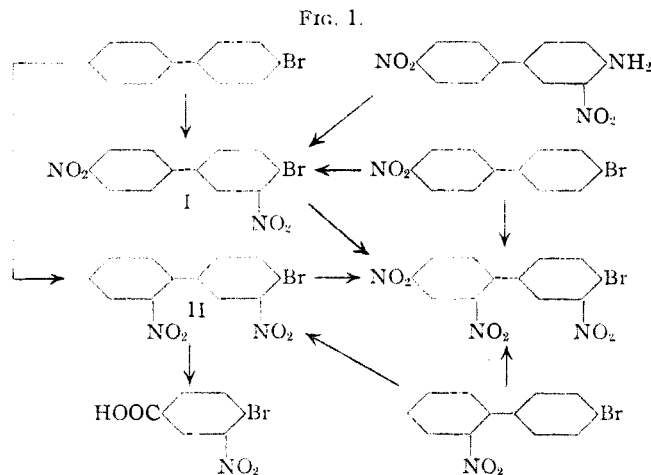


[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF TEMPLE UNIVERSITY]

The Nitration of Certain Halobiphenyls. I. Nitro Derivatives of 4-Bromobiphenyl

BY FRANCIS H. CASE

In 1933 Mascarelli¹ obtained by the nitration of 4-bromobiphenyl two isomeric dinitrobromobiphenyls I (m. p. 205–206°) and II (m. p. 147–148°) whose structure was undetermined since they resisted oxidation. With a view to clearing up the structure of these compounds, we have repeated the nitration, again obtaining the two isomers with the revised melting points 210–211° and 154–155°, respectively. Isomer I, also obtained by the nitration of 4-nitro-4'-bromobiphenyl, has been shown by us to be identical with the product obtained from 3,4'-dinitro-4-aminobiphenyl by replacement of amino by bromine, and is therefore 3,4'-dinitro-4-bromobiphenyl. A substance² (m. p. 135°), obtained by the nitration of 4-nitro-4'-bromobiphenyl, was previously assigned this structure



without experimental proof. Isomer II has been shown by us to be identical with the dinitrobromobiphenyl obtained by Finzi and Bellavita³ by the nitration of 4-bromo-2'-nitrobiphenyl. They assigned to it the structure 2',3'-dinitro-4-bromobiphenyl on the basis that it reacts with piperidine. We have confirmed this structure by oxidizing this substance to 3-nitro-4-bromobenzoic acid, thus avoiding the piperidine reaction,³ which is sometimes misleading. LeFèvre and Turner⁴ obtained by the nitration of either 4-bromo-2'-nitrobiphenyl or 4-bromo-4'-nitrobiphenyl the

same trinitrobromobiphenyl. Since it reacts with piperidine they assigned to it the structure 2,3',4'-trinitro-4'-bromobiphenyl. This is confirmed without the use of piperidine by the fact that 3,4'-dinitro-4-bromobiphenyl also yields the same substance on nitration.

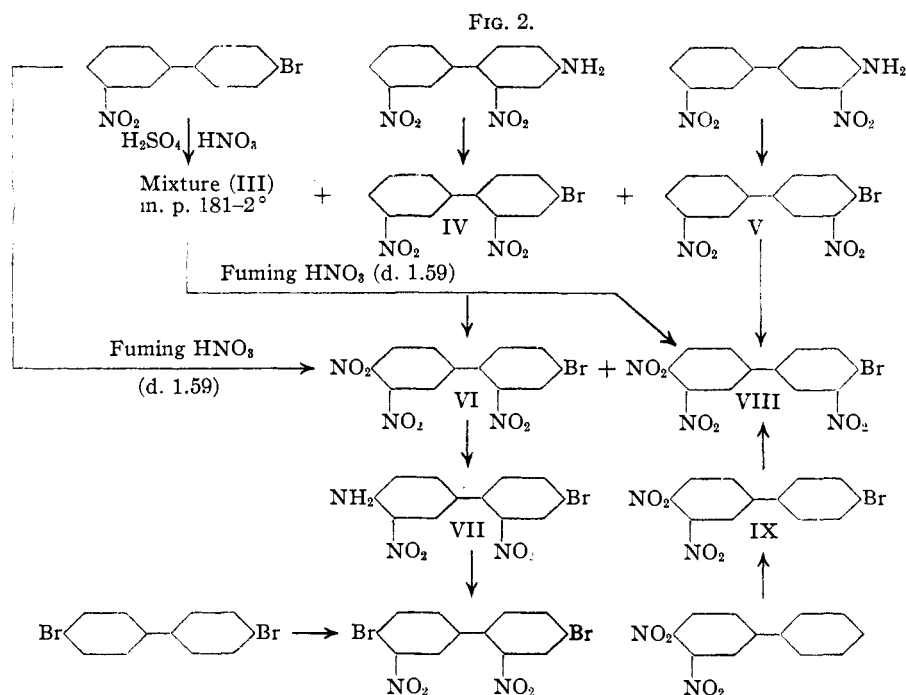
The nitration of 4-bromo-3'-nitrobiphenyl is of interest because in this compound the nitro group is in a position it would not normally assume on the nitration of 4-bromobiphenyl. It was found that if the nitration were carried out according to Mascarelli's general directions, *i. e.*, in a mixture of nitric and sulfuric acids initially kept below 40° but completed at 100° and the product extracted with ether, the ether-insoluble part yielded a constant-melting product III, the analysis of which indicates a trinitrobromobiphenyl mixed with a small amount of a dinitrobromobiphenyl. On oxidation the mixture yields 3-nitro-4-bromobenzoic acid. From the ether soluble portion could be isolated by fractional crystallization a dinitrobromobiphenyl IV (m. p. 143–144°), from alcohol-acetone.

If the nitration were effected under milder conditions, *e. g.*, nitric and sulfuric acids below 40°, nitric acid (sp. gr. 1.5) below 15°, or ethyl nitrate, the reaction product, now soluble in ether, when repeatedly crystallized from alcohol-acetone yielded a constant-melting mixture which analyzed correctly for a dinitrobromobiphenyl. On repeated crystallization from benzene, it yielded a pure isomeric dinitrobromobiphenyl V, m. p. 187–188°. On oxidation the mixture was partially converted into 3-nitro-4-bromobenzoic acid, leaving a residue of the pure isomer IV.

On more drastic nitration with nitric acid (sp. gr. 1.59), at 100°, 4-bromo-3'-nitrobiphenyl is converted into the isomeric trinitrobromobiphenyls VI (predominantly) and VIII.

The structure of isomer IV, suggested by the fact that it does not react with piperidine and on total reduction followed by oxidation yields no acid, was established by the following method: 4-amino-3'-nitrobiphenyl was nitrated to 2,3'-dinitro-4-aminobiphenyl (structure proven by de-

(1) Mascarelli, *Gazz. chim. ital.*, **63**, 654 (1933).(2) LeFèvre, Moir and Turner, *J. Chem. Soc.*, 2330 (1927).(3) Finzi and Bellavita, *Gazz. chim. ital.*, **68**, 77 (1938).(4) LeFèvre and Turner, *J. Chem. Soc.*, 2044 (1926).



amination to 2,3'-dinitrobiphenyl), and the compound resulting from this by replacement of amino by bromine proved identical with IV.

Isomer V was synthesized by nitration of 4-acetamino-3'-nitrobiphenyl to 3,3'-dinitro-4-acetaminobiphenyl (structure proven by hydrolysis and deamination to 3,3'-dinitrobiphenyl) followed by hydrolysis and replacement of amino by bromine.

Isomers IV and V were now separately nitrated further (nitric acid (sp. gr. 1.59) at 100°). The trinitrobromo compound yielded by IV was now found to be identical with VI, obtained by the direct nitration of 4-bromo-3'-nitrobiphenyl under the same conditions. It was found that one nitro group of VI is replaced completely by amino in alcoholic ammonia at 150°. On deamination of the resulting compound (VII), however, IV is regenerated, indicating that the new nitro group is the one attacked by the ammonia. If, however, VII is subjected to the Sandmeyer reaction, the resulting dibromodinitro compound is shown to be identical with 2,3'-dinitro-4,4'-dibromobiphenyl, obtained by the nitration of 4,4'-dibromobiphenyl.^{4,5}

Since the positions of both bromine atoms are known in one compound, and of both nitro groups in the other, the identity of these compounds constitutes a proof of the structure of VI and an inde-

pendent proof of the structure of the dinitration product of 4,4'-dibromobiphenyl.

The replacement of a *p*- instead of a *m*-nitro group by amino in 2,3',4'-trinitro-4-bromobiphenyl seemed somewhat surprising in view of the fact that such compounds as 3,4-dinitromethyl-, iodo-, chloro-, and bromo-benzene all yield *m*-amino derivatives under similar conditions. A study of the reaction of 3,4-dinitrobiphenyl with alcoholic ammonia showed that here, also, the nitro group para to the phenyl nucleus is substituted by amino.

The trinitrobromo compound VIII obtained by the further nitration of V was synthesized as follows: 3,4-dinitrobiphenyl, prepared by the action of copper on phenyl iodide and 3,4-dinitroiodobenzene at 270°, was brominated, and the resulting product (IX) on nitration yielded VIII. Since in IX the position of the two nitro groups is known and in VIII the positions of the bromine atom and of the other nitro group are known, the structures of both VIII and IX are simultaneously proved.

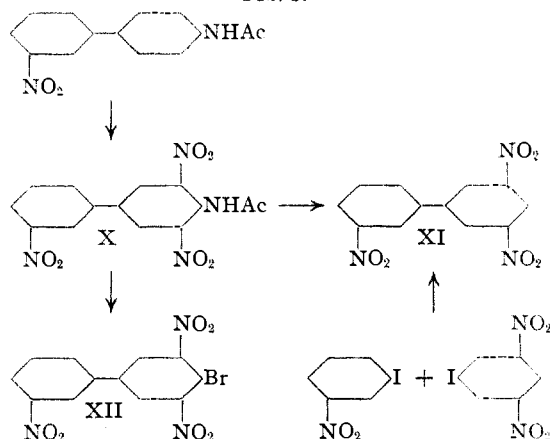
Since on nitration with nitric acid (sp. gr. 1.59) at 100° the previously described mixture (III) yields VIII and in view of the analytical data, it is concluded that it consists largely of VIII mixed with a small amount of a dinitrobromobiphenyl.

The synthesis of 3,3',5'-trinitro-4-bromobiphenyl (XII), another theoretically possible result

(5) Dennett and Turner, *J. Chem. Soc.*, 476 (1926).

of the further nitration of 3,3'-dinitro-4-bromobiphenyl, was accomplished by the dinitration of 4-acetamino-3'-nitrobiphenyl followed by hydrolysis and application of the Sandmeyer reaction. The structure of the intermediate trinitro base (X) was proven by deaminizing it to a trinitrobiphenyl (XI), which proved identical with that obtained by the Ullmann reaction on a mixture of 3,5-dinitroiodobenzene and *m*-nitroiodobenzene. From two moles of 3,5-dinitroiodobenzene, the hitherto undescribed 3,3',5,5'-tetranitrobiphenyl was obtained. It was hoped to reduce one nitro group of this substance and convert it into the trinitro compound mentioned above, but the reduction proved to be unsuccessful.

FIG. 3.



Experimental

Nitration of 4-Bromobiphenyl.—The procedure was the same as that of Mascarelli.¹ Isomer I (ether-insoluble), crystallized from acetone, melted at 210–211°.

Anal. Calcd. for $C_{12}H_7N_2O_6Br$: Br, 24.74. Found: Br, 24.78.

Isomer II (ether-soluble), crystallized from alcohol, melted at 154–155°.

Anal. Calcd. for $C_{12}H_7N_2O_6Br$: Br, 24.74. Found: Br, 24.86.

Synthesis of 3,4'-Dinitro-4-bromobiphenyl (Method of Schoutissen⁶).—To a solution at 0° of 5.2 g. of 3,4'-dinitro-4-aminobiphenyl in 20 cc. of concd. sulfuric acid was added a solution of 2 g. of sodium nitrite in 20 cc. of concd. sulfuric acid. Phosphoric acid (70 cc.) was then added with stirring, keeping the temperature below 2°. After standing one-half hour the resulting solution was poured into a solution of 15 g. of bromine and 15 g. of sodium bromide in 100 cc. of ice-water. After one hour, copper powder was added and the mixture allowed to stand overnight. It was then heated for one hour and the precipitate filtered off and recrystallized from acetone; m. p. 207–208°. This was not depressed by admixture with isomer I, above.

(6) Schoutissen, *THIS JOURNAL*, **55**, 4538 (1933).

Nitration of 4-Nitro-4'-bromobiphenyl.—The procedure was again the same as that of Mascarelli.¹ From 17.7 g. of starting material, the ether-insoluble portion yielded 2.5 g. of pure isomer I.

Nitration of 4-Bromo-2'-nitrobiphenyl.—Six grams of 4-bromo-2'-nitrobiphenyl was added gradually to a mixture of 20 cc. of concd. sulfuric acid and 26 cc. of concd. nitric acid, keeping the temperature below 30°. After one hour of stirring at room temperature the mixture was poured into water and the precipitated solid crystallized from alcohol-acetone; yield 3 g., melting at 154–155°, and unchanged when mixed with isomer II. On oxidation with chromic acid, this substance yields 3-nitro-4-bromobenzoic acid.

Preparation of 2,3',4-Trinitro-4'-bromobiphenyl.—This substance (m. p. 180–181°) was obtained by the action of fuming nitric acid (sp. gr. 1.59) at 100° on each of the following: 3,4'-dinitro-4-bromobiphenyl, 2,3'-dinitro-4-bromobiphenyl, 4-nitro-4'-bromobiphenyl, 2-nitro-4'-bromobiphenyl.

Nitration of 4-Bromo-3'-nitrobiphenyl

Method A.—4-Bromo-3'-nitrobiphenyl (17.7 g.) was added slowly to a mixture of 30 g. of concd. sulfuric acid and 20 g. of concd. nitric acid, keeping the temperature below 40°. The reaction was completed by heating on the steam-bath for one hour. The mixture was then poured into ice-water, filtered, washed and dried. After five extractions with ether, an insoluble residue was obtained which on crystallization from acetone-alcohol yielded 2 g. of a product melting constantly at 181–182°. The analysis indicated it to be an impure trinitro bromo derivative.

Anal. Calcd. for $C_{12}H_6N_3O_6Br$: Br, 21.72; N, 11.42. Found: Br, 22.42; N, 11.08.

On oxidation with chromic acid it yielded 3-nitro-4-bromobenzoic acid.

The ether soluble material was evaporated to dryness, and on repeated crystallization from alcohol-acetone yielded 2.5 g. of a product (IV) melting at 143–144°.

Method B.—Fifteen grams of 4-bromo-3'-nitrobiphenyl was added gradually to a stirred mixture of 30 g. of sulfuric acid and 20 g. of nitric acid, keeping the temperature below 40°. The reaction mixture, which proved to be soluble in ether, was poured into water, washed and dried. After eight crystallizations from benzene 0.4 g. of a product (V) melting at 189–190° was obtained. If the nitration mixture were crystallized from alcohol-acetone, 8.7 g. of a mixture melting at 129–130° was obtained.

Anal. Calcd. for $C_{12}H_7N_2O_6Br$: Br, 24.74. Found: Br, 24.91.

On oxidation with chromic acid the mixture yielded 3-nitro-4-bromobenzoic acid and pure isomer IV.

Method C.—Twenty grams of 4-bromo-3'-nitrobiphenyl was dissolved in 170 cc. of fuming nitric acid (sp. gr. 1.59) and the mixture heated for one hour on the steam-bath. It was then poured into water, and the resulting solid (VI) crystallized four times from alcohol-acetone; yield, 5 g.; m. p. 170–171°.

Anal. Calcd. for $C_{12}H_6N_3O_6Br$: Br, 21.72. Found: Br, 22.01.

From the filtrate of the first crystallization a solid separated on standing which after repeated crystallization from alcohol-acetone yielded 0.7 g. of a solid melting at 191–192° and unchanged when mixed with VIII.

Nitration of the Mixture (III).—Nitration according to the above procedure yielded a trinitrobromobiphenyl (VIII), m. p. 192–193°.

2,3'-Dinitro-4-aminobiphenyl.—Fifteen grams of 3-nitro-4'-aminobiphenyl was dissolved in a mixture of 13 cc. of 15% oleum and 50 cc. of concd. sulfuric acid. Potassium nitrate (7.5 g.) was added slowly, keeping the temperature below 6°. The reaction mixture was then allowed to warm to room temperature, poured into ice water and neutralized with potassium hydroxide. On crystallization from benzene, 11 g. of crude base, m. p. 154°, was obtained. The acetyl derivative was crystallized from alcohol, m. p. 215–216°.

Anal. Calcd. for $C_{14}H_{11}N_3O_5$: N, 13.96. Found: N, 13.84.

The pure base was obtained by hydrolysis of the acetyl derivative in dilute sulfuric acid. It was crystallized from benzene, m. p. 157–158°.

Anal. Calcd. for $C_{12}H_9N_3O_4$: N, 16.22. Found: N, 16.44.

On deamination the above base yielded a product melting unchanged when mixed with 2,3'-dinitrobiphenyl.

2,3'-Dinitro-4-bromobiphenyl.—This was prepared by Schoutissen's⁶ method from 2,3'-dinitro-4-aminobiphenyl. After crystallization from alcohol-acetone it melted at 143–144°. The melting point was unchanged by admixture with isomer IV.

Anal. Calcd. for $C_{12}H_7N_2O_4Br$: Br, 24.74. Found: Br, 24.99.

3,3'-Dinitro-4-aminobiphenyl.—To a solution of 6 g. of 4-acetamino-3'-nitrobiphenyl in 30 cc. of glacial acetic acid and 10 cc. of acetic anhydride at 70° was added a solution of 1.5 cc. of nitric acid (sp. gr. 1.5) in 5 cc. of acetic acid. After one hour of stirring at this temperature, the mixture was poured into ice water, and the precipitated solid recrystallized from glacial acetic acid, yielding 4.5 g., m. p. 241–242°.

Anal. Calcd. for $C_{14}H_{11}N_3O_5$: N, 13.96. Found: N, 13.74.

The free base was liberated by hydrolysis with dilute sulfuric acid at 120°. On crystallization from benzene, it melted at 206–207°.

Anal. Calcd. for $C_{12}H_9N_3O_4$: N, 16.22. Found: N, 16.51.

On deamination the base was converted into 3,3'-dinitrobiphenyl.

3,3'-Dinitro-4-bromobiphenyl.—This was prepared from the above base in the same way as 2,3'-dinitro-4-bromobiphenyl. On crystallization from acetone-alcohol it melts at 187–188°.

Anal. Calcd. for $C_{12}H_7N_2O_4Br$: Br, 24.74. Found: Br, 24.95.

The melting point was unchanged by admixture with isomer V.

2,3',4'-Trinitro-4-bromobiphenyl (VI).—This was prepared from 2,3'-dinitro-4-bromobiphenyl by the same method used to prepare it from 4-bromo-3'-nitrobiphenyl.

2,3'-Dinitro-4'-amino-4-bromobiphenyl.—2,3',4-Trinitro-4-bromobiphenyl (4.5 g.), suspended in a solution of alcoholic ammonia, was heated in a sealed tube for ten hours at 150°. After evaporation of the alcohol, the residue was taken up in benzene and treated with dry hydrogen chloride. From the precipitated hydrochloride the free base was liberated with ammonium hydroxide and crystallized from alcohol-acetone; m. p. 223–224°.

Anal. Calcd. for $C_{12}H_8N_3O_4Br$: Br, 23.65. Found: Br, 23.85.

Deamination.—One gram of the above base suspended in 90 cc. of alcohol was treated with 20 cc. of 1–1 sulfuric acid and 3 g. of solid sodium nitrite. After one hour of heating on the steam-bath, the deaminated product was precipitated in ice-water and recrystallized from alcohol. It melted unchanged when mixed with 2,3'-dinitro-4-bromobiphenyl.

2,3'-Dinitro-4,4'-dibromobiphenyl.—This was obtained from the 2,3'-dinitro-4'-amino-4-bromobiphenyl by the method of Schoutissen as in the case of 2,3'-dinitro-4-bromobiphenyl. It melted at 152–153°, and was shown by mixed melting point to be identical with the product obtained by Dennett and Turner⁵ from the nitration of 4,4'-dibromobiphenyl.

3,4-Dinitrobiphenyl.—The following method of synthesis was adopted after attempts to oxidize 3-nitro-4-aminobiphenyl with Caro's acid, and to apply Sandmeyer's reaction to it had failed. A mixture of 19 g. of 3,4-dinitroiodobenzene, 20 g. of iodobenzene and 22 g. of copper powder was heated for three hours in a sealed tube at 280°. The copper compounds were then removed by extraction with acetone, the acetone evaporated off, and the residue distilled in vacuum. The fraction boiling at 180–210° (3 mm.) was found to be unchanged 3,4-dinitroiodobenzene. The fraction boiling at 210–245° (3 mm.) was recrystallized from methanol, yielding 3.4 g. of 3,4-dinitrobiphenyl, m. p. 86–87°. The pure product melts at 87–88°.

Anal. Calcd. for $C_{12}H_8N_2O_4$: N, 11.48. Found: N, 11.70.

Ammonolysis of 3,4-Dinitrobiphenyl.—3,4-Dinitrobiphenyl (2.5 g.), dissolved in a large excess of alcoholic ammonia, was heated in a sealed tube at 150° for ten hours. After evaporation of the solvent the residue on crystallization from alcohol yielded 1 g. of product melting at 162–163°, or 0.6 g., m. p. 168°. This melted unchanged when mixed with 3-nitro-4-aminobiphenyl. From the filtrate no other pure compound could be isolated.

3,4-Dinitro-4'-bromobiphenyl (IX).—A solution containing 7.1 g. of 3,4-dinitrobiphenyl, 3.5 cc. of bromine, and 0.1 g. of ferric chloride in 30 cc. of glacial acetic acid was heated at 90° for forty hours until the bromine color had disappeared. The mixture was then poured into water, and the resulting solid crystallized eight times from alcohol, yielding 0.5 g. of a product melting at 167–168°. Since very incomplete bromination was indicated, the filtrates were all evaporated down and rebrminated, yielding an additional 1.2 g.

Anal. Calcd. for $C_{12}H_7N_2O_4Br$: Br, 24.74. Found: Br, 24.80.

3,3',4'-Trinitro-4'-bromobiphenyl (VIII).—This was obtained by the nitration of 3,3'-dinitro-4-bromobiphenyl

with nitric acid (sp. gr. 1.59) at 100°. When crystallized from benzene it melts at 192–193°.

Anal. Calcd. for $C_{12}H_6N_3O_6Br$: Br, 21.72. Found: Br, 22.08.

The same product was also obtained by the nitration of IX or of the mixture III.

3,3',5-Trinitro-4-aminobiphenyl (X).—Ten grams of 3,3'-dinitro-4-acetaminobiphenyl was added gradually to 60 cc. of nitric acid (sp. gr. 1.5) keeping the temperature below 8°. On pouring the solution into water and recrystallizing from acetone-alcohol, the acetylated base was obtained yielding 4.5 g., m. p. 241–242°. The pure product melts at 242–243°.

Anal. Calcd. for $C_{14}H_{10}N_4O_7$: N, 16.19. Found: N, 15.83.

This product could also be obtained in a lower state of purity by direct nitration of 4-acetamino-3'-nitrobiphenyl.

The free base was obtained by hydrolysis of the acetamino compound with dilute sulfuric acid at 120°. On crystallization from glacial acetic acid it melted at 233°.

Anal. Calcd. for $C_{12}H_8N_3O_6$: N, 18.43. Found: N, 18.19.

Deamination of 3,3',5-Trinitro-4-aminobiphenyl.—The deamination of 3,3',5-trinitro-4-aminobiphenyl by the simple method used to prepare 2,3'-dinitro-4-bromobiphenyl proved ineffective in this case, as the base was recovered unchanged. The following procedure was therefore adopted: 3.5 g. of the trinitro base, dissolved in 30 cc. of concd. sulfuric acid, was treated at 0° with a solution of 1.5 g. of sodium nitrite in 20 cc. of concd. sulfuric acid. The mixture was treated at 2° with a solution of 70 cc. of phosphoric acid, and then with 40 cc. of 20% oleum, at 15–20°. The resulting solution was poured into 250 cc. of boiling ethanol, and refluxed for one hour. After pouring into ice-water, the resulting solid was filtered and crystallized from methanol-acetone, yielding 1 g. of a product melting at 167–168°. This was further purified by treatment with chromic acid which appeared to remove traces of unchanged base. The melting point of the pure product was 177–178°.

Anal. Calcd. for $C_{12}H_7N_3O_6$: N, 14.54. Found: N, 14.48.

3,3',5-Trinitrobiphenyl (XI).—A mixture of 12 g. of 3,5-dinitroiodobenzene, 7.5 g. of *m*-nitroiodobenzene and 8 g. of copper powder was heated for an hour at 270°. From the ether extract it was possible to obtain by repeated crystallization from alcohol-acetone a small amount of a solid melting at 173–174° and unchanged when mixed with the deamination product of 3,3',5-trinitro-4-aminobiphenyl.

3,3',5-Trinitro-4-bromobiphenyl (XII).—This was prepared from the corresponding base by Schoutissen's method. From 3.5 g. of base was obtained 3 g. of pure product, melting at 222–223° (from alcohol-acetone).

Anal. Calcd. for $C_{12}H_6N_3O_6Br$: Br, 21.72. Found: Br, 22.04.

3,3',5,5'-Tetranitrobiphenyl.—A mixture of 13 g. of 3,5-dinitroiodobenzene and 8.5 g. of copper powder was heated with stirring at 270° for one and one-half hours. The acetone extract, after evaporation, was crystallized from toluene, yielding 0.7 g. of a solid melting at 228–229°.

Anal. Calcd. for $C_{12}H_6N_4O_8$: N, 16.77. Found: N, 16.52.

The nitrogen analyses were carried out by Messrs. Richard Schock and Chester White.

Summary

1. The nitration of 4-bromobiphenyl according to Mascarelli is shown to yield 3,4'-dinitro-4-bromobiphenyl and 2',3-dinitro-4-bromobiphenyl.
2. Depending on conditions, the following substances have been obtained from the nitration of 4-bromo-3'-nitrobiphenyl: 2,3'-dinitro-4-bromobiphenyl, 3,3'-dinitro-4-bromobiphenyl, 2,3',4'-trinitro-4-bromobiphenyl and 3,3',4'-trinitro-4-bromobiphenyl.
3. Proof of the structures of the above substances is given.

PHILADELPHIA, PENNSYLVANIA RECEIVED MAY 11, 1942

[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY, NATIONAL INSTITUTE OF HEALTH, U. S. PUBLIC HEALTH SERVICE]

Syntheses of Epi-lactose and Lactose

BY W. T. HASKINS, RAYMOND M. HANN AND C. S. HUDSON

In continuation of our use of acetone-D-mannosan $\langle 1,5 \rangle \beta \langle 1,6 \rangle^1$ for the synthesis of disaccharides² having their linkage at carbon atom 4, we have now combined this substance with acetobromo-D-galactose and thereby produced, first, the epimer of lactose (4- β -D-galactopyranosido]-D-mannose), which we shall designate epi-lactose for brevity, and, second, lactose (4- β -D-galactopyranosido]-D-glucose) itself.

(1) Knauf, Hann and Hudson, *THIS JOURNAL*, **63**, 1447 (1941).

(2) Haskins, Hann and Hudson, *ibid.*, **63**, 1724 (1941); **64**, 1490 (1942).

pyranosido]-D-glucose) itself. Bergmann, Schotte and Rennert³ discovered epi-lactose by the epimerization of lactose through the reactions *lactose* \rightarrow *acetobromolactose* \rightarrow *hexaacetyl lactal* \rightarrow *lactal* \rightarrow *epi-lactose*. The reverse transformation of epi-lactose to lactose, which has now assumed importance, has been accomplished readily by the reactions *epi-lactose* \rightarrow *acetobromo-epi-lactose* \rightarrow *hexaacetyl lactal* \rightarrow *lactose hexaacetate* \rightarrow *lactose octa-*

(3) Bergmann, Schotte and Rennert, *Ann.*, **434**, 94 (1923).