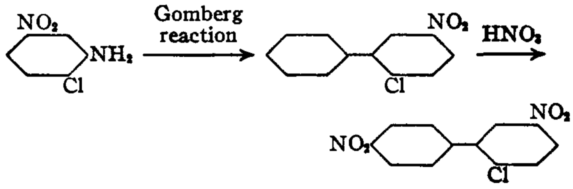
[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF TEMPLE UNIVERSITY]

The Nitration of Certain Halobiphenyls. III. Nitro Derivatives of 2-Chloro- and 2-Bromobiphenyl

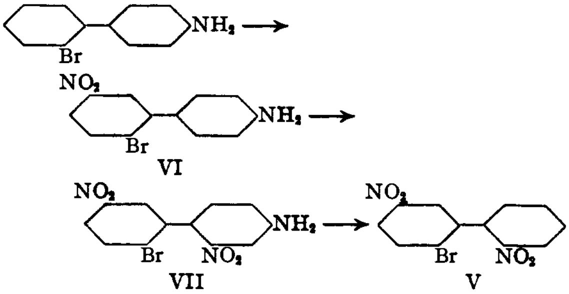
BY FRANCIS H. CASE

The nitration of 2-chlorobiphenyl according to Mascarelli and co-workers[1] leads to the formation of a mononitro I (m. p. 73–74°) and a dinitro II derivative (m. p. 158–159°). To I he assigned the structure 2-chloro-4′-nitrobiphenyl on the basis that it yields *p*-nitrobenzoic acid on oxidation. We have confirmed this structure by synthesizing I from 2-amino-4′-nitrobiphenyl.[2] To compound II Mascarelli assigned the structure 2-chloro-3′,4′-dinitrobiphenyl on the basis that it yields on oxidation 3,4-dinitrobenzoic acid. On repeating this work we find that II is in fact unchanged by prolonged refluxing with chromic anhydride in presence of vanadium oxide in acetic acid solution. Since I on further nitration yields II, it is evident that one nitro group is in the 4′-position relative to chlorine. Reduction of II, followed by oxidation, brought about complete destruction of the molecule. Hence the second nitro group must have been in the ring containing the chlorine atom. Depending on the relative directive influences of the chlorine atom and *p*-nitrophenyl group, the second nitro group might assume a position meta to chlorine as in 2-chloro-4,4′-dinitrobiphenyl III or para to chlorine, as in 2-chloro-4′,5-dinitrobiphenyl. III has now been synthesized from 2-amino-4,4′-dinitrobiphenyl[3] by Sandmeyer's reaction and shown to be different from the nitration product II. 2-Chloro-4′,5-dinitrobiphenyl also has been synthesized by the following method and shown to be identical with II



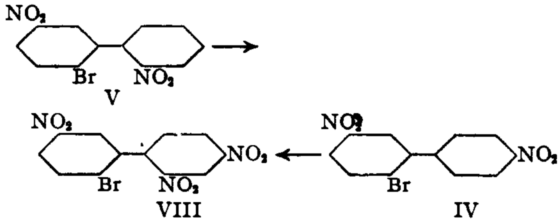
The nitration of 2-bromobiphenyl was found to be best effected by the use of ethyl nitrate in concentrated sulfuric acid. Regardless of whether one or two moles of ethyl nitrate were used it was impossible to isolate any mono-nitro-2-bromobiphenyl. The chief nitration product was 2-bromo-4′,5-dinitrobiphenyl (IV), plus a small amount of 2-bromo-2′,5-dinitrobiphenyl (V). In the course of identification of IV and V, 2-bromo-4,4′-dinitrobiphenyl was also prepared. The structure of IV (already assumed by Finzi and Bellavita,[3] but not proved) depends on the fact that it may be obtained by the nitration of both 2-bromo-4′-nitrobiphenyl and 2-bromo-5-nitrobiphenyl. It was found that the latter compound may be synthesized more conveniently by nitrating 2-*p*-toluenesulfonamidobiphenyl,[4] hydrolyzing and replacing amino by bromine than by the Gomberg method, previously described.[5] The fact that the bromo-nitrobiphenyls prepared by the two methods just described are identical proves definitely for the first time the position taken by the nitro group in Bell,s mono-nitration of 2-*p*-toluenesulfonamidobiphenyl and 2-acetaminobiphenyl and also the structure of 2-acetamino-4′,5-dinitrobiphenyl, which depends on its dual formation[2] from 2-acetamino-5-nitrobiphenyl and 2-acetamino-4′-nitrobiphenyl.

The nitration of 2-bromo-2′-nitrobiphenyl by means of ethyl nitrate in sulfuric acid yields the previously mentioned dinitrobromobiphenyl V, the structure of which was proven in the following manner. It has been found in this Laboratory[7] that 2-bromo-4′-aminobiphenyl on nitration yields 2-bromo-4′-amino-5-nitrobiphenyl VI (proved by deamination to 2-bromo-5-nitrobiphenyl) and this on further nitration forms a dinitrobromoaminobiphenyl, VII.



On deamination VII is converted into V, a fact which proves the structures of both V and VII.

On nitrating with fuming nitric acid (sp. gr. 1.59) both V and, IV yield 2-bromo-2′,4′,5-trinitrobiphenyl VIII whose structure depends on its dual method of synthesis.



The preparation of 2-bromo-3′-nitrobiphenyl[6]

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[1] Mascarelli and Gatti, *Gazz. chim. ital.*, **63**, 654 (1933).

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

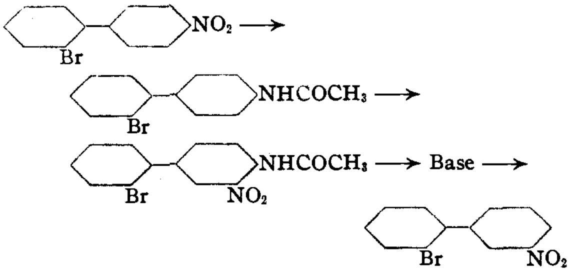
[3] Finzi and Bellavita, *Gazz. chim. ital.*, **68**, 77 (1938).

[4] Bell, *J. Chem. Soc.*, 2770 (1928).

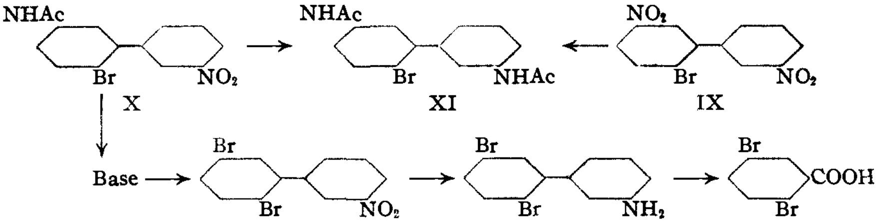
[5] Case, THIS JOURNAL, **58**, 1249 (1936).

[6] Case, *ibid.*, **60**, 424 (1938).

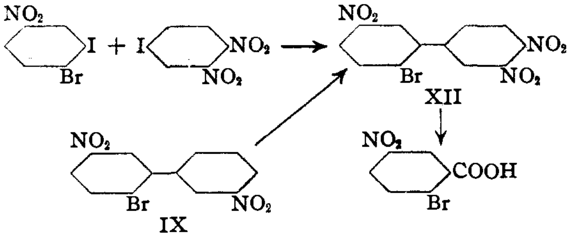
is most conveniently carried out by the following series of reactions



On nitration with ethyl nitrate in concd. sulfuric acid it yields 2-bromo-3',5-dinitrobiphenyl IX. After an attempt to prepare IX by a mixed Ullmann synthesis had failed, the following method was used to establish its structure. By partial reduction of 3,3'-dinitrobiphenyl, followed by acetylation was obtained 3-nitro-3'-acetaminobiphenyl. This was brominated, yielding X. The structure of X is based on the fact that on hydrolysis, replacement of amino by bromine, reduction, and oxidation, 2,5-dibromobenzoic acid resulted. On reduction, followed by acetylation, both IX and X yield 2-bromo-3',5-diacetaminobiphenyl, thus proving the structure of IX.



On drastic nitration, IX yields a trinitrobromobiphenyl XII which, on oxidation, yields 2-bromo-5-nitrobenzoic acid. Its structure was proven by an Ullmann synthesis from 3,4-dinitroiodobenzene and the previously undescribed 2-bromo-5-nitroiodobenzene.



The author acknowledges the assistance of Mr. Richard Schock in connection with the nitration of the chloro derivatives and of Mr. Angelo DiGeorge in connection with the analytical work. This work has been supported by a Grant from the Temple University Committee on Research and Publication.

Experimental Part

2-Chloro-4'-nitrobiphenyl (I).—This was prepared by Sandmeyer's reaction from 2-amino-4'-nitrobiphenyl, and proved to be the same as that obtained by Mascarelli by nitrating 2-chlorobiphenyl (m. p. 74–75°). On nitration by the method of Mascarelli it yielded II (m. p. 159–160°).

2-Chloro-4,4'-dinitrobiphenyl.—This was obtained from 2-amino-4,4'-dinitrobiphenyl by the method of Schoutissen.[7] From 2 g. of base, 0.7 g. of the chloro derivative was obtained, m. p. 153–154° (from acetone–alcohol).

Anal. Calcd. for $C_{12}H_7N_2O_4Cl$: N, 10.06. Found: N, 9.97.

2-Chloro-5-nitrobiphenyl.—Fifty grams of 2-chloro-5-nitroaniline was heated to boiling with 50 cc. of concd. hydrochloric acid and 50 cc. of water. The hot solution was cooled rapidly and the resulting paste diazotized with a solution of 20 g. of sodium nitrite in 40 cc. of water. The temperature was kept below 10°. After fifteen minutes the solution was filtered rapidly and added to 500 cc. of chilled benzene. Using efficient stirring, 54 cc. of 5 *N* sodium hydroxide was added gradually keeping the temperature below 5°. Stirring was continued five hours at room temperature and after standing overnight, the benzene layer was removed, yielding 10.2 g. of a product boiling at 181–190° (6 mm.). On recrystallization from petroleum ether it melted at 59–60°.

Anal. Calcd. for $C_{12}H_8NO_2Cl$: N, 6.00; Cl, 15.17. Found: N, 5.82; Cl, 15.03.

Nitration of 2-Chloro-5-nitrobiphenyl.—Three grams of 2-chloro-5-nitrobiphenyl was dissolved in 30 cc. of fuming nitric acid (sp. gr. 1.5) and heated for five minutes on the steam-bath. The precipitate which formed when the nitrating mixture was poured upon ice was filtered and recrystallized twice from acetone–alcohol; yield, 1.9 g.; m. p. 159–160°, and unchanged when mixed with the product obtained by nitrating 2-chlorobiphenyl by the method of Mascarelli.

Nitration of 2-Bromobiphenyl.—To a solution of 9.3 g. of 2-bromobiphenyl in 80 cc. of concd. sulfuric acid, 3.4 cc. (1 mole) of ethyl nitrate was added slowly, keeping the temperature below 2°. After the temperature had been allowed to rise to 25° the mixture was poured into ice water and the resulting precipitate crystallized from alcohol–acetone; yield, 3 g. of a solid melting at 161°. The pure product melts at 165–166°, unchanged when mixed with the product (IV) obtained by Finzi and Bellavita[3] by nitrating 2-bromo-4'-nitrobiphenyl. By evaporation of the filtrate, 0.7 g. of a solid was obtained melting at 139–140°. This melting point was undepressed on admixture with a specimen (V), obtained by nitrating 2-bromo-2'-nitrobiphenyl.

2-Amino-5-nitrobiphenyl.—This was prepared by the hydrolysis of 5-nitro-2-*p*-toluenesulfonamidobiphenyl[4] in boiling 1–1 sulfuric acid. From 39.5 g. of the *p*-toluenesulfonamido derivative, 17 g. of base was obtained, m. p. 125–126°.

2-Bromo-5-nitrobiphenyl.—A hot solution of 10.7 g. of 2-amino-5-nitrobiphenyl in 100 cc. of glacial acetic acid was quickly cooled to room temperature. It was then diazotized by adding it to 3.8 g. of sodium nitrite in 28 cc. of concd. sulfuric acid, keeping the temperature below 40°. The diazonium solution was added to the mixture obtained by treating a solution of 14.3 g. of hydrated copper sulfate and 6.9 g. of sodium bromide in 45 cc. of water with one of 3.1 g. of sodium metabisulfite and 2.1 g. of sodium hydroxide in 23 cc. of water. The resulting mixture was immedi-

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[7] Schoutissen, THIS JOURNAL, 55, 4531 (1933).

ately treated with 15 cc. of 48% hydrobromic acid and allowed to stand overnight. The precipitate formed was filtered, washed, and crystallized from methanol; yield, 10 g., m. p. 82–83°. The product melted unchanged when mixed with a sample of 2-bromo-5-nitrobiphenyl prepared by Gomberg's method.[5] On further nitration in a nitric-sulfuric acid mixture[1] it yielded a dinitrobromobiphenyl identical with IV.

2-Bromo-4,4′-dinitrobiphenyl.—This was prepared from 2-amino-4,4′-dinitrobiphenyl[8] by a method similar to that just described for 2-bromo-5-nitrobiphenyl. From 4.4 g. of base, 2.5 g. of 2-bromo-4,4′-dinitrobiphenyl was obtained. On crystallization from ethanol, it melted at 148–149°.

Anal. Calcd. for $C_{12}H_7N_2O_4Br$: N, 8.67. Found: N, 8.49.

Nitration of 2-Bromo-2′-nitrobiphenyl.[8]—The procedure, using one mole of ethyl nitrate, was similar to that for the nitration of 2-bromobiphenyl, already described. From 5.56 g. of nitrobromobiphenyl was obtained 3.3 g. of dinitrobromobiphenyl, m. p. 137–138°. The pure product (V), crystallized from ethanol, melts at 140–141°.

Anal. Calcd. for $C_{12}H_7N_2O_4Br$: Br, 24.74. Found: Br, 25.03.

Nitration of 2-Bromo-4′-aminobiphenyl.—To a stirred solution of 30 g. of 2-bromo-4′-aminobiphenyl in 102 cc. of concd. sulfuric acid and 27 cc. of 15% fuming sulfuric acid, 12.5 g. of powdered potassium nitrate was slowly added, keeping the temperature below 6°. After one hour of additional stirring the solution was poured into ice water, and the precipitated product dried and acetylated. On crystallization from methanol, 8 g. of bromonitroacetaminobiphenyl was obtained melting at 176–177°. The pure product melts at 186–187°.

Anal. Calcd. for $C_{14}H_{11}N_2O_3Br$: Br, 23.85. Found: Br, 24.19.

By hydrolyzing the above acetamino compound (8 g.) with boiling dilute sulfuric acid (1 volume of sulfuric acid to 2 volumes of water), the free base, 3.5 g., was obtained. It melts at 111–112° when crystallized from ethanol.

Anal. Calcd. for $C_{12}H_9N_2O_2Br$: Br, 27.28. Found: Br, 27.05.

Deamination of 2-Bromo-5-nitro-4′-aminobiphenyl.—To a suspension of 7.4 g. of the above base in 100 cc. of ethanol was added 25 cc. of dilute sulfuric acid (1-1). The mixture, warmed on the steam-bath, was gradually treated with 4 g. of solid sodium nitrite. The solid product which precipitated on pouring the solution into ice water was dried and distilled *in vacuo.* The fraction boiling at 200–210 (2 mm.) was crystallized from methanol; yield 2.9 g., m. p. 79–80°. It melted unchanged when mixed with a sample of 2-bromo-5-nitrobiphenyl.

Nitration of 2-Bromo-4′-amino-5-nitrobiphenyl.—The directions were similar to those already given for nitrating 2-bromo-4′-aminobiphenyl. The crude dried product obtained from 8.6 g. of 2-bromo-4′-amino-5-nitrobiphenyl was acetylated, yielding 6 g. of a product melting at 237–241°. The pure bromodinitroacetaminobiphenyl on crystallization from alcohol–acetone, melts at 246–247°.

Anal. Calcd. for $C_{14}H_{10}N_3O_5Br$: Br, 21.03. Found: Br, 21.05.

The free base, obtained by the method of hydrolysis already described, melts at 149–150° after crystallization from methanol.

Anal. Calcd. for $C_{12}H_8N_3O_4Br$: Br, 23.64. Found: Br, 23.38.

On deamination, a product melting at 138–139° was obtained, whose melting point was undepressed when mixed with a sample of V.

Nitration of 2-Bromo-2′,5-dinitrobiphenyl (V).—The above substance was heated with fuming nitric acid (sp. gr. 1.59) for an hour on the steam-bath. The nitrated product, VIII, crystallized from ethanol, melts at 140–141°. This melting point was undepressed on admixture of this product with a specimen of the trinitrobromobiphenyl obtained by similarly nitrating 2-bromo-4′,5-dinitrobiphenyl (IV).

Anal. Calcd. for $C_{12}H_6N_3O_6Br$: Br, 21.72. Found: Br, 21.88.

2-Bromo-3′-nitro-4′-acetaminobiphenyl.—A solution of 16 g. of 2-bromo-4′-acetaminobiphenyl in 60 cc. of glacial acetic acid and 19 cc. of acetic anhydride was maintained at 70° during the addition of 3.7 cc. of fuming nitric acid (sp. gr. 1.5) and for forty minutes thereafter. The reaction mixture was poured onto ice, and the precipitate crystallized from ethanol; yield, 10.4 g., m. p. 135–136°.

Anal. Calcd. for $C_{14}H_{11}N_2O_3Br$: Br, 23.85. Found: Br, 24.04.

2-Bromo-3′-nitro-4′-aminobiphenyl.—This base was obtained by the hydrolysis of the above acetamino compound. It crystallized from ethanol, m. p. 145–146°.

Anal. Calcd. for $C_{12}H_6N_2O_2Br$: Br, 27.28. Found: Br, 27.36.

2-Bromo-3′-nitrobiphenyl.—To a solution of 19 g. of 2-bromo-3′-nitro-4′-aminobiphenyl in 200 cc. of ethanol was added 30 cc. of dilute (1-1) sulfuric acid. The mixture, warmed on the steam-bath, was treated gradually with 13 g. of solid sodium nitrite. The product which precipitated on pouring the solution into ice water was dried and distilled *in vacuo.* The fraction boiling at 220° (2 mm.) was crystallized from methanol; yield, 12 g., m. p. 79–80°. This product was identical with that obtained by Ullmann's method.[6]

Nitration of 2-Bromo-3′-nitrobiphenyl.—From the nitration of 8.3 g. of 2-bromo-3′-nitrobiphenyl with one mole of ethyl nitrate was obtained 5.5 g. of dinitrobromobiphenyl IX, m. p. 191–192°. The pure product melts at 194–195° when crystallized from acetone–alcohol.

Anal. Calcd. for $C_{12}H_7N_2O_4Br$: Br, 24.74. Found: Br, 25.06.

3-Nitro-3′-acetaminobiphenyl.—A solution of 20 g. of 3,3′-dinitrobiphenyl in 200 cc. of dioxane was treated with a molten mixture of 24 g. of hydrated sodium sulfide and 4 g. of sulfur. After ten hours of heating on the steam-bath, the dioxane was distilled off and the residue washed with water and extracted three times with dilute (1-1) acetic acid. The dried base obtained by treating the acetic acid extract with dilute sodium hydroxide, was acetylated, yielding 10 g. of a product melting at 164–165°. Pure 3-nitro-3′-acetaminobiphenyl, crystallized from benzene, melts at 165–166°.

Anal. Calcd. for $C_{14}H_{12}O_3N_2$: N, 10.94. Found: N, 10.81.

2-Bromo-3′-nitro-5-acetaminobiphenyl (X).—To a solution of 3 g. of 3-nitro-3′-acetaminobiphenyl in 60 cc. of glacial acetic acid containing 4 g. of anhydrous sodium acetate was added 1.9 g. of bromine. The mixture, after standing overnight, was poured into ice water, and the precipitate crystallized from ethanol; yield, 2.3 g., m. p. 193–194°.

Anal. Calcd. for $C_{14}H_{11}N_2O_3Br$: Br, 23.85. Found: Br, 23.48.

2-Bromo-3′-nitro-5-aminobiphenyl.—This was obtained by the hydrolysis of the above acetamino compound. On crystallization from ethanol, it melts at 112–113°.

Anal. Calcd. for $C_{12}H_9N_2O_2Br$: Br, 27.28. Found: Br, 27.53.

2,5-Dibromo-3′-nitrobiphenyl.—This was obtained from the above base by a method similar to the one used in preparing 2-bromo-5-nitrobiphenyl from 2-amino-5-nitrobiphenyl. From 5 g. of 2-bromo-3′-nitro-5-aminobiphenyl was obtained 3 g. of dibromonitrobiphenyl, melting at 97–98° when crystallized from ethanol.

Anal. Calcd. for $C_{12}H_7NO_2Br_2$: Br, 44.79 Found: Br, 44.45.

The above product when reduced by stannous chloride in alcohol solution, and then oxidized by chromic anhydride in acetic acid, yielded 2,5-dibromobenzoic acid.

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(8) Mascarelli and Gatti, *Gazz. chim. ital.*, **63**, 661 (1933).

2-Bromo-3′,5-diacetaminobiphenyl (XI).—A solution containing 3 g. of 2-bromo-3′-nitro-5-acetaminobiphenyl and 6.5 g. of hydrated stannous chloride in 100 cc. of alcohol was refluxed for ten hours. After removal of alcohol, sodium hydroxide was added, and the base extracted with ether. After removal of the ether, the crude base was acetylated, yielding 1.9 g. of a product which melts at 265–266° when crystallized from glacial acetic acid.

Anal. Calcd. for $C_{14}H_{15}N_2O_2Br$: Br, 23.03. Found: Br, 22.84.

The above product melted unchanged when mixed with the bromo diacetamino derivative obtained from IX by a similar method.

2-Bromo-5-nitroiodobenzene.—A hot solution of 36 g. of 2-bromo-5-nitroaniline[9] in 400 cc. of glacial acetic acid was quickly cooled to room temperature. It was then diazotized by adding it to 13 g. of sodium nitrite in 91 cc. of concd. sulfuric acid, keeping the temperature below 40°. The diazonium solution was added to a solution of 98 g. of potassium iodide and 200 g. of anhydrous sodium acetate in 1100 cc. of ice water. After standing overnight the precipitated crystals were washed and crystallized from methanol; yield, 31 g., m. p. 95–96°. The pure product melts at 97–98°.

Anal. Calcd. for $C_6H_3NO_2IBr$: N, 4.27. Found: N, 4.41.

2-Bromo-3′,4′,5-trinitrobiphenyl (XII).—This was prepared by Ullmann's reaction on a mixture of 3,4-dinitroiodobenzene and 2-bromo-5-nitroiodobenzene. After repeated crystallization from alcohol–acetone a product melting at 222–223° was obtained.

Anal. Calcd. for $C_{12}H_6N_3O_6Br$: Br, 21.72. Found: Br, 21.44.

This product melted unchanged when mixed with the trinitrobromobiphenyl obtained by treating IX with fuming nitric acid (sp. gr. 1.59).

Oxidation of XII with chromic anhydride in acetic acid in presence of vanadium oxide yielded 2-bromo-5-nitrobenzoic acid, m. p. 177°.

Summary

1. The nitration of 2-chlorobiphenyl according to Mascarelli is shown to yield 2-chloro-4′,5-dinitrobiphenyl.
2. The nitration of 2-bromo-2′-nitro-2-bromo-4′-nitro-, and 2-bromo-3′-nitrobiphenyl with ethyl nitrate forms in every case a 2-bromo-5-nitro derivative.
3. The further nitration of the above dinitro products yields in the first two cases 2-bromo-2′,4′,5-trinitrobiphenyl and in the last case 2-bromo-3′,4′,5-trinitrobiphenyl.
4. Proof of the structures of the nitration products is given.

PHILADELPHIA, PA. RECEIVED AUGUST 13, 1943

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[9] Wheeler, *Am. Chem. J.*, **17**, 699 (1895).

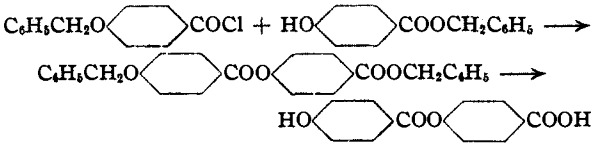
[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF WINTHROP CHEMICAL COMPANY, INC.]

Synthesis of Phenolic Acid Esters. I. Depsides[1]

BY CHESTER J. CAVALLITO AND JOHANNES S. BUCK

The preparation of depsides by the method of E. Fischer[2] involves several disadvantages, notably differential saponification to remove the protecting group, anhydride formation, and migration of certain acyl groups.

Other methods of preparation, such as those of Currie and Russell,[3] and Pepe,[4] yield only the methyl ethers of the depsides.



The present authors have found that, by causing the benzyl ether of a phenolic acid chloride to react with the benzyl ester of a phenolic acid, there is obtained smoothly and in good yield the benzyl ether–benzyl ester of a didepside. This is readily converted by hydrogenolysis under mild conditions into the didepside. By this method, differential saponification, anhydride formation and migration are all avoided. The method is capable of considerable extension. The properties of the compounds involved are listed in the table.

Experimental

Benzyl Esters of *o*-, *m*- and *p*-Hydroxybenzoic Acids.—Fourteen grams (0.1 mole) of the hydroxybenzoic acid was dissolved in 150 cc. of 95% ethanol. To this 100 cc. of 1 *N* sodium hydroxide solution and 13 cc. (0.11 mole) of benzyl chloride were added and the mixture refluxed for two hours, then distilled to about one-third of its volume. Water was added to the residue and the whole chilled until the oily product which first separated became crystalline. The meta and para derivatives were recrystallized from 70% ethanol and the ortho isomer was distilled under reduced pressure.

Benzyl 2,4-Dihydroxybenzoate.—To 31 g. (0.2 mole) of *β*-resorcylic acid was added 250 cc. of 95% ethanol, 50 cc. of 4 *N* potassium hydroxide solution and 25 cc. (0.21 mole) of benzyl chloride. The whole was refluxed for two hours. After cooling, the water insoluble layer was separated and extracted with sodium bicarbonate solution. The oily insoluble residue was distilled under reduced pressure to yield a waxy crystalline solid.

Benzyl 4-Benzyloxybenzoate.—To a solution of 14 g. (0.1 mole) of *p*-hydroxybenzoic acid in 125 cc. of 95% ethanol was added 67 cc. of 3 *N* sodium hydroxide solution and 25 cc. (0.21 mole) of benzyl chloride. The mixture was refluxed for three hours, then cooled. The crystals formed were filtered off, washed with sodium carbonate solution and recrystallized from 95% ethanol.

4-Benzyloxybenzoic Acid.—This could be prepared by saponification of the previously described compound or

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[1] Presented before the Division of Organic Chemistry at the 106th meeting of the American Chemical Society, Pittsburgh, Pennsylvania, Sept. 6, 1943.

[2] E. Fischer, "Untersuchungen über Depside und Gerbstoffe," J. Springer, Berlin, 1919.

[3] T. Currie and A. Russell, *J. Chem. Soc.* 2263 (1932); 140 (1933).

[4] R. O. Pepe, *J. prakt. Chem.*, **126**, 241 (1930); *Chem. Abs.*, **34**, 5426 (1940); **37**, 2723 (1943).