reaction mixture was refluxed for six hours. The resulting reddish solution, after being cooled, was poured into ice-cold water; the solid that separated was collected, crystallized from ethyl alcohol and proved to be the dioxime of 1,3-indandione (identification was carried out by m.p. and mixed m.p. determination with an authentic sample prepared by the action of hydroxylamine hydrochloride on Ia as described above[7]).

Anal. Calcd. for $C_9H_8N_2O_2$: C, 61.36; H, 4.55; N, 15.91. Found: C, 61.25; H, 4.37; N, 15.76.

(b) **IIId.**—Similarly the action of hydroxylamine hydrochloride on IIId yields the dioxime of 1,3-indandione (m.p. and mixed m.p.) together with an oily substance which is under further investigation.

Oxidation of IIIa with Chromic Acid.—IIIa (0.5 g.) was boiled with 50 ml. of glacial acetic acid, 1.5 g. of finely powdered chromic acid was then added and boiling was continued for two hours. The green solution was poured into ice-cold water and, upon standing, a pale-yellow precipitate separated. The precipitate was collected, crystallized from hot water and proved to be phthalic acid.

Action of Heat on IIIa.—IIIa (0.7 g.) was heated for two hours at 220° (bath-temp.) in a test-tube shaped vessel (Pyrex glass) which was connected during pyrolysis to a working oil vacuum pump. The reaction vessel was then allowed to cool in a vacuum. The bottom of the reaction vessel contained a brownish-red residue which upon treatment with a few ml. of cold ether turned into a pale-yellow solid. It was crystallized from benzene as pale-yellow crystals or faint yellow (*ca.* 0.2 g.), m.p. 176°.

Anal. Calcd. for $C_{29}H_{18}O_2$: C, 87.44; H, 4.52. Found: C, 87.34; H, 4.50.

It gives a brown color with concentrated sulfuric acid and is almost insoluble in aqueous sodium hydroxide solution (10%). It is sparingly soluble in cold ethyl alcohol and glacial acetic acid. It is unaffected when treated with hydroxylamine bydrochloride under the same conditions described above.

GIZA, CAIRO, EGYPT

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[7] W. Wislicenus and A. Kötzle, *Ann.*, **252**, 72 (1889), gave m.p. 225° for the same dioxime. When their experiment was repeated and the product was crystallized from alcohol, colorless substances, m.p. 238°, was obtained.

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY, AND THE FRANCIS DELAFIELD HOSPITAL]

Some 4,5- and 5,6-Substituted Benzothiazoles

BY H. B. GILLESPIE, MORRIS ENGELMAN AND SAMUEL GRAFF

RECEIVED OCTOBER 15, 1955

Some substituted benzotriazoles are effective growth inhibitors in certain biological systems. Several new benzotriazoles have been prepared and the structure of the previously reported 5-methoxy-6-nitrobenzotriazole has been shown to be 5-methoxy-4-nitrobenzotriazole. The reduction of β-[4,6-dinitro-3-methoxyphenyl]-hydroxylamine by ammonium sulfide resulted in a *p*-diamine rather than an *o*-diamine as reported in the literature.

The synthesis and some results of preliminary biological assay of several 4,6-substituted benzimidazoles and benzotriazoles has been reported previously.[1] This report describes the preparation of some 4,5- and 5,6-substituted benzotriazoles. In an attempt to obtain 5-methoxy-6-nitrobenzotriazole (II), the nitration of 1-acetyl-5-methoxybenzotriazole (I) was repeated according to Fel'dman and Usovskaya.[2] It seemed to us unlikely that the nitro group should enter the 6-position since halogenation and nitration of 5-hydroxybenzotriazole yield compounds with the entering group in the 4-position and nitration of benzotriazole results in the 4-nitro derivative. On the basis of such evidence, Fries[3] suggested that the benzotriazoles were naphthenoid in character. This idea was supported by the synthesis, from 5-hydroxybenzotriazole, of the 4-carboxylic acid derivative by the Kolbe reaction.[4]

Assuming random nitration, three isomers are possible. These are 5,4- (III), 5,6- (II) and 6,4-methoxynitrobenzotriazole (IV). The latter compound, prepared by an unambiguous synthesis by the action of nitrous acid on 3,4-diamino-5-nitroanisole (V), was found to differ in its properties from the nitration product. To distinguish between the 4,5- and the 5,6-isomers, the preparation of 4-methoxy-5-nitro-*o*-phenylenediamine (VII), from which the 5-methoxy-6-nitrobenzotriazole (VI) could be formed by ring closure, was attempted by the method of Borsche and Feske.[5] These workers reported that the reduction of β-[4,6-dinitro-3-methoxyphenyl]-hydroxylamine (VIII) by ammonium sulfide resulted in an *o*-diamine. On repeating this work, we have found that the product was indeed a diamine IX which formed a diacetyl derivative X. However, it failed to yield a quinoxaline derivative with benzil. The same diamine was synthesized from the corresponding amine, 3-amino-4,6-dinitroanisole (XI), by ammonium sulfide reduction. The diacetyl derivative was the same as that prepared from Borsche and Feske's diamine and treatment of the diamine with benzil did not yield a quinoxaline. However, catalytic reduction converted the nitrodiamine into a triamine which reacted readily with benzil to form 6-amino-2,3-diphenyl-7-methoxyquinoxaline. In addition, 2,5-diacetamido-4-nitroanisole (X) was synthesized by an independent method,[6] and shown by analysis and mixed melting point determination to be identical with the diacetyldiamine of Borsche and Feske. The action of ammonium sulfide on β-[4,6-dinitro-3-methoxyphenyl]-hydroxylamine (VIII) did not result in an *o*-diamine (VII) as reported but in the *p*-diamine, namely, 2,5-diamino-4-nitroanisole (IX).

An investigation of the isomeric 4,5- (VI) and 5,6-aminomethoxybenzotriazoles (XIV) was resorted to for the elucidation of the structure of the

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[1] H. Gillespie, M. Engelman and S. Graff, THIS JOURNAL, **76**, 3531 (1954).

[2] I. Kh. Fel'dman and V. S. Usovskaya, *J. Gen. Chem.* (*USSR*), **19**, 356 (1949); *C. A.*, **43**, 7016d (1949).

[3] K. Fries, H. Guterbock and H. Kuhn, *Ann.*, **511**, 213 (1934).

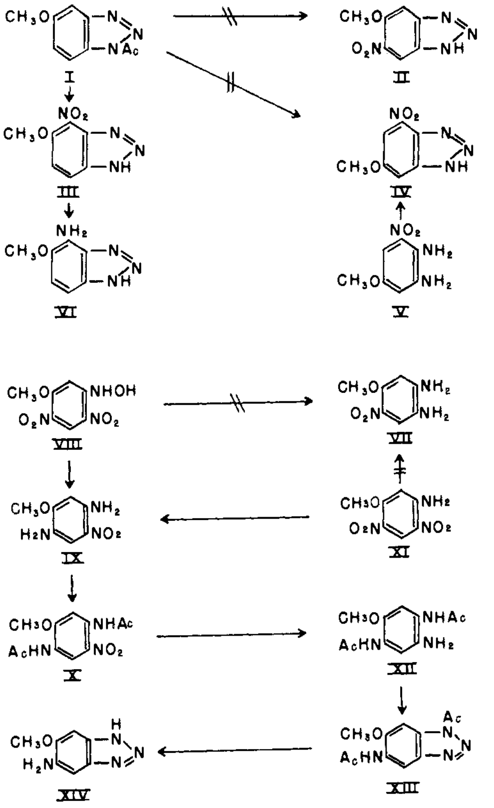
[4] M. Scalera and F. H. Adams, THIS JOURNAL, **75**, 715 (1953).

[5] W. Borsche and E. Feske, *Ber.*, **59**, 816 (1926).

[6] French Patent 966,799, Oct. 18, 1950; *C. A.*, **46**, 6396*g* (1952).

nitration product. An unambiguous synthesis of 5-amino-6-methoxybenzotriazole was possible by catalytic reduction of 2,5-diacetamido-4-nitroanisole (X) to 4-amino-2,5-diacetamidoanisole (XII). Treatment with nitrous acid resulted in 5-acetamido-1-acetyl-6-methoxybenzotriazole (XIII). Acid hydrolysis of the acetamidotriazole gave 5-amino-6-methoxybenzotriazole (XIV) (m.p. 157–158°).

Catalytic reduction of the nitration product of 1-acetyl-5-methoxybenzotriazole gave an amine melting at 202–203°. This amine must be 4-amino-5-methoxybenzotriazole (VI) and the related nitro compound may, therefore, be assigned the structure of 5-methoxy-4-nitrobenzotriazole.



Experimental

6-Methoxy-4-nitrobenzotriazole (IV).—A solution of 550 mg. (3 mmoles) of 3,4-diamino-5-nitroanisole[7] in 30 ml. of hot 2 *N* sulfuric acid was cooled to 5°. The sulfate of the base precipitated. The mixture was treated dropwise with stirring with a solution of 250 mg. of sodium nitrite in 3 ml. of water. After all the nitrite had been added, the mixture was stirred at 5° for one hour and then kept at room temperature overnight. The black precipitate was collected, washed with water, and dried. The crude product (566 mg.) dissolved slowly in 300 ml. of ethanol under reflux for one hour. The hot solution was treated with Nuchar and filtered. From the filtrate, on cooling, there separated 235 mg. (40%) of 6-methoxy-4-nitrobenzotriazole as a light yellow, amorphous powder having m.p. 295° dec.[8]

Anal. Calcd. for $C_7H_6O_3N_4$: C, 43.29; H, 3.09; N, 28.87. Found: C, 43.32; H, 3.33; N, 28.56.

2,5-Diamino-4-nitroanisole (IX).—A mixture of 500 ml. of a freshly prepared 2.6% aqueous solution of ammonium sulfide and 4.3 g. (20 mmoles) of 3-amino-4,6-dinitroanisole[9] was heated with stirring on the steam-bath for three hours. The yellow aminodinitro compound gradually dissolved giving a deep red solution with separation of free sulfur. The mixture was heated to boiling and filtered to remove sulfur. The sulfur was washed with 100–200 ml. of boiling water. A reddish-orange solid precipitated on cooling. This substance was collected, washed with water, then with 25 ml. of carbon disulfide, and finally with 25 ml. of cold 50% alcohol. The crude material (2.5 g.) was crystallized from 75 ml. of ethanol recovering 1.5 g. having m.p. 183–186°. Recrystallized from boiling water, the 2,5-diamino-4-nitroanisole separated as long red needles melting at 188–190°, reported[6] m.p. 190–191°.

2,5-Diacetamido-4-nitroanisole (X).—When 500 mg. of the *p*-diamine IX was refluxed for 15 minutes with 5 ml. of acetic anhydride and the resulting solution poured on ice, 494 mg. of 2,5-diacetamido-4-nitroanisole was obtained. After recrystallization from 50% ethanol the product melted at 258–259°. There was no depression in the m.p. of a mixture containing a specimen of 2,5-diacetamido-4-nitroanisole prepared by another method.[6]

Anal. Calcd. for $C_{11}H_{13}O_5N_3$: C, 49.49; H, 4.87; N, 15.73. Found: C, 49.72; H, 5.11; N, 15.63.

6-Amino-2,3-diphenyl-7-methoxyquinoxaline.—To a solution of 340 mg. (1.6 mmoles) of 2,5-diamino-6-nitroanisole (IX) in 35 ml. of ethanol, 3 ml. of concd. hydrochloric acid and 90 mg. of 10% palladium-on-carbon was added. This mixture was magnetically stirred in the presence of hydrogen at atmospheric pressure for 4 hours. The catalyst was filtered off and the filtrate evaporated to dryness under reduced pressure with exclusion of air. The crude 2,4,5-triaminoanisole trihydrochloride was added to a solution of 425 mg. of benzil in 20 ml. of 50% ethanol containing 410 mg. (5 mmoles) of sodium acetate. The mixture was refluxed for one hour. On cooling, 500 mg. of 6-amino-2,3-diphenyl-7-methoxyquinoxaline separated. Concentration of the filtrate yielded an additional 170 mg.; recrystallized from 50% ethanol, m.p. 196–197°. The same compound was obtained from 3-amino-4,6-dinitroanisole (XI) by catalytic reduction followed by treatment with benzil.

Anal. Calcd. for $C_{21}H_{17}ON_3$: C, 77.06; H, 5.20; N, 12.84. Found: C, 77.21; H, 5.11; N, 12.72.

Reduction of β-[4,6-Dinitro-3-methoxyphenyl]-hydroxylamine (VIII).—A solution of 2.3 g. (10 mmoles) of β-[4,6-dinitro-3-methoxyphenyl]-hydroxylamine[5] in 50 ml. of ethanol was treated with 10 ml. of 10% aqueous ammonium sulfide. The reaction mixture was kept at 50–60° for 2 hours, then diluted with 400 ml. of water. The brown precipitate which separated (761 mg.) was extracted with approximately 200 ml. of boiling water. From the dark red solution, 220 mg. of dark red needles melting at 177–184° separated on cooling. This crude material was refluxed for 15 min. with 5 ml. of acetic anhydride and the solution poured onto ice. This precipitated 148 mg. of material which was recrystallized from ethanol, m.p. 257–258°. By means of a mixed m.p. (258–260°) this was shown to be 2,5-diacetamido-4-nitroanisole[6] indicating that the reduction product was 2,5-diamino-4-nitroanisole (IX).

4-Amino-2,5-diacetamidoanisole (XII).—A suspension of 4.72 g. (17.7 mmoles) of 2,5-diacetamido-4-nitroanisole[6] and 250 mg. of 10% palladium-on-carbon in 500 ml. of ethanol was stirred in the presence of hydrogen at atmospheric pressure overnight. The catalyst was filtered and the filtrate concentrated under reduced pressure to a volume of about 20 ml. On chilling 3.48 g. (83%) of 4-amino-2,5-diacetamidoanisole separated, m.p. 210–211.5°.

Anal. Calcd. for $C_{11}H_{15}O_3N_3$: C, 55.70; H, 6.33; N, 17.72. Found: C, 55.96; H, 6.56; N, 17.57.

5-Acetamido-1-acetyl-6-methoxybenzotriazole (XIII).—A solution of 1.35 g. (5.7 mmoles) of 4-amino-2,5-diacetamidoanisole (XII) in 50 ml. of 1 *N* hydrochloric acid was kept at 5° with stirring while adding dropwise a solution of 394 mg. (5.7 mmoles) of sodium nitrite in 5 ml. of water. After 2 hours, the precipitated triazole was collected, washed with water, and dried *in vacuo* over Drierite. The crude product (1.37 g., 97%) was recrystallized from 40 ml. of ethanol (Nuchar); m.p. 197.5–199.5°.

Anal. Calcd. for $C_{11}H_{12}O_3N_4$: C, 53.23; H, 4.84; N, 22.58. Found: C, 53.32; H, 4.75; N, 22.92.

5-Amino-6-methoxybenzotriazole (XIV).—A solution of 997 mg. (4 mmoles) of 5-acetamido-1-acetyl-6-methoxy-

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[7] F. E. King, R. J. S. Beer and S. G. Waley, *J. Chem. Soc.*, 94 (1946).

[8] All melting points are corrected.

[9] M. M. de Monchy, *Rev. trav. chim.*, **53**, 141 (1934).

benzotriazole in 20 ml. of 3 *N* hydrochloric acid was refluxed for 2 hours. On cooling, 775 mg. of the hydrochloride of 5-amino-6-methoxybenzotriazole separated. After recrystallizing twice from hot water, the free base was obtained by adding aqueous ammonia to a hot concentrated aqueous solution of the hydrochloride. Recrystallized from water, m.p. 157–158°.

Anal. Calcd. for $C_7H_8ON_4$: C, 51.22; H, 4.88; N, 34.15. Found: C, 51.46; H, 4.93; N, 34.40.

4-Amino-5-methoxybenzotriazole (VI).—1-Acetyl-5-methoxybenzotriazole was nitrated according to Fel'dman and Usovskaya.[2] The nitro compound had m.p. 256–257° (lit. m.p. 233–234°). A suspension of 584 mg. (3 mmoles) of the nitro compound and 100 mg. of 10% palladium-on-carbon in 100 ml. of ethanol was stirred for 4 hours in the presence of hydrogen at atmospheric pressure. The catalyst was removed and the filtrate evaporated to dryness. The residue (482 mg.) was recrystallized from 25% ethanol (Nuchar). The 4-amino-5-methoxybenzotriazole separated as dark red needles melting at 202–203°.

Anal. Calcd. for $C_7H_8ON_4$: C, 51.22; H, 4.88; N, 34.15. Found: C, 51.42; H, 4.80; N, 34.12.

Acknowledgment.—This investigation was aided by grants from the American Cancer Society and the Damon Runyon Memorial Fund.

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[Contribution from the Department of Chemistry, Duke University]

Dimeric Olefins *versus* Amines from α-Aryl Alkyl Halides with Alkali Amides in Liquid Ammonia. Intermediate Dimeric Halides and Their Dehydrohalogenation. Imines from Amines[1]

By Charles R. Hauser, Wallace R. Brasen, Philip S. Skell, Simon W. Kantor and Alex E. Brodhag

Received September 29, 1955

Benzyl and benzhydryl chlorides and 9-chlorofluorene are converted to dimeric olefins by alkali amides in liquid ammonia, whereas 2,4,6-trimethylbenzyl chloride yields the corresponding amine. α-Phenylneopentyl bromide forms the corresponding amine, imine and saturated dimeric hydrocarbon. The formation of dimeric olefins is resolved into the self-alkylation of the halide and the dehydrohalogenation of the resulting intermediate dimeric halide. The self-alkylation of benzyl and benzhydryl chlorides furnishes a good method for the synthesis of α,β-diphenylethyl and α,α,β,β-tetraphenylethyl chlorides, respectively. Imines are obtained from amines in two ways. Mechanisms for these various reactions are considered.

It has long been known that certain halides having a relatively reactive α-hydrogen and no β-hydrogen are converted by bases to dimeric olefins. For example, *o*- or *p*-nitrobenzyl chloride is converted by alcoholic potassium hydroxide to a mixture of the *cis*- and *trans*-nitrostilbenes.[2] More recently Bergstrom and Fernelius[3] reported that even benzyl chloride exhibits this type of reaction to form stilbene with potassium amide in liquid ammonia, while Kharasch and co-workers[4] obtained a quantitative yield of this dimeric olefin with sodium amide in this medium (equation 1). The latter workers also showed that certain other halides, including allyl[5] and methylallyl[6] chlorides, react similarly.

$$2C_6H_5CH_2Cl \xrightarrow[\text{liq. NH}_3]{\text{NaNH}_2} C_6H_5CH{=}CHC_6H_5 \qquad (1)$$

I

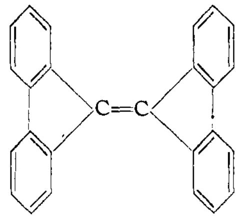
In the present investigation a study of the reactions of certain α-aryl alkyl halides with alkali amides in liquid ammonia was made. It was found that, similar to benzyl chloride, benzhydryl chloride and 9-chlorofluorene produce with sodium amide or potassium amide good yields of the dimeric olefins, II and III,[7] respectively. Moreover, a mixture of benzhydryl chloride and methyl iodide gave the mixed dimeric olefin IV. However, 2,4,6-trimethylbenzyl chloride formed only the corresponding amine V, while α-phenylneopentyl bromide yielded several products including the corresponding amine, imine and the saturated dimeric hydrocarbon VI. Small amounts of imine were obtained also with benzyl chloride and the other halides. The yields of products are summarized in Table I.

$(C_6H_5)_2C{=}C(C_6H_5)_2$

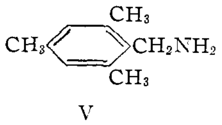
II

$(C_6H_5)_2C{=}CH_2$

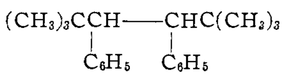
IV



III



V



$$(CH_3)_3C\underset{C_6H_5}{CH}-\underset{C_6H_5}{CH}C(CH_3)_3$$

VI

The reactions listed in Table I were generally carried out by adding the halide to one to two molecular equivalents of the alkali amide. A more thorough study with benzhydryl chloride showed

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[1] Supported by the Office of Ordnance Research, U. S. Army, and by the Office of Naval Research.

[2] C. A. Bischoff, *Ber.*, **21**, 2072 (1888); P. Walden and A. Kernbaum, *ibid.*, **23**, 1958 (1890).

[3] F. W. Bergstrom and W. C. Fernelius, *Chem. Revs.*, **20**, 435 (1947).

[4] M. S. Kharasch, W. Nudenberg and E. K. Fields, This Journal, **66**, 1276 (1944).

[5] M. S. Kharasch and E. Sternfeld, *ibid.*, **61**, 2318 (1939).

[6] M. S. Kharasch, W. Nudenberg and E. Sternfeld, *ibid.*, **62**, 2035 (1940).

[7] This dimeric olefin has been obtained in unreported yield from 9-bromofluorene and alcoholic potassium hydroxide (J. Thiele and A. Wanscheidt, *Ann.*, **376**, 278 (1910)) and in 40% yield from 9-chlorofluorene and liquid ammonia at room temperature (L. A. Pinck and G. E. Hilbert, This Journal, **68**, 379 (1946)).