479. *Compounds related to Thiosemicarbazide. Part VIII.* The Oxidation of Thiosemicarbazones.†*

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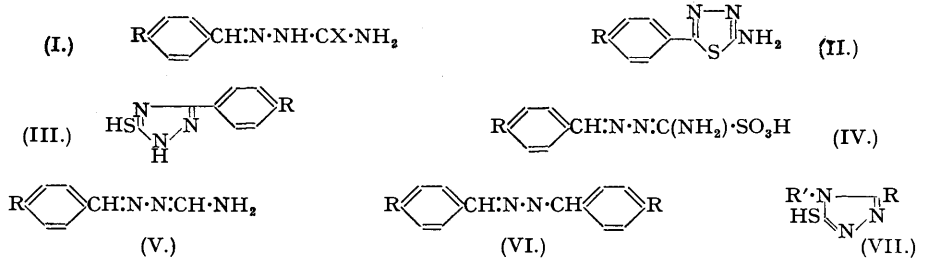
The oxidation of benzaldehyde thiosemicarbazone with hydrogen peroxide in cold acetic acid gives some novel compounds, investigation of which has shown that they are probably derivatives of 2 : 3-diazabuta-1 : 3-diene.

THE oxidation of benzaldehyde thiosemicarbazone (I; R = H, X = S) was first investigated by Young and Eyre (*J.*, 1901, **79**, 54), who found that with aqueous ferric chloride solution, loss of two hydrogen atoms took place very readily to give 2-amino-5-phenyl-1 : 3 : 4-thiadiazole (II; R = H). The formation of a very small amount of an insoluble, high-melting substance was thought to indicate the simultaneous formation of the isomeric 3-phenyl-1 : 2 : 4-triazole-5-thiol (III; R = H). The formation of aminothiadiazoles by oxidation of thiosemicarbazones with ferric chloride has been confirmed by a number of workers including De and Roy Choudhury (*J. Indian Chem. Soc.*, 1928, **5**, 269), who denied that triazoles were also formed. However, these workers claimed that oxidation of thiosemicarbazones with perhydrol in alcohol gave compounds derived from the triazole (III), usually the corresponding disulphide.



Investigation of the oxidation of benzaldehyde thiosemicarbazone showed that perhydrol in cold acetic acid gave two novel oxidation products. One of these was an acid, to which, upon the evidence mentioned below, the constitution 1-amino-4-phenyl-2 : 3-diazabuta-1 : 3-diene-1-sulphonic acid (IV; R = H) was ascribed, and the other an unstable oily base (isolated as its picrate) which was thought to be 1-amino-4-phenyl-2 : 3-diazabuta-1 : 3-diene (V; R = H). Under similar conditions, *p*-methoxybenzaldehyde thiosemicarbazone gave two compounds (IV and V; R = OMe) both of which were crystalline. The basic one, however, was still unstable, and with other thiosemicarbazones examined, only the corresponding sulphonic acids were isolated.

The constitution of the sulphonic acids (IV) followed from the products of their hydrolyses. When heated with concentrated hydrochloric acid, the acids (IV; R = H or OMe) quickly dissolved with almost immediate separation of the corresponding azines (VI; R = H or OMe) and a solution of the same acids in dilute sodium carbonate solution, when boiled, rapidly deposited the corresponding semicarbazones (I; R = H or OMe, X = O). The bases (V; R = H or OMe) were also readily hydrolysed to the azines, and attempts to crystallise (V; R = H) always resulted in formation of benzaldehyde azine. The constitution of the basic compounds was confirmed by their formation from the thiosemicarbazones by " desulphurisation " with Raney nickel catalyst.

Although it is known that in the presence of strong acids thiourea is first oxidised to a salt of " formamidine disulphide " (Preisler and Berger, *J. Amer. Chem. Soc.*, 1947, **69**, 322), yet it was shown by Barnett (*J.*, 1910, **97**, 63) that under approximately neutral conditions hydrogen peroxide gives aminoiminomethanesulphinic acid (" formamidine sulphinic acid ") and that this compound readily loses sulphur dioxide giving (presumably) formamidine. Böeseken (*Rec. Trav. chim.*, 1936, **55**, 1044) showed that aminoiminomethanesulphinic acid could be oxidised by cold peracetic acid to the corresponding sulphonic acid, $NH_2 \cdot C(:NH) \cdot SO_3H$. It

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seems probable, therefore, that the oxidation of thiosemicarbazones by perhydrol in cold acetic acid gives a mixture of the sulphonic acid (IV) and the corresponding sulphinic acid, the latter losing sulphur dioxide during the isolation procedure. It was found by Kitamura (*J. Pharm. Soc. Japan*, 1937, **57**, 51) that thiosemicarbazide was oxidised by perhydrol in *alkaline* solution, giving semicarbazide, and that a similar reaction took place (more slowly) with thiosemicarbazones. It can be supposed that in Kitamura's experiments the sulphonic acids were first formed and suffered hydrolysis. De and Roy Choudhury's oxidations (*loc. cit.*) were effected with perhydrol in alcohol, the mixture being allowed to become hot as reaction took place. Except for benzaldehyde thiosemicarbazone, the thiosemicarbazones examined by these authors carried substituents upon the 4-nitrogen atom of the thiosemicarbazide residue, and all, with the same exception, gave disulphides of 3 : 4-disubstituted 4 : 1 : 2-triazole-5-thiols (VII). In the case of benzaldehyde thiosemicarbazone the product was claimed to be 3-phenyl-1 : 2 : 4-triazole (thought to arise from a corresponding thiol or disulphide by elimination of the sulphur atom) although the melting point of the compound isolated (177°) was not in agreement with that found by other workers (*e.g.*, Young and Oates, *J.*, 1901, **79**, 659). On oxidising benzaldehyde thiosemicarbazone under De and Roy Choudhury's conditions, we found the principal product to be 1-amino-4-phenyl-2 : 3-diazabuta-1 : 3-diene (V; R = H), identified as its picrate and by hydrolysis to benzaldehyde azine. A small amount of a crystalline substance also isolated (m. p. 164°) proved to be unoxidised thiosemicarbazone. Analogous results were obtained by oxidising *p*-anisaldehyde thiosemicarbazone under the same conditions, the base (V; R = OMe) in this case being obtained crystalline and identified by mixed m. p. determination.

Two thiosemicarbazones having a methyl group in position 4 of the thiosemicarbazide residue were oxidised with perhydrol in cold acetic acid. The corresponding sulphonic acids alone were isolated, though there was a considerable basic fraction which could not be induced to crystallise.

Experimental.

Oxidation of Benzaldehyde Thiosemicarbazone.—(*a*) Perhydrol (100 c.c.) and glacial acetic acid (400 c.c.) were stirred at 0°, and finely powdered benzaldehyde thiosemicarbazone (30·0 g.) added during 0·5—0·75 hour. The thiosemicarbazone at first passed into solution but crystals quickly separated and the mixture became quite thick. Stirring was continued for 4—5 hours at 0° and the temperature was then allowed to rise gradually (overnight) to 15—20°. Water (2 l.) was added, and the precipitate (16·0 g.; m. p. 212—214°) collected, washed with a little water, and dried at 80°. The filtrate was concentrated (at 25—30° in a good vacuum) to 200 c.c. and cooled, and concentrated hydrochloric acid added. The precipitate (4·1 g.; m. p. 208—210°) was collected, washed and dried as before, united with the previous precipitate, and dissolved in water (250 c.c.) by stirring and adding solid potassium hydrogen carbonate until effervescence ceased. The clear, filtered solution was made acid with concentrated hydrochloric acid, and the *1-amino-4-phenyl-2 : 3-diazabuta-1 : 3-diene-1-sulphonic acid* (IV; R = H) (17·4 g.) collected and crystallised from alcohol or acetic acid, giving colourless needles, m. p. 254—256° (Found : C, 42·1; H, 4·1; N, 19·0; S, 13·9. $C_8H_9O_3N_3S$ requires C, 42·3; H, 4·0; N, 18·5; S, 14·1%). The filtrate from the second crop of sulphonic acid was cooled strongly and made alkaline with concentrated sodium hydroxide solution, the precipitated oil extracted with ether, dried, and filtered, and the solvent removed (under reduced pressure without heating), giving a clear yellow oil (3·8 g.) which could not be distilled at 0·02 mm. pressure. Attempts to crystallise it gave benzaldehyde azine as yellow plates, m. p. 92° not depressed by an authentic specimen (Found : N, 13·8. Calc. for $C_{14}H_{12}N_2$: N, 13·4%). On storage, a strongly basic smell became apparent and crystals separated which proved also to be the azine. The freshly isolated oil (1·0 g.) was dissolved in cold alcohol (10 c.c.), and the solution filtered and quickly added to a solution of picric acid (2·0 g.) in alcohol (20 c.c.); crystalline aggregates (1·2 g.), m. p. 210—211°, slowly separated (Found : C, 44·7; H, 3·4; N, 22·6. $C_8H_9N_3,C_6H_3O_7N_3$ requires C, 44·7; H, 3·2; N, 22·4%). This *picrate* could not be recrystallised, and attempts to regenerate the base gave only benzaldehyde azine.

When the above sulphonic acid (2·0 g.) was boiled with concentrated hydrochloric acid (20 c.c.) and acetic acid (10 c.c.), a yellow solid (0·8 g., m. p. 90—92°) separated on cooling and neutralisation with potassium hydrogen carbonate. From alcohol, bright yellow needles of benzaldehyde azine, m. p. and mixed m. p. 93—94°, were obtained (Found : C, 80·6; H, 5·7; N, 14·0. Calc. for $C_{14}H_{12}N_2$: C, 80·8; H, 5·8; N, 13·4%). When the sulphonic acid (2·3 g.) was refluxed for 6 hours with 5% sodium carbonate solution (50 c.c.), a solid (1·3 g.; m. p. 218—220°) separated and after cooling was collected and crystallised from alcohol, giving long faintly coloured needles of benzaldehyde semicarbazone, m. p. and mixed m. p. 224—226° (Found : C, 59·2; H, 5·7; N, 26·2. Calc. for $C_8H_9ON_3$: C, 58·9; H, 5·5; N, 25·8%). A solution of 1-amino-4-phenyl-2 : 3-diazabuta-1 : 3-diene in N-hydrochloric acid became cloudy when heated, and, by ether extraction, benzaldehyde azine was isolated; it crystallised from alcohol, giving yellow needles, m. p. and mixed m. p. 92—93°.

(*b*) Finely powdered benzaldehyde thiosemicarbazone (3·6 g.) was added to a well stirred mixture of perhydrol (5 c.c.) and alcohol (50 c.c.) without external cooling, solution taking place with rise of temperature (70—75°). After 0·5 hour's stirring, a small amount of colloidal sulphur was removed (charcoal) and the clear pale yellow filtrate was evaporated at 25° in a good vacuum. The sticky

residue was shaken twice with N-hydrochloric acid (50 c.c.) and ether (50 c.c.), the united extracts filtered from a small insoluble residue, and the ethereal layer separated. The solvent was removed from the ethereal extract and the small residue crystallised twice from aqueous alcohol, giving colourless needles (0·1 g.) of benzaldehyde thiosemicarbazone, m. p. and mixed m. p. 163°. The acid extract was cooled strongly, made alkaline with 10N-sodium hydroxide, and extracted with ether; the extracts were dried and evaporated without being heated, giving a pale yellow oil (1·5 g.). The picrate prepared as above formed yellow aggregates, m. p. 210—212° not depressed by the compound obtained as in (*a*) (Found: C, 44·6; H, 3·1%). The oil (1·2 g.) was refluxed with concentrated hydrochloric acid (10 c.c.) for 5 minutes, cooled, and extracted with ether, and the oil left on evaporation of the solvent crystallised from aqueous alcohol, giving yellow needles (0·65 g.) of benzaldehyde azine, m. p. and mixed m. p. 93—94°.

Oxidation of p-*Anisaldehyde Thiosemicarbazone.*—(*a*) *p*-Anisaldehyde thiosemicarbazone (33·4 g.) being used in place of the benzaldehyde compound in (*a*) above, two crops of a crude acid (27·2 g., m. p. 250—252°; and 1·1 g., m. p. 245—250°) were obtained which were united and purified by solution in dilute potassium hydrogen carbonate solution, giving 1-*amino*-4-p-*methoxyphenyl*-2 : 3-*diazabuta*-1 : 3-*diene*-1-*sulphonic acid* (IV; R = OMe), which crystallised from acetic acid in colourless prisms (18·2 g.), m. p. 256—257° (Found: C, 42·2; H, 4·5; N, 16·4; S, 12·0. $C_9H_{11}O_4N_3S$ requires C, 42·0; H, 4·3; N, 16·3; S, 12·5%). The acid filtrate from the second crop of sulphonic acid was cooled strongly and made alkaline with 10N-sodium hydroxide; the resulting oil was allowed to harden, collected, washed with water, and dried (P_2O_5), and the 1-*amino*-4-p-*methoxyphenyl*-2 : 3-*diazabuta*-1 : 3-*diene* (V; R = OMe) (1·2 g.; m. p. 100—102°) crystallised from benzene–light petroleum (b. p. 60—80°), giving long colourless glistening needles or plates (0·65 g.), m. p. 112—113° (Found: C, 61·3; H, 6·2; N, 24·2. $C_9H_{11}ON_3$ requires C, 61·1; H, 6·2; N, 23·8%). The *picrate*, which slowly separated when warm, filtered, alcoholic solutions of base and picric acid were mixed, formed long yellow needles, m. p. 198—200°, which could not be recrystallised (Found: C, 44·2; H, 3·7; N, 21·0. $C_9H_{11}ON_3,C_6H_3O_7N_3$ requires C, 44·3; H, 3·5; N, 20·7%). Hydrolysis of the sulphonic acid (2·5 g.) with concentrated hydrochloric acid and with 10% sodium carbonate solution as described for the phenyl compound gave respectively, *p*-anisaldehyde azine, which crystallised from xylene in colourless clumps of prisms (1·0 g.), m. p. and mixed m. p. 170° (Found: C, 72·0; H, 6·0. Calc. for $C_{16}H_{16}O_2N_2$: C, 71·7; H, 6·0%), and *p*-methoxybenzaldehyde semicarbazone, which crystallised from alcohol in nearly colourless leaflets (0·7 g.), m. p. and mixed m. p. 211° (Found: N, 22·4. Calc. for $C_9H_{11}O_2N_3$: N, 21·8%). 1-Amino-4-*p*-methoxyphenyl-2 : 3-diazabuta-1 : 3-diene (1·0 g.), heated for a few minutes with concentrated hydrochloric acid, gave *p*-anisaldehyde azine (0·5 g.), m. p. and mixed m. p. 170°.

(*b*) Oxidation of *p*-anisaldehyde thiosemicarbazone (4·2 g.) in place of the benzaldehyde compound in (*b*) above gave unoxidised thiosemicarbazone (0·5 g.), m. p. and mixed m. p. 170—171°, and 1-amino-4-*p*-methoxyphenyl-2 : 3-diazabuta-1 : 3-diene (0·7 g.), m. p. 112—113° (Found: C, 60·9; H, 6·2%). The picrate, formed as previously, gave yellow needles, m. p. 196—198° (Found: C, 44·6; H, 3·5%). There was a considerable resinous residue insoluble in both N-hydrochloric acid and ether from which nothing but a small amount of unoxidised thiosemicarbazone was isolated.

1-*Amino*-4-*phenyl*-2 : 3-*diazabuta*-1 : 3-*diene* (V; R = H).—Benzaldehyde thiosemicarbazone (4·5 g.), alcohol (125 c.c.), and Raney nickel catalyst (*ca.* 20·0 g.) were refluxed for 3 hours with stirring, filtered, and evaporated at 35—40° under reduced pressure. The residual oil (3·2 g.) was dissolved in ether and filtered, and the solvent removed under reduced pressure. The picrate, formed as above, separated as yellow aggregates, m. p. 209—211° (Found: C, 45·3; H, 3·1%). The diene (1·0 g.) was refluxed with concentrated hydrochloric acid (10 c.c.) for 1 hour and cooled, the oil extracted with ether, dried, and evaporated, and the residue crystallised from dilute alcohol, giving benzaldehyde azine, which formed yellow needles (0·5 g.), m. p. and mixed m. p. 93° (Found: C, 80·8; H, 5·9%).

1-*Amino*-4-p-*methoxyphenyl*-2 : 3-*diazabuta*-1 : 3-*diene* (V; R = OMe).—On use of *p*-methoxybenzaldehyde thiosemicarbazone (5·2 g.) in the above experiment, the crystalline residue left on removal of the alcohol at 35—40° crystallised from benzene–light petroleum (b. p. 60—80°) in colourless plates (3·0 g.), m. p. 110—111° (Found: C, 60·8; H, 6·2; N, 24·2%). The picrate, formed as previously, separated as yellow needles, m. p. 198—200° (Found: C, 44·3; H, 3·7%).

The following sulphonic acids were obtained by oxidation of the corresponding thiosemicarbazones with perhydrol in cold acetic acid: 1-*Amino*-4-p-*ethylsulphonylphenyl*-2 : 3-*diazabuta*-1 : 3-*diene*-1-*sulphonic acid hydrate* (IV; R = SO_2Et), small colourless needles (from acetic acid), m. p. 242° (Found: C, 35·8, 35·9; H, 4·5, 4·3; S, 19·1. $C_{10}H_{13}O_5N_3S,H_2O$ requires C, 35·6; H, 4·5; S, 19·0%), which on being dried at 120° in a vacuum gave the anhydrous *acid*, m. p. 242—244° (Found: C, 37·0; H, 4·5. $C_{10}H_{13}O_5N_3S$ requires C, 37·6; H, 4·1%). 1-*Amino*-3-p-*acetamidophenyl*-2 : 3-*diazabuta*-1 : 3-*diene*-1-*sulphonic acid* (IV; R = NHAc), which was insoluble in all ordinary solvents and was purified by solution in cold dilute potassium hydrogen carbonate solution and precipitation with acetic acid, giving micro-needles, m. p. 199—201° (decomp.) (Found: C, 41·7; H, 5·0; S, 11·3. $C_{10}H_{12}O_4N_4S$ requires C, 42·3; H, 4·2; S, 11·3). 1-*Methylamino*-4-*phenyl*-2 : 3-*diazabuta*-1 : 3-*diene*-1-*sulphonic acid*, colourless flat needles, m. p. 232—234° (decomp.) (Found: C, 44·8; H, 4·6. $C_9H_{11}O_3N_3S$ requires C, 44·8; H, 4·5%). 4-p-*Methoxyphenyl*-1-*methylamino*-2 : 3-*diazabuta*-1 : 3-*diene*-1-*sulphonic acid*, colourless leaflets or plates, m. p. 216—218° (slight decomp.) (Found: C, 43·9; H, 5·1; S, 11·6. $C_{10}H_{13}O_4N_3S$ requires C, 44·3; H, 4·8; S, 11·8%).

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