Triazoles. Part III. Mono- and Di-methyl(phenyl)-*1 : 2 : 4*-triazoles.*

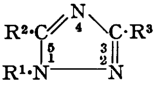
By M. R. Atkinson and J. B. Polya.

Reprint Order No. 5208.]

The structure of *N*-benzimidoyl-*N'*-methylhydrazine is established by its cyclization with ethyl chloroformate to 5-hydroxy-1-methyl-3-phenyl-1 : 2 : 4-triazole. Cyclization of this hydrazine with formic acid or acetic anhydride establishes the structures of the resulting 1-methyl-3-phenyl- and 1 : 5-dimethyl-3-phenyl-1 : 2 : 4-triazoles which differ from the isomeric 1-methyl-5-phenyl- and 1 : 3-dimethyl-5-phenyl-1 : 2 : 4-triazoles prepared from methylhydrazine and *N*-formylbenzamide or *N*-acetylbenzamide respectively. Methylation of 3-phenyl- and 3-methyl-5-phenyl-1 : 2 : 4-triazole by diazomethane affects mainly the " vicinal " nitrogen atom next to the phenyl group, but the other " vicinal " nitrogen atom is preferentially methylated if the sodiotriazoles are treated with methyl iodide. These observations may be correlated with the calculated π-electron densities on the nitrogen centres of 1 : 2 : 4-triazole and its anion.

The unsymmetrical Einhorn–Brunner reaction (Part I, *J.*, 1952, 3418) :

$$R^1{\cdot}NH{\cdot}NH_2 + R^2{\cdot}CO{\cdot}NH{\cdot}CO{\cdot}R^3 \longrightarrow$$



(I)

where $R^2 \neq R^3$ and $R^3{\cdot}CO_2H$ is a stronger acid than $R^2{\cdot}CO_2H$ occurs without the formation of the isomeric triazoles (I; with R^2 and R^3 interchanged) when R^1 = Me, R^2 = Ph, and R^3 = H or Me. The reaction between phenylhydrazine and *N*-acetylurethane, which affords 5-hydroxy-3-methyl-1-phenyl-1 : 2 : 4-triazole (I; R^1 = Ph, R^2 = OH, R^3 = Me), has been described before by Andreocci (*Gazzetta*, 1889, **19**, 448) and confirms the correlation between the orientation of the substituents R^2 and R^3 and the acidities of $R^2{\cdot}CO_2H$ and

---

* Part II, *J.*, 1954, 141.

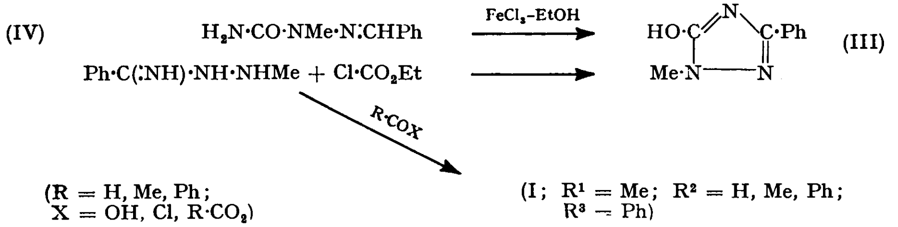
$R^3{\cdot}CO_2H$. Andreocci's work has been repeated under more vigorous conditions but with the same results, confirming earlier observations (Parts I and II) which suggested that reaction times and temperatures do not affect the orientation of substituents.

Structural proofs of the new triazoles described in this paper are based on the unambiguous cyclization of substances containing the N·C·N·N skeleton, in particular amidrazones (II). The usual preparation of amidrazones from imidoates and hydrazines allows two possible structures (II*a* and *b*):

$$R'{\cdot}C(:NH){\cdot}OEt + R''{\cdot}NH{\cdot}NH_2 \longrightarrow \begin{cases} R'{\cdot}C(:NH){\cdot}NH{\cdot}NHR'' & (IIa) \\ R'{\cdot}C(:NH){\cdot}NR''{\cdot}NH_2 & (IIb) \end{cases}$$

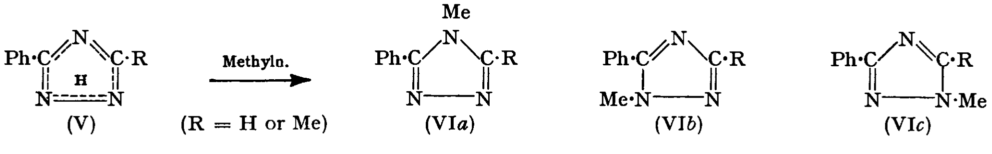
The structure (II*a*) is commonly assumed (Jerchel and Fischer, *Annalen*, 1951, **574**, 85) although structure (II*b*) cannot be dismissed *a priori*, particularly when R'' = Me (cf. the condensation of methylhydrazine with potassium cyanate to $H_2N{\cdot}CO{\cdot}NMe{\cdot}NH_2$; von Brüning, *Annalen*, 1889, **253**, 5). Benzimidoylmethylhydrazine (II; R' = Ph, R'' = Me), prepared from ethyl benzimidoate hydrochloride and methylhydrazine, when treated with ethyl chloroformate, afforded 5-hydroxy-1-methyl-3-phenyl-1 : 2 : 4-triazole (III) which is unambiguously available also from benzylidene-2-methylsemicarbazide (IV) (Young and Oates, *J.*, 1901, **79**, 659); this establishes the structure (II*a*) for the benzimidoylmethylhydrazine.

The triazoles obtained from benzimidoylmethylhydrazine by the action of benzoyl chloride, formic acid, and acetic anhydride are respectively 1-methyl-3 : 5-diphenyl-1 : 2 : 4-triazole (Part II) and the new compounds 1-methyl-3-phenyl- and 1 : 5-dimethyl-3-phenyl-1 : 2 : 4-triazole. The last two are not identical with the triazoles obtained from methylhydrazine sulphate and *N*-formyl- or *N*-acetyl-benzamide in Einhorn–Brunner reactions which must therefore afford 1-methyl-5-phenyl- and 1 : 3-dimethyl-5-phenyl-1 : 2 : 4-triazole respectively. Reference to the last-mentioned four compounds and their known 4-methyl isomers (Young and Oates, *loc. cit.*; Scheuing and Walach, G.P. 541,700, *Chem. Abs.*, 1932, **26**, 2469) permits the identification of the products obtained by the methylation of 3-phenyl- and 3-methyl-5-phenyl-1 : 2 : 4-triazoles (V) which, unlike the triazoles considered in Part II, could give three isomeric *N*-methyl derivatives (VI*a*, *b*, *c*):



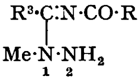
(R = H, Me, Ph; X = OH, Cl, R·CO₂)

(I; R¹ = Me; R² = H, Me, Ph; R³ = Ph)



Methylations were carried out by causing diazomethane to react with the triazoles (V) in ether and by the action of methyl iodide on the sodium derivatives of the triazoles. The 4-methyl derivatives (VI*a*) have not been observed among the products, although our analytical methods (*e.g.*, comparison of products with artificial mixtures of known isomers) were adequate to detect these isomers in amounts above 3—5%. Diazomethane methylates mainly the "vicinal" nitrogen atom next to the phenyl group, giving (VI*b*), although the isomer (VI*c*) is formed in appreciable quantities. Thus 1-methyl-5-phenyl- and 1-methyl-3-phenyl-1 : 2 : 4-triazole are formed from 3-phenyl-1 : 2 : 4-triazole in the proportion 1·6 : 1, and 1 : 3-dimethyl-5-phenyl- and 1 : 5-dimethyl-3-phenyl-1 : 2 : 4-triazole from 3-methyl-5-phenyl-1 : 2 : 4-triazole in the proportion 3·7 : 1. The reaction between methyl iodide and the sodiotriazoles favours the formation of (VI*c*), the proportions of (VI*c*) : (VI*b*) being 2 : 1 from 3-phenyl-1 : 2 : 4-triazole; 3-methyl-5-phenyl-1 : 2 : 4-triazole affords only the isomer (VI*c*) by this method.

The orientation rule observed in the reactions of phenylhydrazine with unsymmetrical diacylamines is consistent with the view that the most nucleophilic centre of the hydrazine ($N_{(2)}$) attacks the more electrophilic carbon centre of the CO·N·CO group in the diacylamine to initiate the reaction. In the case of methylhydrazine one might expect the primary attack to occur from $N_{(1)}$ except that in this case the resulting intermediate (VII) would be less stable than the alternative (VIII*a*–*b*) which would lead to cyclized products that have been found :



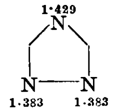
$$\begin{array}{l} R^3{\cdot}C{:}N{\cdot}CO{\cdot}R^2 \\ \quad | \\ Me{\cdot}N{\cdot}NH_2 \\ \quad\ \ 1\quad 2 \end{array}$$

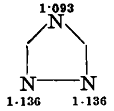
(VII)

(VIII*a*) (VIII*b*)

The annexed calculated values of π-electron densities at the nitrogen centres of the neutral molecule and anion of 1 : 2 : 4-triazole (R. D. Brown and I. M. Bassett, personal communication; cf. Orgell, Cottrell, and Dick, *Trans. Faraday Soc.*, 1951, **47**, 113) may explain the observed trends of *N*-methylation as reported in this paper and Part II. In the neutral molecule the electron density is lowest, and so the acidity highest, on $N_{(1)}$ and $N_{(2)}$; these are the centres attacked by diazomethane and diazoethane. Methylation by the action of methyl iodide on sodiotriazoles involves the triazole anion in which $N_{(1)}$ and $N_{(2)}$, the more nucleophilic centres, are attacked in preference to $N_{(4)}$. Unsymmetrical

(Neutral)





(Anion)

C-substitution of 1 : 2 : 4-triazole by methyl and/or phenyl does not reverse the relative order of π-electron densities on the " vicinal " nitrogen atoms compared with that on $N_{(4)}$ but the π-electron densities of $N_{(1)}$ and $N_{(2)}$ become different. Preferential methylation of neutral (V) to (VI*b*) by diazomethane indicates the reduction of π-electron density on the " vicinal " nitrogen atom nearest to the phenyl group and an increase on that nearest to the methyl group. The same conclusions may be reached on considering the course of the methylation of sodiotriazoles by methyl iodide. The opposite effects of *C*-phenyl and *C*-methyl groups on the π-electron densities of the neighbouring " vicinal " nitrogen atoms account for the greater disparity of the proportion (VI*b*) : (VI*c*) when 3-methyl-5-phenyl-1 : 2 : 4-triazole is methylated by either method.

EXPERIMENTAL

M. p.s are corrected. Extracts in organic solvents were dried with sodium sulphate.

N-*Benzimidoyl*-N′-*methylhydrazine*.—Methylhydrazine was prepared from its sulphate (57·6 g.) and powdered potassium hydroxide (100 g.) in water (50 c.c.). The mixture was distilled until the distillate no longer reduced Fehling's solution. After saturation of the distillate with potassium hydroxide methylhydrazine was separated and boiled under reflux with barium oxide (10 g.) in dry nitrogen for 12 hr. On distillation in nitrogen, anhydrous methylhydrazine (9·2 g., 50%), b. p. 87°/760 mm., was obtained. Further (moist) material could be obtained from the alkaline residues.

Methylhydrazine (4·6 g.) was added to a mixture of ethyl benzimidoate hydrochloride (18·5 g.) and dry pyridine (40 c.c.), with cooling by water. After 0·5 hr. the crystalline mass was filtered off and washed with dry ether (3 × 20 c.c.). *N*-Benzimidoyl-*N*′-methylhydrazine hydrochloride (12·6 g., 68%) was obtained as colourless prisms, m. p. 185° (cf. Jerchel and Fischer, *loc. cit.*). On combination of the pyridine and ether filtrates more of the same material (3·3 g., 18%),

m. p. 185°, was precipitated. The hydrochloride (11·1 g.) was dissolved in 10% aqueous sodium carbonate (50 c.c.), and the solution extracted with chloroform (4 × 50 c.c.). Removal of the solvent below 30° left *N-benzimidoyl-N'-methylhydrazine* (7·0 g., 78% calc. on the hydrochloride) as a colourless oil which decomposed during several hours and more rapidly on heating. This material was used without further purification. When a chloroform solution of the base was shaken with aqueous cobalt chloride (<5 parts per million of Co) a purple colour developed in the organic phase.

N-Benzimidoyl-*N'*-methylhydrazine hydrochloride (3·7 g.) was converted into the free base and immediately treated with ethyl chloroformate (3 c.c.) (cooling) and the mixture was then heated for 10 min. on a steam-bath. Removal of excess of solvent at 20 mm. left a colourless, fibrous solid which was neutralized with 10% aqueous sodium carbonate and extracted with ether (4 × 30 c.c.). Evaporation and crystallization from benzene–light petroleum (b. p. 60—80°; 1 : 1) gave 5-hydroxy-1-methyl-3-phenyl-1 : 2 : 4-triazole (1·9 g., 54%) (Found : C, 61·8; H, 5·1; N, 24·2. Calc. for $C_9H_9ON_3$: C, 61·7; H, 5·2; N, 24·0%), m. p. 219° alone or mixed with material prepared by Young and Oates's method (*loc. cit.*).

Cyclization of N-Benzimidoyl-N'-methylhydrazine to Basic Triazoles.—The benzimidoylhydrazine hydrochloride (3·7 g.) and formic acid (99—100%; 4·6 g.) were mixed at room temperature and after 0·5 hr. were boiled under reflux for 1 hr. Completion of the reaction was ascertained by testing for amidrazone with cobalt chloride. The product was poured into 10% aqueous sodium carbonate (50 c.c.) and extracted with chloroform (3 × 50 c.c.). Distillation of the residue obtained from the chloroform extract gave *1-methyl-3-phenyl-1 : 2 : 4-triazole* (2·2 g., 69%), prisms, m. p. 23°, b. p. 110°/1 mm. (Found : C, 68·3; H, 6·1; N, 26·2. $C_9H_9N_3$ requires C, 67·9; H, 5·7; N, 26·4%). The triazole was evaporated with a chloroform solution of picric acid and the residue recrystallized from ethanol, giving the *picrate*, yellow needles, m. p. 183° (Found : C, 46·4; H, 3·1; O, 28·8. $C_{15}H_{12}O_7N_6$ requires C, 46·4; H, 3·1; O, 28·8%). The same triazole was obtained in inferior yield by using free benzimidoylmethylhydrazine.

Benzimidoylmethylhydrazine [from the hydrochloride (3·7 g.)] and acetic anhydride (3 c.c.) were mixed and initially cooled with water. Reaction was completed during 0·5 hr. on a steam-bath. The product was neutralized with 10% aqueous sodium carbonate. Isolation by chloroform gave *1 : 5-dimethyl-3-phenyl-1 : 2 : 4-triazole* (2·0 g., 58%), m. p. 113°. Crystallisation from benzene and sublimation at 120°/2 mm. gave prisms, m. p. 117° (Found : C, 69·6; H, 6·2; N, 24·6. $C_{10}H_{11}N_3$ requires C, 69·3; H, 6·4; N, 24·3%). The *picrate* crystallized from ethanol as yellow silky needles, m. p. 166° (Found : C, 48·1; H, 3·7. $C_{16}H_{14}O_7N_6$ requires C, 47·7; H, 3·5%).

Benzimidoylmethylhydrazine hydrochloride (0·5 g.) and benzoyl chloride (3 c.c.) were heated together at 120° for 12 hr. The resulting clear solution was poured into 10% aqueous sodium carbonate and extracted with chloroform (3 × 50 c.c.). Removal of the solvent left 1-methyl-3 : 5-diphenyl-1 : 2 : 4-triazole (0·6 g., 94%), m. p. 80°; crystallization from benzene–light petroleum (b. p. 60—80°) gave colourless prisms, m. p. 84° alone or mixed with authentic material (Part II). The substance was characterized further as the picrate, m. p. and mixed m. p. 135°.

Einhorn–Brunner Reactions.—Urethane (66 g.), acetic anhydride (204 g.), and acetyl chloride (1 c.c.) were boiled under reflux for 1 hr. and the product was distilled. *N*-Acetylurethane (80·5 g., 83%), b. p. 105—106°/18 mm., m. p. 78°, was collected (cf. McCreath, *Ber.*, 1875, **8**, 1181). Acetylurethane (11·8 g.) and phenylhydrazine hydrochloride (11·8 g.) were kept at 150—160° for 12 hr. The product was neutralized with 10% aqueous sodium carbonate and extracted with ether (3 × 50 c.c.). 5-Hydroxy-3-methyl-1-phenyl-1 : 2 : 4-triazole (4·3 g., 30%), m. p. 167° (cf. Andreocci, *loc. cit.*), was obtained on evaporation of the extract. Sublimation and recrystallization from ethyl acetate did not raise the m. p.

N-Formylbenzamide (m. p. 112°; 7·5 g.) and methyl hydrazine sulphate (7·2 g.) were kept at 120° for 4 hr. The clear liquid was neutralized with 10% aqueous sodium carbonate and extracted with chloroform (3 × 50 c.c.). Evaporation of the extract left *1-methyl-5-phenyl-1 : 2 : 4-triazole* (5·0 g., 63%), m. p. 57—58°. Crystallization from benzene–light petroleum (b. p. 60—80°) and sublimation at 60°/2 mm. gave colourless prisms, m. p. 59° (Found : C, 67·8; H, 5·6; N, 26·5. $C_9H_9N_3$ requires C, 67·9; H, 5·7; N, 26·4%). The *picrate* crystallized from ethanol as flat yellow needles, m. p. 178° (Found : C, 47·0; H, 3·3. $C_{15}H_{12}O_7N_6$ requires C, 46·4; H, 3·1%). This triazole and its picrate depressed the m. p.s of 1-methyl-3-phenyl-1 : 2 : 4-triazole and its picrate respectively.

N-Acetylbenzamide (m. p. 116°, 6·1 g.) and methylhydrazine sulphate (3·6 g.) were caused to react at 160° for 6 hr. and the product was isolated as in the preceding experiment. After chromatography in benzene on alumina 1 : 3-*dimethyl*-5-*phenyl*-1 : 2 : 4-*triazole* (2·6 g., 65%), m. p. 66—68°, was obtained. Crystallization from benzene–light petroleum (b. p. 60—80°) and sublimation at 60°/2 mm. gave colourless prisms, m. p. 72° (Found : C, 70·0; H, 6·4; N, 24·1. $C_{10}H_{11}N_3$ requires C, 69·3; H, 6·4; N, 24·3%). The *picrate* crystallized from methanol as yellow prismatic needles, m. p. 172° (Found : C, 48·3; H, 3·5; O, 27·3. $C_{16}H_{14}O_7N_6$ requires C, 47·7; H, 3·5; O, 27·8%). The triazole and its picrate depress the m. p.s of 1 : 5-dimethyl-3-phenyl-1 : 2 : 4-triazole and its picrate respectively. The same triazole was obtained in low yield together with much benzamide when the reactants were heated in an acetic acid–sodium acetate buffer (pH 5) for 10 hr.

N-Formylbenzamide (0·55 g.) and semicarbazide hydrochloride (0·42 g.) were kept at 160° for 1 hr. Water (5 c.c.) was added and the mixture was neutralized with solid sodium carbonate. Filtration removed hydrazodicarboxyamide (0·125 g., 29%), m. p. 257° (decomp.). The filtrate was extracted with ether (2 × 50 c.c.) and on evaporation left colourless needles, m. p. 114—115°. Sublimation at 140°/1 mm. gave 3-phenyl-1 : 2 : 4-triazole (0·16 g., 30%), m. p. 118°. This material did not depress the m. p. of 3-phenyl-1 : 2 : 4-triazole, m. p. 119°, prepared according to Hoggarth (*J.*, 1949, 1160), who reports m. p. 121°.

N-Acetylbenzamide (8·2 g.) and semicarbazide hydrochloride (5·6 g.) were caused to react and the products isolated as in the preceding experiment. Hydrazodicarboxyamide (1·2 g., 21%), m. p. 257°, was obtained together with 3-methyl-5-phenyl-1 : 2 : 4-triazole (1·4 g., 18%), m. p. 166° after sublimation at 140°/1 mm. (Heller, *J. pr. Chem.*, 1929, **120**, 49, reports 164·5°) (Found : C, 68·4; H, 5·8. Calc. for $C_9H_9N_3$: C, 67·9; H, 5·7%). Benzamide (121 g.) and acetylhydrazine (74 g.) were mixed and heated in a metal-bath. The internal temperature was raised from 210° to 260° during 12 hr. Water, ammonia, and benzonitrile distilled through a short column. The melt was poured into 5N-hydrochloric acid (500 c.c.). After being heated to boiling, the liquid was cooled and 3 : 5-diphenyl-1 : 2 : 4-triazole (62 g.), m. p. and mixed m. p. 189—191°, was filtered off. The filtrate was partially neutralized with concentrated aqueous ammonia and neutralization was completed with 10% aqueous sodium carbonate. Extraction with benzene (400 c.c.) and removal of the solvent gave a mixture of oil and crystals. The latter were recrystallised from benzene–light petroleum (b. p. 100—120°), giving 3-methyl-5-phenyl-1 : 2 : 4-triazole (21·3 g., 13%), m. p. 165° (from toluene) alone or mixed with material obtained by the Einhorn–Brunner reaction. This was further characterised as the picrate, m. p. 158° (from methanol) (cf. Heller). The same material was prepared from acetamide (18 g.) and benzoylhydrazine (41·5 g.) by Heller's method which afforded 14·4 g. of the substance, m. p. 160—164°; further purification of this material was difficult.

Methylation of 3-*Phenyl*-1 : 2 : 4-*triazole*.—3-Phenyl-1 : 2 4-triazole (2·9 g.) was added to a solution of sodium (0·46 g.) in methanol (10 c.c.). Methyl iodide (2·8 g.) was added and the reactants were kept in a sealed tube for 1 hr. at 20° and 12 hr. at 100°. Methanol was removed by distillation and the residual oil poured into 20% aqueous sodium hydroxide (50 c.c.). Extraction with ether afforded a pale oil (2·9 g.) which was fractionated through a vacuum-jacketed Vigreux column. The fraction of b. p. 114—116°/2—3 mm. had m. p. 55—57° (0·89 g., 28%); after sublimation at 60°/2 mm. it had m. p. 58° and mixed m. p. with 1-methyl-5-phenyl-1 : 2 : 4-triazole 59°. The picrate had m. p. and mixed m. p. 178° (from ethanol). An intermediate fraction (0·1 g.) having been discarded, the fraction of b. p. 120—122°/2—3 mm. (1·79 g., 56%) was collected and sublimed on to a condenser cooled with liquid air. 1-Methyl-3-phenyl-1 : 2 : 4-triazole was obtained as colourless prisms, m. p. and mixed m. p. 23°; its picrate, recrystallized from ethanol, had m. p. 181° and mixed m. p. 181—182°.

3-Phenyl-1 : 2 : 4-triazole (1·45 g.) in dry methanol (10 c.c.) was treated with 3 portions of ethereal diazomethane [generated from 10 g. (total) of nitrosomethylurea] at 2-day intervals. After removal of the solvent the residual oil was fractionated as before, giving 1-methyl-5-phenyl-1 : 2 : 4-triazole (0·89 g., 56%), m. p. 52—55° (picrate, m. p. and mixed m. p. 178°), and 1-methyl-3-phenyl-1 : 2 : 4-triazole (0·54 g., 34%), m. p. 18—20° (picrate, m. p. and mixed m. p. 181—182°).

Methylation of 3-*Methyl*-5-*phenyl*-1 : 2 : 4-*triazole*.—This triazole (7·9 g.) was suspended in a solution of sodium (1·65 g.) in dry methanol (30 c.c.). Methyl iodide (7·1 g.) was added and the reaction was carried out as before. Fractionation under reduced pressure gave a material, b. p. 116—118°/2—3 mm. (8·1 g.), m. p. 111—114°. Recrystallization from benzene–light petroleum (b. p. 60—80°) gave 1 : 5-dimethyl-3-phenyl-1 : 2 : 4-triazole (7·8 g., 90%), m. p. and mixed m. p. 117°. The crude product before distillation gave a picrate, m. p. 164°, which crystallized from ethanol as yellow needles with m. p. and mixed m. p. 166°.

3-Methyl-5-phenyl-1 : 2 : 4-triazole (7·9 g.) in dry methanol (50 c.c.) was treated with diazomethane (from 15 g. of nitrosomethylurea), and the products were isolated as before. The fraction with b. p. 93—96°/1 mm. crystallized and was rubbed with benzene–light petroleum (1 c.c.). This material (3·2 g., 37%) had m. p. and mixed m. p. 70—72° with 1 : 3-dimethyl-5-phenyl-1 : 2 : 4-triazole; the picrate had m. p. and mixed m. p. 170—171°. After discarding of an intermediate fraction (0·15 g.), material with b. p. 105—110°/1 mm. was collected and allowed to solidify. After being washed with benzene–light petroleum (1 c.c.) the substance (0·9 g., 10%) had m. p. and mixed m. p. 113—115° with 1 : 3-dimethyl-5-phenyl-1 : 2 : 4-triazole; the picrate, crystallized from ethanol, had m. p. and mixed m. p. 166°.

The authors acknowledge with thanks an I.C.I.A.N.Z. Research Fellowship (to M. R. A.) and thank Dr. R. D. Brown and Mr. I. M. Bassett of the University of Melbourne who permitted the use of their calculations. Dr. R. D. Brown has also assisted with discussion and advice. The analyses were carried out by the Microanalytical Laboratory of the C.S.I.R.O., Melbourne, under the direction of Dr. K. W. Zimmmermann.

UNIVERSITY OF TASMANIA, HOBART.

[*Received, March* 15*th*, 1954.]