Heterocyclic Imines and Amines. Part XVII.[1] Confirmation of the Structures of Two Aminopyridazinones

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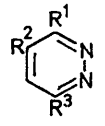
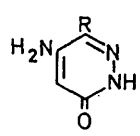
Only the 3-substituent of 4-amino-6-chloro-3-methoxypyridazine was attacked on acidic or alkaline hydrolysis or by thiourea in boiling ethanol. With potassium acetate in acetic acid at 170°, however, 5-amino-6-methoxypyridazin-3(2*H*)-one was obtained, together with 4-amino-1,2-dihydropyridazine-3,6-dione. Heating the former product with hydrazine gave 5-amino-6-hydrazinopyridazin-3(2*H*)-one. A mixture of the two pyridazinones simulated the product from interaction of 3,6-dimethoxypyridazine and hydrazine, so confirming previous tentative conclusions. Heating 4-amino-6-chloro-3-hydrazinopyridazine with potassium acetate in acetic acid gave 8-amino-6-chloro-3-methyl-*s*-triazolo[4,3-*b*]pyridazine.

RECENTLY, we reported [2] that 3,6-dimethoxypyridazine (1) did not react straightforwardly with hydrazine, as claimed,[3] but gave a mixture of two 5-aminopyridazin-3(2*H*)-ones for which we proposed the 6-hydrazino- (2) and -methoxy- (3) structures, largely on the basis of spectroscopic observations. The structures and the nature of the mixture have now been confirmed through a rational synthesis of each compound.

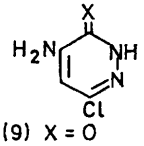
Syntheses might readily be achieved, it appeared, from a 3,4,6-trihalogenopyridazine because the halogeno-substituents were displaceable selectively. Thus treatment of the trichloropyridazine (4) with ammonia was known [4] to yield the 4-amino-compound (5) which with hydrazine and sodium methoxide, respectively, gave 4-amino-6-chloro-3-hydrazino- [4] (6) and 4-amino-6-chloro-3-methoxy-pyridazine [5] (7). Hydrolytic removal of the remaining halogeno-substituent in each compound would then have completed the projected syntheses. However, two difficulties had to be overcome.



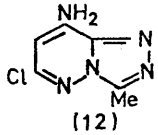
(1) $R^1 = R^3 = OMe$, $R^2 = H$
(4) $R^1 = R^2 = R^3 = Cl$
(5) $R^1 = R^3 = Cl$, $R^2 = NH_2$
(6) $R^1 = NH \cdot NH_2$, $R^2 = NH_2$, $R^3 = Cl$
(7) $R^1 = OMe$, $R^2 = NH_2$, $R^3 = Cl$
(8) $R^1 = R^3 = Cl$, $R^2 = Br$
(11) $R^1 = H$, $R^2 = NH_2$, $R^3 = Cl$



(2) $R = NH \cdot NH_2$
(3) $R = OMe$



(9) X = O
(10) X = S



(12)

First, chloromaleic anhydride, required for preparation of the trichloropyridazine (4), could not be obtained pure by direct chlorination–dehydrochlorination of maleic anhydride and fractionation of the product,[6,7] at least on a small scale; this meant that subsequently a mixture of pyridazines was obtained which could not be separated efficiently. Of various alternatives,[8–10] the halogenation of aqueous sodium maleate [11,12] and distillation of the resulting dihalogenosuccinic acid with phosphorus pentoxide [13] proved most convenient and gave consistently high yields of pure monohalogenomaleic anhydride. The bromo-derivative, so made, was converted into 4-bromo-3,6-dichloropyridazine (8) and thence into compounds (6) and (7).

The second difficulty was that the remaining halogeno-substituent in these two compounds was unreactive. Thus the amino-chloro-methoxy-pyridazine (7) on both alkaline and acidic hydrolysis afforded 4-amino-6-chloropyridazin-3(2*H*)-one (9), the 3-substituent being attacked. Likewise, treatment of the compound (7) with thiourea and then alkali gave the 4-amino-6-chloropyridazin-3(2*H*)-thione (10), which was similarly obtained from the chlorohydrazino-pyridazine (6). Neither of the compounds (6) and (7) was affected by sodium benzyloxide in boiling benzyl alcohol or by boiling morpholine and piperidine, and the chloro-hydrazino-pyridazine (6) was unaffected by attempted acidic hydrolysis. With hot aqueous alkali, however, this compound gave 5-amino-3-chloropyridazine (11), possibly by aerial dehydrogenation of the hydrazino-substituent and then disproportionation to nitrogen and product, or by Wolff–Kishner reduction of the hydrazone tautomer and aerial oxidation of the resulting dihydropyridazine. With acetic acid and potassium acetate at 170°, the chloro-hydrazino-pyridazine (6) gave a product $C_6H_6ClN_5$ for which the *s*-triazolo[4,3-*b*]pyridazine structure (12) was deduced from spectroscopic properties. The same product arose from the action of acetyl chloride in hot pyridine on compound (6). When the chloro-methoxypyridazine (7) was heated (as before) with acetic acid and potassium acetate, the required 5-amino-6-methoxypyridazin-3(2*H*)-one (3) was ob-

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[5] T. Nakagome, T. Hayama, T. Komatsu, and Y. Eda, *Yakugaku Zasshi*, 1962, **82**, 1103 (*Chem. Abs.*, 1963, **58**, 4559g).
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[10] See Beilstein, 'Handbuch der Organischen Chemie,' 4th edn., H **17**, 434, 435; EII **17**, 447.
[11] *Cf.* E. M. Terry and L. Eichelberger, *J. Amer. Chem. Soc.*, 1925, **47**, 1067.
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tained; at a lower temperature, with a prolonged time of interaction, 4-amino-1,2-dihydropyridazine-3,6-dione was a major product, identified with material obtained from the 4-bromo-analogue and ammonia. By heating 5-amino-6-methoxypyridazin-3(2*H*)-one (3) with hydrazine, 5-amino-6-hydrazinopyridazin-3(2*H*)-one (2) was obtained. This was identical with the compound $C_4H_7N_5O$ previously encountered.[2]

A mixture of the hydrazino- and methoxy-pyridazinones (2) and (3), in the ratio 78 : 22, had the same properties, including i.r. spectrum, as the product obtained [2] by heating 3,6-dimethoxypyridazine with hydrazine hydrate, so demonstrating that our previous conclusions concerning this product were correct.

EXPERIMENTAL

Spectra were measured as before.[2]

Dibromosuccinic acid (70—75% from sodium maleate)[12] was distilled (2 ×) from phosphorus pentoxide[13] to give bromomaleic anhydride (80%), b.p. 215° (lit.,[14] 215°), τ ($CDCl_2$) 2·45 (s, CH=) (only), which was converted into 4-bromo-1,2-dihydropyridazine-3,6-dione (82%), m.p. 257°(lit.,[6] 251°), τ [$(CD_3)_2SO$] 2·45 (s, ring H) and —1·6br (NH/OH; treatment of this pyridazine with phosphoryl chloride[15] gave 4-bromo-3,6-dichloropyridazine (8) (65—70%), m.p. 80° (lit.,[16] 80—81°), τ (Me_2CO) 1·80 (s, 5-H), $\nu_{max.}$ 3095 (CH), 1640, 1530, 1340s, 1315, and 1290 cm^{-1}. This compound with ammonia gave 4-amino-3,6-dichloropyridazine[4] (5) (55%), m.p. 204—205° (from water), τ (Me_2CO) 4·20br (NH_2) and 3·19 (s, 5-H), $\nu_{max.}$ 3480 and 3300br (NH_2), 3030w (CH), 1640, 1560, and 1290 cm^{-1}, which (*a*) with hydrazine gave 4-amino-6-chloro-3-hydrazinopyridazine[4] (6) (55%), m.p. 210° (from water) (Found: C, 30·05; H, 3·7; N, 43·8. Calc. for $C_4H_6ClN_5$: C, 30·1; H, 3·9; N, 43·9%), τ [$(CD_3)_2SO$] 5·70br (3-NH·N*H*$_2$), 3·75br (4-NH_2), 3·63 (s, 5-H), and 2·72 (3-N*H*·NH_2), $\lambda_{max.}$ 300 and 263 nm (ε 9000 and 12,000); and (*b*) with methanolic sodium methoxide afforded 4-amino-6-chloro-3-methoxypyridazine[5] (7) (88%), m.p. 197° (from water), τ (MeCN) 5·98 (s, OMe), 4·10br (NH_2), and 3·33 (s, 5-H), $\lambda_{max.}$ 280 and 258 nm (ε 11,600 and 14,800). Stirring the last compound (1·6 g) with 3N-sodium hydroxide (50 ml) at 80—89° for 24 h, neutralisation of the solution (HCl), and keeping it at 0°, provided 4-amino-6-chloropyridazin-3(2*H*)-one[5] (9) (1·3 g), m.p. 283° (from water), τ [$(CD_3)_2SO$] 3·80 (s, 5-H), 3·23br (4-NH_2), and —2·60br (ring NH), $\nu_{max.}$ 3420s and 3320 (NH_2), 3200br (NH), 3060w (CH), 1695s (CO), 1660, 1600br,s, 1550, 1410, and 1310 cm^{-1}. Similar hydrolysis of compound (5) for 3 h gave the same product, m.p. 280°. The same product (0·7 g), m.p. and mixed m.p. 282°, resulted from hydrolysis of compound (7) (1 g) with 3N-sulphuric acid (25 ml) at 80—90° for 24 h. Heating compound (7) (2 g) in ethanol (40 ml) with thiourea (2·5 g) for 4 h under reflux, evaporation of the solution, dissolution of the residue in 3N-sodium hydroxide (20 ml), and, after 2 h, filtration and acidification (HCl) gave yellow 4-amino-6-chloropyridazin-3(2*H*)-thione (10) (1·7 g, 85%), m.p. 225° (from aqueous alkali on acidification) (lit.,[17] 185—195°) (Found: C, 30·1; H, 2·5. Calc. for $C_4H_4ClN_3S$: C, 29·7; H, 2·5%), τ [$(CD_3)_2SO$] 3·80 (s, 5-H), 3·22br (4-NH_2), and —2·65br (ring NH). The same compound (10) (85%), m.p. and mixed m.p. 225°, resulted from similar treatment of compound (6) and also of compound (5), and was further characterised by methylation[18] to give 4-amino-6-chloro-3-methylthiopyridazine, m.p. 213—214° (from water), τ [$(CD_3)_2SO$] 7·60 (s, SMe), 3·63br (NH_2), and 3·32 (s, 5-H). When 4-amino-6-chloro-3-hydrazinopyridazine (6) (1·5 g) was stirred with 3N-sodium hydroxide (50 ml) at 80—90° for 24 h and the solution was neutralised and kept at 0°, 5-amino-3-chloropyridazine (11) separated (0·9 g), m.p. 161—162° (from water) (lit.,[19] 153—154·5°) (Found: C, 36·6; H, 3·2. Calc. for $C_4H_4ClN_3$: C, 37·1; H, 3·1%), τ ($CDCl_3$) 3·55br (NH_2), 3·33 (d, 4-H, $J_{4,6}$ 3 Hz), and 1·46 (d, 6-H).

*8-Amino-6-chloro-3-methyl-*s*-triazolo*[4,3-b]*pyridazine* (12).—4-Amino-6-chloro-3-hydrazinopyridazine (6) (3 g), acetic acid (30 ml), and potassium acetate (3 g; anhydrous) were heated in a Carius tube at 170° for 4 h. The solution was evaporated under reduced pressure and the residue crystallised from water to give the *triazolopyridazine* (2·3 g), m.p. 234—235° (Found: C, 39·0; H, 3·2; N, 38·2. $C_6H_6ClN_5$ requires C, 39·25; H, 3·3; N, 38·1%), τ [$(CD_3)_2SO$] 7·41 (s, 3-Me), 3·86 (s, 7-H), and 2·09br (8-NH_2), $\nu_{max.}$ 3440s and 3300br (NH_2), 3100, 1650s, 1590w, 1560s, 1530w, 1420, 1410, 1340w, and 1240 cm^{-1}, $\lambda_{max.}$ (MeOH) 305 and 234 nm (ε 10,400 and 9000). The same compound (1·7 g), m.p. and mixed m.p. 235° (Found: C, 38·9; H, 3·2; N, 37·95%), was obtained by heating compound (6) (1·6 g) in pyridine (50 ml) with acetyl chloride (1·6 ml) on a steam-bath for 1 h, evaporating the solution under reduced pressure, and crystallising the residue from methanol.

*5-Amino-6-methoxypyridazin-*3(2H)*-one* (3).—4-Amino-3-methoxy-6-chloropyridazine (7) (3 g), acetic acid (20 ml), and potassium acetate (3·5 g; anhydrous) were heated in a Carius tube at 170° for 4 h. Evaporation of the solution under reduced pressure, dissolution of the residue in water, neutralisation, and keeping the solution at 0° afforded *5-amino-6-methoxypyridazin-*3(2H)*-one* (0·8 g, 30%), m.p. 270° (from water) (Found: C, 42·35; H, 5·0; N, 29·7. $C_5H_7N_3O_2$ requires C, 42·6; H, 5·0; N, 29·8%), *m/e* 141, τ [$(CD_3)_2SO$] 6·22 (s, OMe), 4·41 (s, 4-H), 3·71br (5-NH_2), and —1·28br (ring NH), $\nu_{max.}$ 3450s and 3300 (NH_2), 3200br (NH), 1665, 1625s, 1490s, 1425, 1360s, 1285, 1255, and 1215 cm^{-1}, $\lambda_{max.}$ (MeOH) 267 nm (ε 8900). Evaporation of the filtrate from the preceding compound afforded 4-amino-1,2-dihydropyridazine-3,6-dione (1·5 g), m.p. 325° (decomp.) (from water), $\nu_{max.}$ 3400s and 3320br (NH_2), 3200br (NH), 3130w, 1690s (CO), 1610br,s, 1580, 1550, 1405, 1305, and 1200 cm^{-1}, identical (mixed m.p. and i.r. spectrum) with material (m.p. 323°) made[20] from 4-bromo-1,2-dihydropyridazine-3,6-dione. The aminopyridazinedione was the sole product from compound (7) and potassium acetate heated in acetic acid at 140° for 10 h.

*5-Amino-6-hydrazinopyridazin-*3(2H)*-one* (2).—5-Amino-6-methoxypyridazin-3(2*H*)-one (0·7 g) and hydrazine (10 ml) were heated in a Carius tube at 120—130° for 4 h. The excess of hydrazine was distilled off, methanol (10 ml) was added,

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and the solid was washed with water, methanol, and ether to give the pyridazinone (0·5 g, 71%), m.p. 249° (decomp.) (from hydrazine–methanol) [2] (Found: C, 33·8; H, 4·9; N, 49·9. Calc. for $C_4H_7N_5O$: C, 34·1; H, 5·0; N, 49·7%), *m/e* 141, $\lambda_{max.}$ (MeOH) 273 and 232 nm (ε 12,000 and 15,400), identical (mixed m.p. and i.r. spectrum) with the compound encountered before.[2] The *p*-hydroxybenzaldehyde derivative had m.p. and mixed m.p. 270° (decomp.) and an i.r. spectrum as reported.[2]

Product from Interaction of Hydrazine with 3,6-*Dimethoxypyridazine.*—The 6-hydrazino- (2) (0·78 g) and 6-methoxy- (3) pyridazinones (0·22 g) were mixed and the mixture was recrystallised from water several times to give colourless crystals, m.p. 248°. This material was identical [mixed m.p. 248° (decomp.); $\nu_{max.}$ 3390, 3310br, 3200br, 1695s, 1670, 1610br,s, 1565, 1500w, 1440, 1395w, 1317, and 1220br,s cm^{-1}] with the material [2] prepared by heating 3,6-dimethoxypyridazine (2 g) with hydrazine (8 ml) in a Carius tube at 120—130° for 6 h [yield 0·9 g; m.p. 249° (decomp.) (from water)].

We thank Dr. M. A. Smith for a gift of anhydrous hydrazine and gratefully acknowledge study leave and financial support (for S. A.) from the University of Baghdad, Iraq.

[3/2146 *Received*, 19*th October*, 1973]