1081. s-*Triazolopyridazines: Synthesis as Potential Therapeutic Agents.*

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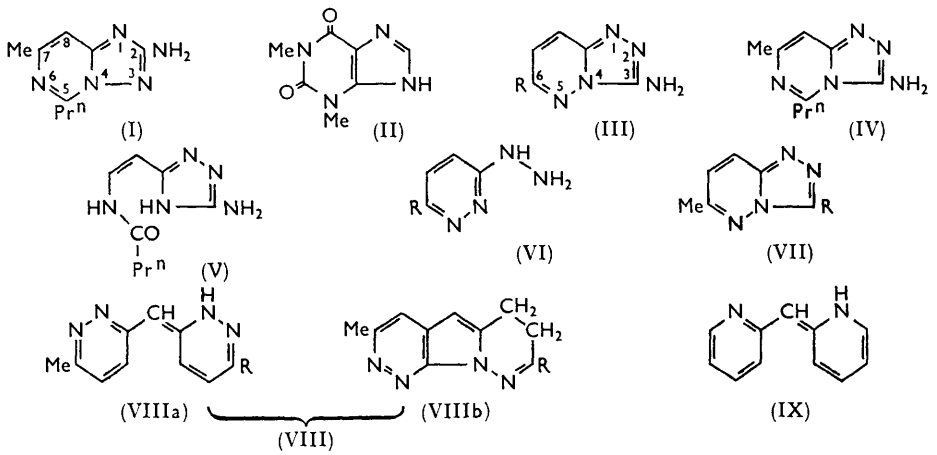
Interaction of cyanogen chloride and 3-hydrazinopyridazines leads to 3-amino-*s*-triazolo[4,3-*b*]pyridazines (III).

Earlier work in these laboratories [1] led to the discovery of bronchodilatory activity in certain triazolopyrimidines, for example, compound (I), and it has been assumed that this effect is associated with the formal structural resemblance shown by this molecule to that of the alkaloid theophylline (II). This research has now been extended to compounds of the *s*-triazolo[4,3-*b*]pyridazine type (III) which are also isosteric with the purine ring system. The *s*-triazolo[2,3-*c*]pyrimidines of type (I), although capable of preparation by direct synthesis, were nevertheless originally made by isomerisation of the corresponding *s*-triazolo[4,3-*c*]pyrimidines (IV), a process which was thought to occur,[1] for example, in hot dilute aqueous acid or alkali, through the intermediate formation of the amidic structure (V). An additional interest, therefore, was to see whether the *s*-triazolo[4,3-*b*]-pyridazines (III) would behave similarly, although a different mechanism would need to be adduced, involving the unlikely rupture of a nitrogen–nitrogen bond. In fact no such isomeric change has been achieved. The initial intermediates for the formation of the compounds (III) would be the corresponding 3-hydrazinopyridazines (VI). Cyclisation of



these with formic acid and ethyl orthoformate, to give triazolopyridazines unsubstituted in position 3, has been studied by earlier workers.[2,3] In the present series, cyanogen chloride was employed, which with the hydrazinopyridazines (VI; R = Cl) [4] and (VI R = Me),[3] in the presence of sodium acetate in dilute aqueous acetic acid, gave the triazolopyridazines (III; R = Cl and Me), while a few 3-amino-*s*-triazolo[4,3-*b*]pyridazine derivatives substituted at position 6 were prepared by nucleophilic displacement of the chlorine atom with different reagents. The 6-methoxy- (III; R = OMe) and 6-n-propoxy-compound (III; R = OPr^n) were obtained by using two equivalents of the sodium alkoxide. The 6-hydrazino- (III; R = $NH{\cdot}NH_2$), 6-piperidino- (III; R = $N[CH_2]_5$), and

[1] Miller and Rose, preceding paper.
[2] Takahayashi, *J. Pharm. Soc. Japan*, (*a*) 1955, **75**, 1242; (*b*) 1956, **76**, 1296; (*c*) 1956, **76**, 765; *Pharm. Bull. Japan*, 1957, **5**, 229.
[3] Libermann and Jacquier, *Bull. Soc. chim. France*, 1962, 355.
[4] Druey, Meier, and Eichenberger, *Helv. Chim. Acta*, 1954, **37**, 121; Takahayashi, *J. Pharm. Soc. Japan*, 1955, **75**, 778.

6-3′-dimethylaminopropylamino-derivatives (III; R = NH·$[CH_2]_3$·NMe_2) were obtained similarly from the appropriate amines.

The availability of the aminotriazolopyridazines prompted the conversion of one of them (III; R = OMe) into the corresponding *N*′-substituted sulphanilamide derivative, by condensation with 4-nitrobenzenesulphonyl chloride in pyridine, followed by catalytic reduction of the nitro-group. An attempt to build a second triazole ring fused to the pyridazine nucleus failed. Thus, refluxing the hydrazinotriazolopyridazine (III; R = NH·NH_2) with formic acid gave only a formyl derivative, the formyl residue presumably being attached to the terminal nitrogen atom of the hydrazino-substituent. Similar behaviour has been recorded for compounds devoid of the 3-amino-group.[2a] A thiol substituent has been introduced into the triazolopyridazine system (VII; R = SH) by the interaction of compound (VI; R = Me) and carbon disulphide in boiling pyridine. Chlorination of the product in a water–chloroform mixture gave the sulphonyl chloride directly, which was then converted into the sulphonamide (VII; R = SO_2·NH_2) by the action of aqueous ammonia. This product was of potential interest as a diuretic agent, but was found to be devoid of activity. The related 6-chloro-3-sulphamoyltriazolo[4,3-*b*]-pyridazine would have been a useful intermediate for further conversion into substances of possible therapeutic interest, but the reaction of the hydrazinopyridazine (VI; R = Cl) with carbon disulphide was found to be complex, whether conducted in pyridine or in a non-basic solvent such as butyl alcohol. The products were high-melting solids which did not lend themselves to further purification, and that obtained with the use of pyridine contained only a trace of chlorine. An attempt to introduce the thiol group through thermal decomposition of the thiosemicarbazide derived from compound (VI; R = Cl) and phenyl isothiocyanate also failed.

The intermediate hydrazinopyridazine (VI; R = Me) referred to above was prepared by the method of Libermann and Jacquier [3] from 3-chloro-6-methylpyridazine. Earlier workers [5] obtained the latter in high yield by heating the corresponding pyridazone in phosphoryl chloride at 100° for 30 minutes. The temperature and duration of this reaction has now been found to be critical. At the b. p., varying yields of the desired chloro-derivative were obtained along with a new yellow crystalline base, the amount of the latter depending upon the length of the reaction time, with longer periods favouring increased formation of the by-product. By separate experiment, it was shown that the new compound was formed in high yield when 3-chloro-6-methylpyridazine was refluxed in phosphoryl chloride for 3 hours. Elemental analysis and molecular-weight determination agreed closely with the molecular formula $C_{10}H_9ClN_4$, and on the basis of spectroscopic evidence and chemical behaviour, the structure (VIIIa; R = Cl) was assigned to the product, the conjugation depicted being proposed to account for its yellow colour. The structure was also in line with that of the dipyridylmethane (IX) prepared by the interaction of 2-pyridone and 2-picoline in the presence of phosphorus pentachloride.[6] Nuclear magnetic resonance studies now in progress, however, have thrown doubt on the structure (VIIIa; R = Cl) and our colleague Dr. G. R. Bedford has proposed the formulation (VIIIb; R = Cl). This strong possibility is being further investigated by him and will be reported later. The failure to achieve condensation of 3-chloro-6-methylpyridazine or 3,6-dichloropyridazine with 2-picoline or with 1,2-dimethylpyridazinium iodide in phosphoryl chloride at temperatures up to 150° also suggested a more complex course for the self-condensation of the chloromethyl compound. In the meantime, the chemistry of compound (VIII; R = Cl) has been examined further. The chlorine atom was labile and readily replaced by mercapto- (VIII; R = SH), piperidino- (VIII; R = NC_5H_{10}), 2-hydroxyethylamino- (VIII; R = NH·$[CH_2]_2OH$), and dimethylamino-residues (VIII; R = NMe_2). A monoquaternary salt was prepared from compound (VIII; R = Cl) and methyl iodide in nitrobenzene at room

[5] Overend and Wiggins, *J.*, 1947, 242; Leanza, Becker, and Rogers, *J. Amer. Chem. Soc.*, 1953, **75**, 4086.

[6] Moir, *J.*, 1925, 2338.

temperature. In the belief that the methylene group of the resultant compound, no matter which nitrogen was quaternised, would be considerably activated, an attempt was made to effect a reaction with *p*-anisaldehyde. A crystalline substance, m. p. 200° (decomp.), was formed in boiling water, having the empirical formula $C_{19}H_{20}ClIN_4O_2$, but the absence of a hydroxyl band, and the presence of an αβ-unsaturated carbonyl band, in the infrared spectrum indicated an addition compound. This view was substantiated by the fact that the compound readily afforded a semicarbazone identical with that from anisaldehyde. Finally, the ready quaternisation of several simple 3,6-disubstituted pyridazines has to be recorded, for example, 3-methyl-6-piperidino- and 3,6-bisdimethylamino-pyridazine, by the action of methyl iodide in benzene or ethyl acetate at room temperature. No work has been done to determine the point of entry of the methyl group. 3-Chloro-6-methylpyridazine has been reported as giving a 3-chloro-1,6-dimethylpyridazinium iodide,[7] but in our hands quaternisation with an excess of methyl iodide at room temperature gave a product that was analytically consistent with 3-iodo-1,6-dimethylpyridazinium iodide. 3,6-Dichloropyridazine failed to quaternise with methyl iodide.

Experimental

Ultraviolet absorption spectra were measured for methanol solutions, unless otherwise stated, on an Optica double-beam spectrophotometer.

3-Amino-s-triazolo[4,3-b]*pyridazine* (III; R = H).—3-Amino-6-chloro-*s*-triazolo[4,3-*b*]-pyridazine (1 g.) in methanol (40 ml.) and ammonia (1·2 ml.; *d* 0·88) was hydrogenated over 5% palladium–charcoal (0·2 g.) during 20 min. The catalyst was filtered off. The filtrate, on concentration, afforded the *product* (0·7 g.) as yellow prisms (from ethanol), m. p. 257°, $\lambda_{max.}$ (in H_2O) 186, 222, and 346 mμ (ε 7700, 3480, and 1380) (Found: C, 44·6; H, 4·4; N, 51·4. $C_5H_5N_5$ requires C, 44·4; H, 3·7; N, 51·8%).

3-Amino-6-chloro-s-triazolo[4,3-b]*pyridazine* (III; R = Cl).—Cyanogen chloride (9·3 g.) was passed into a solution of 3-chloro-6-hydrazinopyridazine (20 g.) and sodium acetate crystals (37·6 g.) in water (200 ml.) and acetic acid (70 ml.), at 0—5°. After 2 hr. the yellow precipitate of the *product* (21 g.) was collected and washed with water. It was sparingly soluble in common organic solvents, but formed yellow prisms, m. p. >350°, from a large volume of aqueous ethanol, and had $\lambda_{max.}$ 242 and 376 mμ (ε 19,800 and 1750) (Found: C, 35·9; H, 2·8; N, 41·3. $C_5H_4ClN_5$ requires C, 35·4; H, 2·4; N, 41·3%).

3-Amino-6-methoxy-s-triazolo[4,3-b]*pyridazine* (III; R = OMe).—3-Amino-6-chloro-*s*-triazolo[4,3-*b*]pyridazine (7·4 g.) and a solution of sodium methoxide (from sodium, 2 g.) in methanol (55 ml.) were heated in a sealed tube at 100° for 5 hr. On cooling, the yellow precipitate of the *methoxy-derivative* was collected. It crystallised from ethanol in pale yellow prismatic needles (4·6 g.), m. p. *ca.* 325° (decomp., sintering at 223°), $\lambda_{max.}$ 235, 276, 288 sh, and 343 mμ (ε 15,400, 2640, 2215, and 2880) (Found: C, 43·9; H, 4·0; N, 42·4. $C_6H_7N_5O$ requires C. 43·6; H, 4·2; N, 42·4%).

3-Amino-6-propoxy-s-triazolo[4,3-b]*pyridazine* (III; R = OPr^n).—3-Amino-6-chloro-*s*-triazolo[4,3-*b*]pyridazine (7·5 g.) was refluxed for 5½ hr. in propan-1-ol (175 ml.) in which sodium (2·0 g.) had been dissolved. The insoluble solid which remained after evaporation of the solvent and addition of water (10 ml.) was combined with the residue extracted from the aqueous filtrate by chloroform; it crystallised from butyl acetate. The *propoxy-derivative* was obtained as pale yellow crystalline flakes (4·6 g.), m. p. 155—156°, $\lambda_{max.}$ 235, 271, 288, and 346 mμ (ε 14,920, 2970, 2570, and 2990) (Found: C, 49·8; H, 5·7; N, 36·5. $C_8H_{11}N_5O$ requires C, 49·7; H, 5·7; N, 36·3%).

3-Amino-6-hydrazino-s-triazolo[4,3-b]*pyridazine* (III; R = $NH{\cdot}NH_2$).—3-Amino-6-chloro-*s*-triazolo[4,3-*b*]pyridazine (3 g.), 100% hydrazine hydrate (6·6 ml.), and ethanol (6·6 ml.) were heated under reflux for 1½ hr. The crystalline product (2·9 g.) was sparingly soluble in common solvents and was purified by the slow addition of dilute aqueous ammonia to a clarified solution in dilute hydrochloric acid. The *hydrazinopyridazine* formed colourless needles, m. p. 293° (decomp.), $\lambda_{max.}$ (in H_2O) 192, 198 sh, 235, and 298 mμ (ε 19,700, 19,600, 15,700, and 5150) (Found: C, 35·9; H, 4·4; N, 59·5. $C_5H_7N_7$ requires 36·4; H, 4·3; N, 59·4%).

[7] Duffin and Kendall, *J.*, 1959, 3789.

3-*Amino*-6-*piperidino*-s-*triazolo*[4,3-b]*pyridazine* (III; R = $N[CH_2]_5$).—3-Amino-6-chloro-*s*-triazolo[4,3-*b*]pyridazine (3 g.), piperidine (11·5 ml.), and water (6 ml.) were refluxed for 1 hr. The precipitate which was formed on partial evaporation of the solvent was treated with water (25 ml.) and filtered off (2·5 g.). A further crop (1·1 g.) was obtained on extraction of the original mother-liquors with chloroform. The *piperidino-derivative* crystallised from water in pale yellow prisms, m. p. 243°, $\lambda_{max.}$ 192 sh, 199, 246, and 293 mμ (ε 18,450, 18,400, 19,000, and 5750) (Found: C, 55·1; H, 6·5; N, 39·0. $C_{10}H_{14}N_6$ requires C, 55·0; H, 6·5; N, 38·5%).

3-*Amino*-6-3′-*dimethylaminopropylamino*-s-*triazolo*[4,3-b]*pyridazine* (III; R = $NH{\cdot}[CH_2]_3{\cdot}NMe_2$).—3-Amino-6-chloro-*s*-triazolo[4,3-*b*]pyridazine (1 g.) and 3-dimethylaminopropylamine (8 ml.) were heated under reflux for 1 hr. The cooled solution was adjusted to pH 10 with 5N-sodium hydroxide, a solid being precipitated. After initial extraction with ether to remove the excess of amine, the mixture was extracted with butan-1-ol. Evaporation of butanol gave the *base* (1·2 g.), which crystallised from ethanol–ethyl acetate in pale yellow needles, m. p. 157°, $\lambda_{max.}$ 239 and 307 mμ (ε 16,800 and 5850) (Found: C, 51·2; H, 7·5; N, 41·7. $C_{10}H_{17}N_7$ requires C, 51·0; H, 7·3; N, 41·7%).

6-*Methoxy*-3-*p*-*nitrobenzenesulphonamido*-s-*triazolo*[4,3-b]*pyridazine*.—*p*-Nitrobenzenesulphonyl chloride (6·8 g.), dissolved in dry pyridine (63 ml.), was added to a stirred suspension of 3-amino-6-methoxy-*s*-triazolo[4,3-*b*]pyridazine (4·6 g.) in dry pyridine (90 ml.) at *ca.* 10°. After the mixture had been kept at room temperature for 20 hr., the excess of pyridine was evaporated under reduced pressure. The residue was treated with water (30 ml.) containing sodium hydroxide (2·4 g.) and filtered off. The filtrate was adjusted to pH 4 with hydrochloric acid, and the crude *sulphonamide* (6 g.), which separated on cooling, was recrystallised from acetone, to yield pale yellow hexagonal plates (3·6 g.), m. p. 255° (Found: C, 41·2; H, 2·9; N, 24·0. $C_{12}H_{10}N_6O_5S$ requires C, 41·1; H, 2·9; N, 24·0%).

6-*Methoxy*-3-*sulphanilamido*-s-*triazolo*[4,3-b]*pyridazine*.—The last-mentioned compound (3·5 g.) in methanol (200 ml.) containing sodium hydroxide (0·5 g.) was hydrogenated over Raney nickel during 2½ hr. The solution obtained after filtration was acidified (pH 5) with hydrochloric acid, and the solvent was removed under reduced pressure. The residue was treated with water (15 ml.) and collected. The *sulphanilamide* (2·3 g.) formed orange prisms (from methanol), m. p. 222—223° (Found: C, 45·0; H, 4·2; N, 26·2. $C_{12}H_{12}N_6O_3S$ requires C, 45·0; H, 3·8; N, 26·2%).

3-*Amino*-6-*methyl*-s-*triazolo*[4,3-b]*pyridazine* (VII; R = NH_2).—Cyanogen chloride (1·6 g.) was passed into a solution of 3-hydrazino-6-methylpyridazine (2·9 g.) and sodium acetate crystals (6·4 g.) in water (15 ml.) and acetic acid (6 ml.) at 0—5°. After 1 hr. the precipitated crude *base* (2·2 g.) was collected; it crystallised from methanol in bright yellow prisms, m. p. 287°, $\lambda_{max.}$ 230 and 354 mμ (ε 20,400 and 1820) (Found: C, 47·7; H, 5·3; N, 47·0. $C_6H_7N_5$ requires C, 48·3; H, 4·7; N, 47·0%).

3-*Mercapto*-6-*methyl*-s-*triazolo*[4,3-b]*pyridazine* (VII; R = SH).—A mixture of 3-hydrazino-6-methylpyridazine (6·7 g.) in pyridine (50 ml.) and carbon disulphide (6·6 ml.) was kept at 60° for 1 hr. After removal of the excess of carbon disulphide, the mixture was finally heated under reflux for 2 hr. The crystalline precipitate (7·7 g.) of the *thiol* was collected, washed with ethanol, and recrystallised from ethanol, to yield yellow prisms, m. p. 260°, $\lambda_{max.}$ 204 sh, 232, 253, 275, and 371 mμ (ε 6420, 11,400, 11,300, 11,000, and 1195) (Found: C, 43·7; H, 3·9; N, 33·7; S, 19·1. $C_6H_6N_4S$ requires C, 43·4; H, 3·6; N, 33·7; S, 19·3%).

6-*Methyl*-3-*sulphamoyl*-s-*triazolo*[4,3-b]pyridazine (VII; R = $SO_2{\cdot}NH_2$).—Chlorine (0·35 g.) was bubbled into a suspension of 3-mercapto-6-methyl-*s*-triazolo[4,3-*b*]pyridazine (0·25 g.) in chloroform (5 ml.) and water (3 ml.) at $<10°$. After the solid had dissolved, the chloroform layer was separated, washed with ice-cold water (3 ml.), and dried ($CaCl_2$). The residue obtained on evaporation of the solvent gave the crystalline *sulphonamide* (0·1 g.), m. p. 217° after stirring with strong aqueous ammonia. It formed colourless prisms, m. p. 217° from ethanol (Found: C, 34·0; H, 3·4; N, 32·4. $C_6H_7N_5O_2S$ requires C, 33·8; H, 3·3; N, 32·9%).

Condensation Product (*presumed* VIII; R = Cl) *of* 3-*Chloro*-6-*methylpyridazine*.—(*a*) 3-Methyl-6-pyridazone (40 g.) and phosphoryl chloride (160 ml.) were heated under reflux for 30 min. The excess of phosphoryl chloride was distilled off under reduced pressure and the residue was added to ice. Concentrated aqueous sodium hydroxide was added to give alkalinity to Brilliant Yellow. The precipitate was filtered off, washed with water, and extracted with ether (3 × 100 ml.). The insoluble residue (10 g.; m. p. 210°) of the condensation *product* gave prismatic needles, m. p. 220°, from methanol (Found: C, 54·3; H, 4·1; N, 25·6; Cl, 15·7.

$C_{10}H_9ClN_4$ requires C, 54·4; H, 4·1; N, 25·4; Cl, 16·1%). It had $\nu_{max.}$ 2970m, 1618w, 1570m, 1536w, 1453vs, 1393s, 1380s, 1340w, 1307w, 1260m, 1192s, 1177s, 962m, and 887m cm.$^{-1}$, τ (Me_4Si standard) 2·41, 3·66 (in Me_2SO), 6·83, 7·22 (in $CHCl_3$) (relative areas 1 : 1 : 4 : 3).

(*b*) 3-Chloro-6-methylpyridazine (16 g.) and phosphoryl chloride (56 ml.) were heated under reflux for 3½ hr. The mixture was worked up as described above, to give the crude product (13·6 g.; m. p. 206°), and finally yellow prismatic needles (10 g.), m. p. 218°, from methanol.

Reaction Products of Compound (VIII; R = Cl) *with Various Reagents.*—(*a*) The chloro-compound (0·54 g.) was refluxed for 2 hr. with 40% aqueous dimethylamine (8 ml.). Addition of sodium hydroxide and extraction with chloroform gave a *dimethylamino-derivative* (0·4 g.) which afforded orange crystals (from benzene), m. p. 193° (Found: C, 62·7; H, 6·5; N, 30·0. $C_{12}H_{15}N_5$ requires C, 62·8; H, 6·6; N, 30·5%). (*b*) A similar experiment with the chloro-compound (3 g.) and piperidine (16·2 ml.) in water (3·6 ml.) gave the *piperidino-derivative* as bright yellow crystals, m. p. 163—164°, from ethyl acetate–ethanol (Found: C, 67·3; H, 7·3; N, 26·2. $C_{15}H_{19}N_5$ requires C, 67·0; H, 7·1; N, 26·0%). (*c*) The chloro-compound (3·9 g.), refluxed in monoethanolamine (15·6 ml.), similarly gave the 2-*hydroxyethylamino-derivative* as yellow prisms, m. p. 179°, from ethanol (Found: C, 58·7; H, 6·5; N, 28·7. $C_{12}H_{15}N_5O$ requires C, 58·7; H, 6·1; N, 28·6%). (*d*) The chloro-compound (4 g.) was refluxed for 2 hr. in a solution of potassium hydroxide (4·1 g.) and methanol (40 ml.), previously saturated with hydrogen sulphide. Evaporation of the solvent and addition of dilute aqueous acetic acid gave the crude *thiol* (4 g.), which was purified [crimson-coloured rhombs, m. p. 130° (decomp.)] by reprecipitation with acetic acid from a clarified solution in dilute aqueous sodium carbonate (Found: C, 54·1; H, 4·9; S, 14·7. $C_{10}H_{10}N_4S$ requires C, 55·0; H, 4·6; S, 14·6%).

Miscellaneous Pyridazines and their Quaternisation Products.—(*a*) 3-Chloro-6-methylpyridazine (2·35 g.) and 40% aqueous dimethylamine (7·6 ml.), were heated together in a sealed tube for 10 hr. at 180°. Evaporation of the solvent from a chloroform extract of the resultant solution gave a gum, which yielded 3-*dimethylamino*-6-*methylpyridazine* as colourless rectangular plates (1·1 g.), m. p. 65—66°, from benzene–light petroleum (b. p. 40—60°) (Found: C, 61·3; H, 8·0; N, 30·1. $C_7H_{11}N_3$ requires C, 61·3; H, 8·1; N, 60·6%). (*b*) 3-Chloro-6-methylpyridazine (7 g.), piperidine (21·7 ml.), and water (4·8 ml.), refluxed for 17 hr. and worked up similarly, gave 3-*methyl*-6-*piperidinopyridazine* as colourless needles, m. p. 63—65°, from light petroleum (b. p. 40—60°) (Found: C, 68·2; H, 8·6; N, 23·3. $C_{10}H_{15}N_3$ requires C, 67·8; H, 8·5; N, 23·7%). A *methiodide* was obtained by leaving a mixture of the amine (5 g.) and methyl iodide (2·2 ml.) in ethyl acetate (30 ml.) overnight at room temperature. The solid which separated formed yellow-orange prisms, m. p. 125—126°, from ethanol–ethyl acetate (Found: C, 41·4; H, 5·8; N, 13·2. $C_{11}H_{18}IN_3$ requires C, 41·4; H, 5·6; N, 13·1%). (*c*) 3,6-Bisdimethylaminopyridazine (2 g.) and methyl iodide (2·2 ml.), kept overnight in benzene (15 ml.), gave a *methiodide* which formed yellow needles, m. p. 188°, from methanol (Found: C, 35·2; H, 5·6; N, 18·2. $C_9H_{17}IN_4$ requires C, 35·1; H, 5·5; N, 18·2%). (*d*) 3-Chloro-6-methylpyridazine (3 g.) and methyl iodide (6 ml.) were refluxed in benzene (15 ml.) for 40 min. The precipitate of the crystalline *methiodide* of 3-*iodo*-6-*methylpyridazine* gave yellow prisms, m. p. 160°, when recrystallised from methanol (Found: C, 20·1; H, 2·1; N, 7·8; I, 69·9. $C_6H_8I_2N_2$ requires C, 19·9; H, 2·2; N, 7·7; I, 70·1%). (*e*) The base (VIII; R = Cl) (2 g.), and methyl iodide (2 ml.), were kept in nitrobenzene (17 ml.) overnight. The crystalline precipitate yielded the *methiodide* as orange-brown crystals, m. p. 223°, from ethanol (Found: C, 36·4; H, 3·1; N, 15·3. $C_{11}H_{12}ClIN_4$ requires C, 36·4; H, 3·3; N, 15·3%).

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