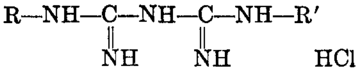
TABLE I

1,5-Diaryl Biguanides



$$R\text{—}NH\text{—}\underset{\substack{\| \\ NH}}{C}\text{—}NH\text{—}\underset{\substack{\| \\ NH}}{C}\text{—}NH\text{—}R' \quad HCl$$

No.	—R	—R′	M.P.[a]	Yield, %	Formula	% N Found	% N Calcd.
1	*p*-Chlorophenyl	*p*-Chlorophenyl	254	70	$C_{14}H_{14}Cl_3N_5$	19.62	19.55
2	3,4-Dichlorophenyl	*p*-Chlorophenyl	248	75	$C_{14}H_{13}Cl_4N_5$	17.68	17.82
3	*p*-Benzenesulfonic acid	*p*-Chlorophenyl	>300	75	$C_{14}H_{15}Cl_2N_5O_3S$	17.52	17.33
4	*p*-Benzenesulfonic acid	*p*-Chlorophenyl	>300	70	$C_{14}H_{15}Cl_2N_5O_3S$	17.18	17.33
5	*p*-Biphenyl	*p*-Chlorophenyl	262	65	$C_{20}H_{19}Cl_2N_5$	17.70	17.54
6	Phenyl	*p*-Chlorophenyl	242	65	$C_{14}H_{15}Cl_2N_5$	21.75	21.90
7	*p*-Biphenyl	Phenyl	180	65	$C_{20}H_{20}ClN_5$	19.01	19.17
8	*p*-Benzenesulfonic acid	Phenyl	>300	70	$C_{14}H_{16}ClN_5O_3S$	18.78	18.98
9	*m*-Benzenesulfonic acid	Phenyl	>300	65	$C_{14}H_{16}ClN_5O_3S$	18.87	18.98
10	Phenyl	Phenyl	220	70	$C_{14}H_{16}ClN_5$	24.37	24.22
11	3,4-Dichlorophenyl	Phenyl	213	65	$C_{14}H_{14}Cl_3N_5$	19.62	19.50
12	*p*-Benzenesulfonic acid	*p*-Benzenesulfonic acid	>300	35	$C_{14}H_{16}ClN_5O_6S_2$	15.80	15.50
13	*m*-Benzenesulfonic acid	*p*-Benzenesulfonic acid	>300	30	$C_{14}H_{16}ClN_5O_6S_2$	15.38	15.50
14	*p*-Biphenyl	*p*-Biphenyl	268	35	$C_{26}H_{24}ClN_5$	16.18	16.00
15	*p*-Biphenyl	*p*-Benzenesulfonic acid	>300	65	$C_{20}H_{20}ClN_5O_2S$	15.91	15.70

[a] All the compounds were crystallized from hot water as white crystals.

render it more resistant to detoxication by the host as well as facilitate absorption and penetration of the drug.

Acknowledgment. The author wishes to express his sincere thanks to Dr. P. C. Guha and Dr. B. H. Iyer for their valuable suggestions and help; the Director of the Indian Institute of Science for the laboratory facilities; and to Dr. V. R. Srinivasan for the pharmacological testing of the compounds.

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[Contribution from the Chemical Laboratory of Queens College]

Replacement of Halogen by Hydrogen in Nitro Aryl Halides: Some Applications in the Thiophene Series[1]

A. H. BLATT, NORMA GROSS, and E. W. TRISTRAM[2]

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The use of bromine as a blocking group during nitration of thiophene derivatives is described. The bromine in the bromonitrothiophenes is removed by treatment with hypophosphorous acid or with copper in acid medium.

The blocking groups commonly used to prevent aromatic substitution in a particular position (the sulfonic acid group which is removed by hydrolysis[3] and the nitro group which is removed by reduction to an amino group and replacement of the latter by hydrogen[4]) are *meta* directing. The methods recently described[5] for the replacement of halogen by hydrogen in nitro aryl halides permit the use of the *o,p*-directing halogens for the same purpose. This use of the halogens as removable blocking groups can be employed either for the determination of structure or for the synthesis of hitherto unavailable substituted aromatic compounds. These applications, which offer the most promise with heterocyclic aromatic compounds, are illustrated in the following paragraphs with examples from the thiophene series.

Thiophene on nitration furnishes almost exclusively the 2-nitro derivative which on further nitration yields, contrary to the usual statements,[6] principally 2,4-dinitrothiophene. The difficultly accessible 3-nitrothiophene furnishes on nitration exclusively 2,4-dinitrothiophene. On attempted further nitration, 2,4-dinitrothiophene is either unattacked or, if the conditions are sufficiently drastic, is destroyed. 2,5-Dinitrothiophene is not affected by attempts at further nitration.

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[1] This work was begun under Contract DA-19-020-ORD-12 with the Office of the Chief of Ordnance and continued under Contract DA-30-069-ORD-1289 with the Office of Ordnance Research.

[2] Present address: Merck & Co., Rahway, N. J.

[3] *o*-Chlorophenol: Takagi and Kutani, *J. Pharm. Soc. Japan*, **517**, 260 (1925) [*Chem. Abstr.*, **20**, 2669 (1926)]. *o*-Bromophenol: R. C. Huston and M. M. Ballard, *Org. Syntheses*, **Coll. Vol. II**, 97 (1943).

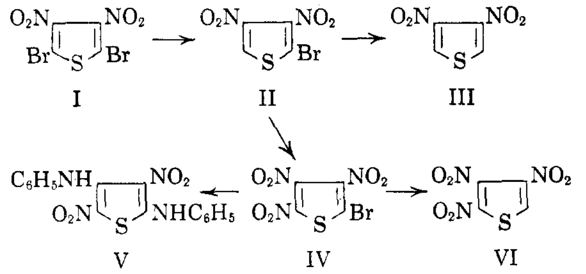
[4] N. Kornblum, *Org. Reactions*, **II**, 262 (1944).

[5] A. H. Blatt and Norma Gross, *J. Org. Chem.*, **22**, 1046 (1957).

[6] A clarification of some inconsistencies in the chemistry of the mononitrothiophenes and the 2,4- and 2,5-dinitrothiophenes is given in the accompanying note, p. 1693.

We undertook to make use of the halogens as temporary blocking groups for the purpose of arriving at more highly nitrated thiophenes. We began with 2,5-dibromothiophene which was nitrated to the known 2,5-dibromo-3,4-dinitrothiophene (I).[7] This completely substituted thiophene undergoes replacement of one bromine by hydrogen on treatment with either hydriodic acid or hypophosphorous acid in acetone at room temperature to furnish 2-bromo-3,4-dinitrothiophene (II) in 88–90% yield. The halogen in the monobromo compound is not removed by hydriodic acid or hypophosphorous acid or by aniline in methanol, but can be removed by heating with copper in an acid medium[8] to furnish 3,4-dinitrothiophene (III).

On treatment with mixed acid the monobromo derivative II is nitrated to 2-bromo-3,4,5-trinitrothiophene (IV) in 90% yield. As would be expected, the halogen in this trinitro derivative is extraordinarily reactive; so reactive that the only solvent suitable for crystallization is concentrated nitric acid. As would also be expected, one nitro group in the trinitro derivative is readily displaced. Most of the reactions of the trinitro derivative lead to intractable products, but the reaction with aniline leads to a dianilino derivative which we formulate as V. The halogen in the trinitrobromothiophene can be replaced by hydrogen to furnish 2,3,4-trinitrothiophene (VI) in 75% yield using hypophosphorous acid as the reagent. This reaction cannot be brought about satisfactorily by hydriodic acid, presumably because the process is complicated by displacement of the central nitro group.



2,3,4-Trinitrothiophene is the first of the two possible trinitrothiophenes to be prepared. One trinitro derivative of thiophene, 2-acetamido-3,4,5-trinitrothiophene, is known.[9] As would be expected of a vicinal trinitro compound, the trinitrothiophene VI contains one very labile nitro group. On treatment with aniline in methanol, potassium acetate in acetic acid, or hydriodic acid in acetone the trinitrothiophene is destroyed. All of these reactions, unfortunately, lead to intractable products. As would also be expected, the trinitrothiophene VI shows the stabilizing and deactivating affects of the nitro groups on the thiophene nucleus. All attempts to nitrate the material failed, and 60% of the starting material could be recovered after heating the compound for four hours at 130° with a mixture of nitric and sulfuric acids containing only 0.1% of water. This resistance to nitration made it impossible to prepare what would have been the first completely nitrated aromatic compound, tetranitrothiophene.

All the dinitro- and trinitro-thiophenes prepared in this work gave the characteristic yellow (dinitro) or red-brown (trinitro) colors with sodium iodide in acetone.[5]

EXPERIMENTAL

Melting points are uncorrected.

Crude 2,5-dibromo-3,4-dinitrothiophene[7] can be crystallized from methanol (30 ml./g.) with a 60% recovery; but it is preferably purified by solution in acetone (2 ml./g.) and treatment with decolorizing carbon, followed by concentration of the filtered solution to half its original volume and dilution with methanol (2 ml./g.).

On treatment with aniline in methanol one bromine atom is displaced by an anilino group to furnish a product which melts at 150.5–151° after crystallization from acetone and water.

Anal. Calcd. for $C_{10}H_6BrN_3O_4$: C, 34.9; H, 1.7. Found: C, 35.1; H, 1.33.

2-Bromo-3,4-dinitrothiophene (II). (a) A solution of 45 g. (0.3 mole) of sodium iodide in 125 ml. of acetone was cooled to 10–15° and added to a similarly cooled solution of 20 g. (0.06 mole) of the dibromodinitrothiophene I in 100 ml. of acetone and 20 ml. of glacial acetic acid. The reaction mixture developed an orange-yellow color and a precipitate (NaBr) formed. After it had been left for one week, the reaction mixture was added to 800 ml. of water containing 10 g. of sodium bisulfite. This removed most of the color and left a gray precipitate of the crude bromodinitrothiophene II that weighed 13.8–14.0 g. (90%) and melted at 87–89°. (b) To a solution of 20 g. (0.06 mole) of the dibromodinitrothiophene I in 200 ml. of acetone that had been cooled to 10–15°, was added 36 ml. (0.3 mole) of 50% hypophosphorous acid. The reaction mixture, which developed an orange-red color, was kept in an ice water bath for 5 min. during which time a mildly exothermic reaction took place, and was then left at room temperature for 2 hr. On pouring the solution into water, 13.5 g. (88%) of the bromodinitrothiophene II, melting at 88–89° was obtained.

2-Bromo-3,4-dinitrothiophene can be crystallized from methanol (2 ml./g.) with an 80% recovery as clusters of stout, almost colorless prisms, or from ether (4 ml./g.) and 30–60° petroleum ether (6 ml./g.). It is soluble in fuming nitric acid at the ordinary temperature and, after remaining in such a solution for 18 hr., can be recovered by dilution with ice and water. Treatment with nitric acid in this way removes impurities and, consequently, the crude material can be used directly for nitration to the bromotrinitrothiophene IV. The analytical sample, which was crystallized from ethanol, melted at 93–94°.

Anal. Calcd. for $C_4HBrN_2C_4S$: C, 18.75; H, 0.5; N, 11.1. Found: C, 19.15; H, 0.88; N, 10.8.

The bromodinitrothiophene II reacts with aniline in ethanol to form a highly colored intractable product. The reaction with potassium acetate in acetic acid also leads to colored, intractable material. The bromine in II is not removed by treatment with either hydriodic acid or hypophosphorous acid. In order to be able to identify the bro-

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[7] R. Mozingo, S. A. Harris, D. E. Wolf, C. E. Hoffhine, Jr., N. R. Easton, and K. Folkers, *J. Am. Chem. Soc.*, **67**, 2092 (1945).

[8] W. T. Smith, Jr., *J. Am. Chem. Soc.*, **71**, 2855 (1949); W. T. Smith, Jr., and L. Campanaro, *J. Am. Chem. Soc.*, **75**, 3602 (1953).

[9] H. M. Priestley and C. D. Hurd, *J. Am. Chem. Soc.*, **69**, 1173 (1947).

mine-free product, 3,4-dinitrothiophene (III), if it were formed we prepared a sample of the material by the reaction between the bromodinitrothiophene II and copper in boiling butyric acid.[8] 3,4-Dinitrothiophene, which has already been prepared in similar fashion from the dinitrodibromothiophene I by Dr. Ellis Brown and which will be described in detail by him later, melts at 94–95° and mixtures of the monobromodinitrothiophene II and the dinitrothiophene III melt below 75°.

2-Bromo-3,4,5-trinitrothiophene (IV). Twenty grams (0.08 mole) of the crude bromodinitrothiophene II was added with stirring during 5 min. to a mixture of 100 ml. of concentrated sulfuric acid and 100 ml. of fuming nitric acid (d. 1.59–1.60). The solid dissolved in the nitrating acid, which was at room temperature, without an appreciable evolution of heat. In about 0.5 hr. the trinitro compound began to precipitate. Stirring was continued for 2 hr., after which time the reaction mixture was left overnight before it was poured onto 300 g. of ice. The yield of crude nitration product, melting at 123–125°, was 21.5 g. (90%).

2-Bromo-3,4,5-trinitrothiophene is a pale yellow solid which is soluble in the common solvents, but apparently with solvolysis; the solutions develop much color and the solute crystallizes poorly or not at all. The only satisfactory procedure for purification is to dissolve the trinitrobromothiophene in concentrated nitric acid (10 ml./g.) by heating on the steam bath. On cooling the filtered solution, the product is obtained with an 80% recovery as lemon yellow crystals melting at 130–131°.

Anal. Calcd. for $C_4BrN_3O_6S$: C, 16.10; H, 0.0; Br, 26.8. Found: C, 16.16; H, 0.0; Br, 26.7.

The trinitrobromothiophene furnishes only intractable material on treatment with potassium acetate in acetic acid. With aniline in methanol it yields a dianilino derivative (V), which is obtained as orange needles melting at 196–196.5° after crystallization from acetone-methanol.

Anal. Calcd. for $C_{16}H_{12}N_4O_4S$: C, 53.9; H, 3.39. Found: C, 54.05; H, 3.46.

2,3,4-Trinitrothiophene (VI). A solution of 5.0 g. (0.017 mole) of the crude bromotrinitrothiophene IV in 100 ml. of acetone was cooled to about 10° and 10 ml. (0.85 mole) of 50% hypophosphorous acid was added. An orange-red color developed at once. The solution was kept at room temperature by immersing the flask in cold water from time to time. After 1 hr. the solution was poured into 800 ml. of water and the tan precipitate was filtered; yield, 2.8 g. (76%), m.p. 138–141°. The product was purified by crystallization from ether (30 ml./g.) and an equal volume of 30–60° petroleum ether. The recovery was 70%.

Anal. Calcd. for $C_4HN_3O_6S$: C, 21.90; H, 0.46. Found: C, 21.93; H, 0.60.

2,3,4-Trinitrothiophene is a colorless solid which melts at 143°. When a small sample of the material in a sealed melting point tube is heated in a free flame it explodes vigorously. The material, which analyzes satisfactorily for carbon and hydrogen, gives low values for nitrogen and sulfur. The trinitrothiophene is unaffected by the ordinary nitric acid–sulfuric acid nitrating mixtures at steam bath temperatures. When one gram of the material was heated at 130° for 1.5 hr. with 10 ml. of concentrated sulfuric acid and 2 g. of potassium nitrate or for 4 hr. with 5 ml. of nitrating acid of the composition 82.3% H_2SO_4–17.6% HNO_3–0.1% H_2O, there was no indication that nitration had taken place and 60% of essentially pure starting material was recovered.

FLUSHING 67, N. Y.

[CONTRIBUTION FROM THE RESEARCH STATION, THE BRITISH PETROLEUM COMPANY LIMITED]

Preparation and Physical Properties of Sulfur Compounds Related to Petroleum. VII. 2-, 6- and 8-Thiabicyclo[3.2.1]octane and 2-Thiabicyclo[2.2.2]octane

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2-, 6-, and 8-Thiabicyclo[3.2.1]octane and 2-thiabicyclo[2.2.2]octane have been synthesized and their physical properties have been recorded. Each sulfide has been characterized by the preparation of derivatives.

In an earlier paper[1], Birch *et al.* reported the isolation from an Agha Jari (S. Persia) kerosine of a sulfide which was apparently 8-thiabicyclo[3.2.1]octane and suggested that other thiabicyclooctanes were also present in this kerosine. It has previously been found possible to identify certain other sulfides as constituents of the kerosine, by comparison of the infrared spectra of the isolated sulfides or sulfide mixtures with those of synthetic compounds which have been prepared in these laboratories.[2] Consequently, the synthesis of 2-, 6- and 8-thiabicyclo[3.2.1]octane (IX, XIII and IV) and 2-thiabicyclo[2.2.2]octane (XVII) was carried out, as reported in the present paper. 3-Thiabicyclo[3.2.1]octane, the fifth member of the group of thiabicyclooctanes containing only five- and six-membered rings and having an atomic bridge, has already been described.[3] The stereochemistry of the thiabicyclo[3.2.1]- and thiabicyclo[2.2.2]octane systems is such that the *trans*- forms would be extremely strained and, as with the corresponding hydrocarbons, it is probable that only one form having a *cis*- configuration can exist.[4] As recently

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[1] S. F. Birch, T. V. Cullum, R. A. Dean, and R. L. Denyer, *Ind. Eng. Chem.*, **47**, 240 (1955).

[2] S. F. Birch, R. A. Dean, N. J. Hunter, and E. V. Whitehead, *J. Org. Chem.*, 20, 1178 (1955).

[3] S. F. Birch and R. A. Dean, *Chem. Ber.*, **585**, 234 (1954) in which this sulfide is referred to as 6-thiabicyclo-[1.2.3]octane.

[4] H. Gilman, *Organic Chemistry*, 2nd. Ed., John Wiley and Sons, Inc., New York, 1948, Vol. 1, p. 485.