[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF DUKE UNIVERSITY]

2-Iodo-4'-chlorobiphenyl

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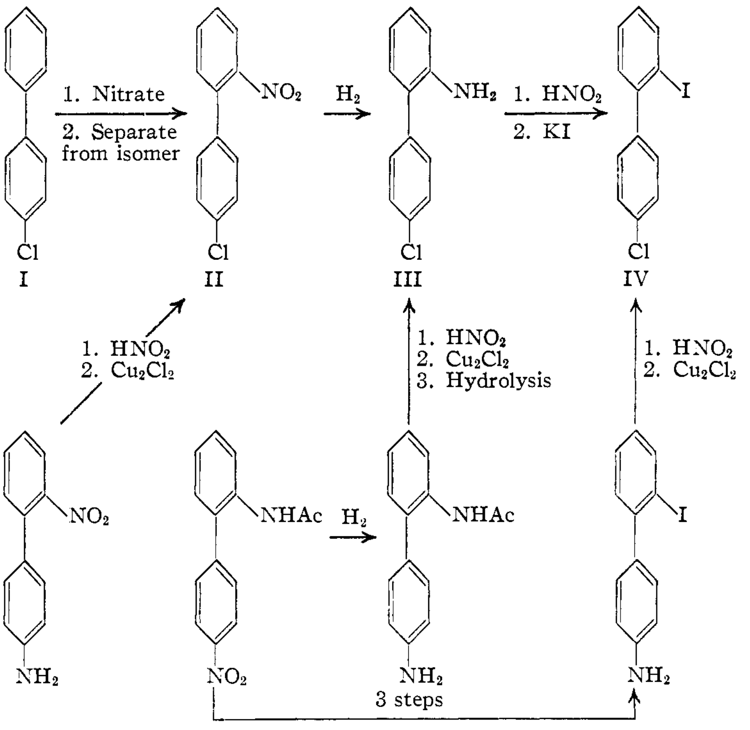
Considerable use has been made of 2-iodobiphenyl as a starting material in the synthesis of phenanthrene hydrocarbons.[2] In order to provide a new means for the preparation of phenanthrene derivatives containing functional groups, and at the same time to determine the effects of these groups on the ease of cyclization, the synthesis of some substituted 2-iodobiphenyls has been undertaken. The present communication deals with the preparation of 2-iodo-4'-chlorobiphenyl (IV).



It would appear that the synthesis of this compound might logically be approached by the application of the diazonium reaction to the previously described 2-iodo-4'-aminobiphenyl (VIII)[3,4] or 2-amino-4'-chlorobiphenyl (III). Diazotization of the former amine (VIII) did afford the desired dihalide, but the poor yield obtained, as well as the great number of steps required in the preparation of this amine, made the route appear unsuitable for large scale preparations. The chloroaminobiphenyl (III), by far the more attractive intermediate, has been prepared previously as one of several products obtained by chlorination of 2-acetamidobiphenyl,[5] by the action of sodium hypobromite on *o*-(*p*-chlorophenyl)-benzamide[6] as well as the reduction of 2-nitro-4'-chlorobiphenyl (II).[7,8] The latter procedure appeared best suited to the preparation of the chloramine (III) in quantity, but since neither 2-nitro-4'-chlorobiphenyl (II) or 4-chlorobiphenyl (I) are yet commercially available, a survey was made of several alternate routes to the amine (III) and the corresponding nitro compound (II). Before completion of these studies, a quantity of 4-chlorobiphenyl was made available to us through the generosity of the Monsanto Chemical Company, making possible the simpler and more direct preparation of the chloroaminobiphenyl.

The preliminary work warrants brief report in that it has afforded several new biphenyl compounds. Our first experiments were directed toward the preparation of 2-amino-4'-chlorobiphenyl (III) using starting materials derived from the commercially available 2-amino- and 2-nitrobiphenyls. Reduction of the 2-acetamido-4'-nitrobiphenyl (VI) of Scarborough and Waters[9] gave the amine (VII) in good yield, but diazotization, treatment with cuprous chloride, and hydrolysis afforded only a small quantity of 2-amino-4'-chlorobiphenyl. It was found that 2-nitro-4'-aminobiphenyl (V) could be converted to the corresponding nitrochlorobiphenyl (III), but the preparation of the required nitroamine (V) by selective reduction[3,10,11] of 2,4'-dinitrobiphenyl proved unsatisfactory on a large scale.

Nitration of 4-chlorobiphenyl (I) and separation of the desired 2-nitro-4'-chlorobiphenyl (II) from its 4-isomer was carried out essentially as described in an unpublished report of the Mon-

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[1] Eli Lilly Fellow (1943–1944).

[2] *E. g.*, Bradsher and Schneider, THIS JOURNAL, **60**, 2960 (1938); Bradsher and Amore, *ibid.*, **63**, 493 (1941); **65**, 2016 (1943); **66**, 1280 (1944); Bradsher and Rapoport, *ibid.*, **65**, 1646 (1943); **66**, 1281 (1944).

[3] Finzi and Bellavita, *Gazz. chim. ital.*, **64**, 335 (1934).

[4] Saka, *Bull. Chem. Soc. Japan*, **10**, 585 (1935).

[5] De Crauw, *Rec. trav. chim.*, **50**, 776 (1931). The melting point recorded for this amine is considerably higher than any subsequently reported, although the melting point of the acetamido derivative has been confirmed (note 6).

[6] Huntress and Seikel, THIS JOURNAL, **61**, 820 (1939).

[7] Raiford and McNulty, *ibid.*, **56**, 680 (1934).

[8] U. S. Patent 2,079,450; *C. A.*, **31**, 4346 (1937).

[9] Scarborough and Waters, *J. Chem. Soc.*, 89 (1927).

[10] Guglialmelli and Franco, *Anales asoc. quím. argentina*, **18**, 190 (1930); *C. A.*, **25**, 4252 (1931).

[11] Schultz, Schmidt and Strasser, *Ann.*, **207**, 348 (1881).

santo Chemical Company.[12] The use of hydrogen in the presence of Raney nickel for reduction of the nitro compound (II) to the corresponding amine was found more convenient than acid-metal combinations.[7,8] The resulting 2-amino-4′-chlorobiphenyl (III) when diazotized and treated with potassium iodide gave 2-iodo-4′-chlorobiphenyl (IV) in 68% yield.

Experimental

2-Nitro-4′-chlorobiphenyl (II).—(a) By diazotization of 2-nitro-4′-aminobiphenyl: A solution of 12.1 g. of 2-nitro-4′-aminobiphenyl[11] in dilute hydrochloric acid was diazotized at 0° by addition of a solution containing 3.5 g. of sodium nitrite. Following addition of cuprous chloride (obtained by reduction of 8.2 g. of cupric chloride), the mixture was allowed to warm up to room temperature. The solid thus obtained was collected and recrystallized from ethanol, yielding 5 g. (38%) of a pale yellow crystalline product, m. p. 59–61°.

(b) By nitration of 4-chlorobiphenyl[8,12]: To a suspension of 209 g. of 4-chlorobiphenyl in a solution containing 365 cc. of concentrated sulfuric acid and 106 cc. of concentrated nitric acid in 198 cc. of water, at 65°, a mixture of 98 cc. of concentrated sulfuric acid and 106 cc. of concentrated nitric acid was added gradually with vigorous stirring. Cooling was applied only when it appeared that the reaction might become too vigorous. Stirring was continued for one hour after which the acid was removed by decantation. The semi-solid product was dissolved in benzene, washed with water and with dilute sodium carbonate solution. The benzene solution was concentrated and the residue was distilled at 10 mm. pressure taking all of the material boiling below 220°. The product was then crystallized from ethanol, the more insoluble 4-nitro-4′-chlorobiphenyl precipitating first at room temperature, and the desired product crystallized at 0° after seeding. The product, m. p. 59–61°, was shown to be identical with that of procedure *a* by a mixed melting point determination; yield 58 g. (22%).

2-Acetamido-4′-aminobiphenyl (VII).—A suspension of 10 ml. of Raney nickel in 200 ml. of ethanol, together with 71 g. of 2-acetamido-4′-nitrobiphenyl[9] was shaken with hydrogen at about 40 lb. pressure until the theoretical quantity had been absorbed. Upon concentration of the solution under reduced pressure, the amine (VII) was obtained as light brown plate-like crystals, m. p. 117–118°; yield 50 g. (80%). This material was used in further reactions, but an analytical sample obtained by recrystallization from dilute ethanol melted at 120–121°.

Anal. Calcd. for $C_{14}H_{14}N_2O$: N, 12.38. Found[13]: N, 11.98.

Acetylation yielded a compound which is presumably 2,4′-diacetamidobiphenyl, m. p. 198–200° (lit.[11] 202°).

2-Amino-4′-chlorobiphenyl (III).—(a) By diazotization of 2-acetamido-4′-aminobiphenyl followed by hydrolysis: A mixture consisting of 75 g. of 2-acetamido-4′-aminobiphenyl and 130 cc. of 9 *M* hydrochloric acid was cooled to 0° and diazotized by addition of a solution of 23 g. of sodium nitrite in water. The diazonium salt was poured into a solution containing an excess of cuprous chloride in hydrochloric acid. After decomposition of the complex, the product was collected, dried and distilled under reduced pressure to yield a yellow-brown solid. This material, presumably 2-acetamido-4′-chlorobiphenyl, was hydrolyzed directly by refluxing in an alcohol-hydrochloric acid mixture. The mixture was neutralized and the base taken up in benzene from which it was precipitated as the salt by passing in hydrogen chloride. The yield was 17 g. (21%) of a hydrochloride salt which, on treatment with ammonium hydroxide, gave the free base, m. p. 42–44° (lit.[8,6,7,5] about 47, 48, 52, 71°).

(b) By reduction of 2-nitro-4′-chlorobiphenyl: To a solution of 142 g. of 2-nitro-4′-chlorobiphenyl, 20 cc. of Raney nickel catalyst was added and the mixture shaken with hydrogen at about 40 lb. pressure. After the theoretical quantity of hydrogen had been absorbed, the catalyst was filtered off and the base precipitated as the hydrochloride by addition of concentrated hydrochloric acid. The salt, washed with cold ether and air-dried, weighed 124 g. (84%) and had a slight yellow-brown color. The free base, liberated as above, melted slightly lower (40–42°) than the preparation in *a*, but the mixed melting point was intermediate between the two.

The 2-benzamido-4′-chlorobiphenyl prepared from the base by the Schotten–Baumann method gave crystals from alcohol, m. p. 171–172°.

Anal. Calcd. for $C_{19}H_{14}ONCl$: C, 74.14; H, 4.56. Found[14]: C, 74.15; H, 4.59.

Apparently the compound obtained upon refluxing[51] the base with acetic anhydride was **2-diacetylamino-4′-chlorobiphenyl.** It crystallized from ethanol–water, m. p. 96–97°.

Anal. Calcd. for $C_{16}H_{14}O_2NCl$: C, 66.77; H, 4.86. Found[15]: C, 66.77; H, 4.82.

2-Iodo-4′-chlorobiphenyl (IV).—(a) By reduction of 2-iodo-4′-nitrobiphenyl followed by diazotization[16]: Reduction of 2-iodo-4′-nitrobiphenyl[3,4] (165 g.) was accomplished essentially as described by Sako.[4] The amine hydrochloride, obtained by addition of a further quantity of concentrated hydrochloric acid to the reduction mixture contained some tin salts, but this did not appear to interfere with the subsequent diazotization. The crude hydrochloride was suspended in dilute hydrochloric acid and diazotized at 0–5° by addition of a solution containing 36 g. of sodium nitrite. The diazonium salt was poured into a hydrochloric acid solution containing an excess of cuprous chloride and the mixture allowed to stand overnight. After a short heating on the steam-bath, the product was taken up in chloroform and the solution washed, dried, and concentrated. Distillation of the residue under reduced pressure gave 51.7 g. (32%) of a light yellow oil, b. p. 175–180° (11 mm.).

(b) By diazotization of 2-amino-4′-chlorobiphenyl: To 40 g. of 2-amino-4′-chlorobiphenyl, 18.5 cc. of concentrated sulfuric acid in 70 cc. of water was added, and the mixture diazotized at 0–10° by slow addition of a solution containing 11.5 g. of sodium nitrite. When the reaction was complete, a solution of 34 g. of potassium iodide in water was added, together with 0.5 g. of copper bronze powder. After decomposition of the complex by heating on the steam-bath, the mixture was extracted with chloroform and the extract washed with sodium hydroxide solution and dried. After removal of the solvent, the residue was distilled under reduced pressure, yielding 35.6 g. (68%) of a pale yellow liquid, n^{22}_D 1.6622, b. p. 170–175° (7 mm.). The analytical sample boiled at 178° (10-11 mm.).

Anal. Calcd. for $C_{12}H_8ClI$: C, 45.82; H, 2.56. Found[13]: C, 46.24; H, 2.64.

Summary

A satisfactory method has been found for the preparation of 2-iodo-4′-chlorobiphenyl, and evidence has been offered in support of the assigned structure.

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[12] Mr. C. F. Booth of the Monsanto Chemical Company has perfected directions for conducting this nitration on a semi-pilot plant scale. These directions, privately communicated to us by Dr. R. L. Jenkins, have been closely followed except with respect to details of the method of isolation. Our slightly modified procedure is published with the permission of, and grateful acknowledgement to the Monsanto Chemical Company.

[13] Analysis by Arlington Laboratories.

[14] Analysis by T. S. Ma, University of Chicago.

[15] Evidently using milder conditions De Crauw (ref. 5) and Huntress and Seikel (ref. 6) obtained the monoacetylated product.

[16] Experiment by William H. Perkins.