XXIX.—*Triazole Compounds. Part II. Methylation of Some* 1-*Hydroxy*-1 : 2 : 3-*benztriazoles.*

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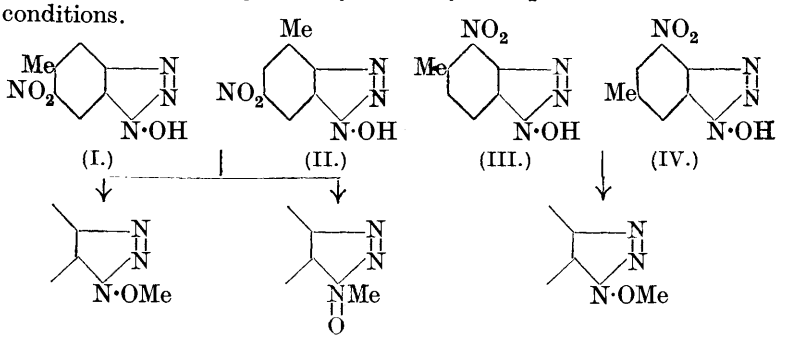
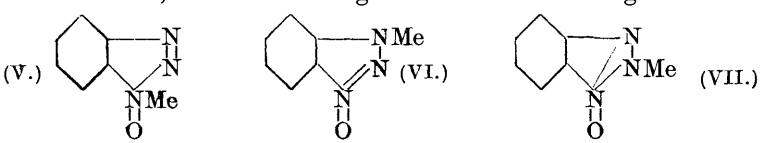
In Part I (J., 1923, **123**, 2258) it was shown that 6-nitro-1-hydroxy-5-methyl- and 6-nitro-1-hydroxy-4-methyl-1 : 2 : 3-benztriazoles (I and II) on methylation gave mixtures of *O*- and *N*-methyl derivatives, the former greatly preponderating, whereas 4-nitro-1-hydroxy-5(or 7)-methyl- and 4-nitro-1-hydroxy-6-methyl-1 : 2 : 3-benztri-

azoles (III and IV) gave only *O*-methyl compounds under similar conditions.

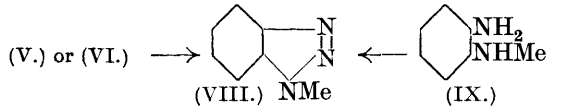


Since in (III) and (IV) the nitro-group in the ortho-position with respect to the triazole ring may be expected to cause the compounds to be stronger acids than (I) and (II), it seems likely that the mechanism of methylation is analogous to that for the oximes (Brady and Goldstein, J., 1926, 2403), that is, the formation of the *O*-methyl derivative is an ionic and of the *N*-methyl derivative a molecular reaction. The former reaction would be favoured by employing a highly dissociated salt of a strong acid. Now the yield of the *N*-methyl compound in the above cases was small and, if these views are correct, 1-hydroxy-1 : 2 : 3-benztriazole should give a much larger proportion of the *N*-methyl derivative. This is so, the ratio of *O*- to *N*-methyl derivative being about 1·6 to 1. Moreover, when the methylation is carried out with the free hydroxybenztriazole in non-ionising solvents the sole product is the *N*-methyl compound, this reaction also being analogous to that of the aldoximes (Brady, Dunn, and Goldstein, J., 1926, 2394). Further, 1-hydroxy-6-methyl-1 : 2 : 3-benztriazole, which should be a weaker acid than 1-hydroxy-1 : 2 : 3-benztriazole, gives a still larger proportion of *N*-methyl derivative, the ratio of *O*- to *N*-compound being about 1·1 to 1. Methyl sulphate in aqueous alkali produces a greater amount of *N*-compound, as compared with *O*-compound, than does methyl iodide in alcoholic sodium ethoxide, but the same relative difference occurs between the two methods of methylation as applied to 1-hydroxy-1 : 2 : 3-benztriazole and 1-hydroxy-6-methyl-1 : 2 : 3-benztriazole.

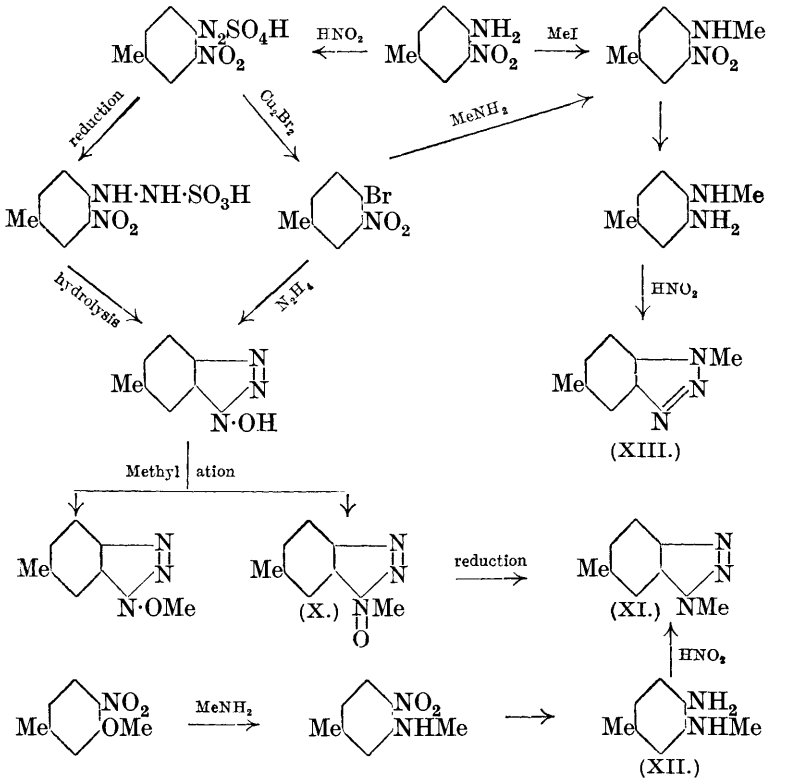
In Part I the constitution of the *N*-methyl compound was left undetermined, the choice being between the following formulæ:



This problem has now been solved. Structure (VII) was rejected because the *N*-methyl compound on reduction gave 1-methyl-1 : 2 : 3-benztriazole (VIII), which is formed from methyl-*o*-phenylenediamine (IX) by the action of nitrous acid.



The choice fell finally on (V) as the result of the consideration of the reduction of 1 : 6-dimethyl-1 : 2 : 3-benztriazole 1-oxide (X) to 1 : 6-dimethyl-1 : 2 : 3-benztriazole (XI), which was synthesised from 4-amino-3-methylaminotoluene (XII), the methyl group in the 6-position enabling a differentiation to be made between the 1- and the 3-position in the triazole ring. The reactions involved were as follows :



3 : 6-Dimethyl-1 : 2 : 3-benztriazole (XIII) was synthesised in the unlikely event of (XI) and (XIII) being tautomeric and was found to be quite distinct from (XI).

EXPERIMENTAL.

1-*Hydroxy*-1 : 2 : 3-*benztriazole*.—*o*-Nitrophenylhydrazine was first prepared by Bischler's method (*Ber.*, 1889, **22**, 2801), but a cleaner and more rapid way was one analogous to that used by Davies (J., 1922, **121**, 715) for the preparation of the *p*-nitro-compound. A solution of *o*-nitroaniline (10 g.) in concentrated hydrochloric acid (21 c.c.) at 100° was cooled to 5° and diazotised (5 g. of sodium nitrite in 35 c.c. of water). The solution was then filtered from a small amount of brown precipitate and run, during 5 minutes, into a solution of crystallised sodium sulphite (41 g.) in *N*-sodium hydroxide (100 c.c.) cooled below 0°. The deep red solution after 5 minutes was treated with concentrated hydrochloric acid (70 c.c.) and warmed to 60°. After 3 minutes, yellow needles separated. The mixture was cooled and kept for 24 hours and the crystalline precipitate, which probably consisted of sodium *o*-nitrophenylhydrazinemonosulphonate, was then collected and heated with concentrated hydrochloric acid (20 c.c.) for 10 minutes on the water-bath. The hydrochloride of *o*-nitrophenylhydrazine that separated on cooling was dissolved in a small quantity of hot water, and a cold saturated solution of sodium acetate added. After cooling, the *o*-nitrophenylhydrazine (7 g.) was collected, washed with water, air-dried, and crystallised from alcohol. Replacing the sodium suphite by ammonium sulphite did not give such a good result, the mono-ammonium sulphonate being more soluble than the corresponding sodium salt.

1-Hydroxy-1 : 2 : 3-benztriazole was prepared in nearly theoretical yield by the action of 25% potassium hydroxide solution on *o*-nitrophenylhydrazine (Zincke and Schwarz, *Annalen*, 1900, **311**, 332), but it can conveniently be obtained from the intermediate product in the above preparation, sodium *o*-nitrophenylhydrazinemonosulphonate. This compound, after being freed from water as completely as possible by means of a water-pump, was boiled under reflux with alcohol (100 c.c.), and an alcoholic solution of potassium hydroxide (rather more than 2 mols.) run in during 30 minutes; the colour then changed from bright yellow through purple to light brown. The alcohol was removed by distillation, the residue dissolved in boiling water, the solution filtered, cooled, and acidified with concentrated hydrochloric acid, and the precipitated hydroxybenztriazole crystallised from hot water containing animal charcoal.

o-Bromonitrobenzene (5 g.) was boiled with alcohol (100 c.c.) and 50% hydrazine hydrate (15 c.c.) under reflux for 30 hours. After distillation of the alcohol, and of the unchanged bromonitrobenzene in steam, the aqueous residue was filtered, evaporated to a small bulk, and acidified with hydrochloric acid; the hydroxytriazole

was then precipitated in 60% yield. The addition of copper bronze during the boiling with hydrazine did not facilitate the reaction.

o-Bromonitrobenzene (5 g.) was heated with 50% hydrazine hydrate solution (10 c.c.) in a sealed tube at 160° for 6 hours. The solution, after being acidified with hydrochloric acid, neither gave a precipitate nor yielded anything to ether. From the solution, made alkaline, chloroform extracted 1 : 2 : 3-benztriazole. At the temperature used, the excess of hydrazine hydrate reduced the hydroxybenztriazole first formed.

1-Hydroxy-1 : 2 : 3-benztriazole is precipitated from a solution of its sodium salt at 0° as an unstable hydrate which loses water on drying in the air.

1-*Acetoxy*-1 : 2 : 3-*benztriazole* was obtained by warming the hydroxybenztriazole (1 g.) with acetic anhydride and one drop of concentrated sulphuric acid on the water-bath and pouring the cooled solution into a saturated solution of sodium carbonate at 0°; the solid obtained, after being washed once with water and dried immediately on a porous tile for a few minutes, crystallised from benzene, containing a few drops of acetic anhydride, in colourless prisms, m. p. 98° (Found : N, 23·7. $C_8H_7O_2N_3$ requires N, 23·7%). The compound is readily hydrolysed by warm dilute sulphuric acid; it decomposes in a few days when left exposed to the air and more slowly in a corked vessel. Nietzki and Braunschweig (*Ber.*, 1894, **27**, 3381) and Zincke and Schwarz (*Annalen*, 1900, **311**, 332) were unable to obtain this acetyl compound and stated that acetic anhydride was without action on the hydroxybenztriazole.

1-*Benzoyloxy*-1 : 2 : 3-*benztriazole*, prepared from the hydroxybenztriazole (1 g.), 2*N*-sodium hydroxide (50 c.c.), and benzoyl chloride (5 g.), crystallised from benzene–light petroleum in colourless needles, m. p. 77° (Found : N, 17·8. $C_{13}H_9O_2N_3$ requires N, 17·6%). This compound, which was also prepared at 0° by the pyridine method of benzoylation, is more stable than the acetyl derivative, but decomposes slowly on exposure to air. On hydrolysis with dilute sulphuric acid, it gives benzoic acid and hydroxybenztriazole.

Reduction of the hydroxybenztriazole. Zincke and Schwarz (*loc. cit.*), by heating the hydroxybenztriazole with hydriodic acid in a sealed tube at 140—150°, obtained a polyiodide of 1 : 2 : 3-benztriazole; but if it (2 g.) is heated with hydriodic acid (6 c.c.; *d* 1·7) and red phosphorus (4 g.) in a sealed tube at 140—150° for 4 hours no polyiodide is formed. After dilution, filtration, evaporation to half bulk, neutralisation with a saturated solution of sodium carbonate, and extraction with chloroform, an almost quantitative yield of 1 : 2 : 3-benztriazole was obtained, which was identified by

conversion into its acetyl derivative and comparison with a specimen prepared from *o*-nitroacetanilide by Bell and Kenyon's method (J., 1926, 954).

Methylation of 1-*Hydroxy*-1 : 2 : 3-*benztriazole*.—There is no mention in the literature of the methylation of the hydroxybenztriazole, but Nietzki and Braunschweig (*Ber.*, 1894, **27**, 3382) stated that ethyl iodide had no action, even at a high temperature.

With methyl sulphate. When the hydroxybenztriazole (2 g.) in 2*N*-sodium hydroxide (50 c.c.) was treated with methyl sulphate (6 g.) in small portions with constant shaking, the temperature rose to 60° and a small amount of white solid separated. The mixture was warmed on the water-bath to complete the reaction and then distilled in steam. The aqueous distillate, in which crystals were floating, was extracted with chloroform and after drying and removal of the solvent the residual oil solidified on cooling. After crystallising from alcohol, 1-*methoxy*-1 : 2 : 3-*benztriazole* was obtained in colourless needles, m. p. 89° (Found: N, 28·2; OMe, 20·2. $C_7H_7ON_3$ requires N, 28·2; OMe, 20·8%). The average yield from a number of experiments was 0·8 g.

From the aqueous residue in the distilling flask, after concentration, repeated extraction with chloroform removed 1-*methyl*-1 : 2 : 3-*benztriazole* 1-*oxide*, which crystallised from alcohol or benzene–light petroleum in colourless needles, m. p. 145° (Found: N, 28·1. $C_7H_7ON_3$ requires N, 28·2%). The average yield was 0·4 g. On heating this compound with hydriodic acid, no methyl iodide was evolved.

The aqueous residue after the chloroform extraction was acidified and the precipitate of unchanged hydroxybenztriazole was collected, dried, and weighed, the average amount being about 0·5 g.; 25% of the triazole is unaccounted for and this loss is probably due to the solubility of the hydroxybenztriazole and the methylbenztriazole 1-oxide in water and to the difficulty of extracting the latter therefrom by chloroform.

The hydroxybenztriazole (1 g.) was heated with pure methyl sulphate (10 g.) at 100° for several hours; after cooling, the addition of ether precipitated an oil, presumably a methosulphate. As this would not crystallise, it was hydrolysed by boiling with dilute hydrochloric acid; the solution then contained sulphuric acid and on exhaustive extraction with chloroform yielded almost pure 1-methyl-1 : 2 : 3-benztriazole 1-oxide. A similar result was obtained when the hydroxybenztriazole was sealed up with methyl sulphate and kept in the dark for 10 weeks (compare Brady, Dunn, and Goldstein, *loc. cit.*).

With methyl iodide. A solution of the hydroxybenztriazole (3 g.),

sodium ethoxide (prepared from 0·35 g. of sodium), and methyl iodide (8 g.) in absolute alcohol was boiled under reflux for 2 to 3 hours. The alcohol was then removed by distillation, and the residue distilled in steam. The aqueous distillate on extraction with chloroform yielded 1·5 g. of the *O*-methyl ether, and the solution remaining in the flask, after being evaporated to small bulk and extracted with chloroform, gave 0·5 g. of 1-methyl-1 : 2 : 3-benztriazole 1-oxide. The aqueous layer, on being acidified, gave no hydroxybenztriazole, indicating complete methylation.

Methylation of the silver salt of the hydroxybenztriazole in alcohol gave a large amount of *O*-ether and only a small quantity of the *N*-methyl compound, and a similar result was obtained by methylation in dry benzene with methyl iodide and dry silver oxide.

The hydroxybenztriazole (1 g.), sealed up with methyl iodide (10 g.), was kept in the dark for 2 months. Some iodine was liberated and the liquid contained dark crystals. Excess of ether was added and the precipitated dark oil was treated with dilute sodium hydroxide solution and a little sodium thiosulphate to destroy free iodine. On distilling in steam no *O*-ether was obtained, so the solution was evaporated to small bulk and extracted with chloroform; the *N*-methyl compound was then obtained. The ethereal solution was evaporated and the residue was treated with dilute sodium hydroxide solution and sodium thiosulphate and distilled in steam, but no *O*-ether was found in the distillate.

Synthesis of 1-*Methyl*-1 : 2 : 3-*benztriazole.*—*o*-Nitromethylaniline has been prepared by previous workers in a number of ways, usually involving sealed tubes. Nitration of methylaniline with copper nitrate trihydrate in acetic anhydride (Menke, *Rec. trav. chim.*, 1925, **44**, 141, 269) was not successful, but the following method, analogous to that of Witt and Utermann (*Ber.*, 1906, **39**, 3903), gave satisfactory results. A mixture of acetic anhydride (3 c.c.), nitric acid (5 c.c.; *d* 1·5), and a small quantity of urea at 0° was slowly added, with mechanical stirring, to methylacetanilide (10 g.) suspended in acetic anhydride (10 c.c.), the temperature being kept below 10°. After being kept at room temperature for 24 hours, the solution was poured into cold water and just neutralised with concentrated ammonium hydroxide. The oil thus produced was extracted with chloroform and boiled under reflux for 2 hours with 50% sulphuric acid (100 c.c.), the red solution being then distilled in steam. The aqueous distillate (2·5—3 l.) on extraction with chloroform gave 5 g. of *o*-nitromethylaniline.

1-*Methyl*-1 : 2 : 3-*benztriazole.* The isolation of the unstable methyl-*o*-phenylenediamine was unnecessary. The following method of reducing *o*-nitromethylaniline is a great improvement on

that of Fischer using tin and hydrochloric acid (*Ber.*, 1892, **25**, 2841). *o*-Nitromethylaniline (5 g.) was suspended in boiling water (75 c.c.), and a solution of sodium hydrosulphite run in slowly until the colour vanished. The solution was made alkaline with sodium hydroxide and extracted with benzene, and the extract shaken with an equal volume of 20% hydrochloric acid. The acid solution of methyl-*o*-phenylenediamine hydrochloride so obtained was cooled to 0° and sodium nitrite (1 g. in 7 c.c. of water) added and when the action was complete the mixture was boiled for 30 minutes. No dark-coloured by-product was obtained as mentioned by Reissert (*Ber.*, 1914, **47**, 676). After cooling, the acid solution was neutralised with sodium carbonate and extracted with chloroform. Removal of the solvent gave an almost theoretical yield of crude 1-methyl-1 : 2 : 3-benztriazole, which was crystallised from benzene–light petroleum.

1-Methyl-1 : 2 : 3-benztriazole 1-oxide (1 g.) was boiled with hydriodic acid (15 c.c.; *d* 1·7) and red phosphorus (3 g.) for 6 hours. The solution was diluted, filtered, made alkaline with sodium hydroxide, and decolorised with sodium thiosulphate. On extraction with chloroform and crystallisation from benzene–light petroleum, 1-methyl-1 : 2 : 3-benztriazole was obtained identical with the above compound.

1-*Hydroxy*-6-*methyl*-1 : 2 : 3-*benztriazole*.—This compound was prepared in an analogous manner to hydroxybenztriazole, but ammonium sulphite gives in this case a better result than sodium sulphite (compare Zincke and Schwarz, and Davies, *locc. cit.*). 4-Bromo-3-nitrotoluene (5 g.), prepared by the Sandmeyer method from 3-nitro-*p*-toluidine (compare Nevile and Winther, *Ber.*, 1880, **13**, 972), was boiled under reflux with alcohol (100 c.c.) and 50% hydrazine hydrate (20 c.c.) for 30 hours, the alcohol distilled off, and the residue distilled in steam. The solution remaining in the flask was filtered while hot, acidified with concentrated hydrochloric acid, and evaporated to small bulk; on cooling, 1-hydroxy-6-methyl-1 : 2 : 3-benztriazole crystallised in 60% yield. One crystallisation from water gave the pure compound.

Acetyl and benzoyl derivatives of 1-*hydroxy*-6-*methyl*-1 : 2 : 3-*benztriazole*. These compounds were obtained in good yield in similar ways to the corresponding hydroxybenztriazole compounds and have similar properties. 1-*Acetoxy*-6-*methyl*-1 : 2 : 3-*benztriazole* crystallised from benzene, containing a little acetic anhydride, in colourless prisms, m. p. 138° (Found: N, 22·4. $C_9H_9O_2N_3$ requires N, 22·0%). 1-*Benzoyloxy*-6-*methyl*-1 : 2 : 3-*benztriazole* crystallised from benzene–light petroleum in colourless prisms, m. p. 129—130° (Found: N, 17·0. $C_{14}H_{11}O_2N_3$ requires N, 16·6%).

Reduction of 1-*hydroxy*-6-*methyl*-1 : 2 : 3-*benztriazole.* This was carried out as in the case of the hydroxybenztriazole and a good yield of 6-methyl-1 : 2 : 3-benztriazole, identified by comparison with a specimen prepared from 3 : 4-tolylenediamine (Ladenburg, *Ber.*, 1876, **9**, 220), was obtained.

Methylation of 1-*Hydroxy*-6-*methyl*-1 : 2 : 3-*benztriazole.* — *With methyl sulphate.* On methylation with methyl sulphate in the presence of 2*N*-sodium hydroxide in exactly the same way as hydroxybenztriazole, 2 g. of 1-hydroxy-6-methyl-1 : 2 : 3-benztriazole gave 0·52 g. of 1-*methoxy*-6-*methyl*-1 : 2 : 3-*benztriazole*, which crystallised from alcohol in colourless needles, m. p. 50° (Found : N, 26·1; OMe, 18·3. $C_8H_9ON_3$ requires N, 25·8; OMe, 19·0%). At the same time, there was obtained 0·47 g. of 1 : 6-*dimethyl*-1 : 2 : 3-*benztriazole* 1-*oxide*, which crystallised from benzene–light petroleum in colourless needles, m. p. 169° (Found : N, 26·0. $C_8H_9ON_3$ requires N, 25·8%). The unmethylated triazole recovered was 0·41 g. As the result of a number of experiments it was found that the ratio of *O*-ether to *N*-methyl-*N*-oxide was less than that for the unsubstituted hydroxybenztriazole. Heating 1-hydroxy-6-methyl-1 : 2 : 3-benztriazole with pure methyl sulphate or keeping it with that reagent for 10 weeks also yielded the *N*-methyl-*N*-oxide and no *O*-ether.

With methyl iodide. By the same method, similar results were obtained to those with hydroxybenztriazole : 2 g. gave 0·84 g. of *O*-methyl ether and 0·4 g. of *N*-methyl-*N*-oxide. Results similar to those with the unsubstituted compound were obtained by using the silver salt, methyl iodide alone or methyl iodide in benzene with silver oxide.

1 : 6-*Dimethyl*-1 : 2 : 3-*benztriazole.*—Zincke and Lawson (*Annalen*, 1887, **240**, 126) claim to have prepared a dimethyl-1 : 2 : 3-benztriazole, but their compound, of which they give no analysis, was probably a mixture of 1 : 6- and 3 : 6-dimethyl-1 : 2 : 3-benztriazole. The following method for preparing the initial material, 4-nitro-*m*-tolyl methyl ether, is a great improvement on those previously described (Reissert, *Ber.*, 1898, **31**, 397; Khotinsky and Jacopson-Jacopmann, *Ber.*, 1909, **42**, 3100). A mixture of 4-nitro-*m*-cresol, methyl iodide (15 g.), dry benzene (75 c.c.), and dry, freshly prepared silver oxide (10 g.) was boiled under reflux for 3 hours. The benzene was distilled off, water and 5 c.c. of 2*N*-sodium hydroxide were added, and the product was distilled in steam. 4-Nitro-*m*-tolyl methyl ether crystallised from the distillate in almost theoretical yield. It is best recrystallised from light petroleum. 4-Nitro-3-methylaminotoluene (3 g.), prepared from the above by heating to 165° with methylamine (Fischer and Rigaud, *Ber.*,

1902, **35**, 1260), was suspended in boiling water (50 c.c.) and reduced with sodium hydrosulphite as in the preparation of 1-methyl-1 : 2 : 3-benztriazole. The hydrochloric acid solution of 4-amino-3-methylaminotoluene was diazotised by the addition below 5° of sodium nitrite (1 g. in 7 c.c. of water). (It is important to keep the solution for 30 minutes to complete the reaction.) After treatment as before, 1 : 6-*dimethyl*-1 : 2 : 3-*benztriazole* was obtained from benzene–light petroleum in colourless plates, m. p. 75° (Found : N, 28·7. $C_8H_9N_3$ requires N, 28·6%). When 1 : 6-dimethyl-1 : 2 : 3-benztriazole 1-oxide was reduced with hydriodic acid in an exactly similar manner to 1-methyl-1 : 2 : 3-benztriazole 1-oxide, a compound identical with the above 1 : 6-dimethyl-1 : 2 : 3-benztriazole was obtained.

3 : 6-*Dimethyl*-1 : 2 : 3-*benztriazole*.—This compound was prepared for comparison by the reduction of 3-nitro-4-methylaminotoluene with sodium hydrosulphite, followed by the action of nitrous acid as before. The initial material is best prepared by heating 4-bromo-3-nitrotoluene (see above) (10 g.) with 33% aqueous methylamine (15 c.c.) for 6 hours in a sealed tube at 150°. The solid product left in the tube, on crystallisation from alcohol, gave 7 g. of pure 3-nitro-4-methylaminotoluene. Gattermann's method (*Ber.*, 1885, **18**, 1487) gave poor yields. 3 : 6-*Dimethyl*-1 : 2 : 3-*benztriazole* crystallised from benzene–light petroleum in colourless plates, m. p. 50° (Found : N, 28·9. $C_8H_9N_3$ requires N, 28·6%).

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