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# SYNTHESIS OF PYRIDAZINE DERIVATIVES—XIII

## FORMATION OF SOME SUBSTITUTED IMIDAZO (1.2-b) PYRIDAZINES[1]

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**Abstract**—Several 2- and 3-substituted imidazo(1.2-b)pyridazines were prepared from 3-amino-6-chloropyridazine and the appropriate α-halo carbonyl compound in a suitable solvent at an elevated temperature (II, VII). Furthermore, many derivatives of these compounds were synthesized and are useful intermediates for further transformations.

RECENTLY, the synthesis of some imidazo(1.2-b)pyridazines and their conversion into new polyazaheterocycles has been described.[2] Since some substituted analogs which are useful intermediates for further synthetic experiments and studies of reactivity had not been reported, the synthesis of these compounds has been investigated. The most suitable method of forming imidazo(1.2-b)pyridazines reported[2] is the formation of the imidazole ring from appropriate pyridazines. This method was recently applied to the synthesis of some substituted imidazo(1.2-b)pyridazines of pharmacological interest.[3,4]

We have now prepared different 2- and 3-substituted imidazo(1.2-b)pyridazines and in addition some transformations are described. The introduction of a Me or Ph group at the position 2 with the simultaneous formation of the imidazole ring (II, R = Me or Ph) was most conveniently performed by condensing 3-amino-6-chloropyridazine (I) with bromoacetone, chloroacetone or phenacyl bromide. It is conceivable that ring closure could take place to give either the 2- or the 3-substituted product. The location of the Me group at position 2 is evident from NMR spectra of this and related compounds.[5] In this connection, an entering alkyl or aryl group was similarly assigned in some related imidazo(1.2-b)azines.

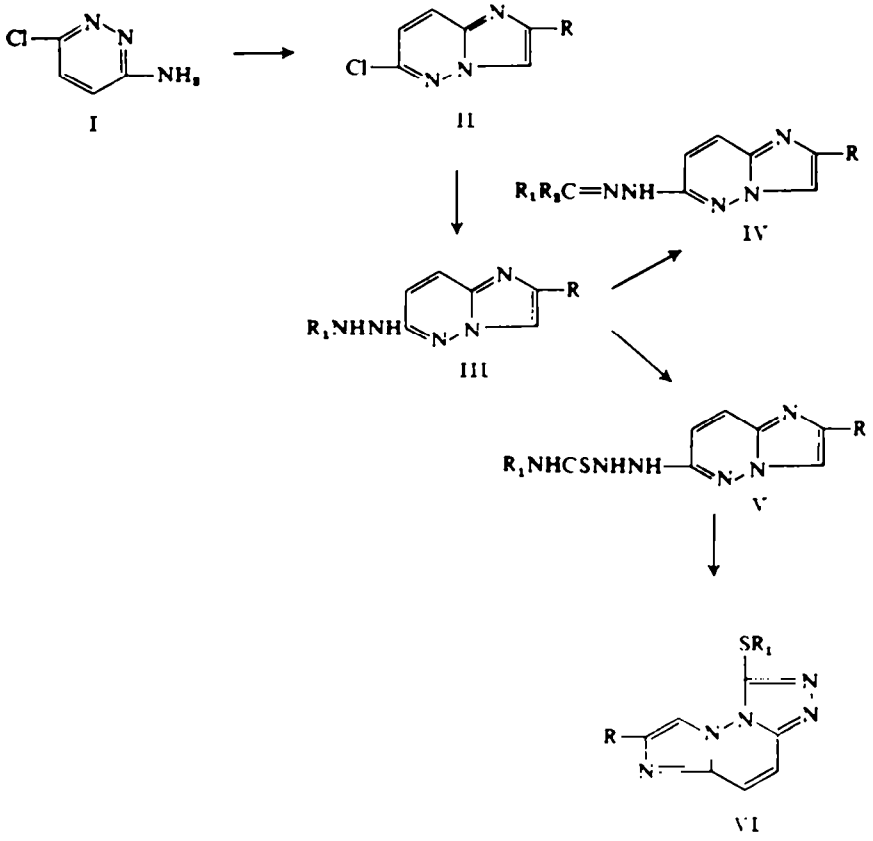
By a nucleophilic displacement of the chlorine at the position 6 the corresponding hydrazino compound III was obtained and this served for the preparation of some arylidene or alkylidene derivatives (IV), suitable for dehydrogenative cyclizations.[6] As in other heterocycles with Me groups in this reaction, the 2-Me group did not condense with aldehydes. This can be attributed to the relative mild reaction conditions under which the reaction was performed.

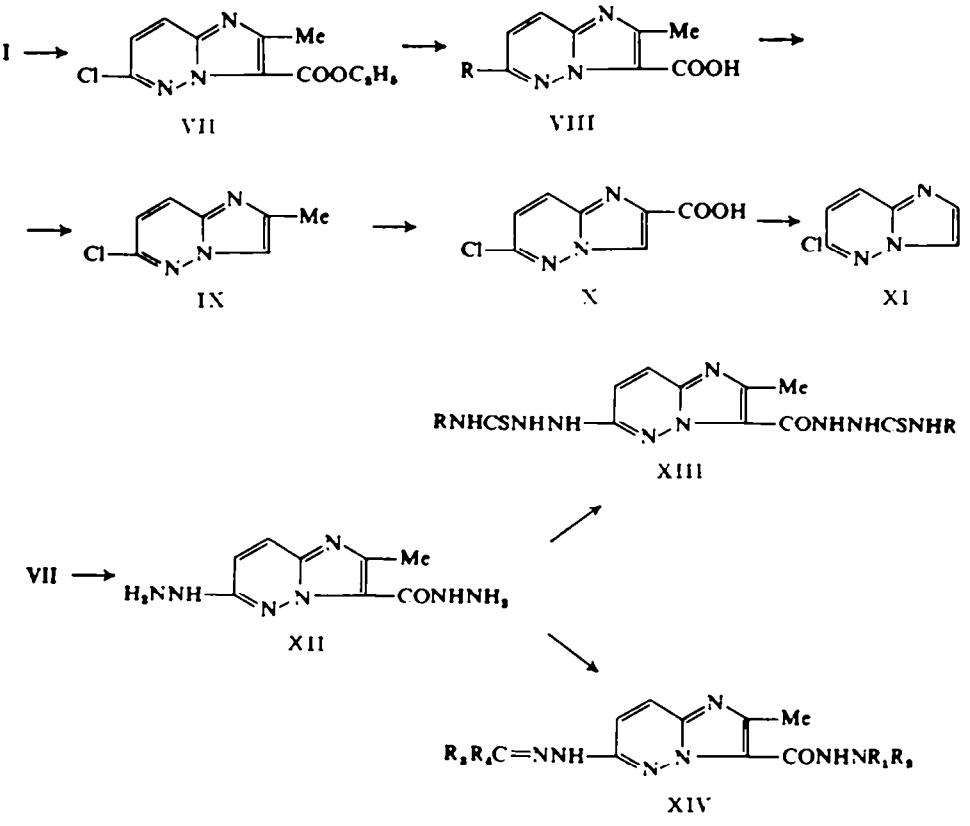
From III and isothiocyanates the corresponding substituted thiosemicarbazides (V)

[1] Paper XLIX on Heterocycles; paper XLVIII: M. Telenc, J. Kobe, B. Stanovnik and M. Tišler, *Monatsh Chem.* in press.
[2] B. Stanovnik and M. Tišler, *Tetrahedron* 23, 387 (1967).
[3] L. Almirante, L. Polo, A. Mugnaini, E. Provinciali, P. Rugarli, A. Gamba, A. Olivi and W. Murmann, *J. Med. Chem.* 9, 29 (1966).
[4] L. M. Werbel and M. L. Zamora, *J. Heterocycl. Chem.* 2, 287 (1965).
[5] B. Stanovnik and M. Tišler, forthcoming paper.
[6] A. Pollak and M. Tišler, *Tetrahedron* 22, 2073 (1966).

were obtained. These, when heated underwent cyclization, with loss of the corresponding amine and 7-substituted 1-mercaptoimidazo(1.2-b)-s-triazolo(3.4-f)pyridazines (VI) were obtained in fairly good yield. The nature of the attached substituent $R_1$ has no influence on the ease of ring closure and this is merely temperature dependent so that cyclization can be performed in boiling ethylene glycol. IR data agreed with the proposed structure of VI ($R_1$ = H) rather than with that of the tautomeric thioamide form.

A convenient route to 3-carbethoxy-2-methyl-substituted imidazo(1.2-b)pyridazines using the same starting pyridazine derivative (I) is the condensation with ethyl 2-bromoacetoacetate. Conversion of the resultant ester VII into the acid VIII followed by decarboxylation gave 6-chloro-2-methylimidazo(1.2-b)pyridazine (IX), identical with the product obtained above in a direct cyclization experiment. The Me group of this compound can be further oxidized and the 2-carboxylic acid (X) thus obtained afforded upon decarboxylation 6-chloroimidazo(1.2-b)pyridazine (XI). This was found identical with the compound obtained in a direct cyclization reaction from I.[2] Treatment of the ester VII with hydrazine hydrate gave the hydrazino-hydrazide (XII) indicating that hydrazinolysis occured also at position 6 with the exchange of the labile chlorine atom. From XII derivatives of the type XIII were easily obtained and with aldehydes condensation to XIV took place. The formation of mono arylidene derivative involving the 6-hydrazino group proceeds only in the cold, as heating yields bis-alkylidene or arylidene derivatives, regardless of the quantity of aldehyde employed.






## EXPERIMENTAL

M.ps: Kofler m.p. apparatus are corrected; IR spectra: Perkin-Elmer Model 21 Spectrophotometer as mulls in Nujol or hexachlorobutadiene.

*6-Chloro-2-methylimidazo*(1.2-b)*pyridazine* (II, R = Me)

Compound I (12·95 g), bromoacetone (13·7 g) and EtOH (100 ml) were heated under reflux for 6 hr. The solvent was evaporated *in vacuo* and the residue was dissolved in the minimum amount of water and neutralized with solid $NaHCO_3$. The liberated free base (yield 34%) was crystallized from water to give colourless needles, m.p. 127–128°. (Found: C, 50·24; H, 3·69; N, 25·22; $C_7H_6ClN_3$ requires: C, 50·17; H, 3·61; N, 25·07%.)

An identical product was obtained if instead of bromoacetone chloroacetone was used. The residue after evaporation of the solvent in the above experiment can be purified by sublimation *in vacuo* and the hydrobromide is identical with the product prepared from the base and hydrobromic acid as indicated below. Alternatively, the crude hydrobromide can be purified by dissolving in a minimum amount of MeOH and diluting with twice the amount of ether, m.p. 238–240°.

The hydrobromide can be obtained from the base in the following manner: a soln of the free base (100 mg) in EtOH (2 ml) was treated with few drops of 48% HBr and the salt separated. Purification was performed as indicated above. (Found: C, 33·63; H, 3·13; $C_7H_7BrClN_3$ requires: C, 33·83; H, 2·84%.)

*6-Chloro-2-phenylimidazo*(1.2-b)*pyridazine* (II, R = Ph)

Compound I (12·95 g) was heated with phenacyl bromide (18·2 g) and EtOH (300 ml) under reflux for 3 hr. Thereafter the solvent was evaporated to half of its original volume and the residue

put on ice. The free base which separated, was collected and recrystallized from EtOH, m.p. 199° (Lit.[6,7] m.p. 199–201° and 200°). (Found: C, 62·94; H, 3·78; N, 18·10; $C_{10}H_8ClN_5$ requires: C, 62·75; H, 3·51; N, 18·29%.)

*6-Hydrazino-2-methylimidazo*(1.2-b)*pyridazine* (III, R = Me, $R_1$ = H)

A suspension of II (R = Me; 5 g) in hydrazine hydrate (20 ml of 80%) was heated to boiling. After complete dissolution refluxing was continued for 10 min. After cooling the separated product was collected and crystallized from water to give the pure compound (4·3 g, 87% yield), m.p. 187–189°. (Found: C, 51·48; H, 5·78; N, 43·06; $C_7H_9N_5$ requires: C, 51·52; H, 5·56; N, 42·92%.)

The compound formed a dihydrochloride (with ethanolic HCl), m.p. 295° (EtOH). (Found: C, 36·62; H, 4·93; N, 29·82; $C_7H_{11}Cl_2N_5$ requires: C, 35·61; H, 4·70; N, 29·66%). Similarly the dihydrobromide was prepared, m.p. 296–299° (EtOH–ether). (Found: C, 25·41; H, 3·54; N, 21·44; $C_7H_{11}Br_2N_5$ requires: C, 25·87; H, 3·41; N, 21·55%.) The sulfate had m.p. 269°. (Found: C, 32·02; H, 4·25; N, 26·67; S, 12·34; $C_7H_{11}N_5O_4S$ requires: C, 32·19; H, 4·24; N, 26·81; S, 12·25%.)

*Benzylidene derivative of 6-hydrazino-2-methylimidazo*(1.2-b)*pyridazine*
(IV, R = Me, $R_1$ = H, $R_2$ = Ph)

To a soln of 0·01 mole of III, (R = Me, $R_1$ = H) in hot EtOH (25 ml) an equiv amount of benzaldehyde and few drops of glacial AcOH were added. The soln was left to cool to room temp and the separated hydrazone was crystallized from N,N-dimethylformamide and washed with hot EtOH, yield of the pale yellow crystals 30%; m.p. 235–236°. (Found: C, 66·91; H, 5·38; N, 27·94; $C_{14}H_{13}N_5$ requires: C, 66·92; H, 5·21; N, 27·87%.)

In essentially the same way the following derivs were prepared and crystallized from N,N-dimethylformamide:

(i) *Ethylidene derivative* IV (R = Me, $R_1$ = H, $R_2$ = Me) in 27% yield, m.p. 218–220°. (Found: C, 57·33; H, 6·07; N, 36·95; $C_9H_{11}N_5$ requires: C, 57·13; H, 5·86; N, 37·01%.)

(ii) *Isopropylidene derivative* IV (R = $R_1$ = $R_2$ = Me), m.p. 198–200°. (Found: C, 59·30; H, 6·51; N, 34·40; $C_{10}H_{13}N_5$ requires: C, 59·10; H, 6·45; N, 34·46%.)

(iii) p-*Hydroxybenzylidene derivative* IV (R = Me, $R_1$ = H, $R_2$ = p-HO—$C_6H_4$), m.p. 287–289°. (Found: C, 63·17; H, 5·18; N, 26·47; $C_{14}H_{13}N_5O$ requires: C, 62·91; H, 4·90; N, 26·20%.)

(iv) p-*Nitrobenzylidene derivative* IV (R = Me, $R_1$ = H, $R_2$ = p-$NO_2$—$C_6H_4$), m.p. 288–289°. (Found: C, 56·82; H, 3·98; $C_{14}H_{12}N_6O_2$ requires: C, 56·75; H, 4·08%.)

*6-Hydrazino-2-phenylimidazo*(1.2-b)*pyridazine* (III, R = Ph, $R_1$ = H)

A mixture of II (R = Ph; 22·95 g), EtOH (250 ml) and hydrazine hydrate (15 ml of 80%) was heated under reflux for about 8 hr until a complete soln resulted. After standing on ice overnight the separated product was collected and washed with EtOH (yield 43%). The filtrate was evaporated and another crop of crystals was obtained giving 17·2 g (76%). Upon crystallization from EtOH the pale yellow crystals had m.p. 208°. (Found: C, 63·69; H, 4·91; N, 30·84; $C_{12}H_{11}N_5$ requires: C, 63·99; H, 4·92; N, 31·09%.)

The compound formed a dihydrochloride, m.p. 255–256°. (Found: C, 48·20; H, 4·33; N, 23·26; $C_{12}H_{13}Cl_2N_5$ requires: C, 48·33; H, 4·29; N, 23·48%.) The dihydrobromide had m.p. 277–279°. (Found: C, 37·06; H, 3·06; N, 17·90; $C_{12}H_{13}Br_2N_5$ requires: C, 37·23; H, 3·38; N, 18·09%.)

*Benzylidene derivative of 6-hydrazino-2-phenylimidazo*(1.2-b)*pyridazine*
(IV, R = Ph, $R_1$ = H, $R_2$ = Ph)

The compound was prepared in the usual way and crystallized from N,N-dimethylformamide, then washed with hot EtOH; m.p. 208–210°. (Found: C, 72·87; H, 5·04; N, 22·20; $C_{19}H_{15}N_5$ requires: C, 72·83; H, 4·82; N, 22·35%.)

Furthermore, the following derivatives were synthesized:

(i) *Ethylidene derivative* IV (R = Ph, $R_1$ = H, $R_2$ = Me), m.p. 206°. (Found: C, 67·05; H, 5·40; N, 27·65; $C_{14}H_{13}N_5$ requires: C, 66·92; H, 5·21; N, 27·87%.)

(ii) *Isopropylidene derivative* IV (R = Ph, $R_1$ = $R_2$ = Me), m.p. 244°. (Found: C, 67·61; H, 5·70; N, 26·40; $C_{16}H_{15}N_5$ requires: C, 67·91; H, 5·70; N, 26·40%.)

[7] F. Yoneda, T. Ohtaka and Y. Nitta, *Bull. Chem. Soc. Japan* **12**, 1351 (1964).

(iii) p-*Hydroxybenzylidene derivative* IV (R = Ph, $R_1$ = H, $R_2$ = *p*-HO—$C_6H_4$), m.p. 295°. (Found: C, 69·31; H, 4·67; N, 21·11; $C_{16}H_{12}N_4O$ requires: C, 69·29; H, 4·59; N, 21·26%.)

(iv) p-*Nitrobenzylidene derivative* IV (R = Ph, $R_1$ = H, $R_2$ = *p*-$NO_2C_6H_4$), m.p. 230°. (Found: C, 63·56; H, 4·27; $C_{16}H_{11}N_5O_2$ requires: C, 63·68; H, 3·94%.)

*Carboxymethylene derivative of* 6-*hydrazino*-2-*methylimidazo*(1.2-b)*pyridazine* (IV, R = Me, $R_1$ = H, $R_2$ = COOH)

A soln of III (R = Me, $R_1$ = H; 1·63 g) in EtOH (10 ml) was treated with a soln of glyoxylic acid (1 g) in water (5 ml). The reaction mixture was gently heated for few min and left at room temp for 30 min. Upon chilling on ice the product separated was filtered off (0·8 g, 35% yield) and crystallized from EtOH; m.p. 218°. (Found: C, 49·22; H, 4·41; $C_9H_9N_5O_2$ requires: C, 49·31; H, 4·14%.)

*Carboxymethylene derivative of* 6-*hydrazino*-2-*phenylimidazo*(1,2-b)-*pyridazine* (IV, R = Ph, $R_1$ = H, $R_2$ = COOH)

Compound III (R = Ph, $R_1$ = H; 2·29 g in 10 ml EtOH) was treated with a soln of glyoxylic acid (1 g) in EtOH (10 ml) as described above. The hydrazone separated was filtered off and washed with hot EtOH giving 1·8 g of pure crystals; m.p. 210–211°. (Found: C, 59·62; H, 4·12; $C_{14}H_{11}N_5O_2$ requires; C, 59·78; H, 3·94; N, 24·90%.)

α-*Methylcarboxymethylene derivative of* 6-*hydrazino*-2-*phenylimidazo*(1.2-b)*pyridazine* (IV, R = Ph, $R_1$ = Me, $R_2$ = COOH)

This compound was prepared in a similar way in 71% yield. Crystallization was effected from EtOH; m.p. 186–187°. (Found: C, 60·88; H, 4·56; $C_{15}H_{13}N_5O_2$ requires: C, 61·01; H, 4·44%.)

6-*Carbethoxyhydrazino*-2-*phenylimidazo*(1.2-b)*pyridazine* (III, R = Ph, $R_1$ = COOEt)

A soln of III (R = Ph, $R_1$ = H; 2·25 g) in EtOH (25 ml) was heated under reflux with ethyl chloroformate (1·1 g) for 10 min. After evaporation of the solvent *in vacuo* to half of its original volume the separated product was filtered off and crystallized from EtOH, yield: 1·65 g; m.p. of the hydrochloride 189°. (Found: C, 53·71; H, 5·10; N, 20·99; $C_{15}H_{16}ClN_5O_2$ requires: C, 53·98; H, 4·83; N, 20·98%.)

2-*Methyl*-6-(4′-*phenylthiosemicarbazido*)*imidazo*(1.2-b)*pyridazine* (V, R = Me, $R_1$ = Ph)

To a hot soln of III (R = Me, $R_1$ = H; 1·63 g) in EtOH (25 ml) an equiv amount (0·01 mole) phenyl isothiocyanate was added dropwise. The mixture was heated under reflux for 10 min, cooled and the product filtered off. Crystallization from N,N-dimethylformamide-water (1:2) yielded colourless microcrystals (39%), m.p. 230°. (Found: C, 56·09; H, 4·41; $C_{14}H_{14}N_6S$ requires: C, 56·37; H, 4·73%.)

In essentially the same way the following substituted thiosemicarbazides were prepared (for crystallization the same solvent mixture as above was used):

(i) 2-*Methyl*-6-(4′-o-*tolylthiosemicarbazido*)*imidazo*(1.2-b)*pyridazine* (V, R = Me, $R_1$ = *o*-$CH_3C_6H_4$) obtained in 24% yield, m.p. 143° (at the temp of m.p. the tricyclic compound VI crystallized from the melt). (Found: C, 57·58; H, 5·19; S, 10·33; $C_{15}H_{16}N_6S$ requires: C, 57·68; H, 5·16; S, 10·25%.)

(ii) 2-*Methyl*-6-(4′-p-*tolylthiosemicarbazido*)*imidazo*(1.2-b)*pyridazine* (V, R = Me, $R_1$ = *p*-

(ii) 2-*Methyl*-6-(4′-p-*tolylthiosemicarbazido*)*imidazo*(1,2-b)*pyridazine* (V, R = Me, $R_1$ = *p*-$CH_3C_6H_4$), obtained in 20% yield, m.p. 138°. (Found: C, 57·58; N, 5·30; H, 26·92; S, 10·15; $C_{15}H_{16}N_6S$ requires: C, 57·68; H, 5·16; N, 26·91; S, 10·25%.)

(iii) 6-(4′-p-*Methoxyphenylthiosemicarbazido*)2-*methylimidazo*(1.2-b)*pyridazine* (V, R = Me, $R_1$ = *p*-$CH_3O$-$C_6H_4$) in 45% yield, m.p. 208°. (Found: C, 54·63; H, 4·82; N, 25·69; S, 9·50; $C_{15}H_{16}N_6OS$ requires: C, 54·87; H, 4·91; N, 25·60; S, 9·74%.)

(iv) 6-(4′-p-*Ethoxyphenylthiosemicarbazido*)2-*methylimidazo*(1.2-b)*pyridazine* (V, R = Me, $R_1$ = *p*-$C_2H_5O$-$C_6H_4$) in 60% yield, m.p. 187°. (Found: C, 56·02; H, 5·61; N, 24·32; S, 9·04; $C_{16}H_{18}N_6OS$ requires: C, 56·13; H, 5·30; N, 24·55; S, 9·34%.)

*1-Mercapto-7-methylimidazo(1.2-b)-s-triazolo(3.4-f)pyridazine* (VI, R = Me, $R_1$ = H)

Compound V (R = Me, $R_1$ = Ph; 2·98 g) when heated in ethylene glycol (20 ml) to temp of b.p. for 10 min decomposes and upon cooling the separated product was collected and washed with EtOH. The pale yellow crystals (yield 64%) did not melt up to 320°. (Found: C, 46·98; H, 3·65; N, 34·09; S, 15·72; $C_6H_7N_5S$ requires: C, 46·83; H, 3·44; N, 34·13; S, 15·60%.) IR Nujol or hexachlorobutadiene: max ($cm^{-1}$) 2500 (SH).

Similarly other above mentioned substituted thiosemicarbazidoimidazo(1.2-b)pyridazines were transformed into the tricyclic compound VI by thermal decomposition.

*1-Methylmercapto-7-methylimidazo(1.2-b)-s-triazolo(3.4-f)pyridazine* (VI, R = $R_1$ = Me)

The above compound VI (R = Me, $R_1$ = H; 820 mg) was dissolved in a hot ethanolic soln of EtONa, prepared from Na (92 mg) and EtOH (15 ml). The filtered soln was treated with MeI (576 mg) and the mixture was shaken at room temp for 1 hr and then poured into water. The collected product (yield 46%) was crystallized from EtOH; m.p. 169–171°. (Found: C, 49·59; H, 4·22; $C_7H_8N_5S$ requires: C, 49·31; H, 4·14%.)

*6-(4'-Cyclohexylthiosemicarbazido)-2-phenylimidazo(1.2-b)pyridazine* (V, R = Ph, $R_1$ = $C_6H_{11}$)

A hot soln of III (R = Ph, $R_1$ = H; 2·26 g) in EtOH (20 ml) was treated dropwise with cyclohexyl isothiocyanate (1·41 g). After addition was complete the mixture was left aside to cool down slowly. The product separated was filtered off and crystallized from N,N-dimethylformamide and finally suspended in EtOH, filtered and washed with EtOH (yield 71%), m.p. 226°. (Found: C, 62·24; H, 6·18; N, 22·69; S, 8·69; $C_{19}H_{22}N_6S$ requires: C, 62·28; H, 6·05; N, 22·94; S, 8·73%.)

In an analogous way the following derivatives were prepared:

(i) *2-Phenyl-6-(4'-o-tolylthiosemicarbazido)imidazo(1.2-b)pyridazine* (V, R = Ph, $R_1$ = *o*-$CH_3C_6H_4$) in 62% yield; m.p. 222°. (Found: C, 63·91; H, 5·07; S, 8·52; $C_{20}H_{18}N_6S$ requires: C, 64·16; H, 4·85; S, 8·55%.)

(ii) *2-Phenyl-6-(4'-m-tolylthiosemicarbazido)imidazo(1.2-b)pyridazine* (V, R = Ph, $R_1$ = *m*-$CH_3C_6H_4$) in 54% yield; m.p. 210°. (Found: C, 64·02; H, 5·15; N, 22·31; $C_{20}H_{18}N_6S$ requires: C, 64·16; H, 4·85; N, 22·45%.)

(iii) *6-(4'-o-Methoxyphenylthiosemicarbazido) 2-phenylimidazo(1.2-b) pyridazine* (V, R = Ph, $R_1$ = *o*-$CH_3O$-$C_6H_4$) in 41% yield; m.p. 215–217°. (Found: C, 61·43; H, 4·92; $C_{20}H_{18}N_6OS$ requires: C, 61·53; H, 4·65%.)

(iv) *6-(4'-p-Ethoxyphenylthiosemicarbazido) 2-phenylimidazo(1.2-b)pyridazine* (V, R = Ph, $R_1$ = *p*-$C_2H_5O$—$C_6H_4$) in 45% yield; m.p. 228–230°. (Found: C, 62·08; H, 4·85; $C_{21}H_{20}N_6OS$ requires: C, 62·36; H, 4·98%.)

*1-Mercapto-7-phenylimidazo(1.2-b)-s-triazolo(3.4-f)pyridazine* (VI, R = Ph, $R_1$ = H)

The compound was prepared from V (R = Ph, $R_1$ = $C_6H_{11}$; 3·6 g) as described in the case of VI (R = Me, $R_1$ = H). The crude product was washed with hot EtOH, yield: 1·2 g, 45%; m.p. 325–327°. (Found: C, 58·26; H, 3·52; N, 26·33; $C_{12}H_8N_6S$ requires: C, 58·43; H, 3·39; N, 26·21%.)

*6-Chloro-2-methylimidazo(1.2-b)pyridazine-3-carboxylic acid ethyl ester* (VII)

To a soln of I (12·95 g) in boiling EtOH (250 ml) ethyl 2-bromoacetoacetate (23 g) was added portionwise and heating was continued for 1 hr. Thereafter $NaHCO_3$ (12·6 g) was added portionwise and the mixture heated under reflux for further 10 min. After cooling the separated product was filtered and washed with few ml of hot EtOH. The combined filtrates were evaporated to about ⅓ of its original volume, filtered while hot, cooled and under vigorous stirring poured into 250 ml of iced water. The separated product was crystallized from water, yield 37%; m.p. 99–100°. (Found: C, 50·24; H, 4·38; N, 17·70; $C_{10}H_{10}ClN_3O_2$ requires: C, 50·10; H, 4·21; N, 17·53%.)

The compound formed a hydrochloride (from EtOH and ether), m.p. 165°. (Found: C, 43·56; H, 4·34; $C_{10}H_{11}Cl_2N_3O_2$ requires: C, 43·49; H, 4·05%.) Similarly the hydrobromide was obtained, m.p. 220° from EtOH and ether. (Found: C, 37·67; H, 3·58; $C_{10}H_{11}BrClN_3O_2$ requires: C, 37·46; H, 3·46%.) These salts are very soluble in water, whereas the sulphate, m.p. 197°, is only slightly soluble. (Found: C, 35·81; H, 3·87; N, 12·54; S, 9·66; $C_{10}H_{12}ClN_3O_6S$ requires: C, 35·66; H, 4·27; N, 12·45; S, 9·49%.)

*6-Chloro-2-methylimidazo*(1.2-b)*pyridazine-3-carboxylic acid* (VIII, R = Cl)

The above VII (2·39 g) was suspended in 10%NaOHaq (10 ml) and the reaction mixture was heated under reflux until the ester layer completely disappeared. After about 15 min the clear brown soln was filtered, cooled and slowly acidified with conc HCl to pH 3–4. The brownish ppt (1·5 g) is slightly soluble in water and common organic solvents, but can be purified with sublimation *in vacuo* (180–190°/1 mm); m.p. 255°. (Found: C, 45·52; H, 3·06; N, 19·65; $C_8H_4ClN_3O_2$ requires: C, 45·41; H, 2·86; N, 19·86%.)

*6-Methoxy-2-methylimidazo*(1.2-b)*pyridazine-3-carboxylic acid* (VIII, R = OMe)

The above VIII (R = Cl; 2·11 g) was dissolved in methanolic MeONa (0·23 g Na were reacted with 10 ml MeOH) and heated under reflux for 30 min. The solvent was evaporated to dryness, water (5 ml) was added and conc HCl until ph 6. The separated product was filtered off and washed free from NaCl with water, yield 1·2 g, 58%. For analytical purposes the crude product was purified by sublimation *in vacuo* at 200–210°/0·1 mm; m.p. 237°. (Found: C, 52·06; H, 4·26; N, 19·81; $C_9H_9N_3O_3$ requires: C, 52·17; H, 4·38; N, 20·28%.)

*Decarboxylation of* VIII (R = Cl) *to 6-chloro-2-methylimidazo*(1.2-b) *pyridazine* (IX)

The acid VIII (R = Cl; 100 mg) was thoroughly mixed with Cu bronze (100 mg) and the mixture heated in a tube in a metallic block at 230–240°. In the cool part of the tube deposited crystals of IX (53 mg), which were found identical with the compound obtained synthetically from I and bromoacetone as described in the case of II (R = Me). A mixed m.p. was undepressed.

*6-Chloroimidazo*(1.2-b)*pyridazine-2-carboxylic acid* (X)

(a) A stirred suspension of IX (3·34 g) in water (50 ml) was heated on water bath until a clear soln resulted. Thereafter, during a period of 20 min $KMnO_4$ (9 g) was added portionwise. The reaction mixture was filtered hot and $MnO_2$ on the filter was washed with few ml of hot water. Upon cooling the acid separated and was subsequently sublimed at 200–220°/0·1 mm; m.p. 260°. From the filtrate, after evaporation *in vacuo* to a small volume, an additional amount of the acid was obtained giving a total yield of 1·1 g. (Found: C, 42·51; H, 2·26; $C_7H_4ClN_3O_2$ requires: C, 42·55; H, 2·04%.)

(b) Compound IX (1·67 g) was dissolved in a mixture of $Ac_2O$ and glacial AcOH (2:1), conc $H_2SO_4$ (1 ml) was added and during 5 min a soln of $CrO_3$ (2 g) in a mixture of $Ac_2O$ and glacial AcOH (2:1, 6 ml) was added dropwise. The reaction mixture was cooled externally with ice and stirred. After the addition was complete, the reaction mixture was left standing on ice for 20 min and thereafter crushed ice (25 g) was added. The product separated was filtered off and a sample for analysis was sublimed *in vacuo* as under (a), m.p. 260° and mixed m.p. with the compound prepared as under (a) was undepressed, yield: 0·6 g.

*Decarboxylation of* X *to 6-chloroimidazo*(1.2-b)*pyridazine* (XI)

The above X (100 mg) was thoroughly mixed with Cu bronze (150 mg) and the mixture was heated in a metallic block at 200–250° in a glass tube. In the cold part of the tube the sublimate deposited in 2 zones. The first, near to the heating block, was identified as the unchanged acid and the second consisted of XI. This was found identical with an authentical sample of 6-chloroimidazo(1.2-b)-pyridazine, prepared directly from I.[8]

*6-Hydrazino-2-methylimidazo*(1.2-b)*pyridazine-3-carboxylic acid hydrazide* (XII)

Compound VII (2·39 g) was treated with hydrazine hydrate (10 ml of 80%) and the mixture heated under reflux for 15 min. Upon cooling the filtered product was washed with cold water (1·8 g) and crystallized from N,N-dimethylformamide to give the pure compound; m.p. 304–307°. (Found: C, 43·20; H, 4·97; N, 44·18; $C_8H_{11}N_7O$ requires: C, 43·44; H, 5·01; N, 44·32%.)

The compound formed a trihydrochloride, m.p. >320°. (Found: N, 29·42; $C_8H_{14}Cl_3N_7O$ requires: N, 29·66%.)

*2-Methyl-6-(4'-phenylthiosemicarbazido)imidazo*(1.2-b)*pyridazinoyl-3-(4'-phenylthiosemicarbazide)* (XIII, R = Ph)

To a soln of XII (2·21 g) in N,N-dimethylformamide (10 ml) phenyl isothiocyanate (1·35 g) was added and the reaction mixture was heated on a water bath for 10 min. Upon cooling the reaction mixture was poured onto ice (30 g) and left overnight on ice. The product was collected and crystallized from N,N-dimethylformamide-EtOH (1:1) to give the pure compound with m.p. 280–282°. (Found: C, 53·74; H, 4·52; N, 25·58; $C_{28}H_{21}N_9OS_2$ requires: C, 53·74; H, 4·31; N, 25·64%.)

*6-(4'-Cyclohexylthiosemicarbazido)-2-methylimidazo*(1.2-b)*pyridazinoyl-3-(4'-cyclohexylthiosemicarbazide)* (XIII, R = $C_6H_{11}$)

The compound was prepared in the same way as described above; m.p. 276–277° from N,N dimethylformamide. (Found: C, 52·80; H, 6·94; N, 24·93; S, 12·58; $C_{28}H_{39}N_9OS_2$ requires: C, 52·44; H, 6·60; N, 25·04; S, 12·74%.)

*6-p-Hydroxybenzylidenehydrazino-2-methylimidazo*(1.2-b)*pyridazine-3-carboxylic acid hydrazide* (XIV, $R_1$ = $R_2$ = $R_3$ = H, $R_4$ = *p*-HO—$C_6H_4$)

Compound XII (2·21 g) was suspended in EtOH (30 ml), *p*-hydroxybenzaldehyde (1·18 g) and few drops of conc HCl were added. The reaction mixture was left at room temp for 24 hr and thereafter poured into water. The separated product (2·5 g) was crystallized from N,N-dimethylformamide–toluene (1:1) to give yellow crystalline powder of m.p. 301–304°. (Found: C, 55·27; H, 4·92; N, 29·89; $C_{15}H_{13}N_7O_2$ requires: C, 55·38; H, 4·65; N, 30·14%.)

*6-Benzylidenehydrazino-2-methylimidazo*(1.2-b)*pyridazine-3-carboxylic acid benzylidenehydrazide* (XIV, $R_2$ = H, $R_4$ = Ph, $R_1R_3$ = =CHPh)

A suspension of XII (2·21 g) in EtOH (25 ml) was treated with benzaldehyde (2·2 g) and few drops of AcOH. The mixture was heated under reflux for 1 hr, the product filtered off and crystallized from N,N-dimethylformamide–toluene (1:2). The colourless microcrystals had m.p. 270–271°. (Found: C, 66·37; H, 5·63; N, 24·90; $C_{22}H_{18}N_7O$ requires: C, 66·48; H, 5·74; N, 24·67%.) In an analogous way the following derivs were prepared:

(i) *6-Isopropylidenehydrazino-2-methylimidazo*(1.2-b)*pyridazine-3-carboxylic acid isopropylidenehydrazide* (XIV, $R_1R_3$ = =$CMe_2$, $R_2$ = $R_4$ = Me) m.p. 290–292° (N,N-dimethylformamide–acetone, 1:1). (Found: C, 55·78; H, 7·62; N, 32·85; $C_{14}H_{19}N_7O$ requires: C, 55·80; H, 7·57; N, 32·54%.)

(ii) *6-p-Bromobenzylidenehydrazino-2-methylimidazo*(1.2-b)*pyridazine-3-carboxylic acid p-bromobenzylidene hydrazide* (XIV, $R_1R_3$ = =$CHC_6H_4Br(p)$, $R_2$ = H, $R_4$ = *p*-$BrC_6H_4$), m.p. 320–321° from N,N-dimethylformamide. (Found: C, 47·84; H, 3·12; N, 17·92; $C_{22}H_{17}Br_2N_7O$ requires: C, 47·57; H, 3·08; N, 17·66%.)

(iii) *2-Methyl-6-p-nitrobenzylidenehydrazino-imidazo*(1.2-b)*-pyridazine-3-carboxylic acid p-nitrobenzylidene hydrazide* (XIV, $R_1R_3$ = =$CHC_6H_4NO_2$-*p*, $R_2$ = H, $R_4$ = $C_6H_4Br$-*p*), m.p. 330° from N,N-dimethylformamide. (Found: C, 54·02; H, 3·82; N, 25·86; $C_{22}H_{17}N_9O_6$ requires: C, 54·20; H, 3·52; N, 25·86%.)

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