TABLE VI

NITROPRUSSIDE TEST FOR SULFHYDRYL GROUP OF CYSTEINE OR THIOGLYCOLATE IN THE PRESENCE OF A 100% EXCESS OF AN UNSATURATED KETONE

++++ Strong red color; +++ Moderate red color; ++ Weak red color; + Faint red color; ± Dubious pinkish color; − No color produced; ? Reaction abnormal. Blue color produced.

Ketone	Sulfhydryl compound	Nitroprusside test 2 hours	Nitroprusside test 24 hours
Mesityl oxide	Cysteine	?	?
	Thioglycolate	++++	++++
Phorone	Cysteine	?	?
	Thioglycolate	++++	++++
Isophorone	Cysteine	++++	++++
	Thioglycolate	++++	++++
Indalone	Cysteine	+++	+++
	Thioglycolate	++++	++++
Benzalacetone	Cysteine	++	+
	Thioglycolate	+++	+++
Furfuralacetone	Cysteine	++	±
	Thioglycolate	++++	++++
Acrylophenone	Cysteine	+	−
	Thioglycolate	−	−
Benzalacetophenone	Cysteine	++	+
	Thioglycolate	+++	+++
Furfuralacetophenone	Cysteine	+++	±
	Thioglycolate	++++	++++
Clavacin	Cysteine	−	−
	Thioglycolate	+	−
Penicillic acid	Cysteine	−	−
	Thioglycolate	±	±

lite or interference with an enzyme system could account for the activity of antibacterial substances. The definite proof by Hellerman, Chinard and Deitz[24] that the inhibition of the enzyme urease by an organic mercurial is a result of the combination of the latter with sulfhydryl groups of the enzyme gives strong support to these hypotheses.

Acknowledgment.—The authors are indebted to Professor Selman A. Waksman for helpful advice, criticism, and encouragement, and to Miss Dorcas Fasan for a portion of the bacteriological testing.

Summary

1. The antibiotic activities of clavacin and of penicillic acid probably are due to their reaction with the sulfhydryl groups of bacterial enzyme systems or with sulfhydryl-containing metabolites essential to the bacteria.

2. Clavacin and penicillic acid are inactivated by an excess of a sulfhydryl compound.

3. Clavacin and penicillic acid, when present in excess, abolish the nitroprusside reaction of cysteine or thioglycolic acid.

4. Certain synthetic α,β-unsaturated ketones, particularly acrylophenone, closely resemble clavacin, both in their bacteriostatic and fungistatic properties, and in their reactivity toward sulfhydryl compounds.

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[24] Hellerman, Chinard and Deitz, *J. Biol. Chem.*, **147**, 443 (1943).

NEW BRUNSWICK, N. J. RECEIVED SEPTEMBER 28, 1944

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF TEMPLE UNIVERSITY]

The Nitration of Certain Halobiphenyls. IV. Nitro Derivatives of 3-Bromobiphenyl

BY FRANCIS H. CASE

The nitration of 3-chlorobiphenyl according to Mascarelli and Gatti[1] yields a dinitro derivative (m. p. 202–203°) of unknown constitution. We have now shown it to be 3-chloro-4,4′-dinitrobiphenyl by synthesizing it from the known 3-amino-4,4′-dinitrobiphenyl.[2] The nitration of either 3-bromobiphenyl or of 3-bromo-4′-nitrobiphenyl with ethyl nitrate yields 3-bromo-4,4′-dinitrobiphenyl (I), whose structure is similarly proved. It was not found possible to isolate any of the expected 3-bromo-4′,6-dinitrobiphenyl (II) from either of these reaction mixtures. This product was synthesized, however, by the following method: 3-acetamino-4′-nitrobiphenyl[2] was converted into 3-acetamino-4′,6-dinitrobiphenyl (III) by nitration with ethyl nitrate in sulfuric acid. Hydrolysis afforded the base, which was then converted into the bromodinitro derivative. The structure of III and hence also of II was proved by the fact that on reduction and acetylation it yielded the same acetyl derivative IV as was obtained by similarly treating 2-acetamino-4′,5-dinitrobiphenyl.[3]

Analysis and molecular weight determination showed this to be a hexa-acetyl derivative. 3-Bromo-4′,6-dinitrobiphenyl also was obtained by brominating 4-nitro-4′-acetaminobiphenyl,[4] hydrolyzing, nitrating the free base, and deaminizing. This product proved to be identical with II, thus proving the structure of the bromodinitro base V.

In another attempt to synthesize II, 2-nitro-5-bromobiphenyl[4a] (m. p. 55–56°) was synthesized from 2-nitro-5-bromoaniline by Gomberg's reaction. Subsequent nitration did not, however, yield any definite product.

In the nitration of 3-bromo-4′-nitrobiphenyl with nitric and sulfuric acids, a small amount of a

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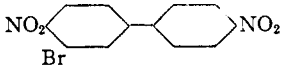
[1] Mascarelli and Gatti, *Gazz. chim. ital.*, **63**, 654 (1933).

[2] Case, THIS JOURNAL, **61**, 767 (1939).

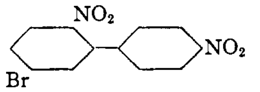
[3] Scarborough and Waters, *J. Chem. Soc.*, 89 (1927).

[4] Case, THIS JOURNAL, **60**, 424 (1938).

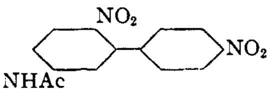
[4a] The compound reported by Campbell, Anderson and Gilmore, *J. Chem. Soc.*, 449 (1940), prepared from 2-amino-5-bromobiphenyl and melting at 230°, is evidently not 2-nitro-5-bromobiphenyl.



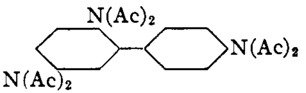
I



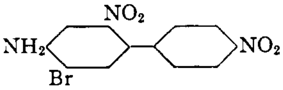
II



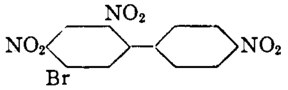
III



IV



V



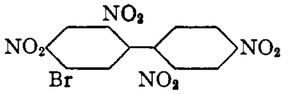
VI

trinitrobromo derivative VI was obtained. It was found that both I and II on nitration with ethyl nitrate (1 mole) yield the same trinitro derivative (VI), thus proving the structure of VI. On drastic nitration (HNO_3 (sp. gr. 1.5) and H_2SO_4) the same tetranitro derivative VII was obtained from I, II and VI.

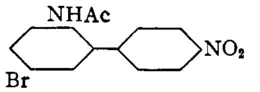
The synthesis of 3-bromo-4′-nitrobiphenyl, previously obtained from 4-nitro-4′-aminobiphenyl,[4] is best carried out by bromination of 2-acetamino-4′-nitrobiphenyl followed by hydrolysis and deamination. The structure of the bromination product was shown to be 3-bromo-4′-nitro-6-acetaminobiphenyl VIII by hydrolysis, conversion of the base to a dibromonitro derivative IX, reduction, and oxidation to 2,5-dibromobenzoic acid.

An attempt was made to prepare 2-nitro-3′-bromobiphenyl from 2,3′-dinitrobiphenyl[5] which has been found in this Laboratory to yield 2-nitro-3′-aminobiphenyl on partial reduction. This method was, however, found less convenient than that of Lesslie and Turner.[6] The nitration of 2-nitro-3′-bromobiphenyl in a nitric–sulfuric acid mixture was found to yield two isomers—X m. p. 156–157°, and XI m. p. 139–140°—which could be separated due to the lower solubility of X in benzene. The structure of XI was proved by oxidation to 3-bromo-4-nitrobenzoic acid, while X was synthesized by a mixed Ullmann reaction from *o*-nitroiodobenzene and 2-nitro-5-bromoiodobenzene. On drastic nitration with fuming nitric acid (sp. gr. 1.5) and sulfuric acid, I, X, and XI, all yield 3-bromo-2′,4,4′,6-tetranitrobiphenyl VII, whose structure is thus proved by its synthesis from different compounds each containing at least two of these radicals in known positions.

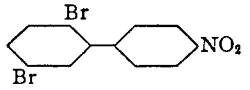
The nitration of 3-bromo-2′,4-dinitrobiphenyl (XI) with ethyl nitrate (1 mole) yields 3-bromo-2′,4,6-trinitrobiphenyl XII, the structure of which depends on the following facts: 2-nitro-3′-acetaminobiphenyl yields on nitration with ethyl nitrate two isomers—3-acetamino-2′,4-dinitrobiphenyl (XIII) and 3-acetamino-2′,6-dinitrobiphenyl (XIV). The structure of XIII is based on the deamination of its base to 2,4′-dinitrobiphenyl, and of XIV on the conversion of its base by the Sandmeyer reaction to X, of known structure. Both XIII and XIV in fuming nitric acid yield the same trinitroacetamino derivative, XV, which is therefore 3-acetamino-2′,4,6-trinitrobiphenyl, due to its dual method of synthesis. The base obtained by hydrolyzing XV yields a trinitrobromo derivative identical with XII.



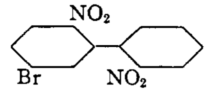
VII



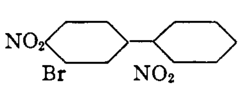
VIII



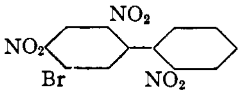
IX



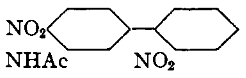
X



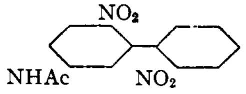
XI



XII



XIII

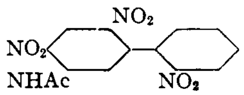


XIV

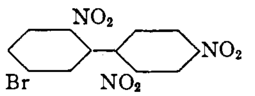
From the nitration of X, 3-bromo-2′,4′,6-trinitrobiphenyl XVI was obtained, in addition to a trace of XII. The structure of XVI is based on the fact that it also results from the nitration of 3-bromo-2′,4′-dinitrobiphenyl XVII, obtained for the first time by a mixed Ullmann reaction.

In preliminary experiments on the preparation of III, 3-*p*-toluene-sulfonamidobiphenyl was nitrated in dilute nitric acid with the idea that the nitro group might be directed to the 6-position. The resulting base, however, proved to be 3-amino-4-nitrobiphenyl, the same product obtained from the nitration of 3-acetaminobiphenyl.[5]

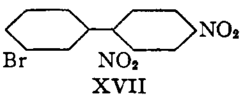
The nitration of 3-acetamino-4′-nitrobiphenyl by means of ethyl nitrate yields chiefly III, but a considerable amount of 3-acetamino-4,4′-dinitrobiphenyl XVIII was also obtained. With fuming nitric acid (sp. gr. 1.6) as the reagent, III was the only dinitro product isolated, but in addition a small amount of 3-acetamino-4,4′,6-trinitrobiphenyl XIX was obtained. The structure of this compound was proved by the fact that it results from the nitration of both XVIII and III.



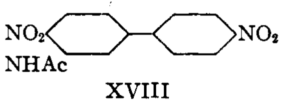
XV



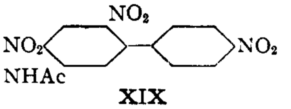
XVI



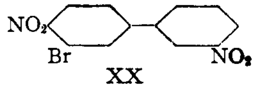
XVII



XVIII



XIX



XX

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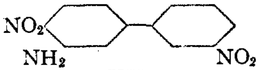
(5) Blakey and Scarborough, *J. Chem. Soc.*, 3005 (1927).

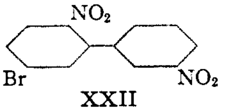
(6) Lesslie and Turner, *J. Chem. Soc.*, 1590 (1933).

It is interesting to note that whereas 3-acetaminobiphenyl yields only XVIII on nitration in fuming nitric acid,[2] only III is obtained when 3-acetamino-4'-nitrobiphenyl is nitrated under similar conditions. This would indicate a tendency (at least in this solvent) on the part of the *p*-nitrophenyl group to orient the entering nitro group para to the acetamino group, whereas the phenyl group directs it to the ortho-position.

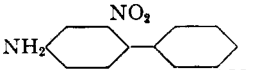
3-Bromo-3'-nitrobiphenyl[7] was synthesized by the deamination of 3-nitro-3'-bromo-4'-aminobiphenyl.[2] From the crude nitration product obtained by treating it with a nitric–sulfuric acid mixture or with ethyl nitrate, it was possible to obtain by repeated crystallization from ethanol a dinitrobromobiphenyl XX. If, on the other hand, the mixture were heated with alcoholic ammonia and the resulting base XXI precipitated out of a benzene solution with dry hydrogen chloride, an isomeric dinitrobromobiphenyl XXII could be obtained from the filtrate. The structure of XX follows from the fact that XXI on deamination yields 3,4'-dinitrobiphenyl, and furthermore XXI has been reconverted to XX by the Sandmeyer reaction.



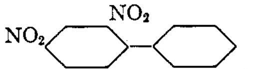
XXI



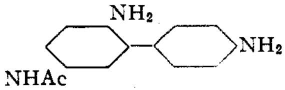
XXII



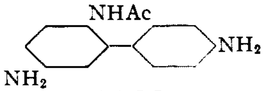
XXIII



XXIV



XXV



XXVI

The synthesis of XXII was accomplished by the following series of reactions: 2,3'-dinitro-4-aminobiphenyl[8] was converted to a monobromo derivative XXIII, which was deaminized, yielding XXII.

Since this method of proof does not eliminate the possibility that the second nitro group might have entered the ring between the bromine and *m*-nitrophenyl linkages, we have synthesized XXII by the Ullmann reaction on a mixture of *m*-nitroiodobenzene and 2-nitro-5-bromoiodobenzene. This proves the structure of XXIII as well as of XXII.

On drastic nitration, XX and XXII as well as 3-bromo-3'-nitrobiphenyl yield 3-bromo-3',4,6-trinitrobiphenyl XXIV, whose structure depends on its dual method of synthesis and the fact that on oxidation it yields *m*-nitrobenzoic acid.

The author gratefully acknowledges the assistance of Messrs. Richard Schock, Marvin Spiro, Isadore Swerlick, Walter Senyshyn, and Bernard Brown in various phases of this work, which has been supported by a grant from the Temple University Committee on Research and Publication.

Experimental Part

3-Chloro-4,4'-dinitrobiphenyl.—The method of Schoutissen[9] was used. To a solution of 2 g. of 3-amino-4,4'-dinitrobiphenyl at 0° in 15 cc. of concentrated sulfuric acid, was added a suspension of 0.6 g. of sodium nitrite in 15 cc. of concentrated sulfuric acid. An 85% solution of phosphoric acid (50 cc.) was then added with stirring, keeping the temperature below 0°. After fifteen minutes the resulting solution was poured into a solution of cuprous chloride made by heating 12.5 g. of copper sulfate, 10 cc. of water, 40 cc. of concentrated hydrochloric acid and 3.5 g. of copper powder. After standing overnight, the reaction mixture was heated to boiling and diluted with water. The precipitate was filtered off and recrystallized from acetone–ethanol: yield, 0.8 g.; m. p. 202–203°, and unchanged when mixed with the dinitration product of 3-chlorobiphenyl.

3-Bromo-4'-nitro-6-acetaminobiphenyl (VIII).—A solution of 198 g. of 2-acetamino-4'-nitrobiphenyl and 200 g. of anhydrous sodium acetate in 2 liters of glacial acetic acid was treated with 43 cc. of bromine and allowed to stand overnight. The precipitate obtained by pouring the solution into ice-water was crystallized from acetone–ethanol: yield, 164 g.; m. p. 208–209°. The pure product melts at 213–214°.

Anal. Calcd. for $C_{14}H_{11}N_2O_3Br$: Br, 23.85. Found: Br, 23.73.

3-Bromo-4'-nitro-6-aminobiphenyl.—This was obtained by hydrolyzing the above-mentioned acetamino compound in a boiling solution of dilute sulfuric acid (one volume of sulfuric acid to two volumes of water). On crystallization from acetone–ethanol, it melts at 151–152°.

Anal. Calcd. for $C_{12}H_9N_2O_2Br$: Br, 27.28. Found: Br, 27.33.

3-Bromo-4'-nitrobiphenyl.—The above-mentioned base (102 g.) was deaminized by treating 1 liter of its warm alcoholic solution acidified with dilute sulfuric acid, with sodium nitrite (40 g.): yield, 33 g.; m. p. 93–94°. It melted unchanged when mixed with a specimen prepared from 4-nitro-4'-aminobiphenyl.[4]

2,5-Dibromo-4'-nitrobiphenyl (IX).—This was prepared from 3-bromo-4'-nitro-6-aminobiphenyl by the same method used in the preparation of 2,5-dibromo-3'-nitrobiphenyl.[10] After crystallization from ethanol it melts at 101–102°.

Anal. Calcd. for $C_{12}H_7NO_2Br_2$: Br, 44.79. Found: Br, 44.75.

2,5-Dibromo-4'-acetaminobiphenyl.—The above-mentioned dibromonitro compound was reduced by stannous chloride in ethanol and acetylated. The product thus obtained melts at 178–179° when crystallized from ethanol.

Anal. Calcd. for $C_{14}H_{11}NOBr_2$: Br, 43.35. Found: Br, 43.34.

2,5-Dibromo-4'-aminobiphenyl.—This was prepared by the hydrolysis of the above-mentioned acetamino derivative. On crystallization from aqueous ethanol, it melts at 94–95°.

Anal. Calcd. for $C_{12}H_9NBr_2$: Br, 48.89. Found: Br, 48.47.

Oxidation of the crude base yielded a product melting unchanged when mixed with 2,5-dibromobenzoic acid.

Nitration of 3-Bromobiphenyl.—To a solution of 9.3 g. of *m*-bromobiphenyl in 80 cc. of concentrated sulfuric acid, 3.4 cc. (1 mole) of ethyl nitrate slowly was added, keeping the temperature below 2°. After one hour the crude reaction product was separated by pouring the nitration mixture into ice-water. Crystallization from acetone–ethanol yielded 1.3 g. of 3-bromo-4,4'-dinitrobiphenyl;

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(7) Mascarelli and Gatti, *Atti R. Accad. Scienze Torino*, **65**, 143 (1930).

(8) Case, This Journal, **64**, 1848 (1942).

(9) Schoutissen, This Journal, **55**, 4531 (1933).

(10) Case, This Journal, **65**, 2138 (1943).

m. p. 201–202°. From the filtrate after repeated crystallization, 0.2 g. of 3-bromo-2′,6-dinitrobiphenyl was obtained, identified with X by mixed melting point.

Nitration of 3-Bromo-4′-nitrobiphenyl.—The crude material from the nitration of 8.8 g. of 3-bromo-4′-nitrobiphenyl with 2.8 cc. of ethyl nitrate in 63 cc. of concentrated sulfuric acid (below 2°) was extracted with warm ethanol. The insoluble part, after crystallization from acetone–ethanol, yielded 3.4 g. melting at 199° or above. Pure 3-bromo-4,4′-dinitrobiphenyl melts at 205–206°. No other product could be isolated from the reaction mixture.

Anal. Calcd. for $C_{12}H_7N_2O_4Br$: N, 8.67. Found: N, 8.77.

The nitration was also carried out as follows: eight grams of 3-bromo-4′-nitrobiphenyl was added slowly to a mixture of 40 g. of sulfuric acid and 28 g. of nitric acid. The reaction mixture, worked up as before, yielded 1.6 g. of 3-bromo-4,4′-dinitrobiphenyl; m. p. 204–205°. From the ethanol-soluble part after repeated crystallization from ethanol 0.4 g. of 3-bromo-4,4′,6-trinitrobiphenyl (VI) (m. p. 152–153°) was obtained. This melted unchanged when mixed with the nitration product of 3-bromo-4,4′-dinitrobiphenyl (see below).

3-Acetamino-4′,6-dinitrobiphenyl (III).—From 36 g. of 3-acetamino-4′-nitrobiphenyl[2] dissolved in 250 cc. of sulfuric acid and nitrated with 11.9 cc. of ethyl nitrate at 2°, was obtained 18 g. of the above-mentioned acetamino dinitrobiphenyl (m. p. 239–240°) by crystallization of the crude nitration mixture from acetone–ethanol.

Anal. Calcd. for $C_{14}H_{11}N_3O_5$: N, 13.96. Found: N, 13.80.

The evaporated filtrate from the above-mentioned compound on extraction with benzene and crystallization from ethanol yielded 4.6 g. of a crude product, m. p. 178°, which on hydrolysis yielded 2.8 g. of pure 3-amino-4,4′-dinitrobiphenyl, melting at 250–251° and unchanged when mixed with a sample prepared by nitrating 3-acetaminobiphenyl with fuming nitric acid.[2]

3-Amino-4′,6-dinitrobiphenyl.—This was prepared by hydrolyzing the acetamino derivative with dilute sulfuric acid. When crystallized from acetone–ethanol, it melts at 216–217°.

Anal. Calcd. for $C_{12}H_9N_3O_4$: N, 16.22. Found: N, 16.38.

3-*p*-Toluenesulfonamidobiphenyl.—To a cooled solution of 42.5 g. of 3-aminobiphenyl in 79 g. of pyridine was added 52.5 g. of *p*-toluenesulfone chloride in small portions, keeping the temperature below 20°. After three hours of stirring, the mixture was poured into 300 cc. of concentrated hydrochloric acid in 1 liter of ice-water. The reaction product solidified after two days. On recrystallization from ethanol, 48 g. was obtained, m. p. 115–116°.

Anal. Calcd. for $C_{19}H_{17}O_2NS$: S, 9.92. Found: S, 9.83.

4-Nitro-3-*p*-toluenesulfonamidobiphenyl.—A suspension of 45 g. of 3-*p*-toluenesulfonamidobiphenyl in 50 cc. of concentrated nitric acid and 500 cc. of water was warmed for several hours on the steam-bath. The resulting gummy product was crystallized from ethanol; yield, 8 g.; m. p. 174–175°. The pure product melts at 175–176°.

Anal. Calcd. for $C_{19}H_{16}O_4N_2S$: S, 8.71. Found: S, 8.69.

The base obtained by hydrolyzing the above nitrosulfonamide with hot dilute sulfuric acid, has the same melting point (116–117°) as that prepared by the method of Blakey and Scarborough,[5] and on deamination yields 4-nitrobiphenyl.

3-Acetamino-4,4′,6-trinitrobiphenyl (XIX).—Nitration of 3-acetamino-4′-nitrobiphenyl (5 g.) in 150 cc. of fuming nitric acid (sp. gr. 1.6) at −1° yielded 3 g. of crude material which was extracted with benzene. The benzene-insoluble portion on crystallization from ethanol yielded 1.2 g., m. p. 229–230°. By further purification the melting point was raised to 236° (with sintering). On admixture with III, the melting point was not depressed. From the benzene soluble part, by repeated crystallization from ethanol, 0.3 g. of 3-acetamino-4,4′,6-trinitrobiphenyl (m p. 193–194°) was obtained.

Anal. Calcd. for $C_{14}H_{10}N_4O_7$: N, 16.19. Found: N, 16.37.

The same product, as shown by mixed melting points, resulted from a similar nitration of either 3-acetamino-4,4′-dinitrobiphenyl, or 3-acetamino-4′,6-dinitrobiphenyl.

3-Amino-4,4′,6-trinitrobiphenyl.—This resulted from the hydrolysis of XIX with hot dilute sulfuric acid. After crystallization from ethanol it melted at 208–209°.

Anal. Calcd. for $C_{12}H_8N_4O_6$: N, 18.43. Found: N, 18.56.

3-Bromo-4′,6-dinitrobiphenyl (II).—A hot solution of 4.2 g. of 3-amino-4′,6-dinitrobiphenyl in 60 cc. of glacial acetic acid was cooled quickly to room temperature. It was then diazotized by adding it to 1.5 g. of sodium nitrite in 13 cc. of concentrated sulfuric acid, keeping the temperature below 40°. The diazonium solution was added to the mixture obtained by treating a solution of 5 g. of hydrated copper sulfate and 2.5 g. of sodium bromide in 18 cc. of water with one of 1.2 g. of sodium metabisulfite and 0.7 g. of sodium hydroxide in 9 cc. of water. The resulting mixture was immediately treated with 6 cc. of 48% hydrobromic acid and allowed to stand overnight. The precipitate formed was filtered, washed with dilute ammonium hydroxide, dried and crystallized from petroleum ether (90–100°); yield, 1.4 g.; m. p. 121–122°. When crystallized from ethanol the product retained ethanol of crystallization.

Anal. Calcd. for $C_{12}H_7N_2O_4Br$: Br, 24.74. Found: Br, 24.41.

3-Bromo-4-amino-4′,6-dinitrobiphenyl (V).—A solution of 15 g. of 3-bromo-4-amino-4′-nitrobiphenyl[4] in 85 cc. of concentrated sulfuric acid and 22 cc. of 15% fuming sulfuric acid was gradually treated with 5.3 g. of potassium nitrate at 5°. After pouring into water the dried, crude reaction product was crystallized from acetone–ethanol; yield, 10 g.; m. p. 181–182°. The pure product melts at 182–183°.

Anal. Calcd. for $C_{12}H_8N_3O_4Br$: Br, 23.64. Found: Br, 23.55.

Deamination of V.—A solution of 6 g. of the above-mentioned base dissolved in 32.6 cc. of concentrated sulfuric acid and 30 cc. of water was diazotized at 10° by the addition of 6 g. of solid sodium nitrite. To this solution was then added 30 cc. of 20% oleum at 20°. The resulting mixture was poured into 400 cc. of ethanol and refluxed for two hours. The dry, crude product obtained by removal of ethanol and addition of water was crystallized from petroleum ether (90–100°); yield, 1.2 g.; m. p. 122–123°, and unchanged when mixed with 3-bromo-4′,6-dinitrobiphenyl obtained by the Sandmeyer reaction.

3-Acetamino-4′,6-diaminobiphenyl (XXV).—This was prepared by the catalytic reduction of 3-acetamino-4′,6-dinitrobiphenyl using Adams catalyst. The base, on crystallization from water, melts at 180–181°.

Anal. Calcd. for $C_{14}H_{15}N_3O$: N, 17.43. Found: N, 16.97.

2-Acetamino-4′,5-diaminobiphenyl (XXVI).—Prepared as above from 2-acetamino-4′,5-dinitrobiphenyl.[11] The base, crystallized from ethanol, melts at 178–179°.

Anal. Calcd. for $C_{14}H_{15}N_3O$: N, 17.43. Found: N, 17.31.

2,4′,5-Tri-(diacetamino)-biphenyl (IV).—This was prepared by refluxing either of the above-mentioned acetamino-diaminobiphenyls with glacial acetic acid in the presence of anhydrous sodium acetate. On crystallization from acetone–ethanol, the hexa-acetyl derivative melts at 173–174°. The products obtained from the two reactions melt unchanged when admixed.

Anal. Calcd. for $C_{24}H_{25}N_3O_6$: N, 9.31; mol. wt., 451. Found: N, 9.59; mol. wt.,[12] 458, 426.

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(11) Scarborough and Waters, *J. Chem. Soc.*, 89 (1927).

(12) Determination by Carl Tiedcke.

2-Nitro-5-bromobiphenyl.—A suspension of 45 g. of 2-nitro-5-bromoaniline in 70 cc. of concentrated hydrochloric acid and 20 cc. of water was diazotized by the addition of a saturated solution of 18 g. of sodium nitrite. To the clear solution (after removal of a small amount of unchanged base) mixed with 200 cc. of benzene, 100 cc. of 5 *N* sodium hydroxide was added slowly with stirring, keeping the temperature below 5°. At the conclusion of the reaction the layers were separated and the benzene removed by distillation. The residue on vacuum distillation yielded 19.5 g. of a liquid, b. p. 140–190° (3 mm.), from which crystals separated on standing. On crystallization from methanol 6 g. was obtained of a product melting at 54–55°. The pure product melts at 55–56°.

Anal. Calcd. for $C_{12}H_8NO_2Br$: Br, 28.75. Found: Br, 28.84.

3-Bromo-4,4′,6-trinitrobiphenyl (VI).—This was obtained by the nitration with one mole of ethyl nitrate in concentrated sulfuric acid of either 3-bromo-4,4′-dinitrobiphenyl or 3-bromo-4′,6-dinitrobiphenyl. On crystallization from acetone–ethanol, it melts at 153–154°.

Anal. Calcd. for $C_{12}H_6N_3O_6Br$: Br, 21.72. Found: Br, 21.99.

3-Acetamino-2′-nitrobiphenyl.—Hydrogen sulfide was passed into a suspension (at 50–60°) of 56 g. of 2,3′-dinitrobiphenyl in 1 liter of ethanol and 400 cc. of 28% ammonia until complete solution resulted. After one hour of standing, the solvent was nearly all removed by distillation, and the residue extracted twice with dilute (1-1) hydrochloric acid. The base, precipitated by the addition of sodium hydroxide, was dried and acetylated; yield, 17 g.; m. p. 141–142°. The pure base, crystallized from methanol, melts at 142–143°.

Anal. Calcd. for $C_{14}H_{12}N_2O_3$: N, 10.94. Found: N, 11.15.

Oxidation of the above-mentioned acetamino compound yielded *o*-nitrobenzoic acid, thus proving that the nitro group in 3-position was reduced.

3-Amino-2′-nitrobiphenyl.—This was prepared by the hydrolysis of the above-mentioned acetamino compound in boiling dilute sulfuric acid containing one-third by volume of concd. sulfuric acid. On crystallization from ethanol–water, it melts at 82–83°.

Anal. Calcd. for $C_{12}H_{10}N_2O_2$: N, 13.09. Found: N, 13.01.

3-Bromo-2′-nitrobiphenyl.—This was prepared from the base by a method entirely analogous to that used for the preparation of 2-bromo-5-nitrobiphenyl.[10] From 3 g. of 3-amino-2′-nitrobiphenyl was obtained 0.8 g. of 3-bromo-2′-nitrobiphenyl, m. p. 54° and undepressed when mixed with a specimen prepared by the method of Lesslie and Turner.[6]

Nitration of 3-Bromo-2′-nitrobiphenyl.—The method was the same as that used for the nitration of 3-bromo-4′-nitrobiphenyl—sulfuric–nitric method. The crude nitration product from 12 g. of 3-bromo-2′-nitrobiphenyl was dried and extracted with benzene. The insoluble part, crystallized from acetone–ethanol, melted at 156–157°; yield, 2.8 g.

Anal. Calcd. for $C_{12}H_7N_2O_4Br$: Br, 24.74. Found: Br, 24.63.

The benzene-soluble part was evaporated and repeatedly crystallized from ethanol, yielding 1.7 g. of a product melting at 138–140° The pure product melts at 141–142°.

Anal. Calcd. for $C_{12}H_7N_2O_4Br$: N, 8.67. Found: N, 8.75.

On oxidation this isomer yielded 3-bromo-4-nitrobenzoic acid.

3-Bromo-2′,6-dinitrobiphenyl (X).—This was prepared by the Ullmann reaction on a mixture of 2-nitro-5-bromoiodobenzene and 2-nitroiodobenzene. It melted unchanged when mixed with the high melting isomer (156–157°) obtained from the nitration of 3-bromo-2′-nitrobiphenyl.

3-Bromo-2′,4,6-trinitrobiphenyl (XII).—This was prepared by the nitration of 2.2 g. of 3-bromo-2′,4-dinitrobiphenyl with one mole of ethyl nitrate in sulfuric acid. On crystallization of the crude nitration product from acetone–ethanol 0.9 g. was obtained of a substance melting at 137–138°.

Anal. Calcd. for $C_{12}H_6N_3O_6Br$: Br, 21.72. Found: Br, 21.62.

Nitration of 2-Nitro-3′-acetaminobiphenyl.—To a solution of 16.5 g. of 2-nitro-3′-acetaminobiphenyl in 100 cc. of concentrated sulfuric acid was added 5.7 cc. of ethyl nitrate keeping the temperature below −1°. After pouring into ice-water, the reaction product was dried and extracted with benzene. The insoluble part after crystallization from ethanol yielded 10 g. of 3-acetamino-2′,6-dinitrobiphenyl (XIV), melting at 180–181°. The pure substance melts at 182–183°.

Anal. Calcd. for $C_{14}H_{11}N_3O_5$: N, 13.96. Found: N, 14.09.

The benzene-soluble part on evaporation and crystallization from ethanol yielded 2 g. of 3-acetamino-2′,4-dinitrobiphenyl XIII, melting at 163–164°. The pure material melts at 167–168°.

Anal. Calcd. for $C_{14}H_{11}N_3O_5$: N, 13.96. Found: N, 13.45.

3-Amino-2′,6-dinitrobiphenyl.—This was obtained by the hydrolysis of XIV in hot dilute sulfuric acid. On crystallization from benzene it melts at 130–131°.

Anal. Calcd. for $C_{12}H_9N_3O_4$: N, 16.22. Found: N, 16.59.

By Schoutissen's method this base was converted to a product melting unchanged when mixed with 3-bromo-2′,6-dinitrobiphenyl, X.

3-Amino-2′,4-dinitrobiphenyl.—Prepared by hydrolyzing XIII. On crystallization from acetone–ethanol it melts at 167–168°.

Anal. Calcd. for $C_{12}H_9N_3O_4$: N, 16.22. Found: N, 16.23.

On deamination the above base yields 2,4′-dinitrobiphenyl.

3-Acetamino-2′,4,6-trinitrobiphenyl (XV).—This was obtained by adding either XIII or XIV to fuming nitric acid (sp. gr. 1.5) at 2°. On crystallization from ethanol the pure product melts at 141–142°. The products obtained from XIII and XIV melted unchanged when mixed.

Anal. Calcd. for $C_{14}H_{10}N_4O_7$: N, 16.19. Found: N, 16.51.

3-Amino-2′,4,6-trinitrobiphenyl.—This was obtained by hydrolysis of XV in hot dilute sulfuric acid. On crystallization from benzene it melted at 180–181°.

Anal. Calcd. for $C_{12}H_8N_3O_6$: N, 18.43. Found: N, 17.97.

By Schoutissen's method the above-mentioned base was converted into a bromo derivative which melted unchanged when mixed with XII, obtained by nitration.

3-Bromo-2′,4′,6-trinitrobiphenyl (XVI).—A solution of 1.7 g. of 3-bromo-2′,6-dinitrobiphenyl in 20 cc. of concentrated sulfuric acid was nitrated at 2° with 0.5 cc. of ethyl nitrate. The crude nitration product, precipitated with ice-water, was extracted with ethanol. The insoluble part yielded on crystallization from acetone–ethanol, 0.8 g. of a substance melting at 214–215°

Anal. Calcd. for $C_{12}H_6N_3O_6Br$: Br, 21.72. Found: Br, 21.92.

From the ethanol-soluble material after repeated crystallization from ethanol was obtained 0.1 g. of a compound melting at 137–138°, and unchanged when mixed with XII.

3-Bromo-2′,4′-dinitrobiphenyl (XVII).—A mixture of 22 g. of 2,4-dinitroiodobenzene, 27 g. of *m*-bromoiodobenzene and 21 g. of copper powder was heated at 260° for one and a half hours with stirring. The reaction product, after extraction with acetone and evaporation, was distilled *in vacuo.* The fraction (6.5 g.) boiling at 240–260° (4 mm.) was crystallized from methanol, yielding 3 g. melting at 88°.

Anal. Calcd. for $C_{12}H_7N_2O_4Br$: Br, 24.74. Found: Br, 24.82.

Nitration of 3-Bromo-2′,4′-dinitrobiphenyl (XVII).—From 3 g. of XVII nitrated with 1 mole of ethyl nitrate was obtained an ethanol-insoluble product which after crystallization from acetone–ethanol yielded 0.3 g.; m. p. 215–216°, and unchanged when mixed with XVI. From the alcoholic filtrate was obtained 0.8 g. of a trinitrobromobiphenyl melting at 145–146°. This was not further investigated. On further nitration it yielded VII.

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

3-Bromo-2′,4,4′,6-tetranitrobiphenyl (VII).—This was obtained by warming any one of the following substances on the steam-bath with equal volumes of concentrated sulfuric and nitric (sp. gr. 1.5) acids: 3-bromo-4′-nitrobiphenyl, 3-bromo-2′,6-dinitrobiphenyl, 3-bromo-2′,4-dinitrobiphenyl, 3-bromo-4,4′-dinitrobiphenyl, 3-bromo-4′,6-dinitrobiphenyl, 3-bromo-4,4′,6-trinitrobiphenyl, 3-bromo-2′,4,6-trinitrobiphenyl and 3-bromo-2′,4′,6-trinitrobiphenyl. On crystallization from acetone–ethanol, it melts at 159–160°.

Anal. Calcd. for $C_{12}H_5O_8N_4Br$: Br, 19.35. Found: Br, 19.56.

3-Bromo-3′-nitrobiphenyl.—A solution of 17.5 g. of 3-nitro-3′-bromo-4′-aminobiphenyl in 200 cc. of ethanol was treated with 50 cc. of dilute (1–1) sulfuric acid. Solid sodium nitrite (8 g.) was gradually added, and the mixture refluxed for one hour on the steam-bath. It was then poured into ice-water, and the precipitate dried and distilled *in vacuo.* The fraction boiling at 230–240° (3 mm.) was crystallized from methanol; yield, 14.5 g.; m. p. 97–98°. This melted unchanged when mixed with 3-bromo-3′-nitrobiphenyl prepared by a mixed Ullmann reaction.

Nitration of 3-Bromo-3′-nitrobiphenyl.—Ten grams of 3-bromo-3′-nitrobiphenyl nitrated in a sulfuric–nitric acid mixture as before yielded after repeated crystallization from acetone–ethanol 0.9 g. of a product melting at 137–138°.

Anal. Calcd. for $C_{12}H_7N_2O_4Br$: Br, 24.74. Found: Br, 24.86.

The combined filtrates from the above-mentioned crystallization were evaporated to dryness and a 3-g. portion heated with saturated alcoholic ammonia at 200° for ten hours. The residue from evaporation of the alcohol was dissolved in dry benzene and the solution saturated with dry hydrogen chloride. The precipitate was treated with sodium hydroxide solution and the resulting base crystallized from acetone–ethanol. It melts at 210–211°.

Anal. Calcd. for $C_{12}H_9N_3O_4$: N, 16.22. Found: N, 16.48.

On deamination this base yielded 3,4′-dinitrobiphenyl. By Schoutissen's method it was reconverted to XX. Evaporation of the benzene filtrate from the precipitation of the hydrochloride of the above base, followed by crystallization from acetone–ethanol, yielded 1.3 g. of XXII; m. p. 148–149°.

Anal. Calcd. for $C_{12}H_7N_2O_4Br$: Br, 24.74. Found: Br, 24.97.

In another experiment, 5.56 g. of 3-bromo-3′-nitrobiphenyl, dissolved in 40 cc. of concentrated sulfuric acid, was nitrated by the slow addition of 1.8 cc. of ethyl nitrate, keeping the temperature below 0°. The yield of XX (m. p. 137–138°) in this case was 1.7 g.

3-Bromo-3′,6-dinitro-4-acetaminobiphenyl.—Since 2,3′-dinitro-4-acetaminobiphenyl was unaffected by bromine in glacial acetic acid, the corresponding base (22.2 g.) was dissolved in 450 cc. of glacial acetic acid containing 24 g. of anhydrous sodium acetate and treated with 4.5 cc. of bromine. After standing overnight the mixture was poured into ice-water and the precipitate crystallized once from ethanol, after removal of tarry matter. It was then acetylated, yielding 6 g. of a product melting at 235–236° when crystallized from acetone–ethanol. The pure product melts at 240–241°.

Anal. Calcd. for $C_{14}H_{10}N_3O_5Br$: Br, 21.03. Found: Br, 21.13.

The above-mentioned acetamino compound on hydrolysis with dilute sulfuric acid yielded 3-bromo-3′,6-dinitro-4-aminobiphenyl, XXIII, which melted at 184–185° when crystallized from acetone–ethanol.

Anal. Calcd. for $C_{12}H_8N_3O_4Br$: Br, 23.65. Found: Br, 23.62.

From the filtrate from the crystallization of 3-bromo-3′,6-dinitro-4-acetaminobiphenyl an isomer was obtained, m. p. 203–204°; yield, 4 g. Its structure was not investigated but it is believed to be 3-bromo-2,3′-dinitro-4-acetaminobiphenyl.

Anal. Calcd. for $C_{14}H_{10}N_3O_5Br$: Br, 21.03. Found: Br, 21.09.

The base was prepared from the acetamino derivative as before. On crystallization from acetone–ethanol, it melted at 195–196°.

Anal. Calcd. for $C_{12}H_8N_3O_4Br$: Br, 23.65. Found: Br, 23.69.

3-Bromo-3′,6-dinitrobiphenyl (XXII).—This was obtained by the deamination of 3-bromo-3′,6-dinitro-4-aminobiphenyl by a process similar to that used in the preparation of 3-bromo-3′-nitrobiphenyl; also by the Ullmann reaction on a mixture of *m*-nitroiodobenzene (9 g.) and 2-nitro-5-bromoiodobenzene (10 g.). The chief product of the Ullmann reaction was 2,2′-dinitro-5,5′-dibromobiphenyl (1.1 g.), m. p. 206–207°.

Anal. Calcd. for $C_{12}H_6N_2O_4Br_2$: Br, 39.77. Found: Br, 39.75.

In the alcoholic filtrate after repeated crystallization was isolated 0.2 g. of a product melting at 149–150°, and unchanged when mixed with XXII obtained by deamination as above described, or from the nitration of 3-bromo-3′-nitrobiphenyl.

3-Bromo-3′,4,6-trinitrobiphenyl (XXIV).—This was obtained by the nitration of any one of the following compounds in fuming nitric acid (sp. gr. 1.59) 3-bromo-3′-nitrobiphenyl, 3-bromo-3′,4-dinitrobiphenyl, and 3-bromo-3′,6-dinitrobiphenyl. On oxidation it yields *m*-nitrobenzoic acid.

Summary

The nitration of 3-bromo-4′-nitrobiphenyl proceeds through the successive stages of 3-bromo-4,4′-dinitrobiphenyl, 3-bromo-4,4′,6-trinitrobiphenyl, and 3-bromo-2′,4,4′,6-tetranitrobiphenyl VII.

The nitration of 3-bromo-2′-nitrobiphenyl yields 3-bromo-2′,4-dinitrobiphenyl XI and 3-bromo-2′,6-dinitrobiphenyl X. Further nitration of XI yields 3-bromo-2′,4,6-trinitrobiphenyl XII, while X yields largely 3-bromo-2′,4′,6-trinitrobiphenyl XVI. Both XII and XVI on further nitration yield VII.

The nitration of 3-bromo-3′-nitrobiphenyl yields 3-bromo-3′,4-dinitrobiphenyl and 3-bromo-3′,6-dinitrobiphenyl. On further nitration both of these compounds yield 3-bromo-3′,4,6-trinitrobiphenyl.

The nitration of 3-acetamino-4′-nitrobiphenyl and of 3-acetamino-2′-nitrobiphenyl is described.

The methods of preparation of the three nitrobromobiphenyls are described.

PHILADELPHIA, PA. RECEIVED AUGUST 4, 1944