not be allowed to rise above 218°, for at this temperature in the presence of copper iodine is liberated from the 2-iodo-5-methylanisole. The crude acids obtained were separated by extracting them with hot benzene in which 2-nitro-6-carboxy-2'-methoxy-4'-methyldiphenyl was soluble and the 2,2'-dinitro-6,6'-dicarboxydiphenyl was insoluble. The 2-nitro-6-carboxy-2'-methoxy-4'-methyldiphenyl was recrystallized from a mixture of benzene and petroleum ether, m. p. 171–172°; yield, 1.5–2 g.

Anal. Calcd. for $C_{15}H_{13}O_5N$: N, 4.88. Found: N, 4.91.

2-Nitro-6-carboxy-2'-methoxy-4'-chlorodiphenyl.—This compound was prepared from 20 g. of 2-iodo-5-chloroanisole and 10 g. of 1-nitro-2-bromo-3-carbomethoxybenzene in exactly the same way as the 2-nitro-6-carboxy-2'-methoxy-4'-methyldiphenyl. The 2-nitro-6-carboxy-2'-methoxy-4'-chlorodiphenyl was recrystallized from petroleum ether and benzene, m. p. 160–160.5°; yield, about 2 g.

Anal. Calcd. for $C_{14}H_{10}O_5NCl$: N, 4.54. Found: N, 4.71.

2-Nitro-6-carboxy-2'-methoxy-4'-bromodiphenyl.—The 2-iodo-5-bromoanisole was coupled with the 1-nitro-2-bromo-3-carbomethoxybenzene at a temperature of 240–250° for two hours. The rest of the procedure was the same as given for the 2-nitro-6-carboxy-2'-methoxy-4'-methyldiphenyl. The 2-nitro-6-carboxy-2'-methoxy-4'-bromodiphenyl was recrystallized from petroleum ether and benzene and melted at 160–161°; yield, about 2 g.

Anal. Calcd. for $C_{14}H_{10}O_5NBr$: N, 4.33. Found: N, 4.30.

The Method of Resolution.—The diphenyl was accurately weighed and dissolved in a suitable solvent. The exact equivalent quantity of cinchonine (anhydrous) was dissolved in the same solvent. The two warm solutions were mixed and filtered. This solution was set aside and allowed to crystallize slowly. Usually three crops of crystals were separated, but in every case only one optically active form was obtained. The quantity of material used, the solvent, and the physical constants of the salt are given in the tables. The optically active acids were obtained from the salts by the method of Yuan and Adams[4] (see Tables II and III).

TABLE III

PREPARATION AND PROPERTIES OF CINCHONINE SALTS

4'-Substituted 2-nitro-6-carboxy-2'-methoxydiphenyl	Anhydrous solvent	Yield of salt, %	M. p. of cinchonine salt, °C.	Formula	N analyses of cinchonine salt	
					Calcd.	Found
4'-methoxy	MeOH	71	198–205	$C_{34}H_{35}O_7N_3$	7.04	7.08
4'-methyl	EtOAc	76	201–204	$C_{34}H_{35}O_6N_2$	7.17	7.35
4'-chloro	EtOAc	85	192–193.5	$C_{33}H_{32}O_6N_3Cl$	6.97	6.84
4'-bromo	EtOAc	85	193–195 dec.	$C_{33}H_{32}O_6N_3Br$	6.66	6.75
4'-nitro	EtOH or dil. EtOH	85	188–189	$C_{33}H_{32}O_8N_4$	9.15	9.21

Summary

A comparison of the rates of racemization of derivatives of 2-nitro-6-carboxy-2'-methoxydiphenyl having methyl, methoxyl, chlorine, bromine and nitro groups in the 4' position indicate (1) the order of stability to racemization to be unsubstituted $< CH_3 < OCH_3 < Cl < Br < NO_2$, (2) that the 4' are less stable than the corresponding 5' and much less stable than the corresponding 3' derivatives, (3) that the order of increase in stability follows the order of increase of the dipole moments of the groups substituted in the 4'-position.

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