

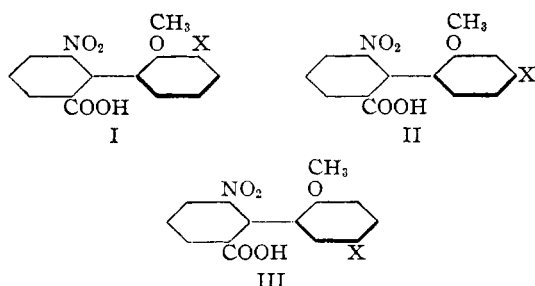
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

Stereochemistry of Biphenyls.¹ XLIII. The Effect of Substituents in the 4-Position of 2-Nitro-6-carboxy-2'-methoxybiphenyl

BY ROGER ADAMS AND H. R. SNYDER

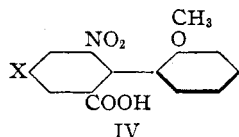
The effect of a substituent group X, where X = NO₂, Br, Cl, CH₃, and OCH₃, in the 3'-, 4'-, and 5'-positions of 2-nitro-6-carboxy-2'-methoxybiphenyl upon the rate of racemization of such molecules has been described previously.²

The substituents in the 3'-position (I) have a greater influence in slowing the rate of racemization of 2-nitro-6-carboxy-2'-methoxybiphenyl than those in the 4'- (II) or 5'- (III) position.



The relative influence of each group is qualitatively in the order listed above with the nitro showing the greatest, and the methoxyl group the least, effect.

The groups NO₂, Br, Cl, CH₃ have now been substituted in the 4-position (IV) in 2-nitro-6-



carboxy-2'-methoxybiphenyl. The results are striking in comparison with those just discussed. The rate of racemization of the parent molecule is only very slightly modified; the chlorine decreases the rate to a minor degree, the bromine is ineffective, the nitro and methyl groups increase the rate. The comparison of the data is shown in Table I.

It is noticeable that the order of effectiveness of the groups upon the racemization rate is entirely different in the 4-series from the 3'-, 4'-, or 5'-series. When in the 4- or 4'-position, the sub-

TABLE I

HALF-LIFE PERIODS IN MINUTES OF SUBSTITUTED 2-NITRO-6-CARBOXY-2'-METHOXYBIPHENYL

For racemization studies the solvent was ethanol in all except the 4'-series, where acetone was used.

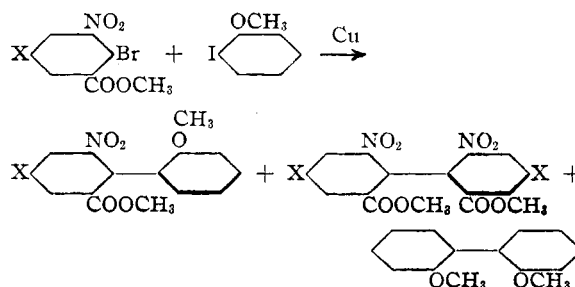
Position of substituent	Nitro	Bromine	Chlorine	Methyl	Methoxyl
3'	1905	827	711	331	98
4'	115	25	12	2.6	3.6
5'	35	32	31	11.5	10.8
4	4.3	9	11.6	5.1	..

No substituent—Half-life period, 9.4

stituents hold an identical location relative to the linkage between the benzene rings. Nevertheless, the effect upon the molecule is quite different. Thus, it is demonstrated that the difference must be due primarily to the influence of the new substituent upon the groups originally present as they effect racemization. From these experiments and others, it is clear that the relative positions of the same substituents in any particular restricted biphenyl molecule is an important factor influencing the observed rate of racemization.

The alkaloidal salts of the acids described in this communication exhibit mutarotation and the half-life periods of mutarotation are of the same order as the rate of racemization of the free acids. The detailed results are given in Table II.

The compounds were prepared by condensing with copper the bromo or iodo esters and *o*-iodoanisole. The desired compound was then isolated from the mixture.



The intermediate halogenated compounds containing in the *p*-position to the halogen a CH₃, Cl or Br all were synthesized through the proper isatoic anhydride by the following series of reactions.

(1) For last paper in this series see Hsing and Adams, *THIS JOURNAL*, **58**, 587 (1936).

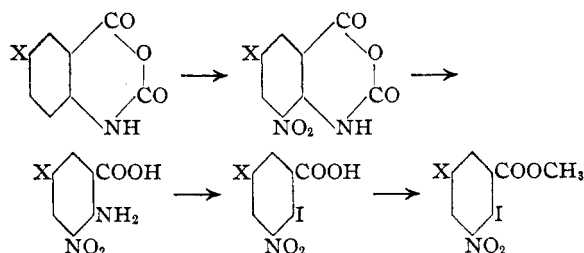
(2) Yuan and Adams, *ibid.*, **54**, 2966, 4434 (1932); Chien and Adams, *ibid.*, **56**, 1787 (1934); Searle and Adams, *ibid.*, **56**, 2112 (1934); Hanford and Adams, *ibid.*, **57**, 1592 (1935).

TABLE II

ROTATIONS OF 4-SUBSTITUTED 2-NITRO-6-CARBOXY-2'-METHOXYBIPHENYLS AND THEIR STRYCHNINE SALTS

The temperature for the rotations was 28°. The K was calculated according to the formula used in previous papers since comparative values are more significant than absolute values. The values of velocity constants, based on an equation derived on the assumption that the racemization is a reversible monomolecular reaction, are somewhat higher (H. Gilman, "Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1938, Vol. I, p. 178).

4-Group	Wt. made to 10 cc., g.	Min. before initial reading	Initial α_D $l = 1$	Final α_D	Calcd. for zero time α_D	Final $[\alpha]_D$	Average K	Average deviation K	Half-life period, min.
Strychnine Salts in Chloroform									
Br	0.1055	2	-1.55	-0.27	-1.74	-165.0	-25.6	0.0302	± 0.0011
	.1236	2	-1.85	-.35	-2.07	-167.6	-28.3	.0294	$\pm .0014$
Cl	.0992	2	-1.02	-.31	-1.11	-111.9	-36.6	.0263	$\pm .0010$
	.1176	2	-1.30	-.37	-1.42	-120.8	-31.5	.0268	$\pm .0018$
CH ₃	.1614	2	-1.55	-.49	-1.85	-114.6	-30.4	.0408	$\pm .0018$
	.1042	2	-0.94	-.31	-1.05	-100.8	-28.7	.0347	$\pm .0017$
NO ₂	.2066	3	-2.67	-.45	-3.95	-190.7	-21.8	.066	$\pm .0020$
	.1151	2	-1.65	-.26	-2.15	-186.7	-22.6	.067	$\pm .0013$
	.1595	2	-2.18	-.46	-2.86	-179	-28.8	.072	$\pm .0012$
Free Acids in Absolute Alcohol									
Br	0.1471	5	-0.46		-0.668	-45.8		0.0324	± 0.0014
	.1297	5	-.40		-.60	-46.2		.0348	$\pm .0035$
Cl	.1170	2	-.25		-.282	-24.1		.0261	$\pm .0015$
	.1710	2	-.37		-.416	-24.6		.0254	$\pm .0039$
CH ₃	.0946	1	-.25		-.285	-30.2		.0576	$\pm .0057$
	.1989	1	-.54		-.62	-31.2		.0601	$\pm .0017$
NO ₂	.2303	1	-.20		-.232	-10.1		.0638	$\pm .0023$
	.2019	1	-.26		.31	-14.8		.0751	$\pm .0074$



The methyl 2-bromo-3,5-dinitrobenzoate was prepared by direct nitration of 2-bromo-3-nitrobenzoic acid, followed by esterification.

Experimental

5-Bromoisatoic Anhydride.—A mixture of 60 g. of crude 5-bromoisatin³ and 600 cc. of glacial acetic acid was stirred mechanically and cooled with ice water. To this, 150 g. of chromic anhydride was added in small portions over a period of thirty minutes, with the temperature maintained at 10–15°. Acetic acid was added from time to time to wash down the sides of the flask until a total of 300 cc. had been introduced. The reaction mixture was stirred for twelve hours at 15°, then for one and one-half hours at 40° and finally for one hour at 75°, cooled and poured into 2250 cc. of ice and water. The light-yellow powder which separated was filtered and washed with water until free from chromium compounds and weighed 41 g. (62% theory). It melted with decomposition at 286–288° and was used without purification in the next step.

(3) Sandmeyer, *Helv. Chim. Acta*, **2**, 234 (1919).

7-Nitro-5-bromoisatoic Anhydride and 2-Amino-3-nitro-5-bromobenzoic Acid.—A solution of 41 g. of 5-bromoisatoic anhydride in 500 cc. of cold concentrated sulfuric acid was cooled to 5° and with mechanical stirring 16.7 g. of finely ground sodium nitrate was added in small portions over about thirty minutes. Stirring at 5–10° was continued for two hours and the reaction mixture was then poured onto 2 liters of cracked ice. The crude precipitate which weighed 24 g. was a mixture of 7-nitro-5-bromoisatoic anhydride and 2-amino-3-nitro-5-bromobenzoic acid. The anhydride could be obtained pure by repeated recrystallization from alcohol; yellow needles, m. p. 94°.

Anal. Calcd. for C₈H₅O₄N₂Br: N, 9.76. Found: N, 9.39.

The mother liquor was diluted with water to about 4.5 liters and allowed to stand overnight. A precipitate separated which weighed 16.5 g. and proved to be crude 2-amino-3-nitro-5-bromobenzoic acid. It was added to the crude nitrobromoisatoic anhydride and the mixture dissolved in 300 cc. of hot glacial acetic acid containing about 100 cc. of concentrated hydrochloric acid. After refluxing the solution for two hours, it was allowed to cool when 34 g. (77%) of yellow crystals separated. They were purified from glacial acetic acid, m. p. 245–247°.

Anal. Calcd. for C₇H₅O₄N₂Br: N, 10.74. Found: N, 10.52.

2-Iodo-3-nitro-5-bromobenzoic Acid.—A mixture of 10 g. of 2-amino-3-nitro-5-bromobenzoic acid and 4.2 g. of potassium meta-bisulfite was ground in a mortar to a fine homogeneous powder. The mixture was added over about one hour to 18 cc. of fuming nitric acid, cooled in ice

to 0–10°. Mechanical stirring was used and the temperature was maintained at 0–10° for fifteen minutes after the addition. The reaction mixture was then poured onto 160 g. of ice. To this solution was added with stirring 5.7 g. of iodine and 11.3 g. of potassium iodide in about 20 cc. of water. After standing overnight at room temperature, the mixture was heated for one hour on the steam-bath. The solid was filtered and stirred with dilute sodium bisulfite solution until the iodine color had disappeared. The excess bisulfite was then destroyed with concentrated hydrochloric acid. The precipitate was filtered and purified by dissolving in 70 cc. of alcohol, decolorizing and diluting the hot filtered solution with boiling water until the volume reached 250 cc. On cooling, yellow-green crystals separated; yield, 13 g. (91%). It melted when pure at 213–214.5°.

Anal. Calcd. for $C_7H_5O_4NBrI$: N, 3.76; neut. equiv., 371.9. Found: N, 3.86; neut. equiv., 370.3, 372.2.

Methyl 2-Iodo-3-nitro-5-bromobenzoate.—By esterification of the acid with methanol and sulfuric acid, an oil was obtained which gradually solidified; yield, 20 g. (88%). It was purified from a mixture of methanol and low-boiling petroleum ether; yellow crystals, m. p. 63°.

Anal. Calcd. for $C_8H_5O_4NBrI$: N, 3.63. Found: N, 3.77.

dl-2-Nitro-4-bromo-6-carboxy-2'-methoxybiphenyl.—A mixture of 20 g. of crude methyl 2-iodo-3-nitro-5-bromobenzoate and 41.6 g. of *o*-iodoanisole was stirred mechanically and heated under reflux in a metal bath until the contents of the flask reached a temperature of 210°. With vigorous stirring 60 g. of activated copper-bronze was added over a period of forty-five minutes; the temperature was maintained at 210–215° till all the copper-bronze had been introduced, then raised to 230° for twenty minutes. After cooling, the reaction mixture was extracted with five 150-cc. portions of boiling acetone. The acetone was removed and the residue refluxed for three hours with 500 cc. of alcohol and 200 cc. of 10% aqueous sodium hydroxide. The alcohol was removed by distillation and the residue was diluted to 600 cc. with water. Insoluble material was filtered and the solution was extracted four times with ether and the extracts discarded. Upon acidification of the aqueous solution, 16 g. of light-brown product was obtained. It was purified by dissolving in 100 cc. of 10% aqueous sodium bicarbonate, heating with decolorizing carbon, filtering and regenerating with acid. It was crystallized once from 15 cc. of glacial acetic acid and twice from dilute alcohol: light-yellow crystals, m. p. 181°; yield, 5.2 g. (27%).

Anal. Calcd. for $C_{14}H_{10}O_4NBr$: N, 3.97; Br, 22.7; neut. equiv., 352. Found: N, 3.98; Br, 22.5; neut. equiv., 353.

Strychnine Salt of l-2-Nitro-4-bromo-6-carboxy-2'-methoxybiphenyl.—A mixture of 2.0 g. of the acid, 1.9 g. of strychnine and 75 cc. of methanol was heated for a few minutes till solution was complete. Upon standing for three to four hours, light-yellow crystals separated, weight 3 g. By chilling the mother liquor, a second crop of 0.56 g. was obtained. Upon recrystallization from methanol (2.9 g. in 60 cc.), a pure yellow crystalline product which melted at 139° with decomposition resulted.

Anal. Calcd. for $C_{35}H_{32}N_8O_7Br$: N, 6.12. Found: N, 5.81.

l-2-Nitro-4-bromo-6-carboxy-2'-methoxybiphenyl.—To 60 cc. of 6 *N* hydrochloric acid at –10° was added 0.70 g. of pure strychnine salt. The mixture was shaken vigorously from time to time over a period of five hours, maintaining a temperature of –10°.

The solid was separated by filtration on sintered glass and again treated with 6 *N* hydrochloric acid at –10° for five hours. It was then removed by filtration and suspended in a fresh portion of 6 *N* hydrochloric acid at –10°. After ten hours it was collected on sintered glass and washed with acid until the washings gave a negative test for strychnine. It was dried *in vacuo* over phosphorus pentoxide; yellowish powder; yield 0.28 g.

5-Chloroisatoic Anhydride.—5-Chloroisatin was made in a similar manner to the corresponding bromoisatin previously described. The crude product was converted to 5-chloroisatoic anhydride by oxidation of 54 g. of chloroisatin with 100 g. of chromic anhydride as described for the bromo analog. The yield was 79%. Purified from dilute dioxane it formed a light-yellow solid, m. p. 267° with vigorous decomposition.

Anal. Calcd. for $C_8H_4O_3NCl$: N, 7.08. Found: N, 6.71.

7-Nitro-5-chloroisatoic Anhydride.—Nitration of 5-chloroisatoic anhydride was carried out as described for the bromo derivative. The crude product was a mixture of anhydride and 2-amino-3-nitro-5-chlorobenzoic acid. By recrystallization from methanol, it formed long bright-yellow needles, m. p. 85°.

Anal. Calcd. for $C_8H_5O_5N_2Cl$: N, 11.5. Found: N, 11.31.

2-Amino-3-nitro-5-chlorobenzoic Acid.—A 93% yield was obtained from the crude 7-nitro-5-chloroisatoic anhydride by hydrolysis as described for the bromo derivative. It was purified from glacial acetic acid in the form of golden needles, m. p. 240°.

Anal. Calcd. for $C_7H_5O_4N_2Cl$: N, 12.93. Found: N, 12.8.

2-Iodo-3-nitro-5-chlorobenzoic Acid.—This was prepared from 2-amino-3-nitro-5-chlorobenzoic acid as described for the bromo analog. From 32 g. of amino acid, 16.2 g. of potassium meta-bisulfite, 70 cc. of fuming nitric acid, 22 g. of iodine and 43.6 g. of potassium iodide, 43 g. (89%) of yellow iodo acid was obtained. It was purified from benzene, m. p. 204°.

Anal. Calcd. for $C_7H_3O_4NClI$: N, 4.28; neut. equiv., 327. Found: N, 4.34; neut. equiv., 333.

Methyl 2-Iodo-3-nitro-5-chlorobenzoate.—It formed yellow crystals from petroleum ether (b. p. 35–65°), m. p. 66–67°.

Anal. Calcd. for $C_8H_5O_4NClI$: N, 4.12. Found: N, 4.12.

dl-2-Nitro-4-chloro-6-carboxy-2'-methoxybiphenyl.—From 20 g. of methyl 2-iodo-3-nitro-5-chlorobenzoate, 48 g. of *o*-iodoanisole, 68 g. of activated copper-bronze, using the same procedure as for the bromo compound, 7.3 g. (45%) of light-yellow crystals was obtained. Purified by crystallization, once from glacial acetic acid and then once from dilute alcohol with norite, it melted at 171°.

Anal. Calcd. for $C_{14}H_{10}O_5NCl$: N, 4.55; Cl, 11.53; neut. equiv., 307.5. Found: N, 4.87; Cl, 11.90; neut. equiv., 306.1.

Strychnine Salt of 1-2-Nitro-4-chloro-6-carboxy-2'-methoxybiphenyl.—A mixture of 3.0 g. of acid, 3.26 g. of strychnine and 200 cc. of methanol was heated until solution took place. After cooling overnight, 6.1 g. of yellow crystals was obtained. These were recrystallized from 100 cc. of absolute ethanol by allowing to stand overnight at 5°; m. p. 137°, with decomposition.

Anal. Calcd. for $C_{38}H_{32}N_3O_7Cl$: N, 6.54. Found: N, 6.32.

1-2-Nitro-4-chloro-6-carboxy-2'-methoxybiphenyl.—The active acid was obtained from the salt in the same way as the corresponding bromo acid from its salt; light-yellow powder.

7-Nitro-5-methylisatoic Anhydride.—The procedure of Panaotovic⁴ was used for preparing 5-methylisatoic anhydride but more explicit directions than his are given for the preparation of the nitro derivative.

To 100 cc. of colorless nitric acid cooled to 0°, was added slowly 20 g. of 5-methylisatoic anhydride, keeping the temperature below 10°. The resulting solution was allowed to stand for four hours in the ice-bath and for fifteen hours at room temperature. After addition to ice and water, light-yellow crystals separated; yield 12.2 g. The product on crystallization from ethanol melted at 177° (Panaotovic reports 175°). It is absolutely necessary to use colorless nitric acid to obtain good results.

2-Amino-3-nitro-5-methylbenzoic Acid.⁵—A mixture of 28 g. of 7-nitro-5-methylisatoic anhydride, 20 cc. of concentrated hydrochloric acid and 100 cc. of water was warmed with stirring in a 1-liter beaker. After foaming ceased, the reaction mixture was boiled for ten minutes, cooled, neutralized with concentrated aqueous ammonia and then made slightly acid with acetic acid. Upon cooling, the product separated. Purified from dilute alcohol it formed white crystals, m. p. 256–257° (with decomposition); yield, quantitative.

Anal. Calcd. for $C_8H_8N_2O_4$: N, 14.28. Found: N, 14.34.

Proof of Position of the Nitro Group in 7-Nitro-5-methylisatoic Anhydride.—The replacement of the amino group in 2-amino-3-nitro-5-methylbenzoic acid by hydrogen resulted in 3-nitro-5-methylbenzoic acid, thus proving the nitro group in the isatoic anhydride to be in the 7-position.

A mixture of 11.5 cc. of 95% of ethanol, 2.9 cc. of concentrated sulfuric acid and 1 g. of 2-amino-3-nitrobenzoic acid was stirred and cooled in an ice-bath. A solution of 0.7 g. of sodium nitrite in 5 cc. of water was added over a period of twenty minutes. After complete addition, stirring was continued for twenty minutes and 0.5 g. of copper-bronze introduced. Gas was evolved in the cold. The solution was allowed to warm to room temperature and then refluxed for ten minutes. The hot solution was filtered and the alcohol evaporated. A yellow product separated which was purified by several crystallizations from water, m. p. 175.5–176.5°.

(4) Panaotovic, *J. prakt. Chem.*, [2] **33**, 58 (1886).

(5) This compound and its derivatives described below were first prepared by Dr. W. E. Hanford (Ph.D. thesis, University of Illinois, 1936).

Anal. Calcd. for $C_8H_7O_4N$: N, 7.84. Found: N, 7.96.

The recorded melting point of 3-nitro-5-methylbenzoic acid is 167°⁶ and 174°.⁷

2-Iodo-3-nitro-5-methylbenzoic Acid.—A mixture of 12.6 g. of 2-amino-3-nitro-5-methylbenzoic acid and 7.1 g. of potassium metabisulfite was ground together to a very fine powder in a mortar. This powder was added slowly over a period of forty minutes to 23 cc. of fuming nitric acid (sp. gr. 1.5) which had been cooled to 0°. The temperature must be maintained below 10° at all times. The solution was poured into 200 g. of ice and an ice-cold aqueous solution of 19 g. of potassium iodide and 9.5 g. of iodine was added. After standing overnight at room temperature and then heating on a steam-bath for thirty minutes, the free iodine was removed with a little sodium bisulfite. The light-yellow solid was purified by crystallization from dilute alcohol, m. p. 207–209°, yield 15.6 g. Traces of the hydroxy compound may have been present in this product.

Anal. Calcd. for $C_8H_5NO_4I$: N, 4.56. Found: N, 4.80.

Methyl 2-Iodo-3-nitro-5-methylbenzoate.—A solution of 12 g. of 2-iodo-3-nitro-5-methylbenzoic acid in 100 cc. of absolute methanol was saturated with hydrogen chloride. After refluxing overnight, cooling and diluting, an oil separated which after removal solidified and was purified by crystallization from methanol and water: light-yellow needles; m. p. 43–44°; yield 10 g.

Anal. Calcd. for $C_9H_9O_4NI$: N, 4.36. Found: N, 4.49.

dl-2-Nitro-4-methyl-6-carboxy-2'-methoxybiphenyl.—To a mixture of 10 g. (0.031 mole) of methyl 2-iodo-3-nitro-5-methylbenzoate, 60 g. (0.256 mole) of *o*-iodoanisole and 50 cc. of nitrobenzene, maintained at its boiling point (about 215°) was added 50 g. of activated copper-bronze over a period of forty-five minutes and then the reaction mixture was heated for one and one-half hours longer. When cool, the mixture was extracted with several 100-cc. portions of boiling benzene. The benzene solution was evaporated to dryness and the residue was dissolved in 200 cc. of ethanol, 200 cc. of 10% aqueous potassium carbonate was added and the mixture refluxed for five hours. Upon acidification, solid acids precipitated. These were dried, dissolved in benzene and boiled with norite. After filtration, petroleum ether (b. p. 35–65°) was added to turbidity. Tan-colored material separated which was purified by crystallization from glacial acetic acid, m. p. 179°, yield 2 g.

Anal. Calcd. for $C_{16}H_{13}O_5N$: N, 4.88. Found: N, 5.13.

Strychnine Salt of 1-2-Nitro-4-methyl-6-carboxy-2'-methoxybiphenyl.—This salt was prepared from equivalent amounts of acid and base in absolute alcohol according to the directions given for the bromo analog. The salt melted at 143° with decomposition.

Anal. Calcd. for $C_{38}H_{35}N_3O_7$: N, 6.76. Found: N, 6.51.

1-2-Nitro-4-methyl-6-carboxy-2'-methoxybiphenyl.—The salt was decomposed as described for the other salts. Light yellowish powder, m. p. 175–178°.

(6) Thol, *Ber.*, **18**, 360 (1885).

(7) Müller, *ibid.*, **42**, 432 (1909).

2-Bromo-3,5-dinitrobenzoic Acid.⁸—A solution of 30 g. of 2-bromo-3-nitrobenzoic acid in 125 cc. of concentrated sulfuric acid was prepared by warming in a beaker on a steam-bath. To this, while still warm, was added slowly with continuous stirring, a mixture of 20 cc. of fuming nitric acid, and 20 cc. of concentrated sulfuric acid. The solution became pasty after a few minutes and was then warmed for fifteen minutes on a steam-bath. After cooling, it was poured onto ice. The product was filtered, dissolved in dilute aqueous sodium hydroxide, reprecipitated with dilute hydrochloric acid and then purified by recrystallization from 50% ethanol. The product was nearly white; m. p. 215–216°; yield 33 g. (93% theory). Meisenheimer⁹ gives a m. p. of 213°.

Methyl 2-Bromo-3,5-dinitrobenzoate.—A solution of 33 g. of 2-bromo-3,5-dinitrobenzoic acid in 200 cc. of absolute methanol containing 3% by weight of dry hydrogen chloride was refluxed for four hours, cooled and poured into ice and aqueous sodium hydroxide. The product was purified by recrystallization from ethanol, m. p. 106–108°.

Anal. Calcd. for $C_8H_3O_6N_2Br$: N, 9.18; Br, 26.20. Found: N, 9.16; Br, 26.15.

dl-2,4-Dinitro-6-carboxy-2'-methoxybiphenyl.—The procedure for condensing methyl 2-iodo-3-nitro-5-bromobenzoate and *o*-iodoanisole with copper was used with 25 g. of methyl 2-bromo-3,5-dinitrobenzoate, 50 g. of *o*-iodoanisole and 75 g. of copper. In the hydrolysis sodium carbonate in dilute alcohol was used in place of sodium hydroxide. The yield of 2,4-dinitro-6-carboxy-2'-methoxybiphenyl was 6 g. (23%). It was purified from 70% ethanol; yellow crystals, m. p. 185°.

Anal. Calcd. for $C_{14}H_{10}O_7N_2$: C, 52.83; H, 3.17; N, 8.81; neut. equiv., 318. Found: C, 53.01; H, 3.34; N, 8.92; neut. equiv., 320.

(8) This compound and its derivatives described below were prepared first by Dr. D. B. Holmes (Ph.D. thesis, University of Illinois, 1934).

(9) Meisenheimer, *Ann.*, **446**, 205 (1925).

Strychnine Salt of l-2,4-Dinitro-6-carboxy-2'-methoxybiphenyl.—To a hot solution of 2.0 g. of the acid in 75 cc. of 95% ethanol and 37.5 cc. of water was added 2.1 g. of strychnine. The clear solution that resulted was cooled overnight at 5° and 3.95 g. of yellow crystals separated, m. p. 136° (dec.). Recrystallization from 95% ethanol did not change the melting point.

Anal. Calcd. for $C_{38}H_{32}O_9N_4$: C, 64.37; H, 4.95; N, 8.58. Found: C, 63.92; H, 5.19; N, 8.51.

If the strychnine salt was prepared in absolute ethanol by the method used for the previous salts, a product, m. p. 206–208°, with decomposition, was obtained which showed no mutarotation.

Rotation.—0.1054 g. made up to 10 cc. in chloroform at 28° gave $\alpha_D -0.30^\circ$; $l = 1$; unchanged after fifty-one minutes, $[\alpha]^{28}_D -28.4^\circ$.

Anal. Calcd. for $C_{14}H_{10}O_7N_2$: N, 8.5. Found: N, 8.5.

l-2,4-Dinitro-6-carboxy-2'-methoxybiphenyl.—The active acid was obtained by hydrolysis as previously described for other salts; yellowish crystals; m. p. 182–185°.

Summary

Four derivatives of 2-nitro-6-carboxy-2'-methoxybiphenyl have been prepared, namely, those with a NO_2 , Br, Cl, and CH_3 group in the 4-position. The rates of mutarotation of the salts and the rates of racemization of the active acids were determined.

The chlorinated acid racemizes a little more slowly, the brominated at about the same rate, and the methyl and nitro compounds more rapidly than 2-nitro-6-carboxy-2'-methoxybiphenyl itself. The influence of a substituent in the 4-position is much less than in the 3'-, 4'- or 5'-position.

URBANA, ILLINOIS

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Derivatives of Coumaran. II. Condensation of Aliphatic Aldehydes and Ketones with 6-Methoxycoumaran-3-one. Reduction of 2-Isopropylidene-6-methoxycoumaran-3-one

BY R. L. SHRINER AND JOHN ANDERSON

Since coumaran-3-ones condense readily with aromatic aldehydes to give 2-benzalcoumaran-3-ones,¹ it seemed reasonable that similar condensations involving aliphatic aldehydes and ketones should take place providing favorable experimental conditions could be found. In the present work a study of the condensation of simple aldehydes and ketones with 6-methoxycoumaran-3-one was made.

It has been found that aliphatic ketones and

aldehydes do react with the active methylene group in coumaran-3-ones in a manner analogous to the well-known Knoevenagel condensation,² although a previous report on this reaction had been unfavorable.³ In glacial acetic acid solution, with hydrochloric acid as the condensing agent, 6-methoxycoumaran-3-one (I) combined with ketones to give 2,2'-bis-(6-methoxycoumaran-3-one)-dialkylmethanes (II). Three ke-

(2) Knoevenagel, *Ber.*, **31**, 2585 (1898).

(3) Feist and Siebenlist, *Arch. Pharm.*, **265**, 196 (1927).

(1) Von Auwers and Pohl, *Ann.*, **405**, 243 (1914).