s-Triazolopyrazines

By S. E. Mallett and F. L. Rose

Several 3-amino-*s*-triazolo[4,3-*a*]pyrazines have been prepared and their isomerisation to members of the *s*-triazolo[2,3-*a*]pyrazine series examined and, in part, achieved.

THE work described in this Communication is an extension of earlier related studies on triazolopyrimidines [1-3] and triazolopyridazines.[4] The former were concerned with the preparation of compounds of types (I) and (II), and their conversion by means of an isomerisation type of reaction to the triazolopyrimidines (III) and (IV), respectively. There was good reason to believe that this reaction, whether induced under anhydrous or hydrolytic conditions, required the intermediate formation of a 3-substituted triazole, schematically represented, for example, by structure (V) derived from the triazolo-[4,3-*c*]pyrimidine (I), which then ring-closed at the 2-position of the triazole residue to form the isomeric triazolo[2,3-*c*]pyrimidine system (III). No such effect was observed with the triazolo[4,3-*b*]pyridazines (VI), nor would it be expected, since the formation of a linear intermediate corresponding to (V) would require the unlikely rupture of the N–N bond. On the other hand, derivatives of the related triazolo[4,3-*a*]pyrazine (VII) might reasonably be expected to rearrange to the isomeric triazolo[2,3-*a*]pyrazines (VIII), and this type of reaction has indeed now been shown to occur. As in the earlier analogues studied, the individual compounds selected for initial investigation were derived from the corresponding hydrazinopyrazines (IX), by the action of cyanogen chloride so that the substituent R^1 in the [4,3-*a*]-isomer (VII) was the primary amino-group. This reaction proceeded smoothly in buffered aqueous acetic acid. The assignment of a [4,3-*a*]-configuration

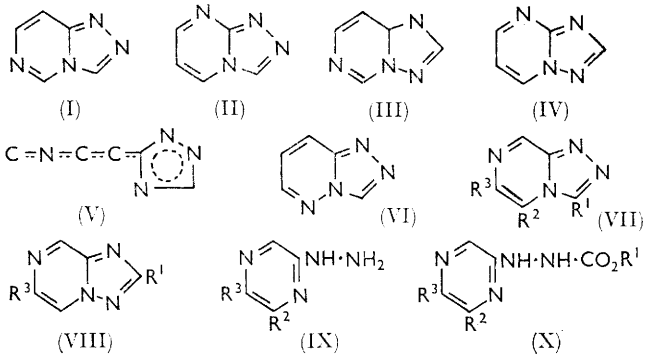
[1] Part I, G. W. Miller and F. L. Rose, *J. Chem. Soc.*, 1963, 5642.

[2] Part II, G. W. Miller and F. L. Rose, *J. Chem. Soc.*, 1965, 3357.

[3] Part III, W. Broadbent, G. W. Miller, and F. L. Rose, *J. Chem. Soc.*, 1965, 3369.

[4] N. K. Basu and F. L. Rose, *J. Chem. Soc.*, 1963, 5660.

to the three compounds formed in this way (VI; $R^1 = NH_2$, $R^2 = R^3 = H$, Me, and Ph) was based partly on subsequent chemical behaviour, but in the case of the triazolopyrazine (VII; $R^1 = NH_2$, $R^2 = R^3 = Ph$) on

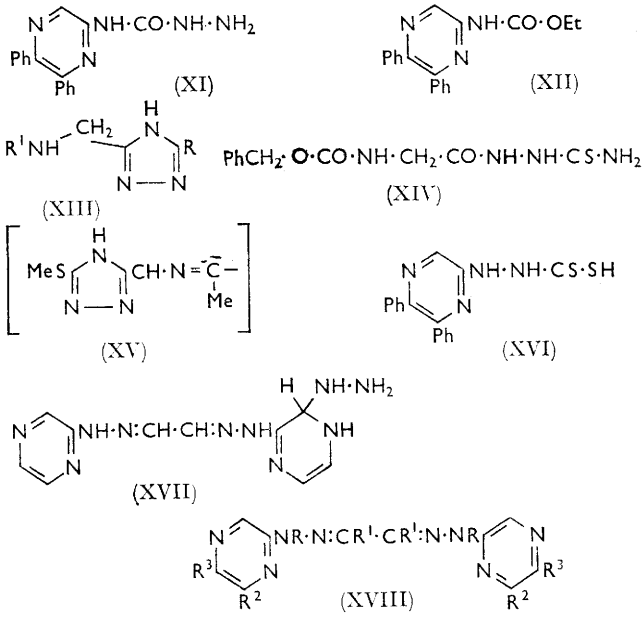


(I) (II) (III) (IV) (V) (VI) (VII) (VIII) (IX) (X)

mass spectral data. These showed a parent peak *m/e* 287 and the loss of a fragment of 40 mass units (N_2C) from this to give the base peak *m/e* 247, supported by a metastable peak *m/e* 213. Fragmentation in this manner was not considered possible from the [2,3-*a*]-structure (VIII; $R^1 = NH_2$, $R^2 = R^3 = Ph$).

Rearrangement in the triazolopyrimidine series was generally brought about by heat in the 200—250° range (conveniently in boiling nitrobenzene), or by the action of hot dilute aqueous hydrochloric acid, sodium carbonate, or sodium hydroxide. In the case of the pyrazine (VII; $R^1 = NH_2$, $R^2 = R^3 = Ph$), only acid treatment was successful, but the product isolated was the hydroxyl derivative (VIII; $R^1 = OH$, $R^2 = R^3 = Ph$) in the lactam form (band at 1685 $cm.^{-1}$). The nuclear magnetic resonance spectrum was in agreement with this structure, while the marked change in the ultraviolet spectrum gave further support to the configurational change to the triazolo[2,3-*a*]pyrazine system. Conclusive evidence for this course of events was provided by the synthesis of the other isomeric hydroxytriazolo[4,3-*a*]pyrazine (VII; $R^1 = OH$, $R^2 = R^3 = Ph$) from the action of phosgene on the hydrazine (IX; $R^2 = R^3 = Ph$), and also by ring-closure of the urethane (X; $R^1 = Et$, $R^2 = R^3 = Ph$), itself prepared from the hydrazine and ethyl chloroformate. As expected, the ultraviolet spectra of the hydroxy- and amino-triazoles in the [4,3-*a*]-series closely resembled one another. Attempts to bring about direct isomerisation of the hydroxytriazolo[4,3-*a*]pyrazine, whether by the action of heat or of acids or alkalis, failed completely, from which it was concluded that this change occurred at the aminotriazole stage, and was followed immediately by the rapid hydrolysis of the amino-group (possibly present in the imino-form). Failure also accompanied attempts to prepare the hydroxytriazolo[2,3-*a*]pyrazine by the elimination of ammonia from the semicarbazide (XI). The intermediate to the latter compound was the urethane (XII). This substance came from the interaction of the aminodiphenylpyrazine and ethylchloroformate in pyridine. The possible alternative configuration in which the ethoxycarbonyl group was attached to the ring nitrogen was discounted because of the stability shown by the product towards hot aqueous hydrochloric acid. This treatment would almost certainly have hydrolysed the 2-imino-group necessarily present in such a structure.

Parallel experiments with the hydrazinodimethylpyrazine (IX; $R^2 = R^3 = Me$) likewise gave in turn the aminotriazolo[4,3-*a*]pyrazine (VII; $R^1 = NH_2$, $R^2 = R^3 = Me$) leading to the hydroxytriazolo[2,3-*a*]pyrazine (VIII; $R^1 = OH$, $R^2 = R^3 = Me$) on treatment with acid, and the hydroxytriazolo[4,3-*a*]pyrazine (VII; $R^1 = OH$, $R^2 = R^3 = Me$) from phosgene and the hydrazinopyrazine. Infrared data showed the former hydroxy-derivative to exist in the lactim form, and the latter as the lactam. Once again, the one could not be rearranged to the other by direct means. Instability, presumably facile hydrolytic breakdown, made it impossible to bring about isomerisation of the parent aminotriazolopyrazine (VII; $R^1 = NH_2$, $R^2 = R^3 = H$). Likewise the action of phosgene on the corresponding hydrazinopyrazine (IX; $R^2 = R^3 = H$) led not to the expected hydroxytriazolopyrazine but to a compound corresponding to the carbamic acid (X; $R^1 = R^2 = R^3 = H$). The unusual stability of this substance could be attributed to salt formation by transfer of a proton from the carboxylic acid group to the adjacent ring-nitrogen atom.



(XI) (XII) (XIII) (XIV) (XV) (XVI) (XVII) (XVIII)

An additional approach to the synthesis of triazolopyrazine envisaged the condensation of an α-dicarbonyl reagent with an aminomethyltriazole (XIII; $R^1 = H$), although it could not be readily predicted whether such a reaction would lead to a member of the [4,3-*a*]- or the [2,3-*a*]-series. Further, if R was an amino-substituent, the formation of an iminazole rather than a pyrazine was a possibility. For this reason, it was proposed to have present in this position a group readily capable of nucleophilic displacement after the initial condensation

reaction, and methylthiol was selected as suitable. The *p*-nitrophenyl ester of *N*-benzyloxycarbonylglycine condensed smoothly with thiosemicarbazide to give compound (XIV) which on treatment with aqueous sodium carbonate at the boil was converted into the triazole (XIII; $R^1 = PhCH_2{\cdot}O{\cdot}CO{\cdot}NH{\cdot}CH_2{\cdot}CO^-$, R = SH). Methylation gave the corresponding methylthiol (R = SMe), which compound was also prepared by a route starting from the *p*-nitrophenyl ester and *S*-methylthiosemicarbazide. Treatment with hydrochloric acid removed the protective group to yield the required aminomethyltriazole (XIII; R = SMe, R^1 = H), but attempts to convert this substance to a triazolopyrazine by condensation with diacetyl, for example, gave the bistriazole (XV) as the only definable reaction product. A related approach to a thiol-substituted triazolopyrazine was by way of the action of carbon disulphide on the hydrazinopyrazine (IX; $R^2 = R^3$ = Ph). Nelson and Potts [5] attempted a similar reaction in pyridine and obtained a thiocarbazide. On the other hand, Broadbent, Miller, and Rose [3] were able to achieve a triazolopyrimidine synthesis in this way with 4-hydrazinopyrimidines in butanol at 130° but these conditions with the hydrazinopyrazine gave only the dithiocarboxyhydrazinopyrazine (XVI). This substance yielded a dimethyl derivative (compare the similar behaviour of phenylhydrazine [6]), but neither compound could be induced to cyclise, with the loss of hydrogen sulphide and methylmercaptan, respectively, to the triazole.

The three hydrazinopyrazines used in this investigation were prepared essentially in the manner described by Nelson and Potts,[5] but employing condensations between the chloropyrazines and aqueous hydrazine rather than anhydrous hydrazine in ethanol. Closer examination of some of the reaction mixtures revealed the presence of other products. Thus, from the preparation of the parent (IX; $R^2 = R^3$ = H) an adduct of hydrazine and the glyoxal dipyrazinylhydrazone was isolated. Ultraviolet and nuclear magnetic resonance spectra suggested the structure (XVII) for this substance. Treatment with acids removed the hydrazine moiety, leaving the parent hydrazone (XVIII; $R = R^1 = R^2 = R^3$ = H). This compound gave a deep red solution with sodium hydroxide in aqueous dimethyl sulphoxide from which a crystalline dimethyl derivative (XVIII; R = Me, $R^1 = R^2 = R^3$ = H) precipitated on reaction with methyl iodide. The formation of the same substance as a by-product from the reaction of chloropyrazine and methylhydrazine eliminated the other possible alternative structure involving methylation of a ring nitrogen atom. A similar sequence of events was observed in the preparation of the hydrazinodimethylpyrazine (IX; $R^2 = R^3$ = Me), although the presence of the hydrazine adduct was only inferred from the presence of acid-labile material (giving the hydrazone) in the crude hydrazinopyrazine initially isolated. Some attention was also given to improvement of the yields of the parent hydroxypyrazines by a modification of the general method due to Karmas and Spôerri.[7]

EXPERIMENTAL

2-Hydrazinopyrazine.—Chloropyrazine (5 g.) and a solution of hydrazine hydrate (10·9 g.) in water (20 ml.) were heated in a sealed tube at 92° for 3 hr., after which the mixture was evaporated to dryness under reduced pressure. The solid crystallised from benzene (100 ml.) to give hydrazinopyrazine (2·8 g.), m. p. 108—114° (lit.,[5] m. p. 112—113°). Water (50 ml.) was added to the benzene insoluble residue, which then crystallised from water to give the *hydrazine adduct of glyoxal dipyrazinylhydrazone* as pale yellow needles (0·11 g.), m. p. 236—237° (Found: C, 43·9; H, 5·0; N, 50·8. $C_{10}H_{14}N_{10}$ requires C, 43·8; H, 5·1; N, 51·0%), $\lambda_{max.}$ (EtOH), 240—242 and 317·5 mμ (log ε 4·00, 4·69), $\nu_{max.}$ 3340 and 3110 cm.$^{-1}$. The n.m.r. spectrum in dimethyl sulphoxide showed four areas of absorption: a singlet at τ 2·79 (2CH) a pair of doublets 2·55 and 2·26 (2CH), coupling constant 8·82 c./sec.; a group of three pyrazine aromatic protons τ 1·93, 2·06, and 1·60 (3CH), and a singlet τ 0·87 (NH_2). An aqueous solution of this adduct (0·25 g.) at 60° was made acid with 5N-acetic acid (3 ml.) and the amorphous yellow precipitate of *glyoxal dipyrazinylhydrazone* (m. p. 320°, decomp.) was filtered off. (Found: C, 49·5; H, 4·5; N, 46·8. $C_{10}H_{10}N_8$ requires C, 49·6; H, 4·1; N, 46·3), $\lambda_{max.}$ (dilute HCl), 238·5 and 368·5 mμ (log ε 3·95, 5·14). The n.m.r. spectrum in trifluoroacetic acid recorded four signals of equal intensity: a quartet at τ 1·43, 2 doublets at τ 1·6 and 0·98, and a singlet at τ 1·84. Salicylaldehyde (5 drops)was added to the dilute acid filtrate and disalicylaldehyde hydrazone (0·063 g.) was precipitated. (M. p. 206—210° undepressed with authentic material; infrared spectrum identical.) Glyoxal dipyrazinylhydrazone identical with the above material (m. p., i.r. and n.m.r. spectra) was also formed when glyoxal (0·13 g.) was added to a solution of hydrazinopyrazine (0·5 g.) in water. Methyl iodide was added dropwise with vigorous stirring to the deep crimson solution of this substance (0·3 g.) dissolved in dimethyl sulphoxide (10 ml.) and aqueous sodium hydroxide (40%, 1·24 ml.) to give *glyoxal bis(N'-methylpyrazinylhydrazone)* which formed small orange coloured rosettes from xylene (0·19 g.), sinters 230°, m. p. 300—302° (decomp.) (Found: C, 53·4; H, 5·1; N, 41·3. $C_{12}H_{14}N_8$ requires C, 53·3; H, 5·2; N, 41·5%), $\nu_{max.}$ 1560, 1500, 1470, 1425, 1400, and 1350 cm.$^{-1}$. The n.m.r. spectrum in trifluoroacetic acid showed five signals; three corresponding to pyrazine ring protons, a quartet at τ 1·06, and two doublets at τ 1·88 and 0·88, a singlet at τ 1·93, and another corresponding to methyl groups at τ 6·1. The same substance (m. p., i.r. and n.m.r. spectra) was formed (0·13 g.) when a solution of chloropyrazine (2 g.) and methylhydrazine (4·08 g.) in ethanol was heated under reflux for 8 hr.

2-Hydrazino-5,6-dimethylpyrazine.—2-Chloro-5,6-dimethylpyrazine (5 g.) and hydrazine hydrate (8·7 g.) in water (25 ml.), were heated together in a tube at 110° for 24 hr. The precipitate of colourless plates of *diacetyl bis-(5,6-dimethylpyrazin-2-ylhydrazone)* which formed on cooling was filtered off, washed with water and dried (0·05 g.), m. p. 305° (decomp.) (Found: C, 58·3; H, 7·1;

[5] P. J. Nelson and K. T. Potts, *J. Org. Chem.*, 1962, **27**, 3245.
[6] E. Fisher, *Annalen*, 1877, **190**, 67.
[7] G. Karmas and P. E. Spôerri, *J. Amer. Chem. Soc.*, 1952, **74**, 1582.

N, 34·2. $C_{16}H_{22}N_8$ requires C, 58·9; H, 6·75; N, 34·35%), $\nu_{max.}$ 3180 and 2950 cm.$^{-1}$. The n.m.r. spectrum in trifluoroacetic acid showed two signals at τ 7·53 ($2CH_3$) and 7·33 ($4CH_3$), and a single peak recording pyrazine ring protons 1·27 (2CH). The aqueous filtrate was evaporated to dryness under reduced pressure and the residue was crystallised twice from benzene (80 ml.) to give the hydrazinopyrazine as large colourless plates (2·8 g.), m. p. 116—119°. An aqueous solution of this product (2·8 g.) was adjusted to pH 5 with 5N-acetic acid and a further quantity (0·09 g., m. p. 303° decomp.) of the dipyrazinyl hydrazone (i.r. spectrum) was precipitated. Neutralisation of the acidic filtrate with sodium carbonate, followed by evaporation to dryness, and crystallisation from benzene (40 ml.) gave colourless plates of the pure hydrazinopyrazine (2·1 g.), m. p. 119—120° (lit.,[5] m. p. 119—120°). Methylation of the diacetyl bis(5,6-dimethylpyrazin-2-yl-hydrazone) (0·1 g.) as described above for the parent hydrazone, gave the *diacetyl bis-(5,6-dimethylpyrazin-2-yl-*N′*-methylhydrazone*) (0·091 g., m. p. 185—191°) which crystallised from ethanol as orange needles (0·047 g.), m. p. 189—191° (Found: C, 61·2; H, 8·2; N, 31·1. $C_{18}H_{26}N_8$ requires C, 61·0; H, 7·4; N, 31·6%).

2-*Hydrazino*-5,6-*diphenylpyrazine*.— 2-Chloro-5,6-diphenylpyrazine (10·4 g.), hydrazine hydrate (98%, 18·5 ml.), and butanol (100 ml.) were heated under reflux for 4 hr. Addition of water (100 ml.) after evaporation of the solvent gave the hydrazinopyrazine which was crystallised from benzene (75 ml., charcoal) (yield 8·4 g.), m. p. 155—156° (lit.,[5] m. p. 154—155°).

Aminotriazolopyrazines.—3-*Amino*-5,6-*diphenyl*-s-*triazolo*[4,3-a]*pyrazine*. Cyanogen chloride (0·82 g.) was passed slowly into a solution of hydrazino-5,6-diphenylpyrazine (2 g.) dissolved in a mixture of methanol (50 ml.), 3N-acetic acid (8 ml.), and sodium acetate trihydrate (3·14 g.), kept at 5—10°. A yellow crystalline precipitate of the *triazolopyrazine* (2·14 g., m. p. 244—246°) formed. It crystallised from aqueous ethanol as yellow needles (1·4 g.), m. p. 248—250° (Found: C, 70·6; H, 4·3; N, 24·0. $C_{17}H_{13}N_5$ requires C, 71·1; H, 4·5; N, 24·4%), $\lambda_{max.}$ (EtOH), 210·4, 233·9 (infl.), 262·6, and 354·5 mμ (log ε 4·34, 4·16, 4·19, and 3·50), $\nu_{max.}$ 3430, 3280, and 3050 cm.$^{-1}$. The n.m.r. spectrum in dimethyl sulphoxide recorded the following signals: singlets at τ 2·75 (Ph), 2·45 (Ph), 0·82 (CH), and 5·1 (NH_2).

3-*Amino*-5,6-*dimethyl*-s-*triazolo*[4,3-a]*pyrazine*. Similarly prepared from 2-hydrazino-5,6-dimethylpyrazine (1 g.), cyanogen chloride (0·62 g.), 0·5N-acetic acid (10 ml.), and sodium acetate trihydrate (3·3 g.) at 0—5°, this *product* crystallised from water as orange plates (0·86 g.), m. p. 260—261° (Found: C, 51·3; H, 5·7; N, 42·8. $C_7H_9N_5$ requires C, 51·5; H, 5·5; N, 42·95), $\lambda_{max.}$ (solvent water), 229·5, 257—265 (infl.), and 339 mμ (log ε 4·26, 3·2, and 3·54), $\nu_{max.}$ 3090 and 3230 cm.$^{-1}$.

3-*Amino*-s-*triazolo*[4,3-a]*pyrazine*. Similarly prepared from cyanogen chloride (0·83 g.), 2-hydrazinopyrazine (1 g.), 0·5N-acetic acid (10 ml.), and sodium acetate trihydrate (3·7 g.) at 0—5°, this *product* formed colourless needles (0·42 g., m. p. >320°) from water (Found: C, 44·5; H, 4·7; N, 51·7. $C_5H_5N_5$ requires C, 44·45; H, 3·7; N, 51·85%). $\lambda_{max.}$ (water), 227·5 and 335 mμ (log ε 4·19 and 3·38). $\nu_{max.}$ 3340, 3300, and 3110 cm.$^{-1}$. The n.m.r. spectrum in dimethyl sulphoxide showed the following signals: singlet at τ 3·25 (NH_2), quartet at τ 1·9 (CH), doublet at 2·34 (CH), and doublet at τ 0·93 (CH).

Hydroxytriazolopyrazines.— 2-*Hydroxy*-5,6-*diphenyl*-s-*triazolo*[2,3-a]*pyrazine*. A solution of 3-amino-5,6-diphenyl-*s*-triazolo[4,3-*a*]pyrazine (1 g.) in N-hydrochloric acid (100 ml.) was heated under reflux for 6 hr. The pale yellow plates of the *hydroxytriazolopyrazine* which formed on cooling the mixture were recrystallised from aqueous ethanol (0·15 g., m. p. 246—248° decomp.) (Found: C, 70·2; H, 4·2; N, 19·5. $C_{17}H_{12}N_4O$ requires C, 70·8; H, 4·2; N, 19·45), $\lambda_{max.}$ (EtOH) 203, 240·5, and 288 mμ (log ε 4·43, 4·09, and 3·91), $\nu_{max.}$ 3700—3100, 1685, 762, 736, and 700 cm.$^{-1}$. The n.m.r. spectrum in dimethyl sulphoxide recorded these signals: four singlets at τ 2·63 (Ph), 2·57 (Ph), 0·32 (CH), and 3·6—5·4 (NH). A further quantity (0·52 g.), m. p. 244—248° (decomp.), was obtained when the acid filtrate was adjusted to pH 7·5 with 10% sodium hydroxide solution.

3-*Hydroxy*-5,6-*diphenyl*-s-*triazolo*[4,3-a]*pyrazine*. (*a*) Anhydrous sodium acetate (0·63 g.) was suspended in a solution of 2-hydrazino-5,6-diphenylpyrazine (1 g.) in dry ethyl acetate (30 ml.) at 20°. Dry phosgene (0·6 g.) was passed in during 20 min. The suspension was filtered and the dried solid crystallised from toluene (20 ml.) to give the *triazolopyrazine* as pale-yellow needles (0·76 g.), m. p. 224—226° (Found: C, 70·8; H, 4·5; N, 19·2. $C_{17}H_{12}N_4O$ requires C, 70·8; H, 4·2; N, 19·45), $\lambda_{max.}$ (EtOH) 206·7, 232 (infl.), 266, 288 (infl.), and 365 mμ (log ε 4·34, 3·99, 3·89, and 3·56). The n.m.r. spectrum in dimethyl sulphoxide showed four signals: τ 2·72 (Ph), 2·57 (Ph), 0·92 (CH), and −3·07 (NH).

(*b*) Ethyl chloroformate (4·14 g.) in dry ethyl acetate (20 ml.) was added to a solution of 2-hydrazino-5,6-diphenylpyrazine (5 g.) in dry ethyl acetate (120 ml.) at 20°. After 4 days the yellow precipitate which formed was filtered off, washed with ethyl acetate, and dried at 80° to give 2-(2′-*ethoxycarbonylhydrazino*)-5,6-*diphenylpyrazine hydrochloride* (6·52 g.), m. p. 195—198° (decomp.) (Found: C, 61·2; H, 5·0; N, 14·9. $C_{19}H_{19}ClN_4O_2$ requires C, 61·5; H, 5·1; N, 15·1%). A suspension of the hydrochloride in 10N-sodium hydroxide was extracted with diethyl ether (4 × 50 ml.). The ethereal layer was washed with water, dried over sodium sulphate and evaporated to dryness to give 2-(2′-*ethoxycarbonylhydrazino*)-5,6-*diphenylpyrazine*. The product crystallised from toluene as buff-coloured rhombic crystals (3·17 g.), m. p. 147—149° (Found: C, 68·7; H, 5·2; N, 16·9. $C_{19}H_{18}N_4O_2$ requires C, 68·25; H, 5·4; N, 16·8%), $\lambda_{max.}$ (EtOH), 225·5, 282·5, and 339 mμ (log ε 4·31, 4·16, and 4·02), $\nu_{max.}$ 3300 and 1830 cm.$^{-1}$. The n.m.r. spectrum (in $CDCl_3$) recorded signals at τ 8·71 (CH_3), 5·76 (CH_2), 2·86 (Ph), 2·82 (NH), 0·78 (NH), and 1·8 (CH). A solution of this substance (0·5 g.) in *o*-dichlorobenzene (5 ml.) was heated under reflux for 1 hr. The solution was cooled and poured into light petroleum (b. p. 100—120°, 100 ml.). The yellow precipitate of the hydroxytriazolopyrazine which formed (i.r. and u.v. spectra) was crystallised from toluene (0·13 g., m. p. 217—220°).

2-*Hydroxy*-5,6-*dimethyl*-s-*triazolo*[2,3-a]*pyrazine*. A solution of 3-amino-5,6-dimethyl-*s*-triazolo[4,3-*a*]pyrazine (0·5 g.) in N-hydrochloric acid (20 ml.) was heated under reflux for 1 hr. The solution was cooled and adjusted to pH 7·5—8 by the addition of 10% sodium hydroxide solution. The precipitate (needles) of the s-*triazolo*[2,3-a]*pyrazine* recrystallised from water as pale yellow micro-needles (0·2 g.), m. p. 268—270° (decomp.) (Found: C, 50·7; H, 6·0; N, 34·0. $C_7H_8N_4O$ requires C, 51·2; H, 4·9; N, 34·15%), $\lambda_{max.}$ (EtOH), 210, 250, and 320 mμ (log ε 3·70, 3·69, and 3·68), $\nu_{max.}$ 3420, 3010, 2790, 2660, and 1560 cm.$^{-1}$.

3-*Hydroxy*-5,6-*dimethyl*-s-*triazolo*[4,3-a]*pyrazine*. 2-Hydrazino-5,6-dimethylpyrazine (0·5 g.) and sodium acetate trihydrate (2·2 g.) were dissolved in 0·8N-acetic acid (12 ml.). The mixture was cooled to 0—5° and phosgene (0·42 g.) was passed in during 10 min. The yellow precipitate which formed after 1 hr. was filtered off, washed and recrystallised from ethanol to give the s-*triazolo*[4,3-a]-*pyrazine* (0·32 g., m. p. 249—250°) as small clusters of yellow rods (Found: C, 51·3; H, 5·5; N, 34·3. $C_7H_8N_4O$ requires C, 51·2; H, 4·9; N, 34·15%), $\lambda_{max.}$ (EtOH) 230, 268, 288 (infl.), and 356 mμ (log ε 4·28, 3·40, 3·06, and 3·59), $\nu_{max.}$ 3200—2600, 1760—1710 (doublet) cm.$^{-1}$.

A similar experiment starting with a solution of 2-hydrazinopyrazine (1 g.) and sodium acetate trihydrate (3·7 g.) in 0·5N-acetic acid (10 ml.) gave a yellow precipitate which after extraction with methanol and evaporation of the solvent left the presumed *carbamic acid* as a yellow microcrystalline solid (0·4 g.), m. p. 220—222° (decomp.) (Found: C, 38·0; H, 5·0; N, 36·9. $C_5H_6N_4O_2$ requires C, 39·0; H, 3·9; N, 36·4), $\lambda_{max.}$ (MeOH), 229·3, 277·3, 323, and 332·6 (infl.) mμ (log ε 3·7, 3·8, 3·98, and 3·97), $\nu_{max.}$ 3370—3180 (broad) and 1700 cm.$^{-1}$. Unchanged material (mixed m. p., i.r. spectrum) was recovered after a solution of this substance in 2N-sodium hydroxide had been kept at 20° for 24 hr.

2-*Ethoxycarbonylamino*-5,6-*diphenylpyrazine*.—A solution of ethyl chloroformate (12·1 g.) and 2-amino-5,6-diphenylpyrazine (5·5 g.) in dry pyridine (120 ml.) was kept at 70° for 16 hr., and then at 20° for 24 hr. The pyridine was distilled off at 80° under reduced pressure and the residue was triturated with N-hydrochloric acid. The insoluble yellow solid which formed was filtered off, washed with water, and crystallised from aqueous ethanol to give the *urethane* as yellow needles (4·75 g.), m. p. 126—128° (Found: C, 71·4; H, 5·3; N, 13·2. $C_{19}H_{17}N_3O_2$ requires C, 71·45; H, 5·3; N, 13·2%), $\lambda_{max.}$ (EtOH), 226·5, 276·5, and 326 mμ (log ε 4·44, 4·12, and 4·08), $\nu_{max.}$ 3250 and 1710 cm.$^{-1}$. The n.m.r. spectrum (in $CDCl_3$) showed five signals at τ 8·8 (CH_3), 5·73 (CH_2), 2·68 (Ph), 2·20 (NH), and 0·64 (CH). The urethane (0·5 g.) was recovered unchanged after a solution in ethanol (15 ml.) and hydrazine hydrate (0·8 g.) had been heated under reflux for 19 hr. The use of 2-ethoxyethanol hydrate as solvent regenerated the 2-amino-5,6-diphenylpyrazine. An experiment of shorter duration (1½ hr. at 110°) gave N,N′-*bis*-5,6-*diphenylpyrazin*-2-*ylaminocarbonylhydrazine*, after addition of the reaction mixture to water and successive extraction of the precipitate which formed with ethyl acetate and N-hydrochloric acid. This compound crystallised from butanol as clusters of small plates, m. p. 233—236° (Found: C, 70·1; H, 4·5; N, 19·8. $C_{34}H_{26}N_8O_2$ requires C, 70·6; H, 4·5; N, 19·4%), $\lambda_{max.}$ (EtOH) 225, 275·5, and 333 mμ (log ε 4·63, 4·51, and 4·38), $\nu_{max.}$ 3330, 3130, and 1685 cm.$^{-1}$. The acid filtrate was adjusted to pH 12 with 10% aqueous sodium hydroxide and the resultant white precipitate was filtered off, washed and dried, and then crystallised from butanol to give N′-5,6-*diphenylpyrazin*-2-*ylsemicarbazide* as small rosettes, m. p. 188—191° (Found: C, 67·5; H, 4·9; N, 22·7. $C_{17}H_{15}N_5O$ requires C, 66·9; H, 4·9; N, 22·95), $\lambda_{max.}$ (EtOH), 225·5, 282·5, and 339 (log ε 4·31, 4·16, and 4·02), $\nu_{max.}$ 3300, 3140, and 1685 cm.$^{-1}$. Benzaldehyde (0·18 g.) was added to a solution of the semicarbazide (0·1 g.) in methanol at 60°, and after 1 hr. the needles which precipitated were filtered off, washed with methanol and dried (0·11 g., m. p. 228—234°). Recrystallisation from xylene gave 2-(4′-*benzylidene-semicarbazono*)-5,6-*diphenylpyrazine* as colourless needles, m. p. 232—234° (Found: C, 73·8; H, 4·9; N, 17·6. $C_{24}H_{19}N_5O$ requires C, 73·3; H, 4·8; N, 17·8%), $\nu_{max.}$ 3325, 3170, 3090, and 1698 cm.$^{-1}$. The pyrazinylsemicarbazide (0·3 g.) was kept at 200° for 15 min. in an open tube. Effervescence occurred and the melt solidified after 10 min. Crystallisation of the solid from toluene gave white needles (0·104 g., m. p. 213—216°) of 2-amino-5,6-diphenylpyrazine (mixed m. p. and i.r. spectrum).

N′-(N-*Benzyloxycarbonylglycyl*)*thiosemicarbazide*.—A mixture of benzyloxycarbonylglycine-*p*-nitrophenyl ester (30·0 g.) and powdered thiosemicarbazide (25·1 g.), in dimethyl formamide (120 ml.) was stirred at 20° for 4 days. The mixture was filtered into water (500 ml.) and chilled at 0—5° for 3 hr. The resultant precipitate was filtered off, washed, dried and then triturated with chloroform (2 × 100 ml.). The insoluble residue (26·2 g.) was recrystallised from water to give the *thiosemicarbazide* as colourless plates (20·7 g.), m. p. 164—166° (Found: C, 46·8; H, 5·2; N, 20·0. $C_{11}H_{14}N_4O_3S$ requires C, 46·8; H, 5·0; N, 19·9%), $\nu_{max.}$ 3430, 3360, 3270, 3160, 1730, and 1670 cm.$^{-1}$.

5-(N-*Benzyloxycarbonylaminomethyl*)-3-*mercapto*-s-*triazole*.—The above semicarbazide (0·22 g.) in aqueous sodium carbonate (2%, 2 ml.) was heated under reflux for 4 hr. The cooled suspension was filtered, and the filtrate was adjusted to pH 6·5—7 with 5N-acetic acid. The precipitate which formed was collected, and crystallised from water to give the *mercaptotriazole* as plates (0·11 g.), m. p. 196—198° (Found: C, 49·6; H, 4·3; N, 20·8. $C_{11}H_{12}N_4O_2S$ requires C, 50·0; H, 4·5; N, 21·2%), $\nu_{max.}$ 3320, 2780—2500, and 1695 cm.$^{-1}$.

N′-(N-*Benzyloxycarbonylglycyl*)-S-*methylthiosemicarbazide*.—Methyl iodide (7·6 g.) was added to a solution of the above thiosemicarbazide (5·0 g.) in aqueous sodium carbonate (4%, 14 ml.), and the mixture was shaken for 1½ hr. The white crystalline solid which precipitated was filtered off, washed with water, and crystallised from ethanol to give the nearly pure S-*methylthiosemicarbazide* (3·4 g.) as colourless plates, m. p. 127—128·5°. Treatment with ethyl acetate gave material having m. p. 132—133° (Found: C, 48·5; H, 5·8; N, 18·6; S, 11·1. $C_{12}H_{16}N_4O_3S$ requires C, 48·65; H, 5·4; N, 18·9; S, 10·8%), $\nu_{max.}$ 3330, 3280, 3170, and 1655 cm.$^{-1}$.

5-(N-*Benzyloxycarbonylaminomethyl*)-3-*methylthio*-s-*triazole*.—Recrystallisation of *N*′-(*N*-benzyloxycarbonylglycyl)-*s*-methylthiosemicarbazide (4·0 g.) from water containing a little ethanol gave the s-*triazole monohydrate* as colourless rectangular plates (3·06 g.), m. p. 80—81° (Found: C, 48·9; H, 5·5; N, 19·1. $C_{12}H_{14}N_4O_2S$, H_2O requires C, 48·65; H, 5·4; N, 18·9%), $\nu_{max.}$ 3510, 3400, 3240—3040, and 1700 cm.$^{-1}$. The same substance (i.r. spectrum, mixed m. p.) was obtained when *N*-benzyloxycarbonylglycine-*p*-nitrophenyl ester (1 g.) was heated with *S*-methylthiosemicarbazinium iodide (1·41 g.) in dimethyl formamide (20 ml.) at 100°, in the presence of potassium carbonate (1·25 g.). The crude product which formed on cooling and diluting with water, was crystallised from aqueous ethanol. It was also obtained when a solution of 5-(*N*-benzyloxycarbonylaminomethyl)-3-mercapto-*s*-triazole (0·5 g.) in aqueous sodium carbonate (2%, 20 ml.) was shaken for ½ hr. with methyl iodide (1·1 g.). The *anhydrous triazole* was formed when the monohydrate (4·0 g.) was heated at 80° *in vacuo* over phosphorus pentoxide for 6 hr. (3·75 g.), m. p. 109—111° (Found: C, 52·0; H,

5·4; N, 20·2. $C_{12}H_{14}N_4O_2S$ requires C, 51·8; H, 5·0; N, 20·1%), $\nu_{max.}$ 3325 cm.$^{-1}$. Crystallisation (1 g.) from ethyl acetate gave the triazole as colourless plates (0·6 g.), m. p. 99—101°, $\nu_{max.}$ 3140 cm.$^{-1}$. The n.m.r. spectra (in $CDCl_3$) of the two different solid forms were identical and showed the following signals: τ 7·44 (CH_3), 5·56 (NCH_2), 4·92 (O-CH_2), 3·59 (NH), 1·0 (NH), and 2·7 (Ph). The anhydrous product (0·65 g., m. p. 99—101°) was also formed when *N'*-(*N*-benzyloxycarbonylglycyl)-*s*-methylthiosemicarbazide (1 g.) was kept at 145° for 5 min., and then crystallised from ethyl acetate.

*5-Aminomethyl-3-mercapto-*s*-triazole Hydrobromide.*—5-(*N*-Benzyloxycarbonylaminomethyl)-3-mercapto-*s*-triazole (0·5 g.) was stirred in a solution of hydrogen bromide in glacial acetic acid (29%, 4 ml.) at 200° for 24 hr. The solid was filtered off and washed with glacial acetic acid (2 × 10 ml.) and then diethyl ether (5 × 25 ml.). The s-*triazole hydrobromide* (0·3 g., m. p. 248—251°) was precipitated as fine needles when light petroleum (80 ml., b. p. 100—120°) was added to a solution of the crude product in methanol (20 ml.) (Found: C, 17·4; H, 3·5; N, 26·1. $C_3H_7BrN_4S$ requires C, 17·1; H, 3·3; N, 26·6%), $\lambda_{max.}$ (H_2O) 243·4 mμ (log ε 4·00), $\nu_{max.}$ 3300—2600, and 2550 cm.$^{-1}$.

*5-Aminomethyl-3-methylthio-*s*-triazole Hydrobromide.*—Similarly prepared when 5-(*N*-benzyloxycarbonylaminomethyl)-3-methylthio-*s*-triazole (1·0 g.) was stirred in a solution of hydrogen bromide in glacial acetic acid (29%, 8 ml.) at 20° for 1 hr., the s-*triazole hydrobromide* (0·57 g., m. p. 244—246°) was obtained as microcrystalline needles from a mixture of methanol and diethyl ether (Found: C, 21·2; H, 3·8; N, 24·6. C_4H_9BrNS requires C, 21·45; H, 4·0; N, 25·0) $\lambda_{max.}$ (H_2O) 232 mμ (log ε 3·53) $\nu_{max.}$ 3020 and 3020—2500 cm.$^{-1}$. A dihydrobromide was formed as the precipitate when a more concentrated solution of hydrogen bromide in glacial acetic acid (8 ml., 49%), and a longer reaction time (24 hr.), were employed. The product was obtained as needles, m. p. 218—220° (decomp.) (Found: C, 15·8; H, 3·4; Br, 53·0; N, 18·6. $C_4H_{10}Br_2NS$ requires C, 15·8; H, 3·3; Br, 52·0; N, 18·4%), $\lambda_{infl.}$ (solvent water), 234·6 mμ (log ε 3·45), $\nu_{max.}$ 3250—2300 cm.$^{-1}$.

*Condensation of 5-Aminomethyl-3-methylthio-*s*-triazole with Diacetyl.*—A solution of diacetyl (0·56 g.) and 5-aminomethyl-3-methylthio-*s*-triazole dihydrobromide (1 g.), in pyridine (10 ml.), was kept at 20° for 3 hr. The pyridine was distilled off under reduced pressure and ether (60 ml.) was added to a solution of the residue oil in ethanol (10 ml.). Water (3·5 ml.) was added to the precipitated gum. The solid which formed was collected and crystallised from t-butyl alcohol to give the *di-ketimine* (XV) as straw-coloured rhombic crystals (0·05 g.), m. p. 208—210° (Found: C, 42·8; H, 6·4; N, 32·9; S, 18·7. $C_{12}H_{18}N_8S_2$ requires C, 42·6; H, 5·3; N, 33·1; S, 18·9%), $\lambda_{max.}$ (EtOH) 210, 238, 280, and 310 mμ (log ε 4·17, 3·94, 2·44, and 2·39), $\nu_{max.}$ 3290, 1530, and 1265 cm.$^{-1}$.

Action of Carbon Disulphide on 2-Hydrazino-5,6-diphenylpyrazine.—2-Hydrazino-5,6-diphenylpyrazine (1 g.), carbon disulphide (0·85 g.), and t-butyl alcohol, were heated in a sealed tube at 140° for 20 hr. The yellow crystalline precipitate which formed on cooling was filtered off and recrystallised from t-butyl alcohol to give *5,6-diphenyl-2,2'-dithiocarboxyhydrazinopyrazine* as yellow needles (0·17 g.), m. p. 272—273° (Found: C, 60·5; H, 4·1; N, 16·8; S, 19·5. $C_{17}H_{14}N_4S_2$ requires S, 60·35; H, 4·1; N, 16·6; S, 18·9%), $\nu_{max.}$ 3120, 2700—2500, and 1254 cm.$^{-1}$. A solution of the thiocarbamic acid (0·1 g.) in N-sodium hydroxide (3 ml.) and dimethyl sulphoxide (1 ml.) was shaken with dimethyl sulphate (0·38 g.). The precipitate which formed was filtered off, dried, and recrystallised from ethanol to give *2-bis(methylthio)methylenehydrazino-5,6-diphenylpyrazine* as yellow rods (0·075 g., m. p. 212—214°) (Found: C, 62·9; H, 4·7; N, 15·2; S, 17·4. $C_{19}H_{18}N_4S_2$ requires C, 62·3; H, 4·9; N, 15·3; S, 17·5%). The n.m.r. spectrum (in $CDCl_3$) had a singlet at τ 7·37 (CH_3), another at 7·26 (CH_3), and a multiplet at 2·65 (11 protons).

Hydroxypyrazine.—A solution of glycineamide hydrochloride (11 g.) and glyoxal monohydrate (7·6 g.) in water (50 ml.) was added dropwise during ½ hr. to a stirred solution of sodium hydroxide (12 g.) in water (30 ml.) and methanol (200 ml.), cooled to −30 to −40°. After a further ½ hr., the temperature was allowed to rise over 1 hr. to 22°, and maintained at this for 2 hr. Concentrated hydrochloric acid was added to adjust to pH 6·5, and the resultant solution was evaporated to dryness at 60°. Extraction of the residual solid with ethanol and crystallisation of the extracted product from the same solvent gave the hydroxypyrazine (5·76 g., m. p. 185—187°).

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