Perchloroimidazo[1,2-*b*]pyridazine. Synthesis and Nucleophilic Substitution.

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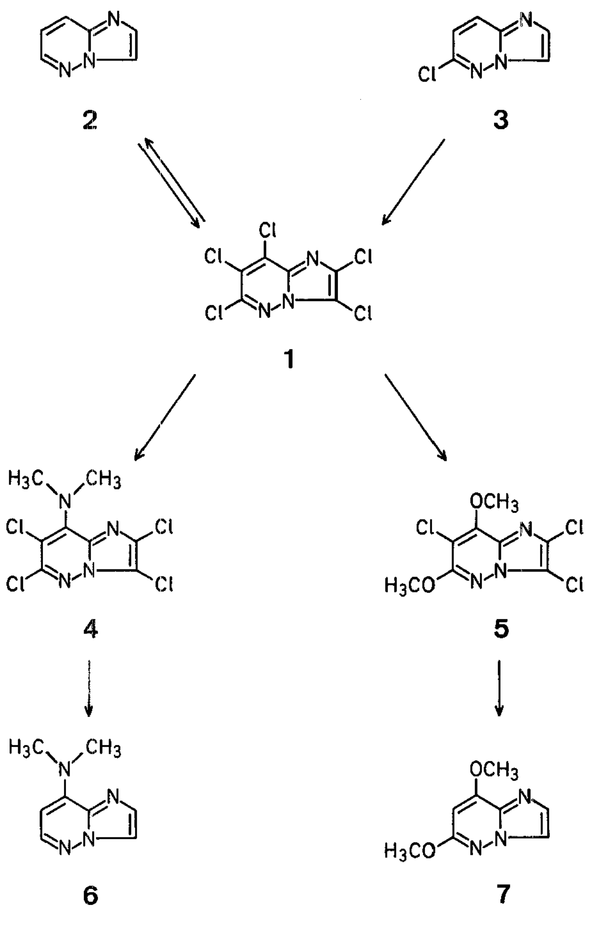
The only halogenated imidazo[1,2-*b*]pyridazines hitherto described are the 3-bromo-[1], 6-chloro-[2], and 3-bromo-6-chloro[2] derivatives. We now report the synthesis of 2,3,6,7,8-pentachloroimidazo[1,2-*b*]pyridazine and the nucleophilic replacement of its chlorine atoms by other functional groups.

2,3,6,7,8-Pentachloroimidazo[1,2-*b*]pyridazine (**1**) was obtained in good yield by treatment of either imidazo[1,2-*b*]pyridazine (**2**) or 6-chloroimidazo[1,2-*b*]pyridazine (**3**) with phosphorus(V)-chloride in a sealed tube at 260–280°. The elemental analysis of **1**, the N.M.R. spectrum (absence of proton signals), and the mass spectrum (parent peak at $m/e = 289$ and a characteristic 5-chlorine isotope pattern) are in agreement with the proposed structure. Hydrogenation of **1** using palladium on carbon as the catalyst gave imidazo[1,2-*b*]pyridazine (**2**); this result indicates that no skeletal change occurs under the reaction conditions employed in the preparation of **1**.



When perchloroimidazo[1,2-*b*]pyridazine (**1**) was treated with dimethylamine in aqueous solution, a mono-dimethylamino-tetrachloroimidazo[1,2-*b*]pyridazine was obtained. Dehalogenation of this compound with hydrogen in the presence of palladium on carbon yielded a dimethylaminoimidazo[1,2-*b*]pyridazine. The N.M.R. spectrum of this latter compound shows an AX pattern at $\tau = 2.11$ and $\tau = 4.25$ ($J_{67} = 5.8$ Hz), due to H_6 and H_7 respectively, an AB pattern at $\tau = 2.45$ and $\tau = 2.18$ ($J_{23} = 0.9$ Hz) characteristic for H_2 and H_3 and a singlet at $\tau = 6.55$ for two equivalent methyl groups. These data together with the absence of the long-range coupling constant J_{38} typical for all imidazo[1,2-*b*]pyridazines unsubstituted on positions 3 and 8[1] show that the compound is 8-dimethylaminoimidazo[1,2-*b*]pyridazine (**6**).

Treatment of perchloroimidazo[1,2-*b*]pyridazine (**1**) with sodium methoxide in methanol gave a dimethoxy compound. The N.M.R. spectrum of the corresponding dehalogenated compound showed two singlets at $\tau = 6.02$ and 6.10 for two methoxy groups at positions 6 and 8, respectively, a singlet at $\tau = 4.15$ corresponding to H_7, an AB pattern at $\tau = 2.65$ and $\tau = 2.47$, due to H_2 and H_3, respectively. The chemical shifts, the magnitude of coupling constants, and the absence of the long range coupling constant J_{38} show that compound is 6,8-dimethoxyimidazo[1,2-*b*]pyridazine (**7**).

Melting points were determined using a Kofler micro hot stage and are corrected. I.R. spectra were recorded on a Perkin-Elmer 137 Infracord as KBr discs, N.M.R. spectra of a solution in $CDCl_3$ were taken on a JEOL JNM-C-60HL spectrometer using TMS as an internal standard, mass spectra were recorded on a CEC 21-110 C instrument using direct sample insertion into the ion source, which operated at 120°, and an ionization voltage of 70 volt.

2,3,6,7,8-Pentachloroimidazo[1,2-*b*]pyridazine (1):

Method A, from imidazo[1,2-*b*]pyridazine: A mixture of imidazo[1,2-*b*]pyridazine (0.2 g) and phosphorus(V)-chloride (2.0 g) was heated in a sealed tube at 280° for 3 hr. The tube was cooled, opened, and the contents were poured into a mixture of chloroform (20 ml) and ice (20 g). The mixture was neutralized with sodium hydrogen carbonate. The chloroform layer was separated, dried with sodium sulfate, and filtered. The chloroform was evaporated in vacuo and the remaining crystals were recrystallized from ethanol; yield: 0.25 g (52%); m.p. 132°.

$C_6Cl_5N_3$	calc.	C 24.73	H 0.00	N 14.43
(291.35)	found	25.01	0.61	14.72

Mass spectrum: $M^+ = 289$.

Method B, from 6-chloroimidazo[1,2-*b*]pyridazine: A procedure as described under A was employed, except that the sealed tube was heated at 260°.

8-Dimethylamino-2,3,6,7-tetrachloroimidazo[1,2-*b*]pyridazine (4):

Perchloroimidazo[1,2-*b*]pyridazine (0.5 g) was added to a 40% aqueous solution (5 ml) of dimethylamine. The mixture was heated at reflux temperature for 2 hr. The mixture was then cooled and the precipitate collected by filtration and dried under vacuum; yield: 0.47 g (90%); m.p. 157–158° (after sublimation) at 120°/1 mm.

$C_8H_6N_4Cl_4$	calc.	C 32.03	H 2.02	N 18.68
(299.8)	found	32.37	2.35	18.48

Mass spectrum: $M^+ = 298$.

N.M.R. ($CDCl_3$): $\tau = 6.65$ (s) for $—N(CH_3)_2$.

6,8-Dimethoxy-2,3,7-trichloroimidazo[1,2-*b*]pyridazine (5):

Sodium (0.460 g) was added to anhydrous methanol (10 ml). The solution was cooled to room temperature and a solution of perchloroimidazo[1,2-*b*]pyridazine (0.58 g) in anhydrous methanol (10 ml) was added. The mixture was heated at reflux temperature for 1.5 hr. Then water was added until a precipitate began to form. The mixture was cooled in the refrigerator for 1 hr, the precipitate was collected by filtration, dried under vacuum, and recrystallized from methanol; yield: 0.5 g (87%); m.p. 144–146°.

$C_8H_6N_3O_2Cl_3$	calc.	C 34.01	H 2.14	N 14.87
(282.52)	found	33.76	2.34	14.64

Mass spectrum: $M^+ = 281$.

Imidazo[1,2-*b*]pyridazine (2):

Perchloroimidazo[1,2-*b*]pyridazine (0.3 g) was dissolved in methanol (50 ml), and 5% palladium on carbon (0.1 g) was added. The mixture was hydrogenated at room temperature until the theoretical amount of hydrogen was absorbed. The catalyst was removed by filtration and the filtrate evaporated in vacuo. Water (5 ml) was added to the residue, the solution made alkaline by the addition of 5% aqueous sodium hydroxide, and extracted with chloroform (3 × 10 ml). The combined chloroform extracts were dried with sodium sulfate, filtered, and evaporated in vacuo. The residue was purified by sublimation at 50°/1 mm; yield: 40 mg. The product was identical in every respect with compound **2** prepared previously[1].

8-Dimethylaminoimidazo[1,2-*b*]pyridazine (6):

A procedure similar to that described for the preparation of compound **2** was employed; yield: 110 mg (65%). The compound was purified by sublimation at 60°/1 mm; m.p. 69°.

$C_8H_{10}N_4$	calc.	C 59.24	H 6.21	N 34.55
(162.20)	found	58.97	6.29	34.42

Mass spectrum: $M^+ = 162$.

6,8-Dimethoxyimidazo[1,2-*b*]pyridazine (7):

A procedure similar to that described for the preparation of compound **2** was employed; yield: 150 mg (80%); m.p. 157°, from methanol/water (1:1).

$C_8H_9N_3O_2$	calc.	C 53.63	H 5.06	N 23.45
(179.19)	found	53.36	5.24	23.62

Mass spectrum: $M^+ = 179$.

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[1] J. Kobe, B. Stanovnik, M. Tišler, Tetrahedron **24**, 239 (1968).

[2] B. Stanovnik, M. Tišler, Tetrahedron **23**, 387 (1967).