

REACTIVITY OF IMIDAZO[1,2-b]PYRIDAZINE 1-OXIDES

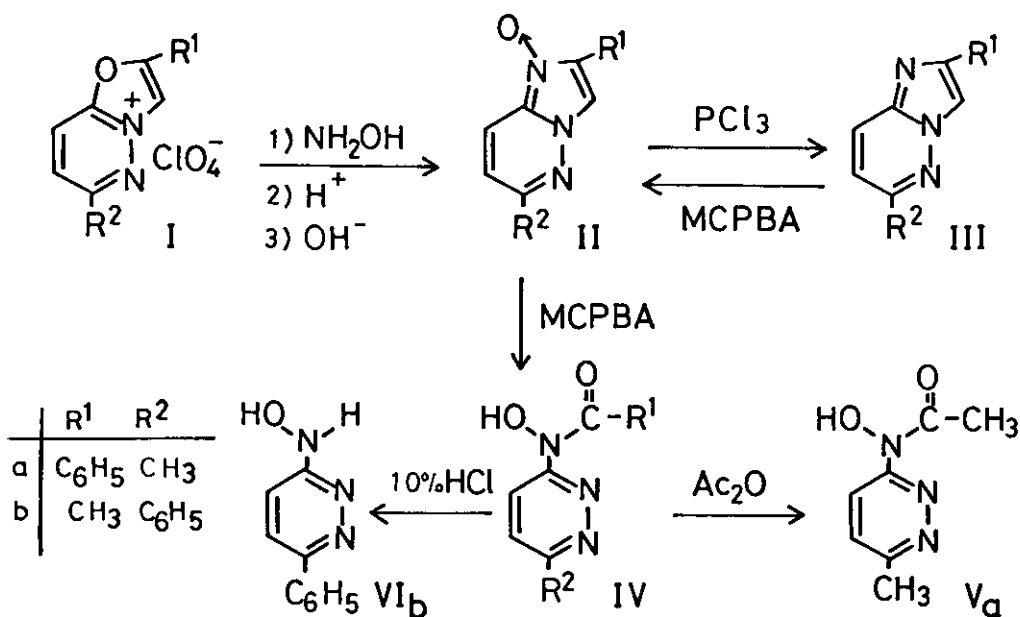
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The treatment of either imidazo[1,2-b]pyridazines(III) or their 1-oxides(II) with excess organic peracid resulted in the oxidative cleavage of imidazole moiety to give 3-(N-acylhydroxylamino)pyridazines(IV). The bromination and nitration of II gave the corresponding 3-substituted N-oxides(VII, IX, X, and XI). Rearrangement reaction of II with phosphoryl chloride or acetic anhydride afforded the deoxygenated 7-substituted imidazopyridazines, XII and XIII, respectively.

In the course of our studies on the synthesis and reaction of pi-deficient heteroaromatics, it was found that oxazolo[3,2-b]-pyridazinium perchlorates (I)¹⁾ reacted with hydroxylamine to furnish imidazo[1,2-b]pyridazine 1-oxides (II),²⁾ which could be potential precursors for physiologically active imidazo[1,2-b]pyridazines with additional functional groups on the ring.³⁾ As very few reports have been published on the reactivity of this

pi-excessive azole N-oxides,⁴⁾ we have now examined the reactivity of this system toward a couple of reagents.

Further oxidation of the N-oxide (IIb) with m-chloroperbenzoic acid (MCPBA) afforded 3-(N-acetylhydroxylamino)-6-phenylpyridazine (IVb) [38% ; mp 215-216°; IR $\nu_{\text{max}}^{\text{KBr}}$ (cm⁻¹) : 3250, 1695; NMR δ (ppm in CDCl₃) : 7.56 (1H, d, J=9Hz), 8.80 (1H, d, J=9Hz), 9.62 (1H, s, OH)] conceivably by oxidation at the 3-position and ring-opening with subsequent decarboxylation. The same compound (IVb) was also formed as the major product by the direct oxidation of the azole (IIIb), the deoxygenated product of IIb with phosphorous trichloride, in the same manner with excess MCPBA. This fact indicates that electrophilic reagents attack at the 3-position of imidazo[1,2-b]pyridazine 1-oxide system. Hydrolysis of IVb with



Scheme 1

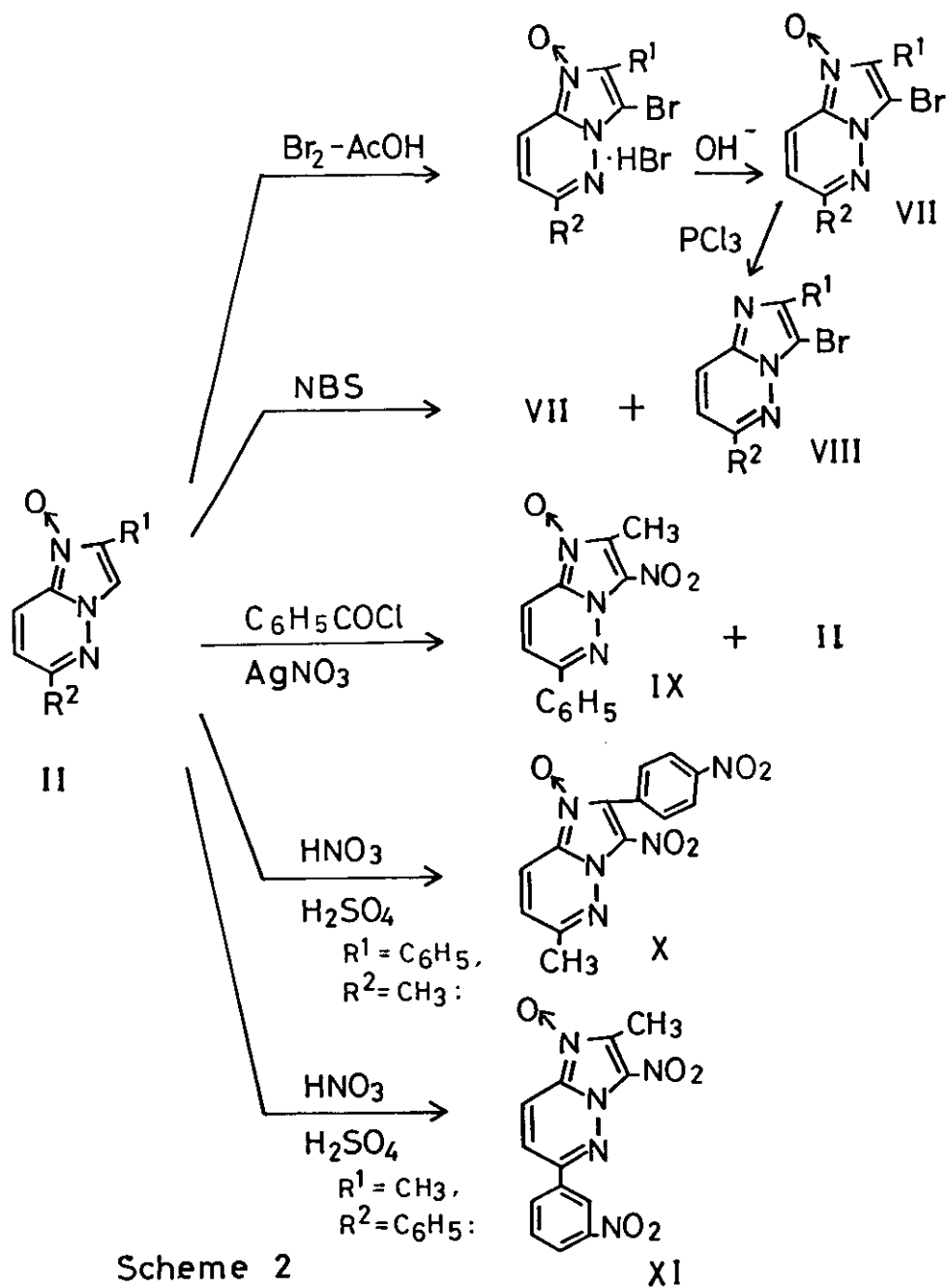
10% HCl gave 3-hydroxylaminopyridazine (VIb) [80% ; mp 185-186°; IR $\nu_{\text{max}}^{\text{KBr}}$ (cm^{-1}) : 3310, 3080 ; NMR δ (ppm in CD_3OD) : 7.40 (1H, d, $J=9\text{Hz}$), 7.75 (1H, d, $J=9\text{Hz}$)]. Heating of the benzamide (IVa) in acetic anhydride gave the corresponding acetamide (V).

Bromination of the N-oxide (IIa) with bromine in acetic acid at room temperature gave the hydrobromide of 3-bromo-N-oxide (VIIa.HBr) [57% ; mp 147-148° ; NMR δ (ppm in CF_3COOH) : 2.90 (3H, s), 7.73 (1H, d, $J=10\text{Hz}$), 8.34 (1H, d, $J=10\text{Hz}$)], which was converted with 5% NaOH into the free base (VIIa) [mp 190-191° ; NMR δ (ppm in CDCl_3) : 2.68 (3H, s), 6.97 (1H, d, $J=10\text{Hz}$), 8.21 (1H, d, $J=10\text{Hz}$)]. The 3-bromo-N-oxide (VIIa) was also obtained by heating of a solution of IIa and N-bromosuccinimide (NBS) in chloroform in 42% yield together with the deoxygenated 3-bromo-compound (VIIIa) [21% ; mp 180-180.5° ; NMR δ (ppm in CDCl_3) : 2.64 (3H, s), 6.94 (1H, d, $J=10\text{Hz}$), 7.80 (1H, d, $J=10\text{Hz}$)]. The similar reaction of IIb with NBS afforded VIIb [79% ; mp 207-208°; NMR δ (ppm in CDCl_3) : 2.58 (3H, s), 7.42 (1H, d, $J=10\text{Hz}$), 8.22 (1H, d, $J=10\text{Hz}$)] together with a trace amount of VIIIb [mp 120-120.5° ; NMR δ (ppm in CDCl_3) : 2.50 (3H, s), 7.48 (1H, d, $J=10\text{Hz}$), 7.86 (1H, d, $J=10\text{Hz}$)]. 3-Bromoimidazopyridazine 1-oxides (VII) were smoothly deoxygenated by heating with phosphorous trichloride in chloroform to give VIII.

Nitration of the N-oxide (IIb) with benzoyl chloride-silver nitrate in chloroform at room temperature gave after 40 days 3-nitro compound (IX) [11% ; mp 221-222°(dec.) ; NMR δ (ppm in DMSO- d_6) : 2.70 (3H, s), 8.23 (1H, d $J=10$ Hz), 8.60 (1H, d, $J=10$ Hz), 7.53-7.70 (3H, arom.), 8.10-8.30 (2H, arom.)] and the starting material was recovered in 70% yield. Nitration of IIa and IIb with $\text{HNO}_3\text{-H}_2\text{SO}_4$ at room temperature gave after 2 days dinitro compound, X [20% ; mp 239-249°(dec.) ; NMR δ (ppm in DMSO- d_6) : 2.71 (3H, s), 7.61 (1H, d, $J=10$ Hz), 8.11 (1H, d, $J=8$ Hz), 8.40 (1H, d, $J=8$ Hz), 8.51 (1H, d, $J=10$ Hz)] and XI [13% ; mp 237-238°(dec.) ; NMR δ (ppm in CF_3COOH) : 3.13 (3H, s), 7.75-8.05 (3H, arom.), 8.17 (1H, d, $J=10$ Hz), 8.33-8.46 (1H, arom.) 8.74 (1H, d, $J=10$ Hz)], respectively.

Heating of the N-oxides, IIa and IIb, in refluxing phosphoryl chloride for 1 hour afforded the deoxygenated 7-chloro compounds, XIIa [46% ; mp 171-173° ; NMR δ (ppm in CDCl_3) : 7.90 (1H, s, $\text{C}_8\text{-H}$), 8.15 (1H, s, $\text{C}_3\text{-H}$)] and XIIb [41% ; mp 134-135° ; NMR δ (ppm in CDCl_3) : 7.75 (1H, s, $\text{C}_3\text{-H}$), 7.96 (1H, s, $\text{C}_8\text{-H}$)] together with the deoxygenated IIIa (16% yield) and IIb (14% yield), respectively. The NMR spectra of 7-chloroimidazopyridazines (XII) showed two singlet peaks at around 8 ppm, indicating that substitution reaction occurred at the 7-position.⁵⁾

Heating of the N-oxide (IIa) in refluxing acetic anhydride gave 7-acetoxyimidazo[1,2-b]pyridazine, XIII [63% ; mp 136-137° ; IR $\nu_{\text{max}}^{\text{KBr}}$ (cm^{-1}) : 1780 ; NMR δ (ppm in CDCl_3) : 2.35 (3H, s), 2.42 (3H, s), 7.65 (1H, s, $\text{C}_8\text{-H}$), 8.14 (1H, s, $\text{C}_3\text{-H}$)] in good yield. The same reaction of IIb gave 2-acetoxymethyl derivative, XIV

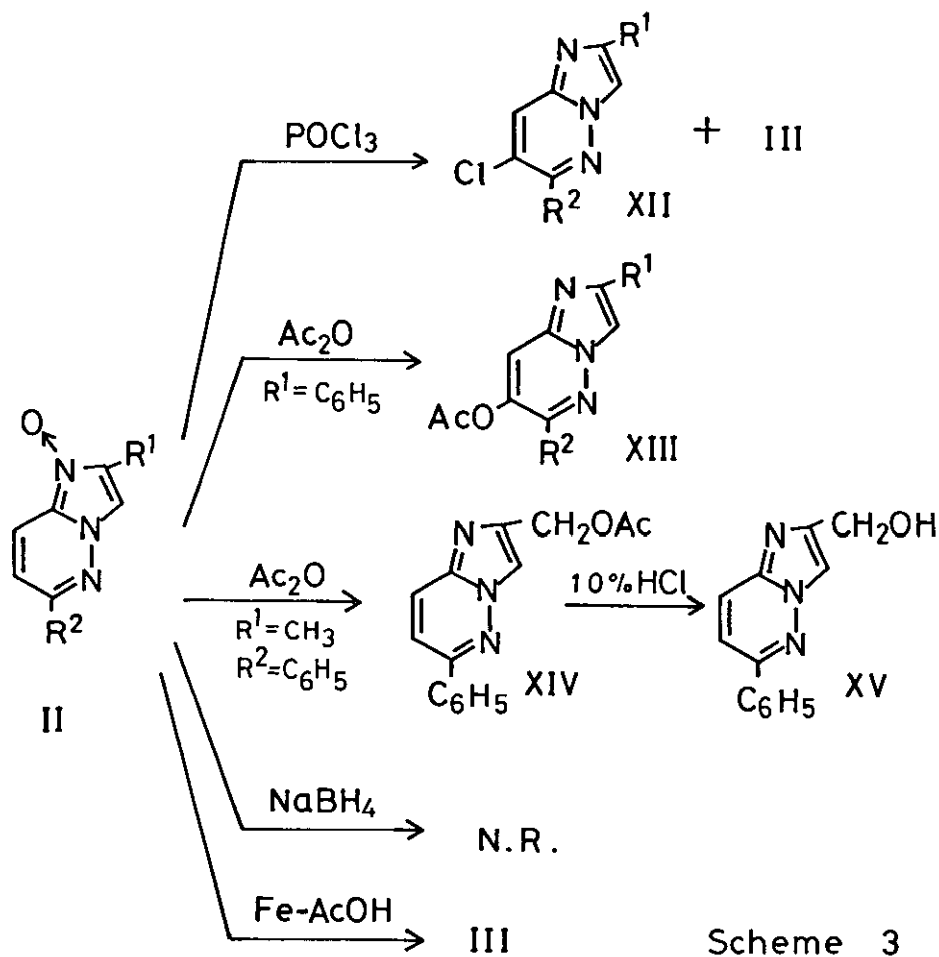


[70% ; mp 81.5-82° ; IR $\nu_{\text{max}}^{\text{KBr}}$ (cm⁻¹) : 1750, 1740 ; NMR δ (ppm in CDCl₃) : 2.13 (3H, s), 5.31 (2H, s), 7.47 (1H, d, J=10Hz), 7.94 (1H, D, J=10Hz), 8.02 (1H, s)], which was hydrolysed into hydroxymethyl derivative, XV [65% (from IIb); mp 147-147.5° ; IR $\nu_{\text{max}}^{\text{KBr}}$ (cm⁻¹) : 3180 ; NMR δ (ppm in CDCl₃) : 3.94 (1H, s, OH), 4.90 (2H, s), 7.42 (1H, d, J=10Hz), 7.92 (1H, d, J=10Hz)] by heating with 10% HCl for 4 hours.

Attempted reduction of the N-oxide (IIa) with NaBH₄ in ethanol failed, however, Fe dust in the presence of acetic acid was effective at room temperature to deoxygenate IIa into IIIa in 83% yield.

Other imidazopyridazine 1-oxides (II, R¹=C₆H₅, R²=Cl; R¹=R²=C₆H₅) reacted in the similar manner with such reagents as bromine, NBS, phosphoryl chloride, and acetic anhydride.

It is well known in the literature⁷⁾ that azine N-oxides react with electrophilic reagents readily in contrast to the case of the corresponding azines. Tišler and coworkers examined some electrophilic substitution reaction on imidazo[1,2-b]pyridazine itself and observed formation of the 3-bromo- and 3-nitro-substituted products under very mild conditions.^{6a)} The authors also recognized that bromination of the azoles (III) with NBS more smoothly proceeded than that of the azole N-oxides (II). It is noteworthy that electrophilic substitution reaction of imidazo[1,2-b]pyridazine 1-oxides (II) require much severer conditions than those of the corresponding azoles (III).



Scheme 3

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