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SYNTHESIS OF IMIDAZO[1,2-b]PYRIDAZINE 1-OXIDES BY REACTION OF OXAZOLO[3,2-b]PYRIDAZINIUM PERCHLORATES WITH HYDROXYLAMINE

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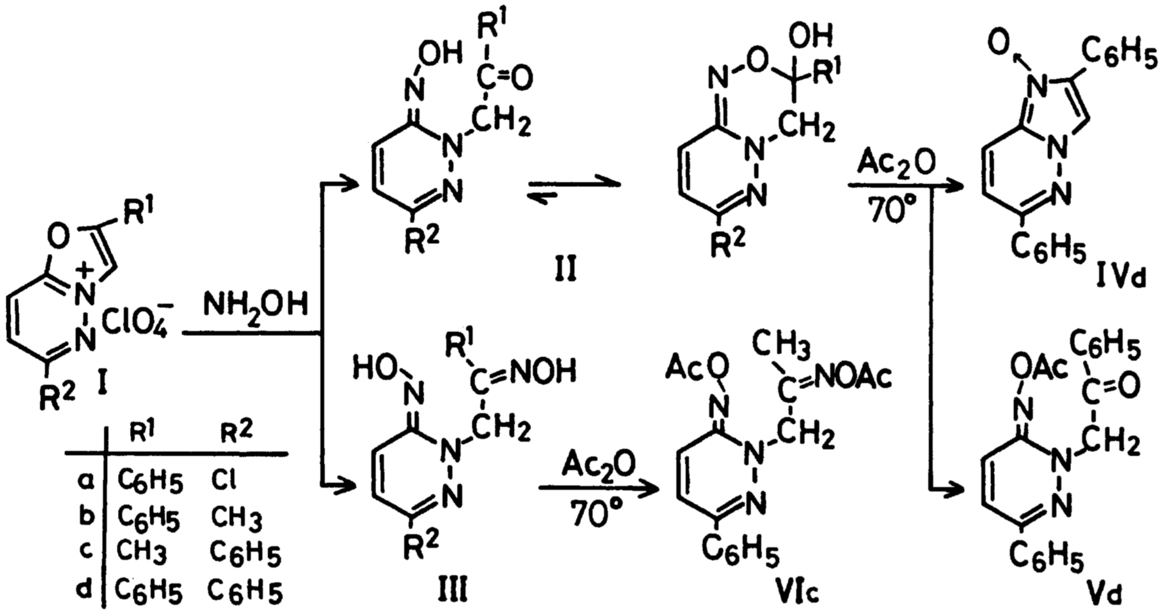
The reaction of oxazolo[3,2-b]pyridazinium perchlorates (I) with hydroxylamine afforded monoximes (II) and dioximes (III), from both of which were synthesized imidazo[1,2-b]pyridazine 1-oxides (IV) by heating in mineral acid. The N-oxides were characterized by converting into the corresponding pyridazines by deoxygenation.

In the course of our studies on the synthesis and reaction of π-deficient condensed thiazolium salts,[1,2,3] it was found that carbanions attack at the C-7 or C-8 position of thiazolo[3,2-b]pyridazinium salts to give quinoid type compounds through oxidative substitution reaction with the participation of triplet oxygen.[1(b)] During examination of the reactivity of oxazolo[3,2-b]pyridazinium perchlorates (I)[4] toward nucleophiles in comparison with that of thiazolopyridazinium salts, hydroxylamine was revealed to attack at the C-8a position of I to give two addition compounds, II and III, both of which were smoothly converted into imidazo[1,2-b]pyridazine 1-oxides (IV) by heating in mineral acid. This procedure constitutes an efficient method for the synthesis of condensed azole N-oxides with a bridge-headed nitrogen, on which very few articles have ever been published.[5] The N-oxides are further of interest as the precursors of phisiologically active imidazo[1,2-b]pyridazines which have recently been reported.[6,7]

The perchlorate (Id) was treated with hydroxylamine hydrochloride and potassium hydroxide in dimethylformamide at room temperature for 20 hours. After evaporation of the solvent the reaction mixture was purified by silica gel column chromatography to give yellow crystals of 2*H*-2-phenacyl-6-phenylpyridazine-3-azanol (IId)[$C_{18}H_{15}O_2N_3$; mp 177-180°; IR $\nu_{max}^{CHCl_3}$ (cm^{-1}): 3000-3580 (OH), 1638 (>C=N-)][8] and



	R^1	R^2
a	C$_6$H$_5$	Cl
b	C$_6$H$_5$	CH$_3$
c	CH$_3$	C$_6$H$_5$
d	C$_6$H$_5$	C$_6$H$_5$

red crystals of 2*H*-2-(2-phenylethylidene)-6-phenylpyridazine-2',3-bisazanol (IIId) [$C_{18}H_{16}O_2N_4$; mp 183-184°; IR ν_{max}^{KBr}(cm^{-1}): 3300 (OH), 1650, 1590 (>C=N-)] in 38 and 16% yields, respectively. The prolonged treatment of the isolated sample of IId with hydroxylamine did not give IIId and the starting material was recoverd quantitatively. The NMR spectrum of IId indicated that the major part of the monoxime was present as cyclized hemiketal, 3,4-dihydro-3-hydroxypyridazino[3,2-c]-1,2,4-oxadiazine; 78% of the methylene protons were observed as two doublet peaks at 3.96 and 4.11 ppm ($J_{7,8}$ =12 Hz). The quarternary salts Ia, Ib and Ic also reacted with hydroxylamine to give the results shown in TABLE I.

By heating IId in acetic anhydride at 70° for an hour yellow crystals of monoacetate (Vd) [mp 158-159°(dec.); NMR δ (ppm in $CDCl_3$): 2.12 (3H, s), 5.59 (2H, s)] and red crystals of IVd were isolated in 53 and 14% yields, respectively, after separation by silica gel column chromatography. Treatment of IId with acetic anhydride at 80° for an hour gave IVd as the major product. By acetylation of IIIc in the same manner yellow crystals of diacetate (VIc) [mp 144-146°; IR ν_{max}^{KBr} (cm^{-1}): 1760 (broad, strong), 1640, 1560; NMR δ (ppm in $CDCl_3$): 2.04 (3H, s), 2.16 (3H, s), 2.19 (3H, s), 4.95(2H, s)] were isolated in 60% yield. The N-oxides (IV) were also formed on treatment of II, III or VIc with mineral acid such as conc. sulfulic acid, 20% hydrochloric acid or 47% hydrobromic acid. The preparative scale experiments were carried out by heating II or III in 47% hydrobromic acid at 80° for half an hour to furnish colorless crystals of hydrobromides of N-oxide (IV) in 60-80%

TABLE I. Reaction products II and III prepared from the quarternary salts (I)

	R^1	R^2	Compound II Mp (°C)	Compound II Yield (%)	Compound II NMR (δ ppm)* CH_2 {q (%) s (%)}	Compound II NMR (δ ppm)* -OH	Compound III Mp (°C)	Compound III Yield (%)	Compound III NMR (δ ppm)* CH_2 s	Compound III NMR (δ ppm)* -OH×2
a	C_6H_5	Cl	123-124	25	{3.93 (78) 5.33 (22)}	7.30	159-162	36	4.91	{9.56 11.50}
b	C_6H_5	CH_3	140-142	52	{3.87 (86) 5.26 (14)}	7.04	178-179	10	4.96	{9.10 11.43}
c	CH_3	C_6H_5	–	–	–		167-168	61	4.60	{9.33 10.73}
d	C_6H_5	C_6H_5	177-180	38	{4.04 (78) 5.45 (22)}	7.22	183-184	16	5.12	{9.40 11.55}

*) Solvent: DMSO-d_6.

yields. These were, then, treated with alkali to give the free N-oxides (IV). The NMR spectra showed an aromatic methine signal at around 8.2 ppm in stead of the methylene signal in those of the starting materials, II and III. The N-O stretching vibration appeared as an absorption in the region of 1190-1250 cm^{-1} in the IR spectra[9] (TABLE II).

The following process was useful as a simplified procedure for the rapid preparation of the N-oxides (IV) in one-step from the quartenary salts (I): I was treated with hydroxylamine in the same manner to give syrupy residure, which, without purification, was heated in 47% hydrobromic acid at 80° for half an hour. After cooling, the reaction mixture was poured onto aqueous solution of sodium hydroxide. The precipitated solid was extracted with dichloromethane to give the free N-oxides in about 50% yield.

The deoxygenation of the N-oxides (IV) was carried out in the usual way by heating with a slight excess of phosphorous trichloride in chloroform for an hour. After evaporation and treatment with alkali, the corresponding imidazo[1,2-b]pyridazines (VIIa [mp 195-196°], VIIb [mp 157-158°], VIIc [mp 152-154°], VIId [mp 164-165°]) were obtained in good yields. The deoxygenated pyridazine (VIIc) was completely identical with specimen derived from 3-amino-6-phenylpyridazine and

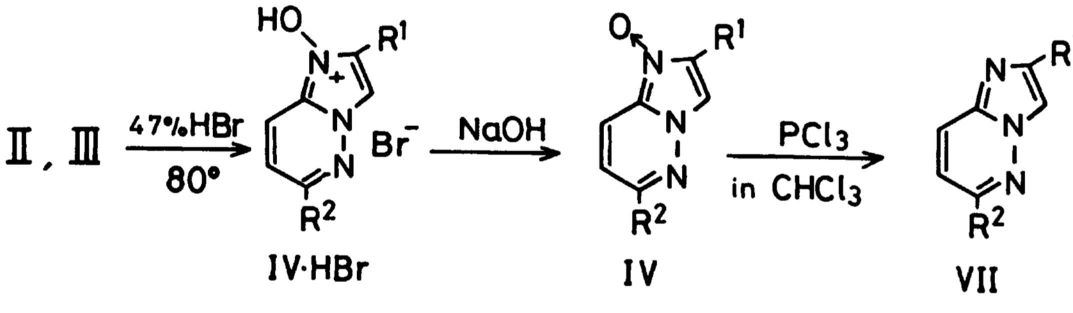


TABLE II. Imidazo[1,2-b]pyridazine 1-oxides (IV)

	R^1	R^2	Mp (°C)	Yield[#] (%)	NMR (δ ppm) C_3-$\underline{H}$(s)	C_7-$\underline{H}$(d)*	C_8-$\underline{H}$(d)*	IR ν_{max}^{KBr} (cm^{-1})
a	C_6H_5	Cl	214-215 (dec.)	51	8.40	7.33	8.27[a)]	1255
b	C_6H_5	CH_3	275-277 (dec.)	56	8.39	7.27	8.13[a)]	1250
c	CH_3	C_6H_5	224-225 (dec.)	52	7.66	7.32	8.29[b)]	1195 1180
d	C_6H_5	C_6H_5	249-250 (dec.)	56	8.42	7.82	8.23[a)]	1250

#) The figures cited are the yields from I through the rapid process.

*) $J_{7,8}$ = ca. 10 Hz. a) Solvent: CD_3OD. b) Solvent: $CDCl_3$.

chloroacetone.

Experiments on thermal and photo-induced isomerization of these newly prepared aromatic amine oxides are now under progress in this laboratory.

REFERENCES AND NOTES

1. a) K. Arakawa, T. Miyasaka, and K. Satoh, Chem. Pharm. Bull., 25, 299 (1977).
   b) K. Satoh, T. Miyasaka, and K. Arakawa, ibid., 25, 307 (1977).
2. H. Ohtsuka, T. Miyasaka, and K. Arakawa, ibid., 23, 3254 (1975), and loc. cit.
3. S. Sawada, T. Miyasaka, and K. Arakawa, ibid., in press.
4. K. Satoh, T. Miyasaka, and K. Arakawa, Yakugaku Zasshi, 97, 422 (1977).
5. a) A. Pollak, B. Stanovnik, and M. Tišler, J. Heterocycl. Chem., 5, 513 (1968).
   b) K. Basič, S. Molan, S. Polanc, B. Stanovnik, J. Stres-Bratoš, M. Tišler, and B. Verček, ibid., 13, 487 (1976).
6. F. Yoneda, T. Ohtaka, and Y. Nitta, Chem. Pharm. Bull., 12, 1351 (1964).
7. L. Almirante, L. Polo, A. Mugnaini, E. Provinciali, P. Rugarli, A. Gamba, A. Olivi, and W. Murmann, J. Med. Chem., 9, 29 (1966).
8. Satisfactory elemental analyses compatible with the structural assignments were obtained for all the compounds with melting point described herein. Melting points were uncorrected.
9. H. Ochiai, "Aromatic Amine Oxides," Elsevier Publishing Company, Amsterdam (1967), p 114. Also cf. reference 5 (a).

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