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SYNTHESIS OF PYRIDAZINE DERIVATIVES—XV

SOME ELECTROPHILIC SUBSTITUTIONS ON IMIDAZO[1,2-b]-PYRIDAZINES[1]

J. KOBE, B. STANOVNIK and M. TIŠLER

Department of Chemistry, University of Ljubljana, Yugoslavia

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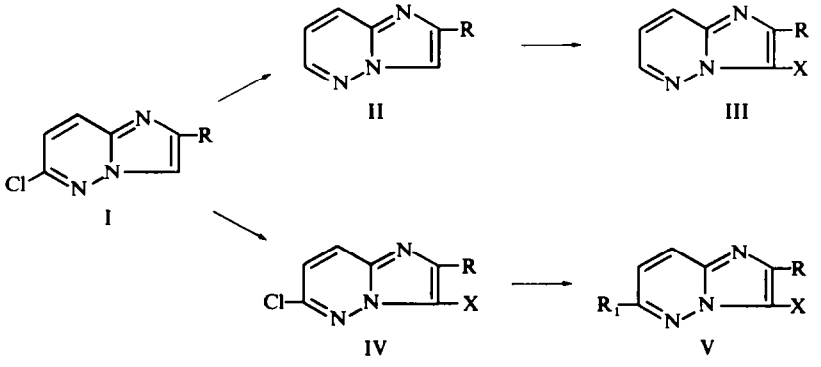
Abstract—Imidazo[1.2-b]pyridazine, which has been prepared for the first time, and several of its analogs were submitted to electrophilic substitution, such as halogenation, nitration and sulphonation. NMR data for several imidazo[1.2-b]pyridazines are included and from these conclusive evidence is obtained that electrophilic substitution occurs at position 3.

THE present investigation is part of a general study of azabicyclic 10 π-electron systems with the specific object to study electrophilic substitution of imidazo[1.2-b]pyridazines which have been prepared recently.[2] In order to examine whether they behave like imidazoles under conditions of electrophilic substitution several compounds have been submitted to halogenation, nitration and sulphonation.

The parent compound II (R = H) has been prepared for the first time by catalytic dehalogenation of its 6-chloro analog I (R = H) and is a weaker base (pK_a = 4·4 in water at 20°) than imidazole or benzimidazole.[3] It is easily brominated by means of bromine in acetic acid or N-bromosuccinimide to give the corresponding 3-bromo derivative III (R = H, X = Br). Likewise, 6-chloro-2-methylimidazo[1.2-b]pyridazine (I, R = Me) is brominated at position 3. This electrophilic substitution which proceeds under relatively mild reaction conditions parallels the reactivity of simple imidazoles. The orientation of the entering halogen is similar to that of the related imidazo(1.2-a)-pyridines[4–6] and its position has been ascertained by means of NMR spectra.

6-Chloro-2-methylimidazo[1.2-b]pyridazine when treated with excess bromine in glacial acetic acid at room temperature formed a complex which analyzes for three atoms of bromine per molecule. The compound liberated iodine from a solution of KI, but the complex is otherwise quite stable and can be crystallized unchanged from



acetic acid. With an ethanolic KOH solution it is transformed into IV (R = Me, X = Br). Such complexes are known with several other azaheterocycles such as pyridine or quinoline,[7] benzothiazole[8] or fused analogs, such as imidazo[2.1-b]-thiazole.[9] Similarly 4-methyl- or 4-phenylcinnoline form with bromine adducts which are believed to be perbromides.[10,11]

Imidazo[1.2-b]pyridazine and its 6-chloro or 6-chloro-2-methyl analogs have been nitrated or sulphonated to give the corresponding 3-substituted derivates. All nitro derivatives are sensitive to light and they do not form salts with mineral acids as do the parent compounds.

As might be expected, a greater reactivity for nucleophilic displacement is observed for the halogen at position 6 and 3-bromo-6-chloroimidazo[1.2-b]pyridazines react readily with hydrazine to form the corresponding 6-hydrazino derivatives. However, controlled catalytic dehalogenation removes first the bromine at position 3.

Relatively mild reaction conditions for the foregoing electrophilic substitutions and correlation of NMR spectra exclude the possibility of substitution in other positions than position 3 of the imidazole ring. For a related ring system, i.e. imidazo-(1.2-a)pyridine the electron density calculations[12] and frontier electron density calculations[5] have successfully predicted position 3 to be the most succeptible for electrophilic substitution. Indeed, this has been verified experimentally. It can be further postulated that the introduction of an extra nitrogen in the 6-membered ring, as in the case of imidazo[1.2-b]pyridazines, would not exert much influence on the electron distribution in the imidazole ring and thus predisposition for electrophilic substitution at position 3 remains unaltered.

NMR spectra of the parent imidazo[1.2-b]pyridazine and its 3-bromo derivative are given in Figs. 1 and 2 and values for chemical shifts and coupling constants are summarized in Table 1.

From the analogy to pyridazine[13] and pyridazine N-oxides[14] the order of chemical shifts in the pyridazine ring of imidazo[1.2-b]pyridazine and its derivatives can be predicted to be $H_6 < H_8 < H_7$, and this holds likewise for the magnitude of the coupling constants. The NMR spectrum of imidazo[1.2-b]pyridazine (Fig. 1) shows three well separated quartets with the coupling constants 10, 4·5 and 2·0 c/s due to an ABX system, in which the chemical shift difference is large when compared to the largest coupling constant. The downfield quartet is ascribed to H_6, since it disappears in the 6-chloro analog.

A decision as to which member of the ABX system is H_7 and H_8 can be reached on account of long range coupling constant $J_{3,8} = 0{\cdot}8$ c/s, which has been observed also in the case of various azaindenes.[5,15,16] On this basis the quartet, which is further split to an octet, is assigned to correspond to H_8. The remaining upfield quartet can therefore correspond only to H_7.

The protons attached on the imidazole ring of imidazo[1.2-b]pyridazine appear in the NMR spectrum as an AB pattern with the coupling constant $J_{2,3} = 1{\cdot}0$. A part of this is split further by a long range coupling constant $J_{3,8} = 0{\cdot}8$ c/s. For this reason it is easly to differentiate between H_2 and H_3. Similarly, the position of substituents on the imidazole ring can be determined.

As already mentioned,[17] 3-amino-6-chloropyridazine could afford with bromo-acetone 2-methyl or the isomeric 3-methyl derivative of 6-chloroimidazo[1.2-b]pyri-dazine, depending upon the direction of cyclization. Since long range coupling constant

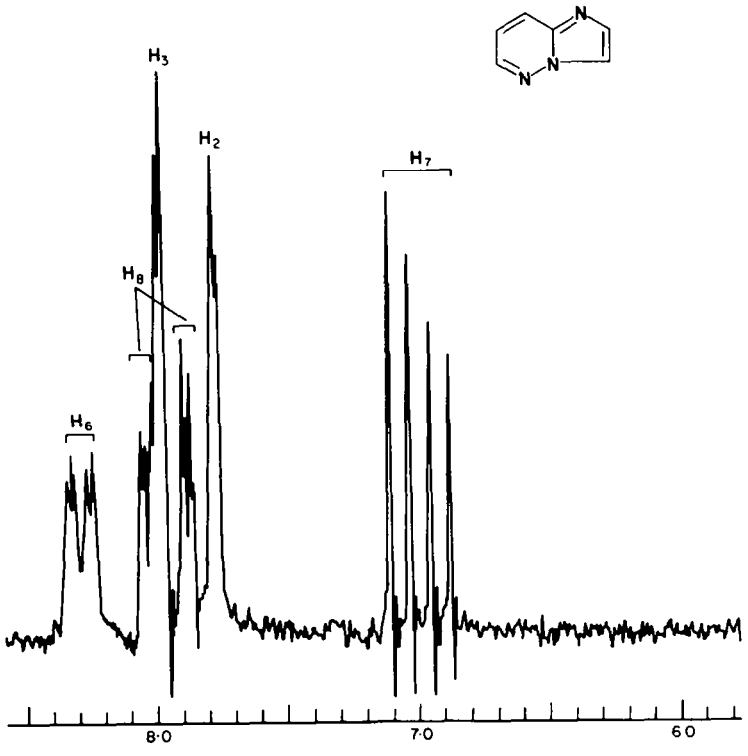


FIG. 1.

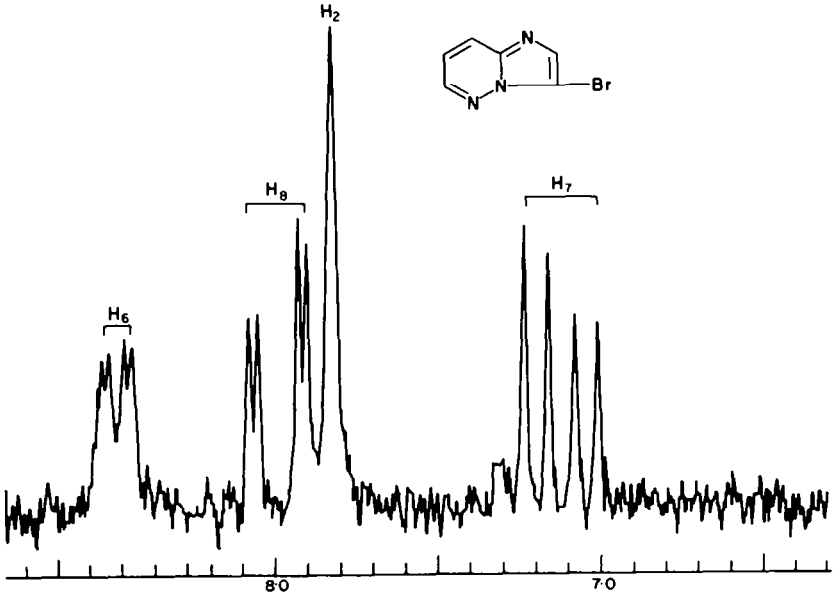


FIG. 2.

TABLE 1.

Compound	Chemical shift $-\tau$						Coupling constants, c/s					
	H_2	H_3	H_6	H_7	H_8	CH_3	$J_{2,3}$	$J_{6,7}$	$J_{7,8}$	$J_{6,8}$	$J_{3,8}$	$J_{H_3,2\text{-}CH_3}$
Imidazo(1.2-b)pyridazine[a]	2·21	2·01	1·70	3·00	2·05		1·0	4·5	10·0	2·0	0·8	
6-Chloroimidazo(1.2-b)pyridazine[b]	2·04	1·72		2·68	1·75		1·0		10·0		0·8	
3-Bromoimidazo(1.2-b)pyridazine[a]	2·21		1·53	2·90	2·03			4·5	10·0	2·0		
3-Bromo-6-chloroimidazo-(1,2-b)pyridazine[c]	1·85			2·40	1·56				10·0			
2-Methylimidazo(1.2-b)pyridazine[a]		2·78	2·32	3·54	2·70	7·67		4·5	10·0	2·0	0·8	0·5
3-Nitroimidazo(1.2-b)pyridazine[a]	1·34		1·22	2·56	1·80			4·5	10·0	2·0		
2-Methyl-6-chloroimidazo-(1.2-b)pyridazine[b]		1·97		2·70	1·91	7·56			10·0		0·8	0·5
2-Methyl-3-bromo-6-chloroimidazo(1.2-b)pyridazine[d]				2·78	2·10	7·90			10·0			

Solvents: [a] $CDCl_3$; [b] CD_3COCD_3; [c] CD_3SOCD_3; [d] $(CF_3CO)_2O$

between H_3 and H_8 is observed ($J_{3\cdot8}$ = 0·8 c/s), the reaction product is unequivocally 2-methyl-6-chloroimidazo[1.2-b]pyridazine.

Another important point, which can be solved by means of NMR spectra is the position of the entering group upon an electrophilic substitution in this heterocyclic system. As the signal for H_8 appears as a clear quartet (instead of an octet in the unsubstituted compound) and the signal for another proton attached to the imidazole ring as a sharp singlet (Fig. 2), the only position on which electrophilic substitution can occur is thus the position 3.

The spectra of all other imidazo[1.2-b]pyridazines are in respect to coupling constants and chemical shifts very similar.

EXPERIMENTAL

NMR spectra of saturated solns of compounds investigated were recorded in CD_3SOCD_3, $CDCl_3$ or $(CF_3CO)_2O$ (TMS as an internal standard) on a Varian A-60 and Perkin–Elmer NMR spectrometer. UV spectra: Beckman Model DU Spectrophotometer; M.ps: Kofler m.p. apparatus and are corrected.

Imidazo[1.2-b]*pyridazine* (II, R = H)

Compound I (R = H; 1·53 g) was dissolved in dry ether (150 ml) and palladized charcoal (0·5 g of 5%) and Et_3N (1·4 ml) were added. The mixture was stirred in an atmosphere of H_2 until 220 ml were absorbed. The suspension was filtered and the solvent evaporated *in vacuo*. The crude product (0·9 g, 75%) was crystallized from pet. ether or purified by sublimation at 40°/15 mm or crystallized from AcOEt and pet. ether (1:2), m.p. 53–55°. (Found: C, 60·28; H, 4·20; N, 34·81; $C_6H_5N_3$ requires: C, 60·49; H, 4·23; N, 35·28%); λ_{max}^{EtOH} 2220 and 3300 Å (ε 19,480 and 3990).

The compound formed a hydrochloride obtained by dissolving the base (1·19 g) in abs. EtOH (3 ml) and then adding a sat. ethereal soln of HCl (80 ml). The colourless hydrochloride had m.p. 240°, yield 93%. (Found: N, 26·99; $C_6H_6ClN_3$ requires: N, 27·01%); λ_{max}^{EtOH} 2240 and 3250 Å (ε 17,750 and 3690).

The hydrobromide (with conc. HBr) was formed similarly, m.p. 285°. (Found: N, 21·14; $C_6H_6BrN_3$ requires: N, 21·00%).

A quaternary salt was obtained from an aqueous soln of the base (0·4 g in 5 ml water) and 1 equiv of MeI and the reaction mixture left aside at room temp for 2 days, and then 1 day on ice. The methyl imidazo(1.2-b)-pyridazinium iodide (0·325 g) was purified by crystallization from EtOH, m.p. 285–286°. (Found: C, 32·50; H, 3·37; N, 16·27; $C_7H_8IN_3$ requires: C, 32·21; H, 3·09; N, 16·09%.)

3-*Bromoimidazo*[1.2-b]*pyridazine* (III, R = H, X = Br)

a. A soln of imidazo[1.2-b]pyridazine (1·19 g) in $CHCl_3$ (10 ml) was treated with N-bromosuccinimide (1·78 g) and the reaction mixture heated under reflux for 5 min. Upon standing for 1 hr at room temp the mixture was made alkaline with a sat Na_2CO_3 aq (10 ml), shaken and the $CHCl_3$ layer separated. After drying over Na_2SO_4, $CHCl_3$ was evaporated and the crude product crystallized from EtOH (1·6 g, 80%), m.p. 163°. (Found: C, 36·59; H, 2·20; N, 21·75; $C_6H_4BrN_3$ requires: C, 36·39; H, 2·04; N, 21·21%); λ_{max}^{EtOH} 2300 and 3340 Å (ε 20,950 and 3,640).

b. A soln of Br (0·54 g) in glacial AcOH (1 ml) was added to a stirred soln of imidazo(1.2-b)pyridazine (0·4 g) in glacial AcOH (3 ml). Heat was evolved and upon cooling the hydrobromide salt of III (R = H, X = Br; 0·43 g, 46%) separated. Upon crystallization from AcOH it had m.p. 284–285°. (Found: N, 15·09; $C_6H_5Br_2N_3$ requires: N, 15·06%); λ_{max}^{EtOH} 2280 and 3320 Å (ε 22,450 and 4,310).

The hydrobromide salt was dissolved in 0·2N NaOH aq, the soln extracted with $CHCl_3$, the $CHCl_3$ layer separated and dried over Na_2SO_4. The solvent was evaporated to dryness and the residue crystallized from EtOH. The compound thus obtained was shown by its m.p. and mixed m.p. to be identical to the compound prepared by method (a).

3-*Nitroimidazo*[1.2-b]*pyridazine* (III, R = H, X = NO_2)

Compound II (R = H; 1·19 g) was added under stirring to conc. H_2SO_4 (4·7 ml) and the mixture cooled to 10° with ice. Stirring was continued and during 5 min HNO_3 (1·4 ml, d = 1·39) was added dropwise.

The reaction mixture was then stirred at room temp for 20 min and poured onto crushed ice (40 g). The separated product was washed thoroughly with water and crystallized from EtOH to give colourless crystals (0·9 g, 55%), m.p. 206–208°. (Found: C, 43·95; H, 2·53; N, 34·22; $C_6H_4N_4O_2$ requires: C, 43·91; H, 2·46; N, 34·14%).

Similar results were recorded when using more concentrated HNO_3 (d = 1·5) and only the mononitro derivative was formed.

Catalytic dehalogenation of 3-bromo-6-chloroimidazo[1.2-b]*pyridazine*

Compound IV (R = H, X = Br; 1·0 g), 5% palladized charcoal (0·6 g) and Et_3N (0·64 ml) in EtOH (150 ml) were stirred in an atmosphere of H_2 until 120 ml were absorbed. The solvent was removed *in vacuo* after filtration and the residue was washed with water. The remaining solid was crystallized from EtOH and crystals of the starting material (0·15 g) were separated. The ethanolic filtrate was evaporated to dryness and the residue crystallized from water. The unpure I (R = H) melted at 109–113° and was purified for analytical purposes by sublimation at 100–115°/1 mm, m.p. 115°, mixed m.p. with an authentic specimen[2] was undepressed.

6-*Chloro*-3-*nitroimidazo*[1.2-b]*pyridazine* (IV, R = H, X = NO_2)

Compound I (R = H; 3·7 g) was mixed with conc. H_2SO_4 (4 ml) under stirring and the mixture cooled on ice below 10°. Stirring was continued and HNO_3 (2·5 ml of d = 1·5) was added dropwise during 5 min. The reaction mixture was stirred thereafter at room temp for 30 min and then poured onto crushed ice (80 g). The crude product was crystallized from EtOH–water (5:1) and the pure compound had m.p. 210°. (Found: C, 36·45; H, 1·90; N, 28·07; $C_6H_3ClN_4O_2$ requires: C, 36·29; H, 1·52; N, 28·21%).

6-*Hydrazino*-3-*nitroimidazo*[1.2-b]*pyridazine* (V, R = H, R_1 = $NHNH_2$, X = NO_2)

The above compound (1·0 g) was suspended in 80% hydrazine hydrate (5 ml) and the mixture heated under reflux for 10 min. Upon cooling on ice a product separated and was crystallized from 50% EtOH, m.p. 188–189°. (Found: C, 37·03; H, 3·36; N, 43·41; $C_6H_6N_6O_2$ requires: C, 37·11; H, 3·11; N, 43·29%).

6-*Chloroimidazo*[1.2-b]*pyridazinyl*-3-*sulfonic acid* (IV, R = H, X = SO_3H)

Compound I (R = H; 1·53 g) was suspended in chlorosulfonic acid (6 ml) and then heated on a water bath until evolution of HCl had subsided (after about 1·5 hr). The reaction mixture was cooled with ice and thereafter poured onto crushed ice (30 g). The product was filtered off to give 1·75 g of the crude acid. For analysis a sample was sublimed at 280°/0·1 mm; m.p. 328–330°. (Found: C, 30·98; H, 2·12; N, 18·18; $C_6H_4ClN_3O_3S$ requires: C, 30·84; H, 1·73; N, 17·99%).

2-*Methylimidazo*[1.2-b]*pyridazine* (II, R = Me)

To a soln of I (R = Me; 1·67 g) in abs. EtOH (50 ml) a soln of KOH (0·56 g) in abs. EtOH (10 ml) and 5% palladized carbon (1·5 g) were added. The suspension was stirred in an atmosphere of H_2 until 225 ml of H_2 were absorbed. Upon filtration the solvent was evaporated *in vacuo* at 45°. The crude base was converted then into the hydrochloride salt by adding a sat ethereal soln of HCl (80 ml), m.p. 205–210°.

The hydrochloride salt was treated with sat Na_2CO_3 aq (10 ml) and extracted 3 times with 25 ml portions of ether. The combined ethereal extracts were dried over Na_2SO_4 and the solvent evaporated *in vacuo* to yield colourless needles (0·9 g, 67%), m.p. 50°. The base may be purified by crystallization from pet ether or by sublimation at 45°/15 mm. (Found: C, 63·02; H, 5·47; N, 31·44; $C_7H_7N_3$ requires: C, 63·14; H, 5·30; N, 31·56%).

3-*Bromo*-6-*chloro*-2-*methylimidazo*[1.2-b]*pyridazine* (IV, R = Me, X = Br)

a. A soln of I (R = Me; 1·67 g) in glacial AcOH (25 ml) was treated dropwise at room temp with excess Br. The product was filtered off and washed with glacial AcOH. Upon crystallization from AcOH (yield 81%) the pure complex melted at 217–220°. (Found: C, 20·17; H, 2·07; N, 10·57; $C_7H_5Br_3ClN_3$ requires: C, 20·69; H, 1·24; N, 10·34%).

b. The above complex (2·03 g) was suspended in an ethanolic soln of KOH (2 g in 30 ml EtOH) and the mixture heated on a water bath under reflux. After some time the product dissolved and soon after a new ppt was formed. It was collected and crystallized from EtOH to give 1·1 g of the pure compound, m.p. 154°. (Found: C, 33·97; H, 2·29; N, 16·89; $C_7H_5BrClN_3$ requires: C, 34·11; H, 2·05; N, 17·04%).

This compound can be obtained by direct bromination at room temp as described under (a), but employing equimolal quantities of Br_2 and the starting compound.

c. To a soln of I (0·84 g) in $CHCl_3$ (10 ml) N-bromosuccinimide (0·87 g) was added and the mixture was heated under reflux for 10 min. To the cooled reaction mixture 15% $NaHCO_3$ aq (20 ml) was added, the $CHCl_3$ layer separated, dried over Na_2SO_4 and the solvent evaporated *in vacuo*. The residue was crystallized from EtOH giving 1·05 g of the pure compound, m.p. 154° (the compound sublimes strongly at temp over 110°). (Found: N, 16·92; $C_7H_5BrClN_3$ requires: N, 17·04%). The compound is identical with the product prepared as described under (b).

6-Chloro-2-methyl-3-nitroimidazo[1.2-b]*pyridazine* (IV, R = Me, X = NO_2)

To stirred conc H_2SO_4 (4 ml), compound I (R = Me; 0·84 g) was added and the mixture cooled to −10° and then conc HNO_3 (1·2 ml, d = 1·5) was added dropwise during 10 min. Thereafter, the mixture was left to warm to room temp and stirring was then continued for another 20 min. The mixture was poured onto ice (40 g) and the resulting ppt was filtered off and crystallized from EtOH to give the pure compound as pale yellow needles (yield 57%), m.p. 196°. (Found: C, 39·64; H, 2·83; N, 26·62; $C_7H_5ClN_4O_2$ requires: C, 39·56; H, 2·37; N, 26·36%).

2-Methyl-3-nitro-6-hydrazinoimidazo [1.2-b]*pyridazine* (V, R = Me, R_1 = $NHNH_2$, X = NO_2)

The above nitro compound (2·12 g) was suspended in EtOH (10 ml), 80% hydrazine hydrate (2 g) was added and the mixture was heated under reflux for 3 hr. The product was crystallized from N,N-dimethylformamide (yield 71%), m.p. 252–255°. (Found: C, 40·11; H, 4·01; N, 40·18; $C_7H_8N_6O_2$ requires: C, 40·38; H, 3·87; N, 40·37%).

The compound formed a *p*-hydroxybenzylidene derivative, m.p. over 340° (from N,N-dimethylformamide). (Found: N, 26·94; $C_{14}H_{11}N_7O_4$ requires: N, 26·91%).

6-(4'-Cyclohexylthiosemicarbazido) 2-methyl-3-nitroimidazo[1.2-b]*pyridazine* (V, R = Me, X = NO_2, R_1 = C_6H_{11}—NHCSNHNH—)

To a hot soln of V (R = Me, R_1 = $NHNH_2$, X = NO_2; 1·05 g) in N,N-dimethylformamide cyclohexylisothiocyanate was added and the mixture was left to cool slowly to room temp. The product was crystallized from N,N-dimethylformamide (yield 66%), m.p. 238–240°. (Found: N, 27·82; $C_{14}H_{19}N_7O_2S$ requires: N, 28·06%.)

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