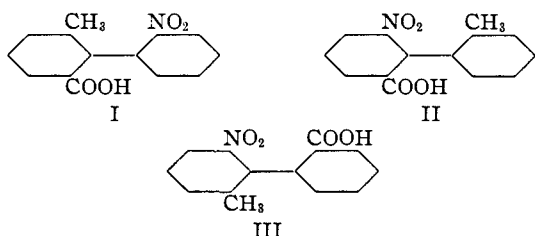


[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Stereochemistry of Biphenyls. XLVIII. A Comparison of the Racemization Rates of Three Isomeric 2,2',6-Nitro-, Carboxy-, Methyl-biphenyls¹BY ROGER ADAMS AND J. B. HALE²

A previous study of various easily racemized biphenyls³ has demonstrated that various substituents in positions other than the 2,2',6,6' materially affect the rate of racemization of the active molecules. A study now has been made of the three possible isomeric 2,2',6-trisubstituted biphenyls (I, II and III) in which the substituents are methyl, nitro and carboxyl groups.



If, in these three compounds, the two phenyl groups are assumed to be rigidly coaxial and the distance between the rings essentially constant, it might be anticipated that the relative rates of racemization would be dependent primarily upon the blocking effect of the two smaller interfering groups present in the 2,2'-positions. Previous study of various substituted biphenyls as well as X-ray data indicate that semiquantitatively the size of the groups is in the following order: nitro > methyl > carboxyl. Accepting these facts, compounds II and III should be of essentially the same stability (CH₃, COOH collision) and both of these should be less stable than compound I (COOH, NO₂ collision).

The actual experimental results failed to conform to this postulation. It was found that compound II was the least stable, compound I more stable, and compound III the most stable. The half-life periods of these three compounds (Table I) were sufficiently different to eliminate the possibility of experimental error.

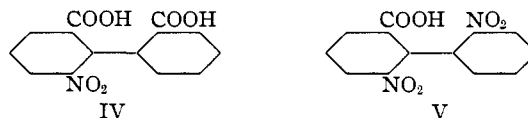
The solvent used in the racemization experiments affects the rate. In Table I acetic acid and *n*-butanol, two solvents which boil within a degree of each other, are compared.

(1) For previous paper see Adams and Finger, *THIS JOURNAL*, **61**, 2182 (1939).

(2) An abstract of a thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in chemistry.

(3) Kuhn and Albrecht, *Ann.*, **455**, 272; **458**, 221 (1927); Chien and Adams, *THIS JOURNAL*, **56**, 1787 (1934); Hanford and Adams, *ibid.*, **57**, 1592 (1935); Yuan and Adams, *ibid.*, **54**, 2996, 4434 (1932).

A comparison of two other 2,2',6-trisubstituted biphenyls also has been made, namely, 6-nitrodiphenic acid (IV) and 2,2'-dinitro-6-carboxybiphenyl (V). As deduced merely from the size of groups, compounds IV and V (COOH, NO₂ collision) should have essentially the same stability. Experimental results indicated that compound IV was more stable in *n*-butanol, less stable in acetic acid, and far less stable in aqueous sodium hydroxide than compound V (Table I).



The conclusion to be drawn from these data is that the relative positions of the different groups to each other is a factor in the rate of racemization of the molecules.

Experimental

2-Methyl-6-nitro-2'-carboxybiphenyl.—The data used in the tables on this compound were those previously described by Stoughton and Adams.⁴

2-Carboxy-6-nitro-2'-methylbiphenyl.—A mixture of 20 g. of methyl 3-nitro-2-bromobenzoate and 34 g. of *o*-iodotoluene in a three-necked flask with reflux condenser and stirrer was heated in a metal bath at 225° (bath temp.). Over a period of one hour, 40 g. of copper powder was added with stirring. The bath temperature was then raised to 230° for thirty minutes. After cooling, the reaction mixture was extracted with three 100-cc. portions of hot ethanol. These filtered extracts were mixed with 400 cc. of 5% aqueous sodium hydroxide and refluxed for eight hours. The solution was then boiled for an additional two hours to remove a large proportion of the ethanol. Upon cooling, an oil separated which was chiefly the excess of *o*-iodotoluene. The aqueous solution was removed, treated with norit, filtered, and acidified with concentrated hydrochloric acid. An oil separated which soon solidified. This crude material was extracted with hot benzene in which the 2-nitro-6-carboxy-2'-methylbiphenyl was soluble, and the 6,6'-dinitrodiphenic acid practically insoluble. The benzene solution was extracted with dilute aqueous sodium hydroxide and the aqueous solution acidified with hydrochloric acid.

The product was purified by several recrystallizations from dilute ethanol: white crystals, m. p. 162–163°; yield, 3 g. (15%).

(4) The data given for compound III are those of Stoughton and Adams, *ibid.*, **52**, 5263 (1930), and were observed at a temperature of 20°.

TABLE I

Compound	Solvent	Sample in g. made up to cc.	l α_D^{25}	$[\alpha]^{25}_D$	Av. K	Half-life period, min.
I	C ₂ H ₅ OH	0.1 (15 cc.)	+1.01	+ 75.7
	CH ₃ COOH	.1 (20 cc.)	+0.49	+ 49.5	.00028	1075
	<i>n</i> -C ₄ H ₉ OH	.1 (20 cc.)	+ .73	+ 73	.00033	913
II	C ₂ H ₅ OH	.0464 (15 cc.)	+ .38	+ 61.5
	CH ₃ COOH	.1 (25 cc.)	- .52	- 65	.00168	179
	<i>n</i> -C ₄ H ₉ OH	.1 (25 cc.)	- .59	- 73.8	.0018	166
III ⁴	C ₂ H ₅ OH	.095 (25 cc.)	- .52	- 68.4
	CH ₃ COOH	.0840 (15 cc.)	- .97	- 86.6	.00015	2007
	<i>n</i> -C ₄ H ₉ OH	.0583 (15 cc.)	- .56	- 72.0	.00115	2510
IV	C ₂ H ₅ OH	.05 (15 cc.)	+ .26	+ 3.90
	CH ₃ COOH	.1 (20 cc.)	- .84	- 84	.0033	91, 90
	<i>n</i> -C ₄ H ₉ OH	.195 (20 cc.)	- .53	- 27.2	.0030	101, 107
	NaOH (0.1 N)	.05 (25 cc.)	+1.17	+293	.066	4.6
V	C ₂ H ₅ OH	.10 (15 cc.)	+2.69	+201.5	.00015	2000
	CH ₃ COOH	.07 (25 cc.)	+1.13	+202	.0024	125, 120
	<i>n</i> -C ₄ H ₉ OH	.07 (25 cc.)	+1.22	+218	.0033	91, 86
	NaOH (0.1 N)	.2 (25 cc.)	-1.49	- 93.0	.0033	91

Anal. Calcd. for C₁₄H₁₁O₄N: C, 65.4; H, 4.28; N, 5.45. Found: C, 65.38; H, 4.1; N, 5.41.

Resolution of 2-Methyl-6-nitro-2'-carboxybiphenyl.—To a boiling solution of 3.28 g. of 2-nitro-6-carboxy-2'-methylbiphenyl in 500 cc. of 60% ethanol was added 4.13 g. of quinine. After standing overnight 3.8 g. of crystals separated which were purified by crystallization three times from 200 cc. of hot 50% ethanol. The salt thus obtained gave a constant rotation and weighed 1.7 g. Before drying, the product had a melting point of 135–140° and after drying, 168–171°.

Rotation (dry *l* salt) 0.05 g. made up to 15 cc. in chloroform at 25°. $\alpha_D -0.89^\circ$; $l = 2$; $[\alpha]^{25}_D -133.5^\circ$.

Anal. Calcd. for C₁₅H₁₃O₆N₃: N, 7.22. Found: N, 7.53.

Rotation (solvated *l* salt) 0.05 g. made up to 15 cc. in chloroform at 25°. $\alpha_D -0.83^\circ$; $l = 2$; $[\alpha]^{25}_D -124.2^\circ$.

On cooling the original mother liquor from the less soluble salt, a small crop of crystals separated which were discarded. The alcohol solution was then allowed to evaporate until the more soluble salt separated. This was purified by three crystallizations from 100 cc. of hot 30% ethanol. The precaution was taken during the first two crystallizations to discard the first third of the salt which separated. The final product gave a constant rotation, m. p. 118–123° before drying and 128–131° after drying.

Anal. (dry *d*-salt) Calcd. for C₁₅H₁₃O₆N₃: N, 7.22. Found: N, 7.12.

Rotation (solvated *d*-salt) 0.10 g. made up to 15 cc. in chloroform at 25°. $\alpha_D -1.40^\circ$; $l = 2$; $[\alpha]^{25}_D -105^\circ$.

The solvation of these salts appeared not to be constant so that the rotations of the solvated salts are not significant.

***d*- and *l*-2-Nitro-6-carboxy-2'-methylbiphenyl.**—A suspension of 2 g. of the less soluble salt in 10 cc. of water was cooled in an ice-bath and treated with 10 cc. of cold dilute hydrochloric acid. After stirring for a few minutes the mixture was extracted with ether and the ether extracts washed several times with dilute hydrochloric acid

and then with water. The ether solution was then treated with 10 cc. of dilute sodium hydroxide and the aqueous alkaline extract acidified in the cold with hydrochloric acid. The *l*-form of the product separated and was recrystallized from dilute ethanol: white crystals, m. p. 153–155°.

Rotation. (*l*-acid) 0.10 g. made up to 25 cc. in ethanol at 25°. $\alpha_D -0.52$; $l = 2$; $[\alpha]^{25}_D -65^\circ$.

The *d*-acid was obtained in a similar manner and had a melting point of 153–156°.

Rotation. (*d*-acid) 0.0464 g. made up to 15 cc. in ethanol at 25°. $\alpha_D +0.38^\circ$; $l = 2$; $[\alpha]^{25}_D +61.5^\circ$.

2-Methyl-6-carboxy-2'-nitrobiphenyl.—*m*-Toluic acid was nitrated to 2-nitro-3-methylbenzoic acid according to the method of Findelee.^{5a} This was esterified^{5b} and then reduced by means of stannous chloride and hydrochloric acid⁶ to the amine. The amino group was replaced by iodine⁷ to give methyl 2-iodo-3-methylbenzoate.

A mixture of 24 g. of methyl 2-iodo-3-methylbenzoate and 60 g. of *o*-iodonitrobenzene was heated in a metal bath with stirring at 230°. Copper-bronze powder (65 g.) was added at such a rate that the temperature of the reaction mixture never rose above 245°. The bath temperature was then raised to 250° and maintained at that temperature for fifteen minutes. After cooling, the reaction mixture was extracted with 300 cc. of hot ethanol, filtered, and refluxed for eight hours with 400 cc. of 5% aqueous sodium hydroxide. The reaction mixture was then boiled for two hours and the ethanol allowed to distill. Upon cooling, a brown semi-solid mass separated and was filtered. The solution was treated with norit, filtered, and acidified with dilute hydrochloric acid. The yellow oil which separated soon solidified. The product thus obtained was dissolved in 200 cc. of hot benzene, filtered, and the desired acid extracted with aqueous sodium hydroxide. After acidification the crude 2-methyl-6-car-

(5) (a) Findelee, *Ber.*, **38**, 3553 (1905); (b) Jurgens, *ibid.*, **40**, 4409 (1907).

(6) Müller, *ibid.*, **42**, 423 (1909).

(7) Mayer, *ibid.*, **44**, 2298 (1911).

boxy-2'-nitrobiphenyl was filtered and crystallized several times from 80% ethanol: yellowish white crystals, m. p. 157°; yield, 12 g. (50%).

Anal. Calcd. for $C_{14}H_{11}O_4N$: N, 5.45; neut. equiv., 257. Found: N, 5.55; neut. equiv., 260.

Resolution of 2-Methyl-6-carboxy-2'-nitrobiphenyl.—A solution of 3 g. of 2-methyl-6-carboxy-2'-nitrobiphenyl in 20 cc. of boiling methanol was mixed with a boiling solution of 5.43 g. of anhydrous brucine in 50 cc. of methanol. After standing for three hours, 5 g. of salt deposited. After three recrystallizations from 50 cc. of methanol a constant rotation was obtained: white crystals, m. p. 165–167°.

Rotation. 0.05 g. made up to 15 cc. in chloroform at 25°. $\alpha_D + 0.32$; $l = 2$; $[\alpha]^{25}_D + 48^\circ$.

Anal. Calcd. for $C_{27}H_{27}N_3O_6$: N, 6.97. Found: N, 7.02.

Upon cooling the mother liquor, 2.4 g. of salt separated. This was dissolved in 40 cc. of methanol and cooled slowly. The first portion of crystals was discarded and finally 1.6 g. of salt was collected. Recrystallization of this from methanol did not change the melting point or the rotation: white crystals, m. p. 153–160°.

Rotation. 0.05 g. made up to 15 cc. in chloroform at 25°. $\alpha_D - 0.34$; $l = 2$; $[\alpha]^{25}_D - 51^\circ$.

Anal. Calcd. for $C_{27}H_{27}N_3O_6$: N, 6.97. Found: N, 6.86.

***d*- and *l*-2-Methyl-6-carboxy-2'-nitrobiphenyl.**—The active acids were formed as previously described for the active 2-carboxy-6-nitro-2'-nitrobiphenyls. The active acids were purified by recrystallization from dilute ethanol, *d*-acid m. p. 179–181°, *l*-acid m. p. 175–179°.

Rotation. (*d*-acid) 0.05 g. made up to 15 cc. in chloroform, $\alpha_D + 0.49$; $l = 2$; $[\alpha]^{25}_D + 73.5^\circ$. (*l*-acid) 0.0485 g. made up to 15 cc. in chloroform. $\alpha_D - 0.47$; $l = 2$; $[\alpha]^{25}_D - 72.6^\circ$.

6-Nitrodiphenic Acid.—This was prepared and resolved according to the method of Bell and Robinson⁸ using morphine.

Rotation. (less soluble salt) 0.1 g. made up to 15 cc. in pyridine at 25°. $\alpha_D - 1.04$; $l = 2$; $[\alpha]^{25}_D - 78^\circ$.

The active acids were liberated from the salt in the way previously described and were purified by dissolving in dilute aqueous ammonia and precipitating with dilute hydrochloric acid.

Rotation. *d*-acid (from less soluble salt) 0.05 g. made up to 15 cc. in ethanol at 25°. $\alpha_D + 0.26$; $l = 2$; $[\alpha]^{25}_D + 39.0^\circ$; $\alpha_{5461} + 0.44$; $l = 2$; $[\alpha]^{20}_{5461} + 66.0^\circ$. *l*-acid (from soluble salt) 0.05 g. made up to 15 cc. in ethanol at 25°. $\alpha_D - 0.25$; $l = 2$; $[\alpha]^{25}_D - 37.5^\circ$.

2,2'-Dinitro-6-carboxybiphenyl.—A mixture of 20 g. of methyl-3-nitro-2-bromobenzoate and 34 g. of *o*-iodonitrobenzene was heated in a metal bath at 220°. Copper-bronze powder (40 g.) was then added at such a rate that the temperature of the reaction mixture did not exceed 225°. The bath temperature was raised to 225° for a period of thirty minutes. After cooling the reaction mixture was extracted with three 100-cc. portions of hot ethanol, the filtered extracts added to 400 cc. of 5% aqueous

sodium hydroxide and the mixture refluxed for eight hours. The reaction mixture was then boiled for about two hours to remove most of the alcohol. On cooling a dark solid mass separated and was filtered. The solution was treated with norit and acidified with concentrated hydrochloric acid to congo red. A crude oil separated which soon solidified. This was extracted with hot benzene in which the by-product of dinitrobiphenyl is practically insoluble. The benzene solution was then extracted with dilute aqueous sodium hydroxide and upon acidification crude 2,2'-dinitro-6-carboxybiphenyl separated. It was purified by crystallization from dilute acetic acid: m. p. 164°; yield, 6 g. (30%).

Anal. Calcd. for $C_{13}H_9O_6N_2$: C, 54.1; H, 2.78; N, 9.72; neut. equiv., 288. Found: C, 53.97; H, 2.89; N, 10.0; neut. equiv., 283.

Resolution of 2,2'-Dinitro-6-carboxybiphenyl.—To a warm solution of 4 g. of 2,2'-dinitro-6-carboxybiphenyl in 800 cc. of 75% ethanol was added with stirring 4.5 g. of quinine. After standing overnight approximately half of the salt separated. It was purified by crystallization twice from 400 cc. of 50% ethanol. The salt then had a constant rotation, m. p. 156–191°. After drying the melting point was 195–197°.

Rotation. (dry *d*-salt) 0.05 g. made up to 15 cc. in chloroform. $\alpha_D + 0.35$; $l = 2$; $[\alpha]^{25}_D + 52.5^\circ$.

Evaporation of the mother liquor from the less soluble salt resulted in the separation of an oil which after standing for a few days gradually solidified. The solid was thoroughly pulverized and allowed to stand in 200 cc. of ethanol with occasional stirring. The solution was filtered and upon evaporation of the solvent the salt obtained solidified rapidly: m. p. 121–125°; yield, 2.5 g.

Rotation. (more soluble salt) 0.1 g. made up to 15 cc. in chloroform at 25°. $\alpha_D - 3.16$; $l = 2$; $[\alpha]^{25}_D - 238^\circ$.

Anal. Calcd. for $C_{22}H_{12}O_6N_4$: N, 9.15. Found: N, 8.96.

***d*- and *l*-2,2'-Dinitro-6-carboxybiphenyl.**—The active acids were liberated from the salts in the manner previously described. The active acids were obtained as oils which solidified upon standing in a vacuum desiccator overnight. They were recrystallized from dilute acetic acid; m. p. of *d*-acid from the less soluble salt was 135–137°; the *l*-acid 127–130°.

Rotation. (*d*-acid) 0.10 g. made up to 15 cc. in ethanol at 25°. $\alpha_D + 2.69$; $l = 2$; $[\alpha]^{25}_D + 201.5^\circ$. (*l*-acid) 0.05 g. made up to 15 cc. in ethanol at 25°. $\alpha_D - 1.33$; $l = 2$; $[\alpha]^{25}_D - 199.5^\circ$.

Summary

The preparation of 2-methyl-6-carboxy-2'-nitrobiphenyl, 2-nitro-6-carboxy-2'-methylbiphenyl, and 2-methyl-6-nitro-2'-carboxybiphenyl is described. They were resolved and the rates of racemization compared. The half-life periods do not correspond to what might be anticipated merely from the relative size of the groups as deduced from X-ray data or from the rates of racemization of previously studied biphenyls. The

(8) Bell and Robinson, *J. Chem. Soc.*, 1695 (1927).

relative positions of the groups have a marked effect on the stability of the molecule. The rate of racemization is modified by the solvent used.

A comparison of the rates of racemization of

optically active 6-nitrodiphenic acid with optically active 2,2'-dinitro-6-carboxybiphenyl also has been made. The latter is the more stable.

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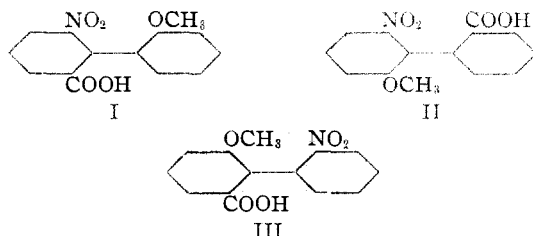
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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Stereochemistry of Biphenyls. XLIX. Comparison of the Racemization Rates of the 2,2',6-Nitro-, Carboxy- and Methoxy-biphenyls¹

BY ROGER ADAMS AND G. C. FINGER²

In the previous paper the relative stabilities of biphenyls containing nitro, methyl and carboxyl in the three possible combinations in the 2,2',6-positions were described. Another similar series has been prepared now in which the nitro, methoxy and carboxyl groups occupy the three possible positions in biphenyl.



Based upon the expectations from the relative size of the groups, compounds I and II (CH₃O, COOH collision) should have essentially the same stability and compound III should be more stable.

mal, and the yields of the acid were poor. It is likely, therefore, that the half-life period is more in error than usual.

The variation in stability of these molecules is concordant with the results described in the previous paper¹ in which the methyl group was present in place of the methoxy.

Experimental

2-Methoxy-6-carboxy-2'-nitrobiphenyl.—The 1-methoxy-2-iodo-3-carbomethoxybenzene was prepared by the method of Stanley, McMahon and Adams.³

In a large Pyrex test-tube a mixture of 5 g. of 1-methoxy-2-iodo-3-carbomethoxybenzene, 4.3 g. of *o*-iodonitrobenzene and 10 g. of copper-bronze powder was heated under reflux in an oil-bath for two hours at 200°. The reaction mixture was extracted with acetone, the acetone solution refluxed with norit, and the solvent concentrated to small volume.

The crude material, which separated, was refluxed for eighteen hours with a mixture of 2 g. of sodium hydroxide

TABLE I
RACEMIZATION OF ACTIVE ACIDS

Compound	Wt. in g. made up to 10 cc. in abs. ethanol	Minutes before initial reading	Initial α_D^{27} ($t = 1$)	Final α_D	Calcd. for zero time α_D	Final α_D	Average K^a	Average dev. K	Half-life period, min.
I	0.0557	7	+0.21	0.0	+0.33	+59.4	0.02936	±0.00081	10.2 ^c
II	.0430	31	-.50	.0	-0.55	-127.9	.001364	±.000048	219 ^c
III	.0473	120	-.76	.0	-1.01	-213.3	.00111	±.00006	271

^a The K value was calculated by the formula $K = \frac{1}{t} \log \frac{\alpha_0 - \alpha_f}{\alpha_t - \alpha_f}$. ^b Stoughton and Adams first prepared this active acid [THIS JOURNAL, 54, 4406 (1932)] and reported 9.4 minutes; Li and Adams found 12.2 minutes [Li and Adams, *ibid.* 57, 1565 (1935)]. ^c *l*-Acid from hydrochloric acid hydrolysis gave 288 minutes.

Experimentally compound I proved to be very unstable while compounds II and III were much more stable. The value of the half-life period obtained for compound II is possibly unreliable due to the fact that the formation of the salt and the decomposition to the active acid was abnor-

mal and 8 g. of sodium carbonate in 350 cc. of water and 50 cc. of ethanol. The saponification mixture was filtered from the alkali-insoluble 2,2'-dinitrobiphenyl. The alkaline filtrate was diluted to 1500 cc. and acidified with dilute sulfuric acid to precipitate the product. The crude material which amounted to about 5 g. was crystallized from 80% ethanol, from which it formed white needles, m. p. 234–236°.

Anal. Calcd. for C₁₄H₁₁O₅: C, 61.53; H, 4.03; N,

(1) For previous paper see Adams and Hale, THIS JOURNAL, 61, 2825 (1939).

(2) An abstract of a thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in chemistry.

(3) Stanley, McMahon and Adams, THIS JOURNAL, 55, 708 (1933).