Heterocyclic Imines and Amines. Part XIII.[1] 3,6-Dihydrazinopyridazine and the Nature of the Reaction between 3,6-Dimethoxypyridazine and Hydrazine

By **J. A. Elvidge** * and **J. A. Pickett**, Joseph Kenyon Laboratory, University of Surrey, Guildford, Surrey

A route to 3,6-dihydrazinopyridazine from dithiomaleohydrazide is confirmed and improved and the product now characterised. Possible alternative routes, *e.g.* from 3,6-dichloro-, -diphenoxy-, and -dimethylthio-pyridazine, yielded the monohydrazino-compounds, whilst 3,6-di-*p*-tolylsulphonyloxypyridazine with hydrazine afforded maleodihydrazide. A previously described method from 3,6-dimethoxypyridazine and hydrazine is shown to yield a mixture of oxygen-containing products, deduced as comprising 6-hydrazino-5-amino-2,3-dihydro-3-oxopyridazine together with some of the 6-methoxy-analogue.

3,6-DIHYDRAZINOPYRIDAZINE (8) was first reported [2] as the product, m.p. 193—195°, from interaction of hydrazine hydrate with dithiomaleohydrazide (1), and then later [3] as having m.p. 220° and being more conveniently prepared from 3,6-dimethoxypyridazine (9). In neither report was the composition of the base (8) established.

The seemingly more-attractive second route was found to give an oxygen-containing product. Various results eventually indicated that this was the 6-hydrazino-derivative (6) of 5-amino-2,3-dihydro-3-oxopyridazine mixed with some of the 6-methoxy-analogue (7). In the meantime other possible routes to the required base (8) were examined, and this led to confirmation of the first route and description (above) and improved yield.

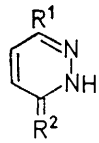
By the action of methanolic hydrazine hydrate on 3,6-dichloropyridazine (10), readily available from maleohydrazide (2), the mono-hydrazino-mono-chloro compound (11) was obtained. Surprisingly, this resisted further treatment with anhydrous hydrazine under vigorous conditions. 3,6-Diphenoxypyridazine (12) likewise gave a mono-substitution product (13) but this was accompanied by traces of a second compound which with acetone yielded the di-isopropylidene derivative (14; $R^3 = R^4 = Me$) of 3,6-dihydrazinopyridazine, as shown by subsequent comparison with an authentic sample. Attempts to increase the yield of dihydrazino-product from (12) by using the better nucleophiles anhydrous hydrazine and sodiohydrazine failed and so an intermediate with a better leaving group than phenoxyl was sought. To this end, maleohydrazide was treated with tosyl chloride in pyridine. This gave in the hot the known mono-*O*- (3) and then in the cold the required di-*O*-tosyl derivative (15), the constitution of the latter being supported by the absence of carbonyl absorption in the i.r. Interaction of the di-*O*-tosyl compound (15) with hydrazine did not however proceed in the manner hoped for but gave maleodihydrazide (5) and toluene-*p*-sulphonohydrazide. Evidently the nucleophile attacked the sulphonyl groups, rather than

[1] Part XII, N. R. Barot and J. A. Elvidge, *J.C.S. Perkin I*, 1972, 1009.

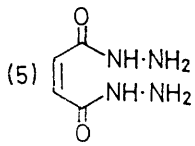
[2] J. Druey, K. Meier, and K. Eichenberger, *Helv. Chim. Acta*, 1954, **37**, 121.

[3] T. V. Gortinskaya and M. N. Shchukina, *Zhur. obshchei Khim.*, 1960, **30**, 1518.

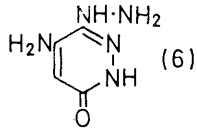
the 3- and 6-positions of the ring, and so gave the last-mentioned compound together with maleohydrazide (2) which would then yield the dihydrazide (5). This last stage, (2) ⟶ (5), was separately demonstrated. Maleodihydrazide (5), which has not hitherto been described, cyclised at once to maleohydrazide (2) in the presence



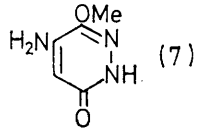
(1) R^1 = SH, R^2 = S
(2) R^1 = OH, R^2 = O
(3) R^1 = OTs*, R^2 = O
(4) R^1 = OEt, R^2 = S



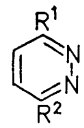
(5)



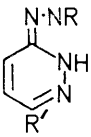
(6)



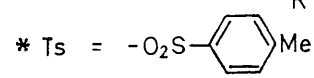
(7)



(8) R^1 = R^2 = NH·NH_2
(9) R^1 = R^2 = OMe
(10) R^1 = R^2 = Cl
(11) R^1 = NH·NH_2, R^2 = Cl
(12) R^1 = R^2 = OPh
(13) R^1 = NH·NH_2, R^2 = OPh
(14) R^1 = R^2 = NH·N:CR^3R^4
(15) R^1 = R^2 = OTs*
(16) R^1 = OEt, R^2 = NH·N:CMe_2
(17) R^1 = R^2 = SMe
(18) R^1 = NH·NH_2, R^2 = SMe
(19) R^1 = R^2 = NH·NH·CO_2Et
(20) R^1 = R^2 = N:N·CO_2Et



(21)

* Ts = 

of acids: even attempted condensation with benzaldehyde gave maleohydrazide, together with benzal azine, a marked contrast with the (normal) behaviour of fumarodihydrazide.[4]

Repetition of Druey, Meier, and Eichenberger's preparation of dithiomaleohydrazide[2] (1) from 3,6-dichloropyridazine (10) and ethanolic potassium hydrogen sulphide in a sealed tube at 140—150° gave only a 30% yield, there being formed rather more (42%) of 6-ethoxy-2,3-dihydro-3-thioxopyridazine (4). The latter reacted with hydrazine hydrate to give 3-ethoxy-6-hydrazinopyridazine which was characterised as the isopropylidene derivative (16). Ninety per cent yields of dithiomaleohydrazide (1) were then achieved by treating 3,6-dichloropyridazine (10) with thiourea in ethanol at 65° and decomposing the resulting bis-isothiouronium salt with aqueous sodium hydrogen carbonate. Methylation gave 3,6-di(methylthio)pyridazine (17) which with hydrazine afforded 3-hydrazino-6-methylthiopyridazine (18). As in previous cases, only mono-substitution appeared to occur. However, from dithiomaleohydrazide itself (1) and hydrazine hydrate, the required 3,6-dihydrazinopyridazine (8) was obtained,[2] now in improved overall yield from (10).

The constitution of the dihydrazinopyridazine (8) was established with the aid of elementary analyses, mass spectrum, and i.r., u.v., and ^{1}H n.m.r. spectra. As expected, the compound condensed with acetone to give the di-isopropylidene derivative (14; R^3 = R^4 = Me) and with glyoxylic acid to give 3,6-di(carboxymethylenehydrazino)pyridazine (14; R^3 = H, R^4 = CO_2H). Ethyl chloroformate acylated the base to form 3,6-di(ethoxycarbonylhydrazino)pyridazine (19), and oxidation of this with nitric acid[5] produced a reddish oil which had i.r. and mass spectral characteristics in accord with the expected bis-azo-structure (20).

From u.v. (aqueous solution) and i.r. (solid state) studies, it has been concluded[6,7] that maleohydrazide (2) and dithiomaleohydrazide (1) exist predominantly in the 2,3-dihydro-ring form (as shown). Each compound absorbs in the u.v. near 305 nm (Table 1). Those non-

TABLE 1

$\lambda_{max.}$/nm (ε) for 3,6-disubstituted pyridazines in MeOH or *H_2O

(1) *	208	(15,000)	(12)	286·5	(2540)
	308	(26,000)	(13)	241	(14,800)
(2) *	206	(13,700)		323	(1480)
	304	(1920)	(14,	284	(32,900)
(8)	245·5	(14,560)	R^3 = R^4 = Me)	354	(1760)
	339	(1370)	(17)	270	(21,790)
(9)	286·5	(2080)	(18)	259	(16,380)
(10)	270	(1200)		332	(1350)
(11)	247	(10,330)			
	324	(1270)			

tautomeric 3,6-di-substituted derivatives with true pyridazine-ring structures (9), (10), (12), and (17) absorb at 270—280 nm. The potentially tautomeric mono-hydrazino-compounds (11), (13), and (18), however, absorb in the 320—330 nm region, and so, allowing for the auxochromic effect of the nitrogenous substituent, it appears that these compounds exist preferentially in the hydrazono-dihydro-ring form (21; R = H_2, R′ = Cl, OPh, and SMe, respectively). Similarly, it appears from the absorption at 339 nm that the dihydrazinopyridazine (8) probably exists in the dihydro-ring form (21; R = H_2, R′ = NH·NH_2) in methanol. However, the ^{1}H n.m.r. spectrum of the compound in deuterium oxide is that of a symmetrically substituted pyridazine, there being one sharp singlet from the two ring protons. The di-isopropylidene derivative (14; R^3 = R^4 = Me) also shows only a single line in the n.m.r. spectrum from the ring protons and only one pair of singlets from the *syn*- and *anti*-methyl groups instead of the more complicated spectrum expected from the structure (21; R = CMe_2; R′ = NH·N:CMe_2). Maleohydrazide (2) in dimethyl sulphoxide likewise shows a single line from the two, apparently non-equivalent ring-protons. Probably there is sufficiently rapid tautomerism in solution at ordinary temperature to make these dihydro-ring structures effectively symmetrical on the n.m.r. time-scale.

[4] R. Radenhausen, *J. prakt. Chem.*, 1895, **52**, 433.
[5] T. Curtius and K. Heidenreich, *Ber.*, 1894, **27**, 773.
[6] D. M. Miller and R. W. White, *Canad. J. Chem.*, 1956, **34**, 1510.
[7] Yu. N. Sheinker, T. V. Gortinskaya, and T. P. Sycheva, *Zhur. fiz. Khim.*, 1957, **31**, 599.

Although Gortinskaya and Shchukina[3] claimed that the product (m.p. 220°) from 3,6-dimethoxypyridazine (9) and hydrazine hydrate was 3,6-dihydrazinopyridazine, their evidence was slender. Satisfactory C and H figures were quoted for a ' hydrochloride hydrate ', but no analysis of the base was obtained, apparently because its recrystallisation was not achieved. Moreover the base was reported to condense with only 1 molecular proportion of an aldehyde or ketone, curious behaviour for a dihydrazino-compound. We found that the so-called hydrochloride hydrate failed to lose water on being heated to its m.p. (232°) and that the nitrogen content was some 10% lower than calculated. Furthermore, the base showed strong carbonyl absorption at 1700 cm^{-1} and its mass spectrum indicated a molecular weight of 141, instead of 140 as required by $C_4H_8N_6$. Combustion analysis results suggested the formula $C_4H_7N_5O$—for which M is indeed 141—but the carbon values were consistently high and the nitrogen low, whilst the hydrogen was correct. The figures were almost unaffected by repeated crystallisation of the material—which proved possible from water and raised the m.p. to 243—245°. Although the material moved as a single spot on a t.l.c. plate, the other findings suggested that it was a mixture or perhaps a molecular compound. If there were two components, these would necessarily each be compounds with $M = 141$ and 7 hydrogen atoms per molecule. That this was indeed so emerged from examination of deuteriated material.

The mass spectrum of a sample twice recrystallised from deuterium oxide showed two molecular-ion peaks, at *m/e* 147 and 144, the latter being the smaller. This confirmed that the original material comprised two components and showed that the main one had 6 exchangeable protons per molecule and the other only 3. The ^1H n.m.r. spectrum (D_2O solvent) showed a line at τ 3·85 and another, which had only *ca.* 2/3rd. the intensity, at τ 6·27. Hence it was concluded that the main component, $C_4H_7N_5O$ (with 6 exchangeable protons), had a single ring-proton and that the minor component still had a methoxy-group present and was necessarily $C_5H_7N_3O_2$. As this had only 3 exchangeable protons, there was also a ring-proton present. The identity of the ring-proton chemical shifts indicated identical immediate environments and so closely similar structures for the two components.

Finally, the major component was isolated as fine needles, m.p. 249° (decomp.) by causing it to crystallise from anhydrous hydrazine by addition of methanol, and the composition was confirmed as $C_4H_7N_5O$. The presence of amino-groups and of an amide carbonyl was shown by the i.r. spectrum, and of a single hydrazino-residue by the condensation with *p*-hydroxybenzaldehyde to give only a monohydrazone $C_{11}H_{11}N_5O_2$. In dimethyl sulphoxide this derivative gave a well-resolved ^1H n.m.r. spectrum of 10 lines, interpretable in terms of the structure (6; $-NH\cdot N{=}CH\cdot C_6H_4\cdot OH$ in place of $-NH-NH_2$). There was a low-field, slightly-broadened singlet at τ −1·83 from the amide proton, comparable to that from maleohydrazide (Table 2). Singlets at τ −0·05, 0·33, and 2·13 were from the hydrazone NH, the phenolic hydroxy and the methine proton of the aldehyde

TABLE 2

^1H Chemical shifts for 3,6-disubstituted pyridazines as 5—10% solutions, measured from internal Me_4Si or $Me_3Si[CH_2]_3SO_3Na$ as appropriate

Compound	Solvent	τ, splitting (J Hz)	Assignment
(1)	Me_2SO	3·07s	4-, 5-H
		2·20brs	NH,
(2)	Me_2SO	3·00s	4-, 5-H
		−1·50brs	NH, OH
(3)	$CDCl_3$	7·55s	Me
		3·03d, 2·74d (9)	4-H, 5-H
		2·63d, 2·17d (8·5)	3′-, 5′-H, 2′-, 6′-H
		−1·50brs	NH
(4)	$CDCl_3$	8·61t, 5·74q (7)	Me, CH_2 of EtO
		3·24d, 2·40d (9)	5-H, 4-H
		−2·20brs	NH
(8)	D_2O	3·00s	4-, 5-H
(9)	$CDCl_3$	5·95s	2 × MeO
		3·01s	4-, 5-H
(10)	$CDCl_3$	2·43s	4-, 5-H
(11)	D_2O	2·88d*, 2·55d (9)	5-H, 4-H
(13)	D_2O(at 90°)	2·74 *ca.* s	Ph
		2·84d*, 2·42d (7)	4-H, 5-H
(14, $R^3 = R^4 = Me$)	$CDCl_3$	8·09s, 7·96s	Me_2
		2·47s	4-, 5-H
		2·25brs	2 × NH
(15)	$CDCl_3$	7·58s	2 × Me
		2·53s	4-, 5-H
		2·69d, 2·15d (8·5)	3′-, 5′-H, 2′-, 6′-H
(16)	$CDCl_3$	8·59t, 5·53q (7)	Me, CH_2 of EtO
		8·08s, 7·97s	Me_2
		3·12d, 2·46d* (9)	4-H, 5-H
		2·20brs	NH
(17)	$CDCl_3$	7·31s	2 × MeS
		2·88s	4-, 5-H

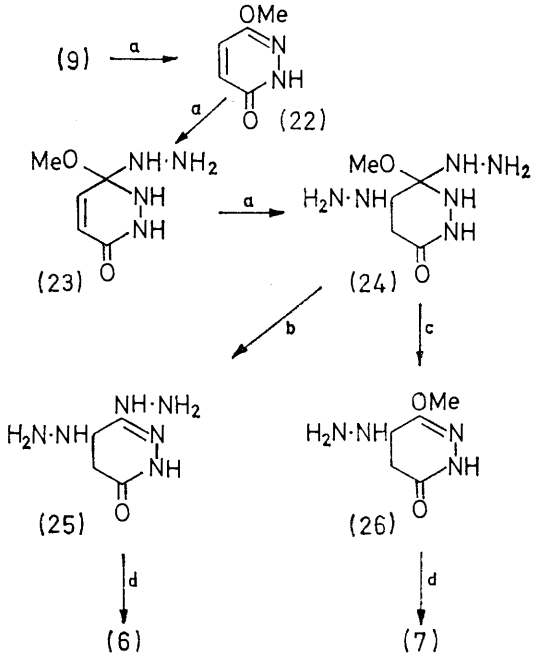
* Slightly broadened by adjacent nitrogenous substituent.

residue, respectively, shifts similar to those found in analogous compounds.[8] There was a 4-proton AB quartet from the protons of the *p*-disubstituted benzene ring, a sharp singlet from the pyridazine ring CH at τ 3·4 and a broadened 2-proton signal at τ 3·72 from the amino-group. The structure of the parent base was therefore (6), the relative positions of the substituents following from the likely mechanism of the compound's formation.

Because 3,6-dimethoxypyridazine (9) was stable to hot water, it seemed unlikely that the loss of methoxyl and appearance of an amidic carbonyl group in the end product (6) occurred by hydrolysis. It was more

[8] *Cf.* G. J. Karabatsos and R. A. Taller, *J. Amer. Chem. Soc.*, 1963, **85**, 3624; T. W. Milligan and B. C. Minor, *J. Org. Chem.*, 1962, **27**, 4663; N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, ' NMR Spectra Catalog,' Varian Associates, Palo Alto, 1962, **1**, No. 233; A. L. Porte, H. S. Gutowsky, and I. M. Hunsberger, *J. Amer. Chem. Soc.*, 1960, **82**, 5057.

likely [9] that the hydrazine was methylated by the methoxy-compound (9) which would then be converted into the mono-amide (22). Analogy with dimethyl sulphate suggested that the remaining 6-methoxy in (22) would not effect further methylation. However, nucleophilic attack by hydrazine at the 6-position could yield an intermediate (23) which would add hydrazine to give (24), similarly to αβ-unsaturated esters.[10] Subsequent elimination of methanol from (24) would then yield a hydrazino-dihydropyridazine (25) which could



a; $NH_2 \cdot NH_2$. b; −MeOH. c; $-NH_2 \cdot NH_2$. d; $-NH_3$.

aromatise [11] by internal hydrogen transfer to give ammonia and the aminopyridazine (6). Alternative elimination of hydrazine from (24) to give (26) and aromatisation would yield a methoxy-compound $C_5H_7N_3O_2$ which would have the pyridazine structure (7). This is very probably the structure of the minor component of the mixture produced from 3,6-dimethoxypyridazine and hydrazine hydrate.

EXPERIMENTAL

I.r. spectra were measured on Nujol mulls, with a Unicam SP 200 spectrophotometer. U.v. and ^1H n.m.r. spectra were recorded with a Unicam SP 800B and a Perkin-Elmer R10 (60 MHz) instrument respectively.

Maleohydrazide [12,13] (2) was treated with phosphorus oxychloride to give 3,6-dichloropyridazine [13] (10) which was sublimed at 100°/10 mmHg. Refluxing with methanolic hydrazine hydrate for 24 h then gave 3-chloro-6-hydrazinopyridazine (11) (85%), m.p. 138—139° (from water) (lit.,[2] 137—138°) (Found: C, 33·2; H, 3·6; Cl, 24·4; N, 38·6. Calc. for $C_4H_5ClN_4$: C, 33·2; H, 3·5; Cl, 24·6; N, 38·8%), *m/e* 146, 144 (1 : 3), $\nu_{max.}$ 3370w and 3300s (NH_2, NH), 1620w, 1580s, 1500, 1280w, 1190w, 1160w, 1150, 1120w, 1070, 1020w, 960, and 840 cm^{-1}. The same product (75%) resulted from refluxing 3,6-dichloropyridazine in anhydrous hydrazine under nitrogen for 24 h. 3-Chloro-6-hydrazinopyridazine was recovered after prolonged refluxing under nitrogen with anhydrous hydrazine containing sodium hydrazide (prepared from sodamide).

3-Hydrazino-6-phenoxypyridazine (13).—3,6-Diphenoxypyridazine [2] (4 g) (prepared using sodium phenolate derived from phenol and sodamide) was refluxed with hydrazine hydrate (30 ml) for 4·5 h. Cooling, and concentrating, afforded *3-hydrazino-6-phenoxypyridazine* (2 g, 65%) which was recrystallised from 2N-sodium hydroxide and then from water to give needles, m.p. 128° (Found: C, 59·3; H, 5·1; N, 27·8. $C_{10}H_{10}N_4O$ requires C, 59·4; H, 5·0; N, 27·7%), *m/e* 202; $\nu_{max.}$ 3270s and 3220 (NH_2, NH), 1620, 1595, 1570, 1500, 1330w, 1275s, 1250w, 1200, 1180w, 1160, 1100w, 1050w, 1030, 1000w, 875, 840, 740, and 680 cm^{-1}. Evaporation of the reaction mother-liquors gave an oil (*ca.* 1 g) which with acetone overnight afforded yellow crystals (0·5 g), identified as 3,6-di-(isopropylidenehydrazino)pyridazine (see later) by the i.r. spectrum and m.p. and mixed m.p. 240° (decomp.).

3-Hydrazino-6-phenoxypyridazine was largely recovered (95%) after 12 h under reflux with an excess of hydrazine hydrate. From the mother liquors (as above) only a trace of 3,6-di-(isopropylidenehydrazino)pyridazine was obtained: no better yield resulted from use of anhydrous hydrazine or hydrazine containing sodium hydrazide.

3,6-Di-p-tolylsulphonyloxypyridazine (15).—Maleohydrazide in boiling pyridine with toluene-*p*-sulphonyl chloride gave 2,3-dihydro-3-oxo-6-*p*-tolylsulphonyloxypyridazine [14] (3), m.p. 162° (from ethanol) (Found: C, 49·5; H, 3·9; N, 10·4. Calc. for $C_{11}H_{10}N_2O_4S$: C, 49·6; H, 3·8; N, 10·5%), $\nu_{max.}$ 3200w (NH), 1695s (C=O), 1670sh, 1600, 1570, 1420, 1390, 1300, 1250w, 1230, 1190w, 1175, 1120w, 1095, 1020, 940br, 860s, 820, 770, 720, and 690 cm^{-1}. This compound (1·3 g) in pyridine (10 ml) was kept with toluene-*p*-sulphonyl chloride (1 g) in pyridine overnight; the solution was poured into water to give *3,6-di-p-tolylsulphonyloxypyridazine* (1·7 g, 83%) as needles, m.p. 125° (from ethanol) (Found: C, 51·4; H, 3·8; N, 6·9. $C_{18}H_{16}N_2O_6S_2$ requires C, 51·4; H, 3·8; N, 6·8%), which was sensitive to moisture; $\nu_{max.}$ 1600, 1580w, 1570w, 1420s, 1310, 1295, 1230, 1195, 1175s, 1120w, 1090, 1040w, 1020w, 960w, 890w, 860s, 840s, 820, 790w, 750, 720, 710w, and 680 cm^{-1}.

Maleodihydrazide (5).—Anhydrous hydrazine (15 ml) reacted vigorously with 3,6-di-*p*-tolylsulphonyloxypyridazine (2 g). After 2 h, the solution was evaporated to half bulk at 100°/10 mmHg, and the liquid was cooled. *Maleodihydrazide* (0·6 g, 87%) formed needles, m.p. 170° (from aqueous ethanol) (Found: C, 33·5; H, 5·4; N, 38·9. $C_4H_8N_4O_2$ requires C, 33·3; H, 5·6; N, 38·9%), $\nu_{max.}$ 3360 and 3230 (NH_2, NH), 1675 (C=O), 1590s (amide-II), 1545s, 1440, 1385, 1320, 1305, 1225w, 1150w, 1120w, 1080w, 1010, 950, 860w, and 840 cm^{-1}; τ (D_2O) 3·07s (2 × CH). Further evaporation of the reaction mother-

[9] J. A. Elvidge and A. P. Redman, *J. Chem. Soc.*, 1960, 1710.
[10] W. O. Godfredsen and S. Vangedal, *Acta Chem. Scand.*, 1955, **9**, 1498; J. Deles and W. Polaczkowa, *Roczniki Chem.*, 1961, **35**, 853.
[11] R. C. Elderfield, 'Heterocyclic Compounds,' Wiley, New York, 1957, **6**, pp. 105, 112, 118.
[12] H. Feuer, E. H. White, and J. E. Wyman, *J. Amer. Chem. Soc.*, 1958, **80**, 3790.
[13] R. H. Mizzoni and P. E. Spoerri, *J. Amer. Chem. Soc.*, 1951, **73**, 1873.
[14] K. Szabo and E. Oswald, *Acta Chim. Acad. Sci. Hungary*, 1958, **15**, 1.

liquors gave an oil which crystallised on being cooled. This solid (1·3 g, 72%) (Found: *m/e* 186. Calc. for $C_7H_{10}N_2O_2S$: *M*, 186) had m.p. 109° and mixed m.p. 110° with authentic toluene-*p*-sulphonohydrazide (lit.,[15] 112°).

Maleohydrazide (0·74 g) with anhydrous hydrazine (3 ml) afforded a gel which crystallised from 50% aqueous ethanol to give maleodihydrazide (0·42 g, 45%), identified by i.r. and mixed m.p.

To a solution of maleodihydrazide (0·37 g) in water, 3N-hydrochloric acid (1 drop) was added. Fine crystals of maleohydrazide separated (0·25 g, 87%), m.p. and mixed m.p. 300° (decomp.) (Found: C, 42·9; H, 3·6; N, 25·0. Calc. for $C_4H_4N_2O_2$: C, 42·9; H, 3·6; N, 25·0%).

To maleodihydrazide (0·45 g) in water, benzaldehyde (0·7 ml) in ethanol was added. Maleohydrazide precipitated (0·3 g, 85%), having the correct i.r. spectrum. Concentration of the filtrate under reduced pressure afforded yellow prisms of benzaldehyde azine (0·4 g, 60%), m.p. 91° (from ethanol–benzene) (lit.,[16] 93°) (Found: N, 13·9. Calc. for $C_{14}H_{12}N_2$: N, 13·5%), *m/e* 208.

Reaction of 3,6-*Dichloropyridazine with Ethanolic Potassium Hydrogen Sulphide*.—The dichloride (3 g) and ethanolic 2N-potassium hydrogen sulphide [17] (33 ml) were heated together in a Carius tube at 140—150° for 6 h. The yellow solid was collected and washed with water. Recrystallisation from ethanol gave 6-ethoxy-2,3-dihydro-3-thioxopyridazine [18] (4) (1·3 g, 42%) as yellow needles, m.p. 190° (Found: C, 46·3; H, 5·2; N, 17·9; S, 20·5. Calc. for $C_6H_8N_2OS$: C, 46·2; H, 5·1; N, 18·0; S, 20·5%), *m/e* 156; $\nu_{max.}$ 1575s, 1440, 1330, 1300s, 1240, 1150, 1120, 1080, 1035, 1020s, 920, 850, 820w, and 720 cm^{-1}.

The filtrate and washings were acidified (HCl) and the yellow precipitate was purified by dissolution in aqueous sodium hydrogen carbonate and reprecipitation with acid to give 2,3-dihydro-6-mercapto-3-thioxopyridazine (1) (0·9 g, 31%) as a yellow powder, m.p. 230—240° (decomp.),[2] with i.r. absorption as reported.[7]

3-*Ethoxy*-6-*hydrazinopyridazine*.— 6-Ethoxy-2,3-dihydro-3-thioxopyridazine (1 g) was refluxed in ethanol (5 ml) with hydrazine hydrate (5 ml) for 6 h. Evaporation under reduced pressure to half bulk and cooling of the solution afforded 3-*ethoxy*-6-*hydrazinopyridazine* (0·4 g, 41%), m.p. 94° (Found: *m/e* 154. $C_6H_{10}N_4O$ requires *M*, 154). To a solution of this compound (0·2 g) in a minimum of ethanol, acetone (1 ml) was added. Next day, the yellow crystals of 3-*ethoxy*-6-*isopropylidenehydrazinopyridazine* (16) (0·11 g, 45%) were collected, m.p. 150—151° (from ethanol) (Found: C, 56·0; H, 7·3. $C_9H_{14}N_4O$ requires C, 55·7; H, 7·2%), *m/e* 194; $\nu_{max.}$ 3200 (NH), 1620 (C=N), 1515, 1435, 1350, 1315w, 1280, 1255, 1125, 1110w, 1085w, 1040w, 1010, 920, and 845 cm^{-1}.

Dithiomaleohydrazide.—3,6-Dichloropyridazine (14·9 g) in ethanol (100 ml) was kept with a solution of thiourea (16 g) in 96% ethanol (100 ml) at 65° for 1 h. Evaporation under reduced pressure left a yellowish brown oil which was dissolved by stirring in water containing sodium hydrogen carbonate (35 g). After several hours, the solution was filtered and acidified (HCl) to litmus, and the yellow-ochre precipitate was collected, washed, and dried (yield 13 g, 90%), m.p. 240—250° (decomp.). Filtration of a solution of this solid in aqueous sodium carbonate–sodium hydrogen carbonate into aqueous hydrochloric acid gave yellow 2,3-dihydro-6-mercapto-3-thioxopyridazine (1), m.p. 250—260° (decomp.) (lit.,[2] 230—240°), with the correct i.r. spectrum.[7] Methylation gave 3,6-bis(methylthio)pyridazine (17), m.p. 128°.[2]

3-*Hydrazino*-6-*methylthiopyridazine* (18).—The bismethylthiopyridazine (0·86 g) was kept with anhydrous hydrazine (3 ml) at 100° for 20 h. On cooling, 3-*hydrazino*-6-*methylthiopyridazine* separated (0·6 g, 77%), m.p. 120° (from water) (Found: C, 38·6; H, 5·2; N, 36·0; S, 20·4. $C_5H_8N_4S$ requires C, 38·5; H, 5·1; N, 35·9; S, 20·5%), *m/e* 156; $\nu_{max.}$ 3280 and 3210sh (NH_2), 1640 (C=N), 1610s, 1570, 1415, 1360, 1315, 1160, 1080, 1025, 970, 840, 750w, and 720w cm^{-1}.

3,6-*Dihydrazinopyridazine* (8) *and Derivatives*.—3,6-*Dihydrazinopyridazine*, prepared [2] from dithiomaleohydrazide and hydrazine hydrate, crystallised from water (charcoal) as lustrous needles, m.p. 195—196° (decomp.) (Found: C, 34·1; H, 5·7; N, 59·8. $C_4H_8N_6$ requires C, 34·3; H, 5·7; N, 60·0%), *m/e* 140; $\nu_{max.}$ 3350sh, 3280, and 3220 (NH_2, NH), 1630 (C=N), 1580w, 1330w, 1310, 1150, 1040, 980, 870, and 840 cm^{-1}.

The 3,6-di-isopropylidene derivative (14; $R^3 = R^4 =$ Me) crystallised from chloroform as fine yellow needles, m.p. 250° (decomp.) [2] (Found: C, 54·3; H, 7·4; N, 38·3. Calc. for $C_{10}H_{16}N_6$: C, 54·6; H, 7·3; N, 38·2%), $\nu_{max.}$ 3200 (NH), 1640w, 1610w, 1590w, 1510s, 1400, 1310, 1280w, 1250, 1210w, 1130, 1070w, 1020, 880, and 850 cm^{-1}.

Ethyl chloroformate (3·5 g) in ethanol was added dropwise to 3,6-dihydrazinopyridazine (2·21 g) in ethanol with stirring, whereupon a thick white precipitate began to separate. After 3 h, the solid was collected (4 g); a further (1·6 g) was obtained by adding ether to the filtrate. A portion (3·5 g) of this hydrochloride was dissolved in a minimum of water and the solution then rendered alkaline to litmus with aqueous sodium carbonate. 3,6-*Di*-(2-*ethoxycarbonylhydrazido*)*pyridazine* (19) separated (2 g, 71%), m.p. 208° (from ethanol) (Found: C, 42·3; H, 5·5; N, 29·7. $C_{10}H_{16}N_6O_4$ requires C, 42·3; H, 5·6; N, 29·6%), *m/e* 284; $\nu_{max.}$ 3350 and 3200 (NH), 1710s and 1690s (C=O), 1630, 1560, 1535, 1500, 1320, 1270s, 1210, 1120w, 1100w, 1050, 1040, 1020w, 980, 900w, 850w, 840, and 770 cm^{-1}.

3,6-Di-(2-ethoxycarbonylhydrazido)pyridazine (0·9 g) was kept with concentrated nitric acid (4 ml) at 0° for 5 h. Water was added, the orange solution was extracted with benzene, and the extract was dried ($MgSO_4$) and evaporated to give 3,6-*di*-(2-*ethoxycarbonylazo*)*pyridazine* (20) as a reddish brown oil (0·7 g), b.p. 80°/2 mmHg with decomp. (Found: *m/e* 280. $C_{10}H_{12}N_6O_4$ requires *M*, 280), $\nu_{max.}$ (liquid film) 3050w, 3000, and 2970 (C–H), 1760s (C=O), 1570w, 1530, 1475, 1450, 1400, 1370, 1250s, 1170, 1100, 1020, 980, 860, 840w, 820w, and 690 cm^{-1}.

Glyoxylic acid monohydrate (0·2 g) in water was added to a solution of 3,6-dihydrazinopyridazine (0·07 g) in a minimum of water. The yellow precipitate (0·12 g, 95%) was dissolved in aqueous sodium hydrogen carbonate and reprecipitated with glyoxylic acid to give yellow 3,6-*di*(*carboxymethylenehydrazino*)*pyridazine* (14; $R^3 = H$, $R^4 = CO_2H$), m.p. 199° (decomp.) (Found: C, 38·0; H, 3·4; N, 33·5. $C_8H_8N_6O_4$ requires C, 38·1; H, 3·2; N, 33·3%), $\nu_{max.}$ 3400 and 3200 (NH), 1700 (C=O), 1590, 1560, 1420, 1320, 1140s, 1000, 920w, 860w cm^{-1}.

The Reaction of Hydrazine with 3,6-*Dimethoxypyridazine*.—By refluxing the dimethoxy-compound (2 g) in hydrazine

[15] K. Freudenberg and F. Blummel, *Annalen*, 1924, **440**, 45.
[16] T. Curtius and R. Jay, *J. prakt. Chem.*, 1889, **39**, 27.
[17] H. Zinner, *Chem. Ber.*, 1953, **86**, 825.
[18] R. N. Castle and K. Kaji, *J. Heterocyclic Chem.*, 1965, **2**, 463.

hydrate (6 ml) for 5 h and then cooling, a basic crystalline product (0·5 g, 25%) was obtained, m.p. *ca.* 227° (lit.,[3] *ca.* 220°); however, *m/e* = 141 and the ' hydrochloride hydrate ' (from aq. HCl), m.p. 232·5° (lit.,[3] 232—233°) [Found: C, 28·95; H, 4·45; N, 37·7. (lit.,[3] C, 25·7; H, 5·4%)], gave at 230° only N_2 + HCl (weight loss, 38%). An identical basic material (2 g, 40%) resulted from heating the dimethoxy-compound (5 g) with hydrazine hydrate (35 ml) in a Carius tube at 120° for 6 h (Found: C, 35·5; H, 5·1; N, 46·8%). Five recrystallisations from water gave a sample, m.p. 243—245° (decomp.) (Found: C, 35·0; H, 4·65; N, 46·9%), not changed by two further crystallisations, *m/e* 141.

3,6-Dimethoxypyridazine (6 g) was heated with anhydrous hydrazine (25 ml) on a steam-bath for 56 h. By pouring the cooled liquid into ethanol, fine crystals separated (2 g), m.p. 245—247° (decomp.); a second crop of product (1·3 g), same m.p., was obtained by evaporation of the mother liquor and addition of water and then ethanol (total yield 55%). T.l.c. in water on silica gel (Merck $PF_{254+366}$) failed to separate this mixture of compounds (6) and (7) (Found: C, 35·7; H, 5·0; N, 44·9%; *m/e* 141, persisting on reduction of source potential. Calc. for 78% of $C_4H_7N_5O$ + 22% of $C_5H_7N_3O_2$: C, 35·9; H, 5·0; N, 45·3%; *M*, 141), $\nu_{max.}$ 3400, 3350, 3200, 1700, 1680, 1610s, 1575 cm^{-1}; $\lambda_{max.}$ 225, 275 nm; τ (D_2O at 90°) 3·85s (*ca.* 4/5th of 1 ring proton of $C_4H_7N_5O$ + 1/5th ring proton of $C_5H_7N_3O_2$), 6·27s (1/5th of MeO of $C_5H_7N_3O_2$). A sample twice recrystallised from deuterium oxide had *m/e* 147, 144 ($C_4HD_6N_5O$ requires *M*, 147. $C_5H_4D_3N_3O_2$ requires *M*, 144).

5-Amino-6-hydrazino-2,3-dihydro-3-oxopyridazine (6).—The preceding mixture of compounds (6) and (7) was heated with anhydrous hydrazine and the solution was filtered into methanol: repetition (3×) afforded *5-amino-6-hydrazino-2,3-dihydro-3-oxopyridazine* as fine crystals, m.p. 247—249° (decomp.) (Found: C, 34·2; H, 5·1; N, 49·5. $C_4H_7N_5O$ requires C, 34·0; H, 5·0; N, 49·7%), $\nu_{max.}$ 3400 and 3330 (NH_2), 3200 (NH), 1700 (C=O), 1610s and 1575 (C=C), 1550w, 1515w, 1410w, 1320, 1210, 1140w, 995, 950, 890, 820, and 775 cm^{-1}.

The *p*-hydroxybenzaldehyde derivative, *5-amino-2,3-dihydro-6-(p-hydroxybenzylidenehydrazino)-3-oxopyridazine* was formed (97%) in hot water and recrystallised (ethanol) to give pale yellow crystals, m.p. 268—269° (decomp.) (Found: C, 54·0; H, 4·5; N, 28·6. $C_{11}H_{11}N_5O_2$ requires C, 53·9; H, 4·5; N, 28·6%), $\nu_{max.}$ 3490 and 3380 (NH_2), 3200br (NH, OH), 1615s and 1590s (C=C and C=N), 1515, 1405, 1350, 1320w, 1300w, 1260, 1240, 1200w, 1165, 1120, 1100, 1000, 950w, 920, 900w, 840, 780w, and 740 cm^{-1}; τ (Me_2SO) −1·83s br (NH·CO), −0·05s (NH–N), 0·33s (OH), 2·13s (CH=N), 2·52d and 3·18d J = 8·5 Hz (2,6- and 3,5-H on benzene ring, respectively), 3·40s (H on pyridazine ring), 3·72s br (NH_2); τ (Me_2SO + 1 drop D_2O) 2·17s (CH=N), 2·50d and 3·18d J = 8·5 Hz (2,6- and 3,5-H on benzene ring), 3·43s (H on pyridazine ring); *m/e* 245.

We thank the University of Surrey and Fisons Industrial Chemicals Ltd. for maintenance grants (to J. A. P.), and Dr. M. A. Smith for his interest and for gifts of hydrazine.

[1/2351 *Received*, 7*th December*, 1971]