

cold, concd. hydrochloric acid, and then 100 ml. of ice water was added. Chlorine was bubbled into the solution, keeping the temperature below 10° throughout by external cooling. The solution became dark brown at first, and the chlorination was complete when the temperature no longer rose and when the color of the solution lightened (two and one-half hours). The solution was then diluted with 1200 g. of ice and water, keeping the temperature still below 10°. The product which separated was filtered, washed with ice water, dried *in vacuo* over phosphorus pentoxide, and recrystallized the same day from ethylene dichloride. The sulfonyl chloride should be dried and recrystallized rapidly to prevent decomposition to the sulfonic acid. An analytical sample melted at 165–166° (d.).

Anal. Calcd. for C₇H₇ClN₂O₂S: N, 11.94; Cl, 15.11. Found: N, 11.75; Cl, 14.97.

Substituted Acetaminopyridinesulfonamides.—2-Sulfonamido-5-acetaminopyridine was prepared by adding one part of the sulfonyl chloride to four parts of concd. ammonia (25%), and evaporating the excess ammonia on the steam-bath. The product crystallized out on cooling; yield, 86%. The guanidine derivative was made by the method of Marshall, Bratton, White and Litchfield¹⁶; yield, 51%. The derivatives of the cyclic amines were prepared in 62–98% yields by adding an equivalent of 5-

(16) Marshall, Bratton, White and Litchfield, *Bull. Johns Hopkins Hosp.*, **67**, 163 (1940).

acetaminopyridine-2-sulfonyl chloride to the cyclic amine dissolved in dry pyridine, the weight of the latter being equal to that of the total solids. Solution took place with evolution of heat and the reactions were completed by warming at 60° for one-half to one hour. The crude derivatives obtained by pouring the dark solutions into ice water were dissolved in one equivalent of aqueous sodium hydroxide, decolorized, and reprecipitated by addition of hydrochloric acid.

Hydrolysis of the N⁴-Acetyl Group.—Six of the acetyl compounds were hydrolyzed by refluxing 0.5 to 1.0 molar solutions containing 2.5 equivalents of sodium hydroxide for two and one-half to three hours. The acetyl derivative of the guanidine condensation product was hydrolyzed with 6-molar hydrochloric acid by the method of Marshall, *et al.*¹⁶

Summary

1. 5-Acetaminopyridine-2-sulfonyl chloride has been prepared and is available as an intermediate for the preparation of a new series of chemotherapeutic agents.

2. The preparation of seven new substituted 5-aminopyridine-2-sulfonamides and their acetyl derivatives is reported.

PHILADELPHIA, PA.

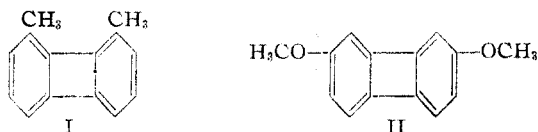
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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF TRINITY COLLEGE]

1,8-Dimethyl and 2,7-Dimethoxybiphenylene

BY WARREN C. LOTHROP

Continuing a line of investigation recently reported,¹ the present paper describes the preparation of two substituted biphenylenes. These new substances were obtained by following the procedure previously worked out for the parent substance, biphenylene, and have been assigned the structures



1,8-dimethylbiphenylene (I) and 2,7-dimethoxybiphenylene (II).

The hydrocarbon (I) was prepared with considerable difficulty and in very poor yield by the pyrolysis of 4,5-dimethylbiphenylene idonium iodide with cuprous oxide. The over-all yield for the whole series of reactions starting with 100 g. of 2-amino-3-nitrotoluene was only 100 mg. of a pale yellow hydrocarbon crystallizing in plates

from methanol. It melted at 79–80° and formed a picrate crystallizing in long crimson needles from ethanol and melting at 126°. It was lower melting and less highly colored than its isomer, 2,7-dimethylbiphenylene,² but otherwise similar.

For the preparation of II, a series of reactions previously reported³ was followed but with variations in procedure materially improving the yields of all steps. Acetylation of *p*-anisidine (97%) followed by nitration with dilute nitric acid at room temperature (78%), and hydrolysis with alcoholic hydrochloric acid (95%) gave 3-nitro-*p*-anisidine⁴ III. This when coupled by the procedure of Atkinson, *et al.*,⁵ gave 2,2'-dinitro-*p,p'*-bianisole IV contaminated by a con-

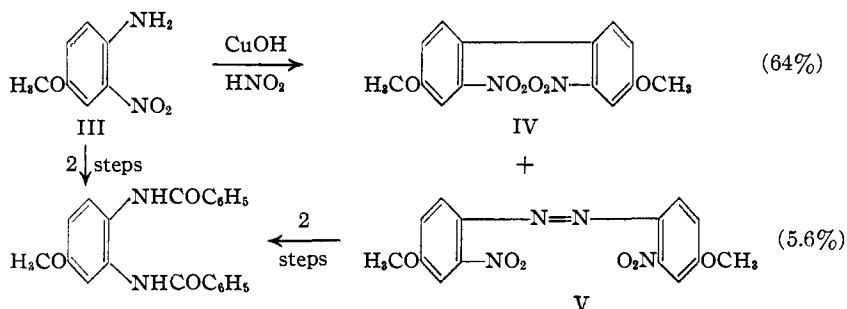
(2) Recrystallization and careful drying of the picrate of this compound gave needles (m. p. 110–111°) which were evidently free of the alcohol of crystallization previously reported.¹ *Anal.* Calcd. for C₁₄H₁₂-C₆H₄O₇N₃: N, 10.27. Found: N, 9.90, 10.43.

(3) Hata, Tatematsu and Kubota, *Bull. Chem. Soc. Japan*, **10**, 425 (1935).

(4) Cf. Reverdin, *Bvr.*, **29**, 2595 (1896).

(5) Atkinson, Lawler, Heath, Kimball and Read, *This Journal*, **63**, 730 (1941).

(1) Lothrop, *This Journal*, **63**, 1187 (1941).



siderable amount of orange material which was evidently 4,4'-azobis-3-nitroanisole V,⁶ since on reduction and benzylation it gave only 3,4-dibenzamidoanisole.

It is interesting to note that Atkinson's coupling procedure applied to 2-amino-3-nitrotoluene yields only 24% of 6,6'-dinitro-*o,o'*-bitolyl and 16% of 2,2'-azobis-3-nitrotoluene, possibly due to steric hindrance; the identity of the latter was proved by its conversion to 2,3-dibenzamidotoluene and comparison with an authentic sample.

Conversion of IV to the diamine and then to the iodonium iodide, followed by the usual pyrolysis, gave dimethoxybiphenylene in 2% yield, as glistening lemon yellow plates melting at 108° and forming a picrate crystallizing from alcohol in black needles melting at 125°. All attempts to convert II into dihydroxybiphenylene failed, since it was inert to alkaline reagents, as expected, and was rapidly cleaved by acids to give solutions of a deep purple color resembling permanganate, and from which only tar could be obtained. Experiments conducted in an atmosphere of nitrogen were identical with those performed in air.

This result may not be entirely unexpected since 2,7-dihydroxybiphenylene is seen to be an isomer of 4,4'-biphenylquinone which was found by Willstätter and Kolb⁷ to be an unstable substance reacting even with warm water to give decomposition products.

Experimental Part

6,6'-Dinitro-*o,o'*-bitolyl was prepared in the manner of Wittig and Stichnoth⁸ by the reaction of 2-iodo-3-nitrotoluene with copper. An attempt to obtain it directly from 2-amino-3-nitrotoluene (11 g.) by following exactly the procedure of Atkinson, *et al.*,⁵ (called by them Method 2) gave a mixed product which was separated by extraction with 40 cc. of boiling alcohol. The alcoholic solution gave 2.4 g. of pale buff needles which after recrystallization

melted at 107–108° and represented a 24% yield of dinitrobitolyl.

The alcohol-insoluble material was recrystallized from glacial acetic acid in bright orange needles weighing 1.8 g.; 16% yield; m. p. 199°. Reduction of this 2,2'-azobis-3-nitrotoluene with zinc dust and boiling acetic acid and benzylation of the water-

soluble diamine by the Schotten-Baumann procedure gave 2,3-dibenzamidotoluene, m. p. 228–229°, which crystallized from acetic acid in white needles. It was identical with the product obtained by reduction and benzylation of 2-amino-3-nitrotoluene.

Anal. Calcd. for $\text{C}_{21}\text{H}_{18}\text{O}_2\text{N}_2$: C, 76.34; H, 5.49; N, 8.48. Found: C, 76.22; H, 5.58; N, 8.22.

6,6'-Diamino-*o,o'*-bitolyl was prepared as previously described⁹ by reduction of the dinitro compound with stannous chloride and hydrochloric acid in acetic acid solution. The best yield obtainable was 55% of white plates, m. p. 132° after two crystallizations from alcohol.

When the above diamine was diazotized and treated with potassium iodide by the same procedure used for biphenylene iodonium iodide, a yield of 67% of crude 6,6'-diiodo-*o,o'*-bitolyl¹⁰ resulted. Since the product was completely soluble in dilute alcohol, it was apparent that no iodonium iodide had been formed in this case, doubtless due to the steric effects of the adjacent methyl groups.

1,8-Dimethylbiphenylene (I) resulted in very poor yield by pyrolysis of the above crude diiodide with cuprous oxide. It was isolated through its picrate which separated from alcohol in long, crimson needles; m. p. 126°.

Anal. Calcd. for $\text{C}_{14}\text{H}_{12}\cdot\text{C}_6\text{H}_5\text{O}_7\text{N}_3$: N, 10.27. Found: N, 10.27.

No trace of 4,5-dimethylphenazone could be found. This is in contrast to all other reaction series where the corresponding phenazone is present as an impurity.

Decomposition of the picrate with ether and ammonia gave a pale yellow hydrocarbon which crystallized from methanol in large, pearly plates, m. p. 79–80°, and had a slight odor reminiscent of biphenylene.

Anal. Calcd. for $\text{C}_{14}\text{H}_{12}$: C, 93.28; H, 6.72; mol. wt., 180. Found: C, 93.30; H, 7.04; mol. wt. (Rast micro), 182.

***p*-Acetamidoanisole** resulted in 97% yield by treatment of a solution of *p*-anisidine hydrochloride with sodium acetate in the presence of acetic anhydride.¹¹

3-Nitro-*p*-acetamidoanisole⁴ was prepared as follows: a sludge of 184 g. of acetaniside in 340 cc. of glacial acetic acid was mixed with a solution of 112 cc. of concentrated nitric acid in 615 cc. of water and allowed to stand at room temperature for one day. During this time the reaction warmed up to 60° spontaneously and all material went into solution while the product crystallized out on cooling in

(6) Cf. Saunders, "The Aromatic Diazo-compounds," Edward Arnold, London, 1936, p. 148.

(7) Willstätter and Kolb, *Ber.*, **38**, 1235 (1905).

(8) Wittig and Stichnoth, *ibid.*, **68**, 928 (1935).

(9) Meisenheimer and Horing, *ibid.*, **60**, 1425 (1927).

(10) Angeletti, *Gazz. chim. ital.*, **63**, 145 (1933).

(11) Cf. Fieser, "Experiments in Organic Chemistry," 2nd ed., D. C. Heath Co., Boston, Mass., 1941, p. 165.

bright yellow needles; m. p. 115° (literature m. p. 117°); yield 183 g. or 78%.

3-Nitro-*p*-anisidine (III) was obtained when 243.5 g. of the acetyl derivative, after refluxing for six hours with 500 cc. of alcohol and 245 cc. of concentrated hydrochloric acid, was neutralized with 300 cc. of concentrated ammonia and cooled. The product separated in deep orange-red needles, m. p. 122° (literature 122°), weighing 183 g. (94%).

2,2'-Dinitro-*p,p'*-bianisole (IV) was prepared from the diazonium solution of the above nitroanisidine by the action of a solution of cuprous hydroxide. When 340 g. of the amine was treated by the procedure described under Method 2⁶ a crude product not entirely soluble in acetic acid resulted. The soluble material crystallized from the solution and weighed 141.5 g. (64%), m. p. 131° and was identical with material prepared by heating 4-iodo-3-nitroanisole with copper powder.³

The insoluble material was crystallized from nitrobenzene in bright orange prisms, m. p. 259°, and was evidently **4,4'-azobis-3-nitroanisole (V)** since on reduction with zinc dust and boiling acetic acid followed by benzylation of the water soluble diamine it gave 3,4-dibenzamidoanisole.¹²

This crystallized from acetic acid in white needles and gave no depression of the m. p. (250°) of an authentic sample.

Anal. Calcd. for C₁₄H₁₃O₆N₄ (V): N, 16.85. Found: N, 17.05.

2,2'-Diamino-*p,p'*-bianisole.³—When 89 g. of dinitrobianisole was reduced by the action of 297 g. of tin, 960 cc. of concentrated hydrochloric acid and 165 cc. of acetic acid, the diamine (m. p. 110°) crystallized from alcohol in pearly plates weighing 53 g. (74% yield).

2,7-Dimethoxybiphenylene idonium iodide was obtained in a crude condition in 77% yield by treatment of the above diamine in the usual manner,¹ so that from 62.5 g. of the diamine, 92 g. of light brown powder resulted. This was not purified further but was subjected to pyrolysis with cuprous oxide.

2,7-Dimethoxybiphenylene (II).—When the crude product of the above pyrolysis was subjected to prolonged steam distillation, 6 g. of yellow crystals was isolated from the distillate (20 liters) by ether extraction. This was fractionally crystallized from alcohol yielding first of all 1.12 g. of pure white plates, m. p. 174°, which were identified as *p,p'*-bianisyl¹³ by comparison with an authentic sample. From the mother liquor the desired product crystallized in lemon yellow plates. These were purified by conversion to the **picrate** which separated from its deep red alcoholic solution in thick needles of a red color so deep as to be almost black; m. p. 125°.

(12) Meldola and Eyre, *J. Chem. Soc.*, **81**, 991 (1902).

(13) Gillmeister, *Ber.*, **30**, 2849 (1897).

Anal. Calcd. for C₁₄H₁₂O₂·C₆H₃O₇N₃: N, 9.52. Found: N, 9.78.

Decomposition of the pure picrate with ammonia and ether gave 1 g. of pure dimethoxybiphenylene crystallizing in large, bright yellow, striated plates from ethanol; m. p. 107–108°.

Anal. Calcd. for C₁₄H₁₂O₂: C, 79.24; H, 5.70; mol. wt., 212. Found: C, 79.07, 79.51; H, 5.80, 5.95; mol. wt., 214 (Rast micro).

2,2'-Diiodo-*p,p'*-bianisyl.—The residue left from the above steam distillation was dissolved in hot glacial acetic acid, treated with norite and after filtration and cooling gave a deposit of pale buff prisms of unreacted diiodide (0.15 g.). Repeated crystallization failed to remove all color but the melting point stayed constant at 131°.

Anal. Calcd. for C₁₄H₁₂O₂I₂: I, 54.45. Found: I, 54.95.

2,7-Dimethoxyphenazone was recovered from the mother liquors as a gummy yellow precipitate which in acetone solution gave an orange picrate; m. p. 231–233°.

Anal. Calcd. for C₁₁H₁₂O₂N₂·C₆H₃O₇N₃: N, 14.92. Found: N, 15.14.

From this the pure dimethoxyphenazone was obtained in fine yellow needles from dilute acetic acid; m. p. 202–203° (literature 197°).³

2,7-Dihydroxybiphenylene.—Attempts to cleave dimethoxybiphenylene were uniformly unsuccessful, alcoholic alkali being without effect, while various acid reagents failed to give workable products. When the diether was treated in acetic acid solution with 48% hydrobromic acid or with concentrated hydrochloric acid, in air or under an atmosphere of nitrogen, a pink color appeared even at room temperature and rapidly turned to a deep purple, requiring about one minute on the steam-bath. From this solution a deep indigoid precipitate was obtained (m. p. above 360°) which was insoluble in alkali and all ordinary solvents and resisted attempts at acetylation. Parallel experiments with biphenylene showed that these effects were due to the methoxyl groups, since the hydrocarbon was untouched by such treatment.

An attempted cleavage in acetic anhydride solution gave a deep green solution and a gummy green precipitate which could not be crystallized.

Summary

Using methods previously employed for the preparation of biphenylene, 1,8-dimethylbiphenylene and 2,7-dimethoxybiphenylene have been prepared. Attempts to cleave the latter to form 2,7-dihydroxybiphenylene were unsuccessful.

HARTFORD, CONN.

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