

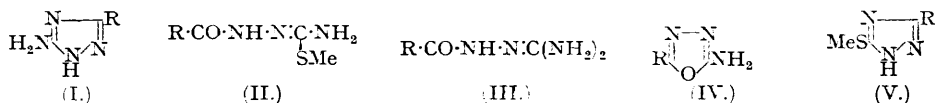
116. Compounds related to Thiosemicarbazide. Part IV.

5-Amino-3-phenyl-1 : 2 : 4-triazoles.

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1-Benzoyl-*S*-methylisothiosemicarbazides (Part III) are cyclised by boiling with alcoholic solutions of organic bases to give a mixture of the 2-amino-5-phenyl-1 : 3 : 4-oxadiazole and 5-methylthio-3-phenyl-1 : 2 : 4-triazole. Piperidine differs from the other amines examined in giving also some of the 5-amino-3-phenyl-1 : 2 : 4-triazole. A new route to the amino-triazoles has been found in the reaction of *S*-methylisothiurea with benzhydrazides, followed by cyclisation of the resultant benzamidoguanidines.

ACCORDING to Benack (Dissert., Munich, 1896, quoted in "Beilstein," First Suppl. Vol., 26, 45) 5-amino-3-phenyl-1 : 2 : 4-triazole (I; R = Ph) is formed by heating aminoguanidine carbonate with benzoyl chloride. This method was found unsatisfactory and it seemed possible that 1-benzoyl-*S*-methylisothiosemicarbazide (II; R = Ph) (Part III, *J.*, 1949, 1918) might react with ammonia or primary or secondary amines to give the benzamidoguanidine (III) or the corresponding alkyl derivatives of (III), which, it was expected, would be readily cyclised to 5-amino-3-phenyl-1 : 2 : 4-triazoles.



When (II; R = Ph) was heated with alcoholic ammonia, *isopropylamine*, or diethylamine, 2-amino-5-phenyl-1 : 3 : 4-oxadiazole (IV; R = Ph) and 5-methylthio-3-phenyl-1 : 2 : 4-triazole (V; R = Ph) were formed in each case. The same reaction was observed when the tertiary bases, pyridine or triethylamine, were used. The *p*-anisoyl compound (II; R = *p*-MeO·C₆H₄) with ammonia or triethylamine gave the corresponding oxadiazole and triazole, but the amount of the latter product was small. 5-Methylthio-3-*p*-chlorophenyl-1 : 2 : 4-triazole was obtained by the action of triethylamine on 1-*p*-chlorobenzoyl-*S*-methylisothiosemicarbazide and also by methylation of the corresponding thiol. These results are in contrast to the behaviour of 1-benzoyl-*S*-methylisothiosemicarbazides with alcoholic solutions of sodium alkoxides (Part III) which under similar conditions give 5-alkoxy-3-phenyl-1 : 2 : 4-triazoles. However, the crude alkoxy-triazoles, prepared in this way, were found to contain a small amount of sulphur which was difficult to remove by crystallisation and necessitated a method of purification involving dissolution in acids and alkalis. It is probable that small amounts of the methylthio-triazoles were formed in this reaction. Since the parent 1-benzoylthiosemicarbazides give the same product (*i.e.*, 3-phenyl-1 : 2 : 4-triazole-5-thiols) with alcoholic solutions of organic bases or sodium alkoxides (Part II, *J.*, 1949, 1163) it might be supposed that the 5-alkoxytriazoles were formed by the action of sodium alkoxides on 5-methylthio-triazoles. This was disproved by showing that 5-methylthio-3-phenyl-1 : 2 : 4-triazole was recovered unchanged after long refluxing with sodium ethoxide solution. The same methylthio-group has been shown (Part I, *J.*, 1949, 1160) not to be replaced on heating the substance with amines and it has now been observed that 5-methoxy-3-*p*-methoxyphenyl-1 : 2 : 4-triazole is not attacked by hot ammonia.

In the above reactions of 1-benzoyl-*S*-methylisothiosemicarbazides with amines, separation of the products was readily effected by dissolution of the triazole in sodium hydroxide solution. In each case, the crude triazole when precipitated from the clarified alkaline solution, had approximately the expected sulphur content. However, when piperidine was used as the amine, the triazole fraction had much less than half of the expected amount of sulphur and was eventually

separated into 5-methylthio-3-phenyl-1 : 2 : 4-triazole (V; R = Ph) and 5-piperidino-3-phenyl-1 : 2 : 4-triazole, which have very similar solubilities.

Benzamidoguanidines (III; R = Ph, *p*-MeO·C₆H₄, or *p*-C₆H₄Cl) were obtained by warming the corresponding benzhydrazides with *S*-methylisothiourea sulphate and alkali, and the compound (III; R = Ph) was also obtained by treatment of aminoguanidine with benzoyl chloride in cold pyridine. These compounds are readily cyclised with loss of water on being heated just below their melting points and in this manner very satisfactory yields of 5-amino-3-phenyl-, 5-amino-3-*p*-methoxyphenyl-, and 5-amino-3-*p*-chlorophenyl-1 : 2 : 4-triazole (I; R = Ph, *p*-MeO·C₆H₄, or *p*-C₆H₄Cl) were obtained. This cyclisation was also carried out with an alcoholic solution of sodium ethoxide (in moderate yield) but could not be effected with sulphuric or phosphoric acid (cf. the cyclisation of 1-benzoylthiosemicarbazides, Part II).

When benzhydrazide was treated with *S*-methyl-*NN*-pentamethyleneisothiourea, 5-piperidino-3-phenyl-1 : 2 : 4-triazole was formed directly. The intermediate benzamidoguanidine in this case appears to be cyclised during the isolation. The corresponding *p*-methoxyphenyl compound was obtained by using *p*-anishydrazide.

EXPERIMENTAL.

Reaction of 1-Benzoyl-S-methylisothiosemicarbazide with Ammonia.—The *S*-methylisothiosemicarbazide (4.2 g.) and alcohol (25 c.c.) containing dry ammonia gas (1.9 g.) were set aside for 12 hours and then refluxed for 4 hours. The solvent was evaporated under reduced pressure, and the residue triturated with *N*-sodium hydroxide (50 c.c.) and filtered. The insoluble residue, which was sulphur-free (2.3 g.; m. p. 236°), was crystallised from alcohol, giving colourless prisms (1.8 g.) of 2-amino-5-phenyl-1 : 3 : 4-oxadiazole, m. p. 243°, not depressed by an authentic specimen (Fehrenbach and Stollé, *J. pr. Chem.*, 1929, 122, 289). The original filtrate was made just acid with acetic acid, and the precipitate collected (0.9 g.; m. p. 158—160°) (Found: S, 15.8%) and crystallised from water containing a little alcohol, giving colourless plates (0.6 g.) of 5-methylthio-3-phenyl-1 : 2 : 4-triazole, m. p. 162° (Part I, *loc. cit.*) (Found: C, 56.4; H, 4.3; S, 17.0. Calc. for C₉H₉N₃S: C, 56.5; H, 4.7; S, 16.75%).

With isopropylamine (5.0 c.c.) in place of ammonia in the above experiment, the amino-oxadiazole (2.0 g.; m. p. 243°) and the methylthio-triazole (0.5 g.; m. p. 161°) were isolated. With diethylamine, triethylamine, or pyridine very similar results were obtained. The percentages of sulphur in the crude alkali-soluble fractions from these and the preceding experiment were 16.0, 16.7, 16.2, and 16.3 respectively.

Reaction of 1-Benzoyl-S-methylisothiosemicarbazide with Piperidine.—When the above experiment was repeated using piperidine (4.0 c.c.) in place of ammonia, the amino-oxadiazole (1.3 g.; m. p. 240°) was isolated as previously (Found: C, 59.6; H, 4.4. Calc. for C₈H₇ON₃S: C, 59.6; H, 4.3%). The crude alkali-soluble fraction (1.4 g.; m. p. 135—140°) (Found: S, 7.2%) was rubbed in a mortar with *N*-hydrochloric acid (10 c.c.) for 1 minute and quickly filtered (the whole dissolved on rubbing with twice as much acid for 15 minutes). The residue (0.3 g.; m. p. 152—154°) (Found: S, 15.6%) was crystallised twice from aqueous alcohol giving colourless leaflets (0.2 g.) of the methylthio-triazole, m. p. 162° (Found: C, 56.5; H, 4.6%). The acid extract was precipitated with potassium hydrogen carbonate, the solid collected (1.0 g.; m. p. 170—180°) (Found: S, 0.2%) and crystallised from benzene-light petroleum (b. p. 60—80°) and then twice from benzene giving colourless needles (0.5 g.) of 5-piperidino-3-phenyl-1 : 2 : 4-triazole, m. p. 196° (Found: C, 68.7; H, 6.8; N, 24.6. C₁₃H₁₆N₄ requires C, 68.4; H, 7.0; N, 24.6%).

Reaction of 1-p-Anisoyl-S-methylisothiosemicarbazide with Ammonia.—The *S*-methylisothiosemicarbazide (4.8 g.) and alcohol (25 c.c.) containing ammonia (1.8 g.) gave the amino-oxadiazole (Part III, *loc. cit.*), which crystallised from alcohol in large colourless needles (2.8 g.), m. p. 246—247°, and the methylthio-triazole (Part III, *loc. cit.*), which crystallised from aqueous alcohol in colourless leaflets (0.1 g.), m. p. 125° (Found: C, 54.2; H, 4.8. Calc. for C₁₀H₁₁ON₃S: C, 54.3; H, 5.0%). A similar result was obtained by using triethylamine (6.3 c.c.) in place of the ammonia, and in both cases the methylthio-triazole was formed in smaller amounts and was more difficult to purify compared with corresponding reactions with 1-benzoyl-*S*-methylisothiosemicarbazide.

Reaction of 1-p-Chlorobenzoyl-S-methylisothiosemicarbazide with Triethylamine.—The *S*-methylisothiosemicarbazide (4.9 g.), alcohol (30 c.c.), and triethylamine (6.3 c.c.) gave, as above, the amino-oxadiazole (Part III, *loc. cit.*) (2.1 g.) which crystallised from alcohol in colourless needles, m. p. 270°, and 5-methylthio-3-*p*-chlorophenyl-1 : 2 : 4-triazole which crystallised from benzene in hard, refractive, colourless prisms (1.2 g.), m. p. 154° (Found: C, 48.2; H, 3.5; S, 14.2. C₉H₈N₃SCl requires C, 47.9; H, 3.5; S, 14.2%). The same methylthio-triazole was obtained by shaking the triazole-thiol (0.7 g.) with *N*-sodium hydroxide (5 c.c.), methyl iodide (0.3 c.c.), and alcohol (1 c.c.). The precipitate, crystallised from benzene, gave colourless prisms (0.5 g.), m. p. 153°, not depressed by the compound as prepared above (Found: C, 48.0; H, 3.6%).

*Attempt to cause 5-Methylthio-3-phenyl- or 5-Methoxy-3-*p*-methoxyphenyl-1 : 2 : 4-triazole to react with Sodium Ethoxide and Ammonia, respectively.*—The methylthiotriazole (1.9 g.) was refluxed with a solution of sodium (0.8 g.) in alcohol (30 c.c.) for 24 hours and evaporated under reduced pressure. The residue was made just acid with acetic acid, and the solid collected and crystallised from aqueous alcohol, giving colourless leaflets (1.6 g.), m. p. 161—162°, not depressed by admixture with starting material.

The methoxy-triazole (Part III, *loc. cit.*) (0.5 g.) and alcohol (20 c.c.) containing ammonia (1.8 g.) were heated in a sealed tube at 110° for 18 hours. The residue left on evaporation of the solvent crystallised from aqueous alcohol in colourless needles (0.35 g.), m. p. 168—169°, not depressed by admixture with starting material.

Benzamidoguanidine (III; R = Ph).—(a) *S*-Methylisothiurea sulphate (13.9 g.) was added with stirring to ice-cold *N*-sodium hydroxide (100 c.c.), followed by benzhydrazide (13.5 g.). After storage for 3—4 days at room temperature (smaller yields were obtained after shorter times) the mixture was slowly heated to 50° and kept for 3 hours at this temperature. Purple-tinged crystals separated. The reaction vessel was cooled in a freezing mixture, a rapid stream of carbon dioxide passed in, and, after neutralisation, the solid was collected, washed with water, and dried (12.2 g.; m. p. 180—182°). *Benzamidoguanidine* was soluble in dilute acids but only sparingly soluble in sodium hydroxide solution, and crystallised from water (charcoal) in large colourless refractive prisms, m. p. 184° (decomp.) (Found: C, 54.2; H, 5.5; N, 31.9. $C_8H_{10}ON_4$ requires C, 53.9; H, 5.6; N, 31.5%).

(b) Aminoguanidine hydrogen carbonate (6.0 g.) in dry pyridine (50 c.c.) was cooled to 0° and stirred whilst freshly distilled benzoyl chloride (6.0 c.c.) was added during 0.5 hour. After 12 hours' stirring at room temperature, the solvent was removed under reduced pressure, and the residue treated with water (50 c.c.) and made strongly alkaline with 10*N*-sodium hydroxide. The solid was collected (3.4 g.; m. p. 180—182°) and crystallised from water giving large colourless prisms, m. p. 185° (decomp.) (Found: C, 53.5; H, 5.7%). The alkaline filtrates were examined for amino-triazole but only benzoic acid (1.4 g.; m. p. 121°) was isolated.

The following were obtained in good yield by method (a): *p*-anisamido- (III; R = *p*-MeO·C₆H₄), colourless prisms which effloresce on drying (from water), m. p. 218—220° (Found: C, 52.0; H, 5.9. $C_9H_{12}O_2N_4$ requires C, 51.9; H, 5.8%), and *p*-chlorobenzamido-guanidine (III; R = *p*-C₆H₄Cl), colourless prisms (from aqueous alcohol), m. p. 194—196° (Found: C, 45.6; H, 4.3; N, 26.5. $C_8H_9ON_4Cl$ requires C, 45.2; H, 4.2; N, 26.4%). *p*-Chlorobenzhydrazide was much less soluble than the other hydrazides used and the reaction liquid was therefore diluted with an equal volume of alcohol and this solvent subsequently removed under reduced pressure at 50°.

5-Amino-3-phenyl-1:2:4-triazole (I; R = Ph).—(a) Benzamidoguanidine (5.0 g.) was heated in an oil-bath at 220°. Water was eliminated with decrepitation and after 5 minutes the residue was crystallised from water, giving colourless silky needles (3.8 g.), m. p. 186—187°, not depressed by a specimen prepared as described by Benack (*loc. cit.*) (Found: C, 59.8; H, 4.9. Calc. for $C_8H_8N_4$: C, 60.0; H, 5.0%). When benzamidoguanidine (1.8 g.) was added to sulphuric acid (98%; 20 c.c.) at 120° (with stirring), a sublimate of benzoic acid formed. After 0.5 hour's stirring, the mixture was poured on ice; the solid was collected (1.1 g.; m. p. 118°) and by crystallisation from water gave benzoic acid (0.6 g.; m. p. 120°). The acid filtrates contained no diazotisable amine. A similar result was obtained with phosphoric acid-phosphoric oxide.

(b) Benzamidoguanidine (1.8 g.) was refluxed with a solution of sodium (1.5 g.) in alcohol (100 c.c.) for 3 hours and the solvent removed under reduced pressure. Water (20 c.c.) was added, the small insoluble residue filtered off, and the filtrate made just acid with acetic acid. The precipitate (0.6 g.; m. p. 184°) was collected and crystallised from water giving colourless needles (0.4 g.), m. p. 186° (Found: C, 60.2; H, 5.2%).

The following were prepared by method (a): *5*-amino-3-*p*-methoxyphenyl- (I; R = *p*-MeO·C₆H₄), small colourless plates (from water), m. p. 224—226° (Found: C, 57.1; H, 5.3. $C_9H_{10}ON_4$ requires C, 56.8; H, 5.3%), and *5*-amino-3-*p*-chlorophenyl-1:2:4-triazole (I; R = *p*-C₆H₄Cl), large colourless needles (from aqueous alcohol), m. p. 227—229° (Found: C, 49.7; H, 3.9. $C_8H_7N_4Cl$ requires C, 49.4; H, 3.6%).

5-Piperidino-3-phenyl-1:2:4-triazole.—*NN*-Pentamethylenethiourea (6.0 g.) and water (10 c.c.) were shaken together and freshly distilled methyl sulphate (6.0 g.) added. On slight warming of the mixture, a vigorous reaction occurred. The clear solution was refluxed for 0.5 hour and evaporated under reduced pressure. The syrup (which could not be crystallised) was cooled in a freezing mixture, and *N*-sodium hydroxide added until the product was just alkaline to brilliant-yellow. Benzhydrazide (5.4 g.) was added, and after 3 days the reaction mixture was stirred and heated at 50° for 3 hours. The supernatant liquid was decanted from the sticky precipitate which was hardened by rubbing it with a little 10% acetic acid. The solid was collected (6.7 g.; m. p. 180°) and crystallised from aqueous alcohol, giving colourless needles (5.2 g.), m. p. 196—198°, not depressed by the compound prepared as above (Found: C, 68.5; H, 6.9%).

5-Piperidino-3-*p*-methoxyphenyl-1:2:4-triazole.—This compound, obtained as was the corresponding phenyl compound, crystallised from aqueous alcohol or benzene-light petroleum (b. p. 60—80°) in colourless platelets, m. p. 206—208° (Found: C, 65.3; H, 6.9. $C_{14}H_{18}ON_4$ requires C, 65.1; H, 7.0%).

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