

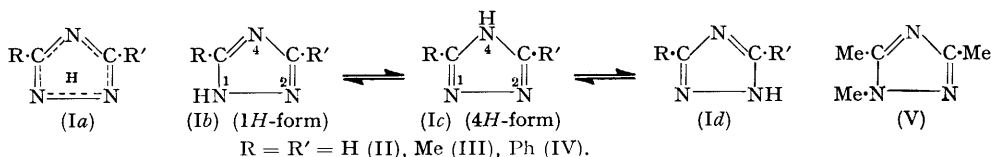
Triazoles. Part II. N-Substitution of Some 1:2:4-Triazoles.*

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1:2:4-Triazole and its 3:5-dimethyl and 3:5-diphenyl derivatives have been methylated, ethylated, and acetylated by various methods. The orientation of the unstable acetyltriangles could not be determined with certainty. Alkylation afforded mainly 1-alkyl-1:2:4-triazoles, the structures of which were established by alternative syntheses and comparison with known isomers. Some new triazole picrates have been prepared.

LIKE the analogous glyoxalines and pyrazoles, "acidic" triazoles (I; R = R' = H, Alkyl, Aryl, etc.) which contain no *N*-substituent are obtained only in one form. This may be due to mesomerism (Ia) or tautomerism (Ib, c, d). Whichever representation is adopted, it appears probable that the acidic hydrogen will not be shared equally between the three nitrogen atoms. Alkylation of 1:2:4-triazole (II) (Pellizzari and Soldi, *Gazzetta*, 1905, **35**, I, 373) or 3:5-dimethyl- (III) or 3:5-diphenyl-1:2:4-triazole (IV) affords exclusively or mainly 1-alkyl-1:2:4-triazoles, that is, derivatives of (Ib = Id). This suggests the uneven distribution of the acidic hydrogen between N₍₁₎ and N₍₄₎, without necessarily proving that the acidic hydrogen is more closely linked with either. More light may be thrown on this by a study of *N*-substitution of triazoles in which R and R' are different which will be reported later.



Methylhydrazine sulphate and diacetimide afford 1:3:5-trimethyl-1:2:4-triazole (V); under the mild conditions of the Einhorn-Brunner reaction (Part I*) rearrangement of methyl from N₍₁₎ to N₍₄₎ is unlikely. It was shown for (V) and all other 1:2:4-triazoles studied in this work that such rearrangements do not occur at higher temperatures and with longer reaction times than those applying in Einhorn-Brunner syntheses. Also the rearrangement of N₍₄₎-substituted 1:2:4-triazoles [*i.e.*, derivatives of (Ic)] to N₍₁₎-substituted triazoles [*i.e.*, derivatives of (Ib, d)] does not occur under such conditions. Methylation of 3:5-dimethyltriazole by diazomethane or by treatment of its sodium salt with methyl iodide affords (V) in good yield and free from the 3:4:5-trimethyl isomer (Meyer, G.P. 574,944; *Chem. Abs.*, 1933, **27**, 4541). Pure (V) with methyl iodide gives a very hygroscopic methiodide which is not obtained by reaction of equimolar amounts of methyl iodide and the sodium salt of the dimethyltriazole.

Ethylation of 3:5-dimethyl-1:2:4-triazole by diazoethane affords an ethyldimethyltriazole in almost quantitative yield. Treatment of the sodium salt with ethyl iodide affords the same main product with, in addition, a small quantity of an isomeric triazole. The latter is identified as 4-ethyl-3:5-dimethyl-1:2:4-triazole by its Pellizzari synthesis from acetylhydrazine and *N*-ethylacetamide. As the two compounds are not interconvertible by heating, the other must be the 1-ethyl isomer.

Methyl iodide and the sodium salt of 3:5-diphenyl-1:2:4-triazole afford 1-methyl-3:5-diphenyl-1:2:4-triazole, the structure of which is established by an alternative synthesis from methylhydrazine sulphate and dibenzimide and by its difference from the isomeric 4-methyl-3:5-diphenyl-1:2:4-triazole (Scheuing and Walach, G.P. 543,026; *Chem. Abs.*, 1932, **26**, 3263). It may be noted in general that trisubstituted 4*H*-1:2:4-triazoles † have considerably higher melting and boiling points than the isomeric 1*H*-1:2:4-triazoles.

* Part I, *J.*, 1952, 3418. † *H* indicates the position of the "extra" ("indicated") hydrogen atom.

Methylation of the sodium salt of 1 : 2 : 4-triazole itself by methyl iodide (Pellizzari and Soldi, *loc. cit.*) gave 1-methyl-1 : 2 : 4-triazole, in agreement with the earlier work.

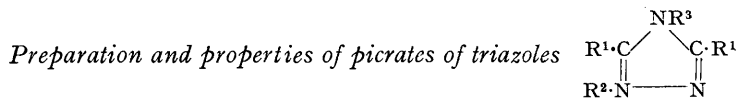
Acylation of 3 : 5-dimethyl-1 : 2 : 4-triazole with acetic anhydride and treatment of its potassium salt with acetyl chloride afford the same acetyltriazole. Reduction of this to an ethyldimethyltriazole with lithium aluminium hydride failed, 3 : 5-dimethyltriazole being the only triazole isolated from the products. An attempted Einhorn-Brunner reaction between acetylhydrazine and diacetimide afforded acetamide and *NN'*-diacetylhydrazine in good yields, but no triazole. The acetyl group of the acetyldimethyltriazole is readily hydrolysed even by atmospheric moisture, but reaction with ethyl iodide in a sealed tube fails to replace acetyl by ethyl. Acetyl-1 : 2 : 4-triazole itself is even more sensitive to moisture; it is decomposed by picric acid in chloroform to give 1 : 2 : 4-triazole picrate. Acetylation of 3 : 5-diphenyltriazole by different methods affords the same acetyldiphenyltriazole (Pinner, *Ber.*, 1894, 27, 984; Wolchow, *Monatsh.*, 1916, 37, 473). This is more resistant to hydrolysis by atmospheric moisture than the two previous acetyl derivatives but it is cleaved by picric acid. The lability of the acetyl groups in these compounds is consistent with their formulation as *N*-acetyltriazoles. The positions of the acetyl groups cannot be stated with certainty. On the analogy of the predominating 1-alkylation (see above) and on consideration of the relatively low melting points, they may be regarded tentatively as 1-acetyl derivatives.

Although the analysis of triazole picrates is difficult and gives high figures for carbon and low figures for nitrogen (probably owing to the incomplete reduction of nitrogen oxides) picrates are possibly the best derivatives for the rapid identification of triazoles.

EXPERIMENTAL

M. p.s are corrected.

The new *picrates* are shown in the Table. The last two were dried at 20°/1 mm., the others at 60—75°/1 mm.



R ¹	R ²	R ³	Cryst. from	M. p.	Composition	Reqd. (%)		Found (%)		Note
						C	H	C	H	
H	H	—	CHCl ₃	168°	C ₉ H ₆ O ₇ N ₆	32.2	2.0	32.8	2.2	<i>a</i>
Me	H	—	C ₆ H ₅ -MeOH	170	C ₁₀ H ₁₀ O ₇ N ₆	36.8	3.1	37.2	3.1	<i>a</i>
Ph	H	—	C ₆ H ₅ -CHCl ₃	171	C ₂₀ H ₁₄ O ₇ N ₆	53.3	3.1	54.4	3.6	<i>b, c, d</i>
Me	Me	—	EtOH	134.5	C ₁₁ H ₁₂ O ₇ N ₆	38.8	3.6	39.2	3.6	<i>b, e</i>
Me	Et	—	EtOH	126	C ₁₂ H ₁₄ O ₇ N ₆	40.7	4.0	40.9	3.9	<i>b</i>
Me	—	Et	EtOH	147	C ₁₂ H ₁₄ O ₇ N ₆	40.7	4.0	41.1	4.4	<i>b</i>
Ph	Me	—	20% EtOH	135	C ₂₁ H ₁₆ O ₇ N ₆	54.3	3.5	54.8	3.5	<i>f</i>
Ph	—	Me	EtOH	155	C ₂₁ H ₁₆ O ₇ N ₆	54.3	3.5	54.5	4.0	<i>b</i>
H	Me	—	EtOH	137	C ₉ H ₈ O ₇ N ₆	34.6	2.6	35.4	2.6	<i>b</i>
Me	Ac*	—	C ₆ H ₅ -CCl ₄	120	C ₁₂ H ₁₂ O ₈ N ₆	39.1	3.3	39.2	3.2	<i>a</i>

* Possibly R³ = Ac. *a* Prep. in CHCl₃. *b* Prep. in EtOH. *c* Forms an unstable chloroform solvate, m. p. 150° (decomp.). *d* Found: O, 24.6. Reqd.: O, 24.9%. *e* Found: N, 24.2. Reqd.: N, 24.7%. *f* Prep. in 20% EtOH.

Substitution of 1 : 2 : 4-Triazole.—1 : 2 : 4-Triazole (10.0 g.) (Pellizzari, *Gazzetta*, 1894, 24, II, 222), dissolved in a solution of sodium (3.33 g.) in methanol (60 c.c.), was treated with methyl iodide (20.6 g.) according to Pellizzari and Soldi (*loc. cit.*), then heated in an autoclave at 120° for 1 hr., and freed from methanol. The residue was extracted with hot benzene (50 c.c.) and then hot chloroform (3 × 50 c.c.). The combined extracts were cooled to precipitate unchanged 1 : 2 : 4-triazole, m. p. 121° (1.86 g., 19%). The filtrate was freed from solvent, and the residue distilled at 177°/755 mm., affording 1-methyl-1 : 2 : 4-triazole (9.44 g., 78%), *d*_D²⁰ 1.105, *n*_D²⁰ 1.4650, in agreement with recorded data.

1 : 2 : 4-Triazole (3.45 g.) was heated under reflux with acetic anhydride (6 c.c.) for 1 hr. The solvents were removed by distillation under atmospheric pressure; the fraction distilling at 178—180°/760 mm. set to colourless, triclinic crystals of *acetyl*-1 : 2 : 4-triazole (4.41 g., 79%), m. p. 38—39°, b. p. 178°/755 mm., which sublimes at 40°/2 mm. (Found: C, 44.5; H, 4.7; N, 37.5. C₄H₅ON₃ requires C, 43.2; H, 4.5; N, 37.8%). Only picric acid was pre-

precipitated when warm chloroform or benzene-carbon tetrachloride solutions of acetyltriazole and picric acid were mixed; the mother-liquor deposited 1 : 2 : 4-triazole picrate after a week.

Sodium (0.23 g.) was dissolved in ethanol (50 c.c.) and after addition of 1 : 2 : 4-triazole (0.69 g.) the solution was evaporated to dryness. The residue was covered with benzene (20 c.c.) and mixed with acetyl chloride (1 c.c.) in benzene (20 c.c.), and the suspension boiled under reflux with stirring for 30 min., then filtered. The residue was washed with benzene (30 c.c.), and the combined filtrate and washings were freed from solvent. The product was purified by distillation at 179—180°/760 mm. and crystallized from benzene-light petroleum (b. p. 40—60°) in triclinic crystals (0.21 g., 19%), m. p. 38—39° alone or on admixture with the former acetyltriazole.

Substitution of 3 : 5-Dimethyl-1 : 2 : 4-triazole.—(a) *Acetyl derivative.* 3 : 5-Dimethyl-1 : 2 : 4-triazole (2.0 g.) (Silberrad, *J.*, 1900, **77**, 1185) and acetic anhydride (4.0 c.c.) were boiled for 1 hr. under reflux, then the solvents were distilled off. The residue, sublimed at 70°/2 mm., gave colourless prisms of *acetyl-3 : 5-dimethyl-1 : 2 : 4-triazole* (2.41 g., 84%), m. p. 90—91°, b. p. 199°/760 mm. (Found : C, 51.9; H, 6.4; N, 30.9. $C_8H_9ON_3$ requires C, 51.8; H, 6.5; N, 30.2%).

3 : 5-Dimethyl-1 : 2 : 4-triazole (1.00 g.) was dissolved in a solution of potassium (0.39 g.) in methanol (10 c.c.). The potassium salt was precipitated with ether (200 c.c.), suspended in benzene (50 c.c.), and treated with acetyl chloride (0.80 g.) in benzene (25 c.c.) as in the preparation of acetyl-1 : 2 : 4-triazole. The product (0.86 g., 60%), purified by sublimation, had m. p. 89—91° alone and on admixture with the preceding sample. The picrates of the two materials were similarly proved to be identical.

Acetyldimethyltriazole (0.76 g.) and ethyl iodide (0.89 g.) were heated in a sealed tube with benzene (2 c.c.) at 100° for 6 hr. Removal of the solvent and sublimation of the residue gave unchanged acetyldimethyltriazole, m. p. 90° (0.71 g., 93%), identified as the picrate, m. p. 120°.

Diacetimide (10.1 g.) and acetylhydrazine (7.4 g.) were dissolved in a mixture of ethanol-free chloroform (100 c.c.) and dry pyridine (10 c.c.), and the solution was set aside at room temperature for a month. The solvent was removed by distillation and repeated evaporation with carbon tetrachloride. Sublimation of the residue at reduced pressure afforded acetamide (4.2 g., 78%), m. p. 78°. The less volatile portion, recrystallized from ether-*isopropyl* alcohol, gave *NN'*-diacetylhydrazine (9.1 g., 78%), m. p. 136° alone and on admixture with material prepared by Stollé's method (*Ber.*, 1899, **32**, 796). No dimethyltriazole or acetyldimethyltriazole could be detected.

Acetyldimethyltriazole (1.75 g.) was added to a slurry of lithium aluminium hydride (1.5 g.) in ether (50 c.c.), and the mixture was refluxed under nitrogen for 20 hr. After decomposition of the mixture with water, followed by 4*N*-sulphuric acid, the aqueous layer was extracted with chloroform (3 × 50 c.c.). Evaporation of the combined extracts left traces of an oil which gave no picrate. Extraction of the aqueous layer made alkaline with 10% sodium hydroxide gave similar results. Extraction of the residue, obtained on neutralization and concentration of the aqueous layer, with chloroform gave dimethyltriazole (0.84 g., 69%), m. p. and mixed m. p. 141—142°.

(b) *Methyl derivative.* Diacetimide (15.0 g.) and methylhydrazine sulphate (14.4 g.) were heated at 145° for 5 hr. Water (5 c.c.) was added, the solution boiled under reflux for another hour, and its pH adjusted to 5 with cold 2*N*-sodium carbonate and then to pH 8 with cold concentrated aqueous ammonia. Extraction with chloroform (3 × 80 c.c.) followed by the removal of the solvent and distillation of the residue at 193—195°/760 mm. left crude 1 : 3 : 5-trimethyl-1 : 2 : 4-triazole which was redistilled at 193°/755 mm. and 72—74°/11 mm. (6.3 g., 57%) and then had d_{20}^{20} 1.037, n_D^{20} 1.4652 (Found : C, 54.5; H, 8.3; N, 37.3. $C_5H_9N_3$ requires C, 54.0; H, 8.2; N, 37.8%).

A solution of trimethyltriazole (0.76 g.) and methyl iodide (3.4 g.) in benzene (20 c.c.) was boiled under reflux for 4 hr. and on cooling afforded very hygroscopic prisms of 1 : 3 : 5-trimethyl-1 : 2 : 4-triazole *methiodide*; dried at 75°/2 mm. and recrystallized twice from methanol-ether (1 : 2) they had m. p. 138° (Found : C, 27.5; H, 5.5; I, 50.2. $C_6H_{12}N_3I$ requires C, 28.5; H, 4.8; I, 50.1%). The hygroscopic nature of the substance no doubt accounts for discrepancies of the carbon and hydrogen analyses; the iodine analysis was carried out in our own laboratory on absolutely fresh material.

Dimethyltriazole (7.50 g.) was dissolved in a solution of sodium (1.78 g.) in methanol (40 c.c.) and caused to react with methyl iodide (11.0 g.) for 1 hr. at room temperature and 1 hr. at 120° (sealed vessel). The products were worked up as before and afforded trimethyltriazole

(6.95 g., 81%) and unchanged dimethyltriazole (0.15 g., 2%); these triazoles and their picrates were identical with those reported in the preceding experiments. Neither this nor a similar experiment in which the reaction temperature did not exceed 100° afforded 3 : 4 : 5-trimethyl-1 : 2 : 4-triazole which has m. p. 81.5° (Meyer, *loc. cit.*). Dimethyltriazole (1.00 g.) in methanol (20 c.c.) was treated with a 10—12-molar excess of ethereal diazomethane in 3 portions during 3 days. After removal of the solvent, 1 : 3 : 5-trimethyl-1 : 2 : 4-triazole was distilled below 70°/1.5 mm., then redistilled at 195—196°/755 mm. (0.93 g., 81%), and identified as the picrate. The residue, triturated with benzene, crystallized, giving unchanged dimethyltriazole (0.14 g., 14%), m. p. 143°.

(c) *Ethyl derivative.* Phosphorus oxychloride (15.3 g.) in dry ethanol-free chloroform (100 c.c.) was added with stirring to *N*-ethylacetamide (8.7 g.) in dry pyridine (16 g.) below 20°. After 12 hr. acetylhydrazine (7.4 g.) in boiling chloroform (200 c.c.) was added; heating and stirring were continued for 1 hr. The cooled product was extracted with water (2 × 100 c.c.) and 10% aqueous sodium hydrogen carbonate (2 × 50 c.c.); the aqueous solutions were united, made strongly alkaline with sodium hydroxide, and extracted with chloroform (4 × 100 c.c.). The combined chloroform extracts were dried and the residue was purified by fractionation at 170—175°/12 mm. and by chromatography in benzene on alumina, followed by elution with benzene-chloroform (20 : 1), which gave 4-ethyl-3 : 5-dimethyl-1 : 2 : 4-triazole (2.84 g., 23%), m. p. 115—116° (Found : C, 56.7; H, 9.6; N, 33.8. C₆H₁₁N₃ requires C, 57.6; H, 8.9; N, 33.6%). The substance is hygroscopic; its picrate gives better analytical results.

Dimethyltriazole (10.0 g.) in a solution of sodium (2.37 g.) in ethanol (60 c.c.) was ethylated with ethyl iodide (16.1 g.) for 1 hr. at room temperature and 1 hr. at 120° in a sealed vessel. Distillation at 196°/755 mm., then 80.5—81.5°/12 mm., afforded 1-ethyl-3 : 5-dimethyl-1 : 2 : 4-triazole (7.50 g., 58%), d_{20}^{20} 0.990, n_D^{20} 1.4690 (Found : C, 57.2; H, 8.9; N, 33.7%). The hygroscopic residue from the distillation gave a picrate which did not depress the m. p. of the picrate of 4-ethyl-3 : 5-dimethyl-1 : 2 : 4-triazole prepared in the preceding experiment. The picrate was decomposed by 4*N*-hydrochloric acid; extraction with chloroform and chromatographic purification gave the expected base (0.15 g., 1%), m. p. and mixed m. p. 115°.

Ethylation of dimethyltriazole by diazoethane was carried out in the same manner as the methylation with diazomethane, but an 18-molar excess was used. This gave 1-ethyl-3 : 5-dimethyl-1 : 2 : 4-triazole (1.20 g., 93%), b. p. 194.5°/745 mm., and unchanged dimethyltriazole (0.03 g.); the isomeric ethyldimethyltriazole could not be detected.

Substitution of 3 : 5-Diphenyl-1 : 2 : 4-triazole.—The preparation of acetyldiphenyltriazole by the acylation of 3 : 5-diphenyl-1 : 2 : 4-triazole (1.2 g.) (Pellizzari, *Gazzetta*, 1911, **41**, II, 20) with acetic anhydride (2.0 g.) and sodium acetate (1.0 g.) by Wolchowe's method (*loc. cit.*) gave the expected compound (0.85 g., 60%), m. p. 108° after recrystallization from ether-light petroleum (b. p. 60—80°). Diphenyltriazole (0.54 g.) and acetic anhydride (2.0 g.) were boiled under reflux for 4 hr. The acetic anhydride was distilled off and the residue sublimed at 100°/1 mm. This gave acetyldiphenyltriazole (0.60 g., 93%), m. p. 107—108° alone or when mixed with the first preparation.

Diphenyltriazole (4.4 g.) was dissolved in a solution of sodium (0.46 g.) in methanol (10 c.c.). The solution was evaporated to dryness and the residue was boiled with acetyl chloride (1 c.c.) in benzene (30 c.c.) for 1 hr. The sodium chloride was filtered off and washed with ether (2 × 20 c.c.). The combined filtrate and washings were evaporated to dryness and the residue, recrystallized from ether-light petroleum, afforded acetyldiphenyltriazole (2.38 g., 45%), m. p. 107°, identical with the preceding two preparations.

Diphenyltriazole (2.21 g.) was dissolved in a solution of sodium (0.23 g.) in methanol (5 c.c.), mixed with methyl iodide (1.42 g.), and heated to 120° for 15 hr. The product was made into a slurry with 5% aqueous sodium carbonate and stirred with benzene-ether (1 : 1; 3 × 30 c.c.). After removal of solvents from the extract the residue was dissolved in benzene, filtered through a column of alumina, and evaporated to dryness. Crystallization from benzene-light petroleum (b. p. 40—60°) gave 1-methyl-3 : 5-diphenyl-1 : 2 : 4-triazole (1.47 g., 63%), m. p. 85° (Found : C, 76.8; H, 5.6; N, 18.0. C₁₅H₁₃N₃ requires C, 76.6; H, 5.5; N, 17.9%).

Dibenzimide (2.25 g.) and methylhydrazine sulphate (1.44 g.) were heated together at 160° for 4 hr. A suspension of the product in water (100 c.c.) was brought to pH 6 with sodium carbonate and extracted with benzene-ether (2 : 1; 4 × 25 c.c.). The extract was dried and evaporated. The residue, recrystallized from light petroleum (b. p. 60—80°), gave 1-methyl-3 : 5-diphenyl-1 : 2 : 4-triazole (0.95 g., 40%), m. p. 85°, identical with the preceding preparation. Both preparations are clearly different from 4-methyl-3 : 5-diphenyl-1 : 2 : 4-triazole which has m. p. 242° (243° according to Scheuing and Walach).

All the triazole preparations were heated at 140—165° for 4—6 hr. without change of physical constants.

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