Studies of Heterocyclic Compounds. VIII.[1] Synthesis and Tautomerism of 2-Hydroxypyrazolo[1,5-*a*]pyridine

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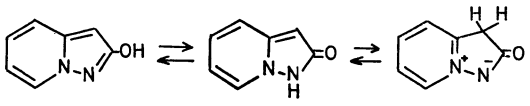
2-Hydroxypyrazolo[1,5-*a*]pyridine (I) was synthesized by reaction of ethyl 2-pyridylacetate (IV) with hydroxylamine-*O*-sulfonic acid. I was shown to undergo nitrosation, nitration and bromination at C-3 position. Methylation of I with diazomethane gave 2-methoxypyrazolo[1,5-*a*]pyridine (V), while methylation of I with dimethyl sulfate gave a mixture of V and 1-methyl-1,2-dihydropyrazolo[1,5-*a*]pyridin-2-one (VI). The enol form was found to be predominant tautomeric species of I in solution. Treatment of I with acetic anhydride afforded 2-acetoxypyrazolo[1,5-*a*]pyridine (XIII) exclusively. 1-Acetyl-1,2-dihydropyrazolo[1,5-*a*]pyridin-2-one (XIV) dose not seem to intervene in the formation of thermally stable *O*-acetylated product (XIII).

In connection with the synthesis and reactivity of pyrazole derivatives[2,3] it seemed to us of interest to examine the chemical properties of 2-hydroxypyrazolo-[1,5-*a*]pyridine (I) as well as possible tautomerization including 1,2-dihydropyrazolo[1,5-*a*]pyridin-2-one (Ib), a pyrazolone form and a ylide form (Ic) (Scheme 1).

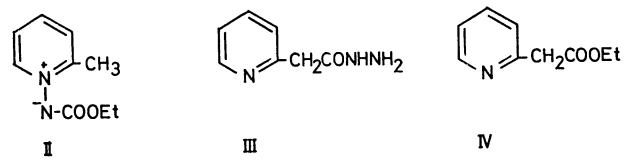


I I-b I-c

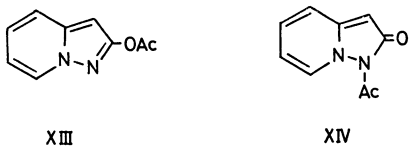
Scheme 1.

Although many papers have appeared on the synthesis of pyrazolo[1,5-*a*]pyridines,[4] only a few deal with the synthesis of condensed pyrazolone system functionalized at 2-position.[5-7]

2-Picoline is considered to be an easily available starting material for the synthesis. Attempts to form I by cyclization of 2-pyridylacetyl azide through the intermediacy of the nitrene (II) or by that of 2-pyridylacetohydrazide (III) with a strong base were unsuccessful. However, *N*-imination of ethyl 2-pyridylacetate (IV) with potassium salt of hydroxylamine-*O*-sulfonic acid (HAS)[8,9] afforded the desired bicyclic system as colorless fluorescent crystals (mp 127—128 °C), whose elemental analysis and mass spectrum agreed with the molecular formula $C_7H_6ON_2$.



II III IV



XIII XIV

The preparation of I was best carried out by adding an aqueous solution of HAS into 3 molar equivalents of 2-pyridylacetate (IV), extraction of the reaction product with a 10% aqueous sodium carbonate solution and recrystallization from benzene–hexane after stirring for 30 h at room temperature. The IR spectrum lacked an ester carbonyl band at around 1700 cm^{-1}, but showed a broad band at 3000 cm^{-1} (associated –O–H) and a strong band at 1635 cm^{-1} (–C=N–), indicating the presence of enol instead of carbonyl grouping. The NMR spectrum displayed a one proton singlet at δ5.83 ppm (C_3–H), a one proton broad doublet at δ 8.29 ppm (C_7–H, $J_{6,7}$=6 Hz) and other signals at δ 6.61 (C_6–H), 7.11 (C_5–H) and 7.34 ppm (C_4–H). Mass spectrum of this compound displayed molecular ion (*m/e* 134) which was the base peak and other ions of *m/e* 105 $[M-CHO]^+$, 91 $[C_6H_5N]^+$ and 79 $[C_5H_5N]^+$ (Fig. 1, Scheme 2).

Treatment of I with an ethereal solution of diazo-

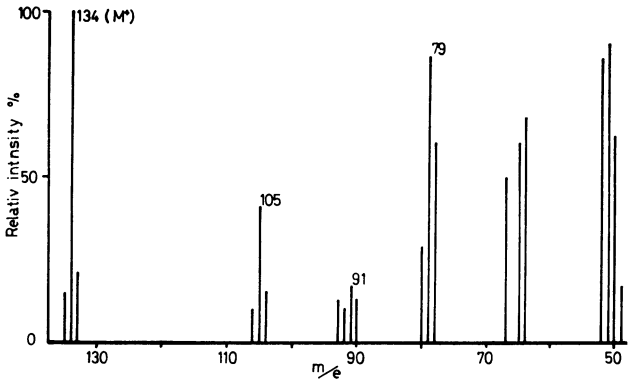
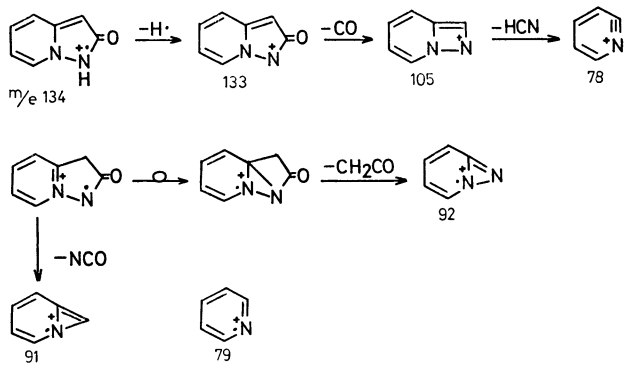


Fig. 1. Mass spectra of 2-hydroxypyrazolo[1,5-*a*]pyridine.



Scheme 2. Mass fragmentation pattern of 2-hydroxypyrazolo[1,5-*a*]pyridine.

methane gave an oily substance $C_8H_8ON_2$ which displayed a single spot on the TLC plate. The IR spectrum lacked a carbonyl band. The NMR spectrum showed an *O*-methyl signal at δ 3.98 ppm, indicating *O*-methylation of I to give 2-methoxypyrazolo[1,5-*a*]-pyridine exclusively. Methylation of I with dimethyl sulfate in aqueous sodium carbonate gave a (3: 1) mixture of two monomethyl derivatives. Separation through a silica gel column afforded the major component which was identical with the *O*-methyl derivative (V) and the minor component which was revealed to be 1-methyl-1,2-dihydropyrazolo[1,5-*a*]pyridin-2-one (VI) by the IR (>C=O 1660 cm^{-1}) and by the NMR spectra (δ 3.64 ppm, 3H, s) (Tables 2, 3).

Katritzky and Maine reported the tautomerism of substituted 3-hydroxypyrazoles.[10] The IR and the NMR spectra demonstrate that both keto and enol forms are present in nonprotic solvents such as chloroform in the case of 3-hydroxy-2-methylpyrazoles. However, enol form is present predominantly in the case of 3-hydroxy-1-methylpyrazoles. The UV spectrum of I in methanol as well as in cyclohexane had maxima at 232, 280 and 310 nm (log ε; 4.59, 3.09 and 3.10, respectively) and was very close to the spectrum of 2-methoxypyrazolo[1,5-*a*]pyridine (V). However, the UV spectrum of VI had maxima at the longer wave length: 241.5, 280.5, 288 and 341 nm (log ε: 4.47, 3.89, 3.88 and 3.32, respectively). By addition of a sodium hydroxide solution to the methanolic solution of I, the maxima shifted to the longer wave length of 260, 280 and 335 nm, respectively. This suggests a phenolic character of the hydroxyl group at 2-position. Thus the enol form was a predominant tautomeric species for I in solution.

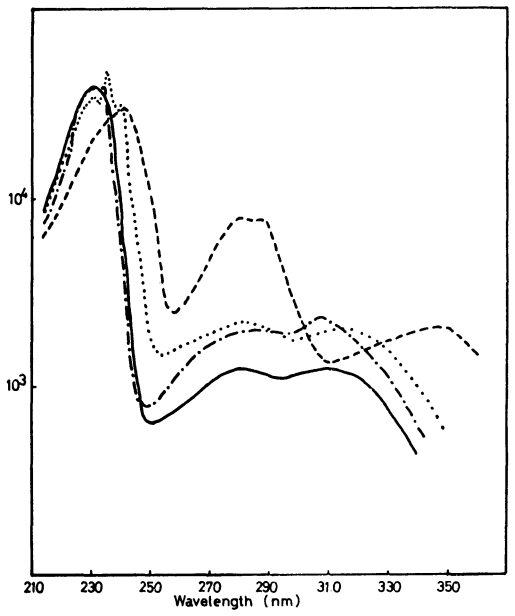
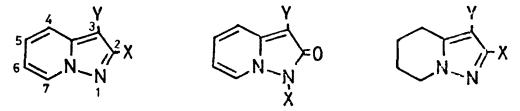


Fig. 2. UV spectra of I (——), V (-·-·-), and VI (------) in methanol and I (·····) in cyclohexane.

The electrophilic substitution of mono-cyclic 3-hydroxypyrazoles usually takes place at 4-position. Nitrosation, nitration and bromination of I afforded exclusively 3-monosubstituted products, 3-nitroso, 3-nitro- and 3-bromo-2-hydroxypyrazolo[1,5-*a*]pyridines (VII), (VIII) and (IX), respectively. The NMR spectra lacked the C_3-proton signals at δ 5—7 ppm (Table 2). Bromination of I with two molar equivalents of bromine gave dibromo compound (X) identical with the further brominated product of monobromide (IX). The IR and the NMR spectra indicated this to be 1,3-dibromo-1,2-dihydropyrazolo[1,5-*a*]pyridin-2-one.

Table 1. Derivatives of pyrazolo[1,5-*a*]pyridine



A B C

Compd	Form	X	Y	Mp °C
I	A	H	H	127—128
V	A	OCH_3	H	oil
VI	B	CH_3	H	165—167
VII	B	H	NO	>280
VIII	A	OH	NO_2	243 (decomp.)
IX	A	OH	Br	188.5—190.5
X	B	Br	Br	162 (decomp.)
XI	A	Cl	H	oil
XII	C	OH	H	172—174
XIII	A	$OCOCH_3$	H	oil

Table 2. NMR spectral data of pyrazolo-[1,5-*a*]pyridine

Compd	Solv.	3	4	5	6	7	$-CH_3$
I	$CDCl_3$	5.83	7.34	7.11	6.61	8.29	
V	$CDCl_3$	5.78	7.25	7.00	6.52	8.19	3.98
VI	$CDCl_3$	5.40	7.11	7.03	6.52	7.70	3.64
VII	DMSO-d_6		8.20	7.83	7.69	8.62	
VIII	DMSO-d_6		8.12	7.82	7.28	8.70	
IX	DMSO-d_6		7.25	7.20	6.72	8.38	
X	DMSO-d_6		8.24	8.02	7.78	8.69	
XI	CCl_4	6.28	7.32	7.02	6.62	8.25	
XIII	$CDCl_3$	6.38	7.42	7.11	7.72	8.26	2.36

Chemical shifts are expresed by δ ppm from TMS.

Table 3. Coupling constant

Compd.	$J_{4,5}$	$J_{4,6}$	$J_{4,7}$	$J_{5,6}$	$J_{5,7}$	$J_{6,7}$
I	8	1	1	7	1	6
V	8	1	1	7	1	7
VI						7
VII	7	1	1	7	1	6
VIII	8	1	1	7	1	7
IX						6
X	8.5	1	1	7	1	7
XI	8.5	1	1	7	1	7
XIII	9	1	1	7	1.5	7

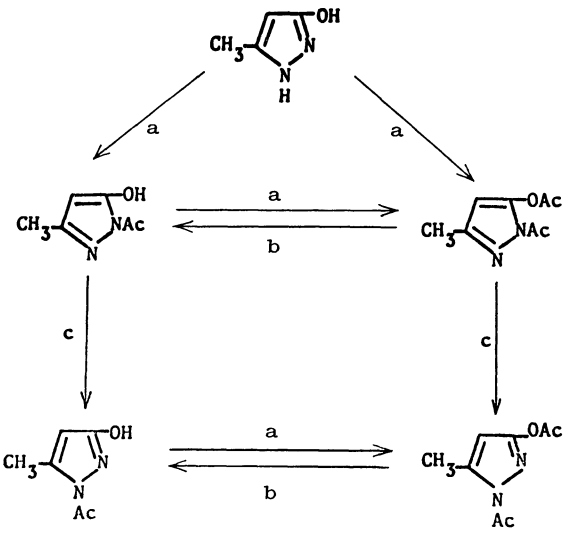
Coupling constants, J, in terms of unit Hz.

Substitution of the hydroxy group of I with chlorine was carried out in the usual way by heating in refluxing phosphoryl chloride only to recover the starting material. By heating in a sealed tube at 145 °C for 6 h I was converted into 2-chloropyrazolo[1,5-*a*]pyridine (XI) in

72% yield.

Catalytic hydrogenation of I with platinum oxide in acetic acid gave colorless crystals (mp 172—174 °C) after sluggish absorption of two molar equivalents of hydrogen. The NMR spectrum (δ 1.90, 2.68, and 3.85 ppm, 8H) indicated that the hydrogenation took place upon the pyridine nucleus to furnish 2-hydroxy-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridine (XII). The hydroxypyrazole moiety of I seems to be relatively electron-sufficient and the electron-deficient pyridine moiety seems reactive enough to undergo hydrogenation exclusively.

Arakawa *et al.* reported on the structure of the acetylated products of 3-hydroxy-5-methylpyrazole which had eight potential tautomeric forms[2] and also on the acetyl transfer reaction of 3-acetoxy-1-acetyl-5-methylpyrazole and the related compounds.[3] Among the four mono- and diacetyl derivatives the 2-acetyl-3-hydroxy-5-methylpyrazole formed initially were kinetically controlled products, which gave by thermal treatment 1-acetyl-3-hydroxy-5-methylpyrazole and 3-acetoxy-1-acetyl-5-methylpyrazole as the thermally more stable products (Scheme 3). We have tried acetylation of the bicyclic hydroxypyrazole (I) in order to examine the possible isomeric acetates responsible for the three conceivable tautomers (Scheme 1).



a : Acetylation
b : Basic Hydrolysis
c : Thermolysis

Scheme 3.

Hydroxypyrazole (I) gave an oily acetate (XIII) by heating in refluxing acetic anhydride for 2 h, which displyayed one spot on the TLC plate. The IR spectrum had one peak in the carbonyl region (ν_{max} 1780 cm^{-1}, $-\dot{C}=\dot{C}-O-COCH_3$). Elemental analysis and the NMR spectrum (δ 2.36 ppm, 3H, s) also indicate the compound to be 2-acetoxypyrazolo[1,5-*a*]pyridine. The time-course of acetylation was followed spectrophotometrically in a sample-tube for NMR measurement by observing the singlet signals at δ 5.78 and at δ 6.41 ppm of the C_3-protons of I and XIII, respectively. The signal at δ 5.78 ppm of the spectrum of I in acetic acid started diminishing slowly in its area-intensity as soon as acetic anhydride was added to the mixture. A new peak appearing at δ 6.41 ppm increased greatly in intensity, its spectrum changing completely into that of XIII after being heated 3 h at 35 °C (Fig. 3). Since no signal was observed in the region during the course of reaction, 1-acetyl-1,2-dihydropyrazolo[1,5-*a*]pyridin-2-one (XIV) did not seem to intervene in the formation of the thermally stable *O*-acetylated product (XIII).

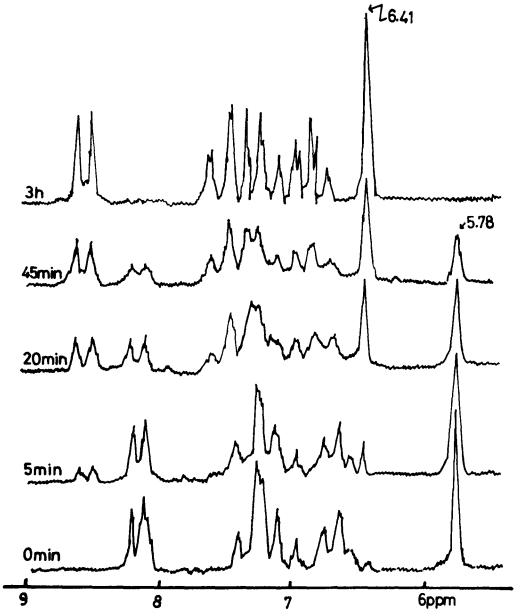


Fig. 3. NMR spectra during the time-course of changing I into XIII in a mixture of acetic acid and acetic anhydride at 35 °C.

Experimental

All the melting points were measured in capillary tubes and were uncorrected. The NMR spectra were measured on Hitachi R-20 60 MHz and Hitachi R-22 90 MHz spectrophotometers, using tetramethylsilane as an internal reference. The IR and the UV spectra were measured on a JASCO IRA-I spectrophotometer and a Hitachi EPS-3 spectrophotometer, respectively.

2-Hydroxypyrazolo[1,5-a]pyridine (*I*). After a mixture of ethyl 2-pyridylacetate (3.00 g), HAS (0.60 g) and water (3 ml) was stirred at room temperature for 30 h, it was extracted with CH_2Cl_2. The aqueous layer was made alkaline with 10% Na_2CO_3 to pH 9 and was extracted with CH_2Cl_2. The organic extracts were combined, and after drying over $MgSO_4$ the solvent was evaporated. The residual oil was shaken with Et_2O–10% Na_2CO_3. After the ether-layer was dried over $MgSO_4$, the solvent was evaporated to give the starting ethyl 2-pyridylacetate (2.11 g, 70.5% yield). The pH of the basic aqueous layer was adjusted to 5 by adding AcOH to precipitate brown powder (0.36 g, 45.9% yield, based upon the consumed starting material). Recrystallization from benzene–hexane gave 2-hydroxypyrazolo[1,5-*a*]pyridine (0.32 g, 40.7%) mp 127—128 °C, as colorless leaflets. UV λ_{max}^{MeOH} nm (log ε): 232 (4.59), 280.5 (3.09), 310 (3.10). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3000, 1635, 1535, 1258. Found: C, 62.53; H, 4.48; N, 20.98%. Calcd for $C_7H_6ON_2$: C, 62.68; H, 4.51; N, 20.89%.

2-Methoxypyrazolo[1,5-a]pyridine (*V*). To a solution of

I (134 mg) in MeOH (5 ml) was added an excess solution of CH_2N_2 in ether[11] and the mixture was left to stand in an ice-box for a day. Evaporation of the solvent gave colorless oil (135 mg) which exhibited a single spot on a TLC plate (R_f= 0.89, 5% MeOH–$CHCl_3$ silica gel G. F. nach Stahl). Purification by passing a short column of SiO_2 gave colorless oil (118 mg, 80.5% yield). UV λ_{max}^{MeOH} nm (log ε): 234 (4.57), 282 (3.30), 307 (3.31). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3000, 1640, 1540, 1360. Found: C, 64.57; H, 5.31; N, 18.71%. Calcd for $C_8H_8ON_2$: C, 64.85; H, 5.44; N, 18.91%.

Treatment of I with Dimethyl Sulfate–Sodium Carbonate, 2-Methoxypyrazolo[1,5-a]pyridine (V) and 1-Methyl-1,2-dihydropyrazolo-[1,5-a]pyridin-2-one (VI). After alternate portionwise addition of dimethyl sulfate (250 mg) and a solution of Na_2CO_3 (2.40 g) in H_2O (6 ml) to a stirred solution of I (268 mg) in EtOH (14 ml), the mixture was stirred at room temperature for 48 h. The precipitate was filtered off and the filtrate was evaporated *in vacuo* to give a brown residue, which was shaken with CH_2Cl_2 and H_2O. Drying and evaporation of the organic layer gave a brown residue, which was fractionated by passing through a SiO_2-column to first give colorless oil (186 mg, 62.8% yield) and next colorless prisms (48 mg, 16.2% yield). The former was found to be identical with V by comparison of TLC, IR and NMR spectra. The latter was recrystallized from benzene to give crystals (VI) melting at 165—167 °C. UV λ_{max}^{MeOH} nm (log ε): 241.5 (4.47), 280.5 (3.89), 288 (3.88), 341 (3.32). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2960, 1660, 1630 (br). Found: C, 64.59; H, 5.32; N, 18.68%. Calcd for $C_8H_8ON_2$: C, 64.85; H, 5.44; N, 18.91%.

Nitrosation of I, 2-Hydroxy-3-nitrosopyrazolo[1,5-a]pyridine (VII). To an ice-cold stirred solution of I (100 mg) in a mixture of MeOH (2 ml) and 6M-HCl (2 ml) was added dropwise a solution of $NaNO_2$ (15 mg) in H_2O (0.7 ml). After stirring under ice-cooling for 30 min and at room temperature for 1 h the reaction mixture was cooled in ice-salt mixture to deposit a yellow precipitate, which was collected by filtration and washed with cold water. Recrystallization from MeOH gave golden feather-like crystals (63 mg, 52% yield). Mp>280 °C. UV λ_{max}^{MeOH} nm (log ε): 273 (4.30), 316.5 (3.76). IR ν_{max}^{KBr} cm^{-1}: 3040, 1700, 1680, 1635, 1020. Found: C, 51.53; H, 3.32; N, 27.50%. Calcd for $C_7H_5O_2N_3$: C, 51.54; H, 3.09; N, 27.60%.

Nitration of I, 2-Hydroxy-3-nitropyrazolo[1,5-a]pyridine (VIII). To an ice-cold stirred solution of I (70 mg) in concd HNO_3 (d=1.38) (1 ml) was added dropwise fuming nitric acid (d= 1.50) (0.5 ml). After stirring in an ice-bath for 30 min and at room temperature for 1 h the reaction mixture was poured onto ice–water to give a precipitate, which was collected by filtration. Recrystallization of the powder (61 mg) thus obtained from MeOH gave light brown leaflets (45 mg, 48.2 % yield) mp 243 °C (dec). UV λ_{max}^{MeOH} nm (log ε): 220 (4.30), 276 (3.51), 354 (4.16). IR ν_{max}^{KBr} cm^{-1}: 3440, 1645, 1580, 1360, 1220. Found: C, 46.71; H, 3.07; N, 23.21%. Calcd for $C_7H_5O_3N_3$: C, 46.93; H, 2.81; N, 23.46%.

Bromination of I with Equimolar Amount of Bromine, 3-Bromo-2-hydroxypyrazolo[1,5-a]pyridine (IX). To a stirred mixture of I (134 mg) and $NaOAc \cdot 3H_2O$ (140 mg) in AcOH (4 ml) was added dropwise a solution of Br_2 (160 mg) in AcOH (2 ml). After addition of ice–water the precipitated solid was collected by filtration. The pink-colored powder (146 mg) were recrystallized from MeOH to give prisms (126 mg, 56.3% yield), mp 188.5—190.5 °C. UV λ_{max}^{MeOH} nm (log ε): 235 (4.02). IR ν_{max}^{KBr} cm^{-1}: 1630, 1560 (br), 1520 (br). Found: C, 39.32; H, 2.32; N, 13.34%. Calcd for $C_7H_5ON_2Br$: C, 39.44; H, 2.35; N, 13.15%.

Bromination of I with Excess Brimine, 1,3-Dibromo-1,2-dihydropyrazolo[1,5-a]pyridin-2-one (X). To a stirred solution of I (134 mg) in AcOH (2 ml) was added dropwise at 15 °C a solution of Br_2 (320 mg) in AcOH (2 ml). After stirring for 1 h the reaction mixture was poured onto ice–water. The precipitate was collected by filtration and washed with cold water to give yellow powder (230 mg). Recrystallization from MeOH gave yellow scales (183 mg, 62.7% yield), mp 162 °C (dec). UV λ_{max}^{MeOH} nm (log ε): 249 (4.18), 308.5 (3.62), 350 (3.61). IR ν_{max}^{KBr} cm^{-1}: 1660, 1650, 1640. Found: C, 28.88; H, 1.55; N, 9.76%. Calcd for $C_7H_4ON_2Br_2$: C, 28.76; H, 1.71; N, 9.59%.

Attempted Chlorination of I by Refluxing in Phosphoryl Chloride. After a mixture of I (100 mg) and phosphoryl chloride (5 ml) was heated under reflux for 2 h the reaction mixture was treated in the usual way. The starting material (82 mg) was recovered unchanged.

Reaction of I with Phosphoryl Chloride at 145 °C, 2-Chloropyrazolo-[1,5-a]pyridine (XI). After a mixture of I (100 mg) and phosphoryl chloride (3 ml) was heated in a seald tube at 145 °C for 6 h, the reaction mixture was poured onto ice–water. Extraction with CH_2Cl_2, drying and evaporation of the solvent *in vacuo* afforded red oil (93 mg). Purification of the oil by passing through a column of SiO_2 gave colorless oil (82 mg, 72% yield). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1640. Found: C, 54.91; H, 3.52; N, 18.52%. Calcd for $C_7H_5N_2Cl$: C, 55.08; H, 3.28; N, 18.36%.

Catalytic Hydrogenation of I, 2-Hydroxy-4,5,6,7-tetrahydropyrazolo-[1,5-a]pyridine (XII). A solution of I (134 mg) in AcOH (20 ml) was shaken in the presence of Pt which was prereduced from PtO_2 (100 mg) under atmospheric pressure. The absorption of hydrogen ceased after uptake of 2 mmol of hydrogen. After filtration of the solvent the residual colorless crystals (145 mg) were recrystallized from acetone–Et_2O to give colorless scales (89 mg, 69% yield), mp 172—174 °C. UV λ_{max}^{MeOH} nm (log ε): 228.5 (3.72), 260 (3.48). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1540, 1035, 955. NMR δ ppm (in $CDCl_3$): 1.90 (4H, m), 2.68 (2H, t, J=5 Hz), 3.85 (2H, t, J=5 Hz), 5.26 (1H, s), 10.20 (1H, br. s, exchangeable with D_2O). Found: C, 60.62; H, 7.42; N, 20.09%. Calcd for $C_7H_{10}ON_2$: C, 60.85; H, 7.30; N, 20.28%.

Acetylation of I, 2-Acetoxypyrazolo[1,5-a]pyridine (XIII). A mixture of I (150 mg) in Ac_2O (10 ml) was heated under reflux for 2 h. After evaporation of solvent *in vacuo*, the residual oil was purified by passing through a column of SiO_2 to give colorless oil (188 mg, 97% yield). UV λ_{max}^{MeOH} nm (log ε): 222.5 (4.60), 286 (3.59). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1780, 1645, 1380. Found: C, 61.48; H, 4.43; N, 16.12%. Calcd for $C_9H_8O_2N_2$: C, 61.36; H, 4.58; N, 15.90%.

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