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

Stereochemistry of Biphenyls. L. Comparison of the Interference of a Methoxyl and an Hydroxyl Group[1]

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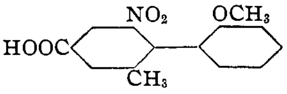
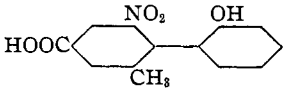
The groups on the 2,2′,6,6′ atoms attached to the rings in biphenyls exhibiting restricted rotation have a definite steric effect. Thus, a comparison of the methoxy, ethoxy and propoxy derivatives of 2-nitro-6-carboxy-2′-alkoxybiphenyl indicated a marked difference in the racemization rates. The order of effectiveness in restricting the rotation was as follows: $CH_3O < C_2H_5O < C_3H_7O$.[3] Similarly, the substitution of the carboxyl groups in 2,2′-dicarboxy-6,6′-dimethoxybiphenyl by $COOC_2H_5$, $CONH_2$, $CONHCH_3$, $CON(CH_3)_2$, etc., resulted in all cases in molecules which racemized more slowly than the original molecule.[4]

A comparison has now been made of the optical stability of two molecules differing only by an hydroxyl and a methoxyl in the 2 position. The molecules used are shown in formulas I and II.



I



II

Compound I was resolved and the active acid racemized in glacial acetic acid at 25° with a half-life of two hundred and seven minutes. On the other hand, the hydroxyl derivative (II) could not be obtained in optically active form. In these molecules it may be concluded, therefore, that the methoxyl is larger than the hydroxyl group.

On the basis of a comparison of the racemization rates of various restricted biphenyls, it was deduced that the internuclear distance of a benzene carbon and a methoxyl was about 1.45 Å. Internuclear distances calculated from Pauling's tables of atomic radii, utilizing estimates of the oxygen bond angle in water and in ethers, were 1.67 Å. for methoxyl and 1.45 Å. for hydroxyl groups.[5] The difference in their values, 0.22 Å., when taken into account in the empirical calculation of the restriction[6] in the two compounds studied, indicates the probable resolution of I and non-resolution of II. This agrees with the experimental facts.

The brucine salt of compound I exhibited an unusual phenomenon. When prepared in ethanol solution and when the solvent was evaporated gradually, several crops of crystals were taken. All gave essentially the same rotation. This was interpreted as the isolation of a single salt, the less soluble one, due to mutarotation. However, no fraction of the salt exhibited mutarotation, yet each on decomposition yielded an active acid of the same rotation. The explanation of this is difficult. If the salt which crystallizes from the ethanol is one of constant composition made up of the *ld* and *ll* salts, with the latter in larger amount, the decomposition product would have the *l*-acid in predominance. The fact that under various conditions for decomposition of the salt, the active product had the same rotation makes this explanation seem unlikely. The salt could be made to crystallize only from various alcohols. It was observed that it was solvated under these conditions and that the alcohol was very difficult to remove from the crystals. It seems probable, therefore, that the *ll*-salt forms in solution, then solvates and is thus stabilized so that it no longer reverts to the *ld* modification.

Compounds I and II were prepared by the following series of reactions.

The orientation of the groups in compound V was established by hydrolysis to the known 3-methyl-4-hydroxy-5-nitrobenzoic acid.

Experimental

3-Methyl-4-bromobenzonitrile.—This product was prepared according to the procedure described for synthesizing tolunitrile from *p*-toluidine.[7] From 100 g. of 3-methyl-4-bromoaniline[8] was obtained 52.3 g. (48%) of 3-methyl-4-bromobenzonitrile, b. p. 107–110° (3 mm.); m. p. 54–55° (cor.).

Anal. Calcd. for C_8H_6NBr: N, 7.14. Found: N, 7.53.

3-Methyl-4-bromo-5-nitrobenzonitrile.—To a mixture of 39.2 g. of 3-methyl-4-bromobenzonitrile and 125 cc. of

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[1] For previous paper in this series see Adams and Finger, THIS JOURNAL, **61**, 2828 (1939).

[2] An abstract of a thesis submitted in partial fulfillment of the degree of Doctor of Philosophy in Chemistry.

[3] Li and Adams, THIS JOURNAL, **57**, 1565 (1935).

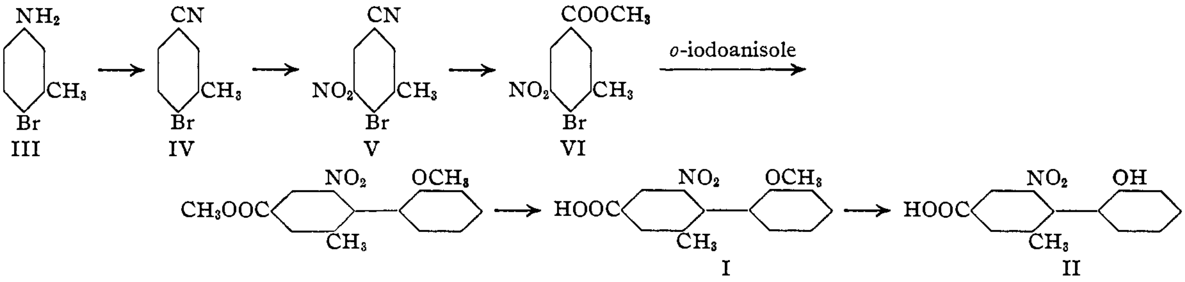
[4] Hsing and Adams, *ibid.*, **58**, 587 (1936).

[5] Pauling, *Proc. Nat. Acad. Sci. U. S.*, **20**, 336 (1934); Pauling and Huggins, *Z. Krist.*, **87**, 205 (1934); Pauling, THIS JOURNAL, **53**, 1367 (1931); Sutton and Brockway, *ibid.*, **57**, 474 (1935).

[6] Adams and Stanley, *ibid.*, **52**, 1200 (1930).

[7] "Organic Syntheses," Coll. Vol. I, 1932, p. 500.

[8] Huston and Hutchinson, THIS JOURNAL, **54**, 1504 (1932).



concentrated sulfuric acid cooled in an ice-bath to 10°, was added dropwise over a period of one hour, with vigorous stirring, a mixture of 150 cc. of concentrated sulfuric acid and 150 cc. of concentrated nitric acid. The temperature of the reaction mixture was kept at all times below 15°. After the addition, stirring was continued for three hours and then the reaction mixture was poured into water. A gummy precipitate formed which slowly crystallized. It was purified by recrystallization from ethanol: yellow needles, m. p. 100–103° (cor.); yield 34 g. (70%).

Anal. Calcd. for $C_8H_5O_2NBr$: N, 11.62. Found: N, 11.67.

3-Methyl-4-hydroxy-5-nitrobenzonitrile.—A mixture of 1 g. of 3-methyl-4-bromo-5-nitrobenzonitrile, 1 g. of freshly fused sodium acetate and 2 g. of acetamide was fused at 200° according to the method of Borsche.[9] Extraction of the resulting mass with hot water followed by acidification with hydrochloric acid gave a brown precipitate. It was purified by recrystallization from ethanol: yellow prisms, m. p. 125–126° (cor.); yield 0.085 g. (11.5%).

Anal. Calcd. for $C_8H_6O_3N_2$: N, 15.73. Found: N, 15.44.

3-Methyl-4-hydroxy-5-nitrobenzoic Acid.—Anhydrous hydrogen chloride was passed into a solution of 0.04 g. of 3-methyl-4-hydroxy-5-nitrobenzonitrile in 10 cc. of anhydrous methanol while it refluxed for two hours. After cooling and pouring into water, methyl 3-methyl-4-hydroxy-5-nitrobenzoate separated as a yellow powder and was purified by recrystallization from methanol; yellow crystals, m. p. 102–103°. Pfister[10] reports m. p. 103°.

The ester just prepared was refluxed with 20% aqueous sodium hydroxide for thirty minutes. On acidification and cooling, yellow needles formed, m. p. 238–240° (cor.). Pfister reports 240°.[10]

3-Methyl-4-bromo-5-nitrobenzoic Acid.—A mixture of 34 g. of 3-methyl-4-bromo-5-nitrobenzonitrile, 105 cc. of concentrated sulfuric acid and 105 cc. of water was refluxed for thirty minutes. The product separated, during refluxing, as brownish needles. After cooling, the product was filtered, yield 31.5 g. (88.5%). For purification it was recrystallized from ethanol, treated with Norit in dilute aqueous sodium hydroxide, followed by three crystallizations from dilute ethanol; white needles, m. p. 212–213° (cor.).

Fittig, Ahrends and Mattheides[11] reported m. p. 175–176° when prepared by another method.

Anal. Calcd. for $C_8H_6O_4NBr$: C, 36.93; H, 2.31. Found: C, 36.49; H, 2.28.

Methyl 3-Methyl-4-bromo-5-nitrobenzoate.—A mixture of 30 g. of 3-methyl-4-bromo-5-nitrobenzoic acid and 100 cc. of thionyl chloride was refluxed until a clear solution resulted and the excess thionyl chloride was distilled. To this residue was added cautiously 50 cc. of anhydrous methanol and then the mixture was refluxed for two hours. Upon cooling, the ester separated. It was purified by crystallization from methanol: white needles, m. p. 81–81.5°; yield 25.5 g. (81%).

Anal. Calcd. for $C_9H_8O_4NBr$: C, 39.42; H, 2.92. Found: C, 40.00; H, 3.02.

2-Methyl-4-carboxy-6-nitro-2′-methoxybiphenyl.—A mixture of 13.7 g. of methyl 3-methyl-4-bromo-5-nitrobenzoate and 26 g. of *o*-iodoanisole[3] was heated to 240° in a Wood's metal bath. With constant stirring, 40 g. of activated copper bronze[12] was added in small portions over a period of forty-five minutes maintaining the temperature at 240–250°. The temperature was then raised to 270° for fifteen minutes. The cooled reaction mixture was broken up and extracted for eighteen hours with 200 cc. of ethanol in a Soxhlet extractor. The extract was evaporated to half its original volume, treated with 200 cc. of 10% aqueous sodium carbonate and refluxed for five hours. It was now decanted through a moist filter and acidified with dilute hydrochloric acid.

The black tarry product which gradually solidified was dissolved in 10% aqueous sodium carbonate and treated with Norit. After acidification, filtration and drying, the material was extracted with 200 cc. of boiling benzene in 40-cc. portions. The benzene extract was evaporated to small volume and cooled. The precipitate used directly for subsequent reactions was further purified from ethanol. It was obtained as pale yellowish crystals, m. p. 227–229° (cor.), yield 4.0 g. (28%).

Anal. Calcd. for $C_{15}H_{13}O_5N$: C, 62.72; H, 4.53. Found: C, 63.09; H, 4.24.

2-Methyl-4-carboxy-6-nitro-2′-hydroxybiphenyl.—A mixture of 60 cc. of 40% aqueous hydrobromic acid, 25 cc. of glacial acetic acid, 21 cc. of a saturated solution of hydrogen bromide in glacial acetic acid and 0.80 g. of 2-methyl-4-carboxy-6-nitro-2′-methoxybiphenyl was refluxed for two hours. The solvent was then evaporated to dryness *in vacuo*. The residue was dissolved in benzene, filtered, concentrated and allowed to crystallize slowly. The product was purified by recrystallization from benzene: pale yellowish prisms, m. p. 180–181° (cor.); yield 0.450 g. (60%).

Anal. Calcd. for $C_{14}H_{11}O_5N$: C, 61.54; H, 4.03. Found: C, 61.10; H, 4.14.

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[9] Borsche, *Ber.*, **50**, 1339 (1917).

[10] Pfister, THIS JOURNAL, **43**, 375 (1921).

[11] Fittig, Ahrends and Mattheides, *Ann.*, **147**, 328 (1868).

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

Resolution of 2-Methyl-4-carboxy-6-nitro-2′-methoxybiphenyl.—A mixture of 1.0 g. of *dl*-acid in 30 cc. of absolute ethanol and 1.372 g. of brucine in 30 cc. of absolute ethanol was evaporated to half its volume and allowed to stand in a refrigerator. After twelve hours 1.88 g. of yellow prisms separated, m. p. 145–147° (cor.). Obviously it contained ethanol of crystallization.

Anal. Calcd. for $C_{38}H_{39}O_9N_3 \cdot C_2H_5OH$: N, 5.78. Found: N, 5.77. *Rotation.* 0.1001 g. made up to 10 cc. with chloroform at 25° gave α_D −0.156; *l*, 2; $[\alpha]^{25}_D$ −7.8°.

The rotation did not change on recrystallization of the salt from ethanol.

A second crop obtained from the mother liquor of the original salt preparation weighed 0.3417 g. and gave the same melting point and rotation. Recrystallization of this salt gave no change in rotation.

No mutarotation at room temperature was observed for any of the salt fractions and only very minor differences occurred in the rotation of the salt fractions.

***l*-2-Methyl-4-carboxy-6-nitro-2′-methoxybiphenyl.**—The different samples of salt were decomposed at 0° with iced hydrochloric acid until free from brucine; white crystals, m. p. 227–228° (cor.). This acid racemized gradually in solution. Several duplicate experiments gave consistent results. A typical experiment follows. *Rotation.* 0.0768 g. of *l*-acid made up to 10 cc. with glacial acetic acid at 25° after 5 minutes gave α_D −0.114°; *l*, 2; $[\alpha]^{25}_D$ −7.43°: 44 min., −6.51°; 84 min., −5.87°; 129 min., −4.95°; 199 min., −4.04°; 309 min., −2.74°; 459 min., −1.82°. Calculated half-life, 215 min.; $[\alpha]^{25}_D$ (calcd. to 0 time) −7.55°. At the temperature of boiling glacial acetic acid the half-life approximated eleven minutes.

Anal. Calcd. for $C_{15}H_{13}O_5N$: C, 62.72; H, 4.53. Found: C, 63.03; H, 4.86.

Other Salts of 2-Methyl-4-carboxy-6-nitro-2′-methoxy biphenyl.—The salts other than that of brucine were not so easily crystallized. They were made in essentially the same way. None mutarotated.

Anal. (Strychnine salt.) Calcd. for $C_{36}H_{35}O_7N_3$: N, 6.66 Found: N, 6.73. *Rotation.* 0.1281 g. made up to 10 cc. with chloroform at 25° gave α_D −0.12°; *l*, 1; $[\alpha]^{25}_D$ −13.4°.

Anal. (Cinchonine salt.) Calcd. for $C_{34}H_{35}O_6N_3$: N, 7.23. Found: N, 7.54. *Rotation.* 0.0749 g. made up to 10 cc. with chloroform at 25° gave α_D +0.70°; *l*, 1; $[\alpha]^{25}_D$ 140.0°.

Decomposition of these salts gave an active acid of essentially the same rotation as that obtained from the brucine salt.

Attempted Resolution of 2-Methyl-4-carboxy-6-nitro-2′-hydroxybiphenyl.—The brucine salt was prepared in absolute ethanol and four fractions of salt were isolated. All had the same rotation and none mutarotated. The salt softened at 169° and melted at 205° (cor.).

Anal. Calcd. for $C_{37}H_{37}O_9N_3$: N, 6.30. Found: N, 6.55. *Rotation.* 0.0708 g. made up to 10 cc. with chloroform at 25° gave α_D −0.316°; *l*, 2; $[\alpha]^{25}_D$ −22.4°.

Decomposition of this salt with cold hydrochloric acid gave inactive 2-methyl-4-carboxy-6-nitro-2′-hydroxybiphenyl.

The strychnine salt, made in a similar manner, gave fractions all of which after one recrystallization had the same rotation; yellow plates, m. p. 223–227°.

Anal. Calcd. for $C_{35}H_{33}O_7N_3$: N, 6.80. Found: N, 6.51. *Rotation.* 0.0621 g. made up to 5 cc. with chloroform at 25° gave α_D −0.18; *l*, 2; $[\alpha]^{25}_D$ −14.2°.

Summary

The two compounds, 2-methyl-4-carboxy-6-nitro-2′-methoxybiphenyl and 2-methyl-4-carboxy-6-nitro-2′-hydroxybiphenyl, have been synthesized. The former was resolved and an active acid was obtained which racemized with a half-life of two hundred and seven minutes; the latter could not be resolved. Thus, it is concluded that the methoxyl is larger than the hydroxyl group.

The brucine salt of the methoxy compound was obtained in a single form only, but in spite of this fact it did not mutarotate. The postulation is made that this salt first forms then solvates and becomes stabilized so that it will not revert to its diastereoisomer.

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