[Chem. Pharm. Bull.]
21(10)2146—2160(1973)

UDC 547.771'821.057.09 : 615.28.011.5

Synthetic Antimicrobials. II.^{1a)} Synthesis of Pyrazolo[1,5-*a*]pyridine Derivatives. (I)

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(Received January 22, 1973)

2-Alkyl-3-acyloxypyrazolo[1,5-*a*]pyridines (III) were prepared by refluxing 1-amino-2-hydroxymethylpyridinium chloride (Ia) in excess acyl anhydride in the presence of a base. III were converted into 2-alkyl-3-hydroxy derivatives (IVa—f) by acid hydrolysis. Ia was refluxed with ethyl orthoformate in acetic acid containing sodium acetate to give 3-hydroxy derivative (IVg).

Reaction of Ia with benzoyl chloride in $H_2O-K_2CO_3$ gave mainly O,N-dibenzoyl ylide (VIIa) and 2-phenyl-3-benzoyloxypyrazolo[1,5-*a*]pyridine (IXa). Pyrolysis of VIIa gave 2-phenyl-3-hydroxy derivative (VIIIa), which was also obtained from 1-benzimidido-2-hydroxymethylpyridine (VIa) by treatment with H_2SO_4 , followed by alkali treatment. Further the compound (VIIIa) was prepared by the reaction of 1-benzimidido-2-picoline (XVIIa) with I_2 in pyridine. Analogously various 2-substituted-3-hydroxy derivatives (VIIIb—l and IVa) were obtained.

1-Anilinothiocarbonylimino-2-hydroxymethylpyridine (XIXa) was converted into cyclic pyridinium salt (XXa) by treating with H_2SO_4 , and XXa was treated with K_2CO_3 to give 2,2'-dianilinopyrazolo[1,5-*a*]pyridine-3,3'-disulfide (XXIIa). XXIIa was converted into 2-anilino derivative (XXIIIa) by Raney Ni reduction. Analogously 2-benzamido derivative (XXIIIb) was obtained from 1-benzamidothiocarbonylimino-2-hydroxymethylpyridine (XIXa) by the same procedure. 2-Acetamido derivative (XXIX) was obtained by heating pyridine-2-acetamidoxime (XXVII) with acetic anhydride. The compounds (XXIIIa and XXIX) were also converted into the corresponding 3-thiocyano and 3-nitro derivatives (XXIV, XXV, XXXIb and XXXIc).

The tuberculostatic activities of the pyrazolo[1,5-*a*]pyridine derivatives were also indicated.

It has been found that 3-acetoxy-2-methylpyrazolo[1,5-*a*]pyridine (IIIa), which was obtained during the preparation of 1-acetimidido-2-acetoxymethylpyridine (II) described in the preceding paper,^{1a)} had a potent growth inhibitory activity *in vitro* against mycobacteria. Then an interest in the formation, and chemical and physiological properties of the novel pyrazolo[1,5-*a*]pyridine derivatives led us to further studies on this ring system.

Concerning the synthesis of pyrazolo[1,5-*a*]pyridine ring system, Potts, *et al.*,³⁾ recently reported a method by treatment of 2-alkyl-1-aminopyridinium salts with acyl chlorides in about 20% yield, and other earlier procedures were also presented in his report. However, there has been no report regarding the biological activities of the pyrazolo[1,5-*a*]pyridine derivatives.

The present paper is on the novel synthesis of pyrazolo[1,5-*a*]pyridine derivatives and their tuberculostatic activities.

Reaction of 1-amino-2-hydroxymethylpyridinium chloride (Ia) with acetic anhydride mainly provided II together with a small amount of IIIa. When the reaction was carried out in the presence of a basic substance, such as sodium acetate and pyridine, the reaction afforded IIIa in a good yield.

- 1) a) Part I: S. Suzue, M. Hirobe, and T. Okamoto, *Yakugaku Zasshi*, **93**, 1331 (1973); b) A part of this work was presented at the 89th Annual Meeting of the Pharmaceutical Society of Japan, Nagoya, April 1969.
- 2) Location: Hongo, 7-3-1, Bunkyo-ku, Tokyo; a) Present address: Kyorin Chemical Laboratory, Ukima, 1-3, Kila-ku, Tokyo.
- 3) K.T. Potts, U.P. Singh, and J. Bhattacharyya, *J. Org. Chem.*, **33**, 3766 (1968).

Chart 1

Chart 2

In the same manner, 3-acyloxy-2-alkyl derivatives (IIIb, c, e, and f) were obtained in a moderate yield (about 50%) as shown in Chart 1. These compounds (III) were readily hydrolyzed to 2-alkyl-3-hydroxy derivatives (IVa—f) on warming in aqueous hydrochloric acid solution. Trifluoromethyl derivative (IIIId) underwent deacylation to IVd during the purification by silica gel chromatography. 3-Hydroxy derivative (IVg) unsubstituted in the 2-position was also prepared in 40% yield by refluxing Ia with ethyl orthoformate in acetic acid containing sodium acetate. Further, IVa was converted into 3-methoxy derivative (Va) by treatment with dimethyl sulfate in aqueous sodium hydroxide solution. The compounds (Vb and c) were also prepared from the corresponding 3-hydroxy derivatives (IVe and g) by treatment with acid anhydrides.

TABLE I. Reaction of Ia with Benzoyl Chloride in $\text{H}_2\text{O}-\text{K}_2\text{CO}_3$

Molar ratio of BzCl/Ia	Yield (%)			
	VIa	VIIa	VIIIa	IXa
1.6	12.2	8.9	3.2	3.7
2.4	0	38.2	1.8	12.8
3.0	0	40.4	0	27.8

On the other hand, when Ia was allowed to react with 1.6 moles of benzoyl chloride in aqueous potassium carbonate solution at room temperature, four products were separated by column chromatography over alumina. The first product was found to be 1-benzimido-2-hydroxymethylpyridine (VIa) by elemental analysis, nuclear magnetic resonance (NMR) spectrum, and infrared (IR) spectrum. VIa showed a characteristic absorption band at 1520 cm^{-1} as was seen in the case of 1-acyliminopyridine derivatives⁴⁾ and at $3200\text{--}2600\text{ cm}^{-1}$ attributed to a hydroxyl group in its IR spectrum. The second product was proved to be 1-benzimido-2-benzoyloxymethylpyridine (VIIa) on the basis of analytical data and IR spectrum, which exhibited carbonyl band of the benzoyl group on the ylide-type nitrogen at 1555 cm^{-1} and ester band at 1730 , 1290 , and 1125 cm^{-1} . The third product (VIIIa) showed no carbonyl band but the hydroxyl absorption in the region of 3000 cm^{-1} in its IR spectrum.

TABLE II. Reaction of Ia with 3 moles of Substituted BzCl in $\text{H}_2\text{O}-\text{K}_2\text{CO}_3$

Compound VII, IX	X	Yield of VII (%)	Yield of IX (%)
e	<i>m</i> -F	72.3	10.6
f	<i>m</i> -Cl	67.5	9.1
g	<i>m</i> -Br	67.3	11.4
h	<i>m</i> -I	55.4	7.9
i	<i>p</i> -Cl	58.3	16.7
j	<i>p</i> -CH ₃ O	52.5	23.3

4) T. Okamoto, M. Hirobe, C. Mizusima, and A. Ohsawa, *Yakugaku Zasshi*, **83**, 308 (1963).

NMR spectrum of its methyl ether (Xa), prepared by treating VIIa with dimethyl sulfate in aqueous sodium hydroxide solution, was consistent with that of 3-methoxy-2-phenylpyrazolo[1,5-*a*]pyridine (Xa).³⁾ On the basis of above data together with elemental analyses, VIIa was culminated to be 3-hydroxy-2-phenylpyrazolo[1,5-*a*]pyridine. The fourth product, which gave VIIa and benzoic acid on hydrolysis, was proved to be 3-benzoyloxy-2-phenyl derivative (IXa). The ratio of the formation of these products was influenced by the amount of benzoyl chloride as shown in Table I.

Analogous to the above reaction, Ia was allowed to react with 3 moles of various substituted benzoyl chlorides to produce O,N-diacyl ylides (VIIe—j) and pyrazolo[1,5-*a*]pyridine derivatives (IXe—j), and the results are summarized in Table II.

TABLE III. Analytical Data of VIIa—j

Compd.	X	Y	mp (°C)	Formula	Analysis (%)						IR $\nu_{\text{max}}^{\text{KBr}}$ cm ⁻¹	
					Calcd.			Found			$\begin{array}{c} \text{O} \\ \parallel \\ \text{--N--C--} \end{array}$	$\begin{array}{c} \text{O} \\ \parallel \\ \text{--O--C--} \end{array}$
					C	H	N	C	H	N		
VIIa	H	H	146—147 ^{a)}	C ₂₀ H ₁₆ O ₃ N ₂	72.28	4.85	8.47	72.30	4.88	8.47	1555	1730
VIIb	<i>p</i> -NO ₂	H	186—188 ^{b)}	C ₂₀ H ₁₅ O ₅ N ₃	63.66	4.01	11.14	63.58	4.07	11.38	1580	1730
VIIc	<i>p</i> -NO ₂	<i>p</i> -NO ₂	192—193 ^{c)}	C ₂₀ H ₁₄ O ₇ N ₄	56.87	3.34	13.27	56.51	3.33	13.30	1580	1740
VIIId	H	<i>p</i> -NO ₂	168—169 ^{d)}	C ₂₀ H ₁₅ O ₅ N ₃	63.66	4.01	11.14	63.55	4.03	11.24	1600	1735
VIIe	<i>m</i> -F	<i>m</i> -F	164 ^{e)}	C ₂₀ H ₁₄ O ₃ N ₂ F ₂	—	—	7.62	—	—	7.95	1560	1720
VIIIf	<i>m</i> -Cl	<i>m</i> -Cl	128—129 ^{a)}	C ₂₀ H ₁₄ O ₃ N ₂ Cl ₂	59.81	3.52	6.98	59.73	3.50	6.68	1550	1720
VIIg	<i>m</i> -Br	<i>m</i> -Br	129—130 ^{a)}	C ₂₀ H ₁₄ O ₃ N ₂ Br ₂	49.00	2.88	5.71	48.82	2.86	5.56	1545	1715
VIIh	<i>m</i> -I	<i>m</i> -I	139—141 ^{a)}	C ₂₀ H ₁₄ O ₃ N ₂ I ₂	41.15	2.42	4.80	40.55	2.40	5.28	1530	1710
VIIi	<i>p</i> -Cl	<i>p</i> -Cl	157 ^{d)}	C ₂₀ H ₁₄ O ₃ N ₂ Cl ₂	59.81	3.52	6.96	60.21	73.50	6.82	1590	1730
VIIj	<i>p</i> -CH ₃ O	<i>p</i> -CH ₃ O	74—76 ^{f)}	C ₂₂ H ₂₀ O ₅ N ₂	67.33	5.14	7.14	67.28	5.38	6.89	1600	1720

a) recrystallized from AcOEt as colorless needles

b) recrystallized from AcOEt as pale yellow needles

c) recrystallized from MeOH as colorless needles

d) recrystallized from MeOH as pale yellow needles

e) recrystallized from AcOEt-*n*-hexane as colorless needles

f) recrystallized from AcOEt as colorless rods

The data in Table I suggest that an intermediate in the course of the cyclization to VIIa or IXa would be not VIIa but VIa, since the rate of formation of VIIa did not decrease with increased quantity of benzoyl chloride. In order to confirm this suggestion, the following reaction was carried out. First, VIa was treated with benzoyl chloride under the similar reaction condition as described in the reaction of Ia with benzoyl chloride to give the cyclization products, and VIIa and IXa were obtained. The same treatment of VIIa did not give the cyclization product and the starting material was recovered. Further, in order to confirm the introduction of the phenyl group at 2-position of IXa, VIa was reacted with 2.2 moles of *p*-nitrobenzoyl chloride under the same condition, and three kinds of ylide-type compounds (VIIb—d) and two kinds of pyrazolo[1,5-*a*]pyridine derivatives (VIIa and IXb) were obtained as shown in Chart 2. These results indicate the probable course of the cyclization as shown in Chart 3.

Chart 3

The primarily formed N-benzoyl-ylide (VIa) would be able to react further with benzoyl chloride to produce VIIa, XII, and XIII. The compound (VIIa) would not be undergone further conversion under such condition, but might give N,N-dibenzoylimino derivative (XI), which would be hydrolyzed easily to VIIa again, because VIIc was obtained in the reaction of VIa with *p*-nitrobenzoyl chloride. The compound (XII) might be convertible into VIIa as the result of N→O rearrangement of the benzoyl group, as supported by the formation of VIId in the above reaction. The compound (XIII) would collapse very easily to a six-membered cyclic pyridinium salt (XIV), which would be deprotonated to XV under alkaline condition. The compound (XV), having 12 π ring system, might be recycled to a more stable VIIIa possessing a 10 π ring system *via* an intermediate (XVI) as shown by arrows. The possibility of the formation of VIIIa from XIII *via* the anhydro base (XIII') was also considered, but it was difficult to support this possibility, since VIIa which would have a tendency to form the corresponding anhydro base more easily than VIa, could not be converted into IXa on treatment with benzoyl chloride in aqueous potassium carbonate solution which was the identical condition as that in the reaction of VIa and benzoyl chloride to form VIIIa.

Next, on the basis of the above assumption, an attempt was made to obtain 3-hydroxypyrazolo[1,5-*a*]pyridine derivatives from a substance capable of being converted into the intermediate (XV) *via* cyclic pyridinium derivative (XIV) under a suitable condition and three successful routes were found as shown in Chart 4.

First, VIIa was heated at 190° for 15 min to afford VIIIa and benzoic acid in approximately equal amounts (80%), together with a small amount (2.5%) of IXa. VIa was then treated with sulfuric acid, followed by alkali treatment, to obtain VIIIa in 71% yield. The same compound (VIIIa) was obtained in 26% yield by refluxing 1-benzimidazo-2-picoline (XVIIa) with an equimolar amount of iodine in pyridine. In a similar manner, various 3-hydroxypyrazolo[1,5-*a*]pyridine derivatives (VIIIe-1, IVa) were obtained and converted further into the corresponding 3-acetoxy derivatives (XVIIIe-1) by treating with acetic anhydride for antimicrobial evaluation as shown in Chart 4.

Chart 4

The scope of the cyclization method was extended to 1-thiocarbonylimino-2-hydroxymethylpyridine derivatives. 1-Anilinothiocarbonylimino-2-hydroxymethylpyridine (XIXa), which was prepared from Ia and phenyl isothiocyanate, was treated with sulfuric acid at room temperature and the resulting mixture was poured into ice water. Crystalline product that separated out was proved to be the cyclic pyridinium salt, 2-anilinopyridinium[1,2-*d*]-1,3,4-thiadiazine hydrogensulfate (XXa), which was hitherto postulated as an intermediate during the formation of pyrazolo[1,5-*a*]pyridines in our cyclization methods. Its structure

Chart 5

was proved by IR and NMR spectra, and from elementary analysis. The NMR spectrum of XXa (in DMSO- d_6) revealed a broad singlet at 5.30τ (2H) due to methylene group, a broad singlet at -0.98τ (1H), which disappeared by deuterium oxide treatment, assignable to the NH group, a multiplet at 0.8τ (1H) ascribable to C-6 proton of pyridine ring, and signals of the aromatic protons at 1.35 – 3.00τ (8H). The IR spectrum showed the absorption bands at 3400 – 3000 cm^{-1} attributed to the salts, at 1530 cm^{-1} due to $-\text{C}=\text{N}-$ group, and no thio-carbonyl group which existed in the spectrum of XIXa at 1440 cm^{-1} . When XXa was treated with alkali in water, a disulfide (XXIIa), which would result from the corresponding thiol (XXIa), was obtained in 88% yield. The structure of XXIIa was confirmed by elemental analyses and mass spectral data, which exhibited a weak molecular ion peak ($m/e=536$) and a strong (M/2) peak (268), and others. On treatment with Raney nickel in acetone, XXIIa was converted into 2-anilinopyrazolo[1,5-*a*]pyridine (XXIIIa), whose NMR spectrum indicated the C-3 proton at 2.73τ (1H) as a singlet and others (see Table V).

In a similar manner, 1-benzamidothiocarbonylimino-2-hydroxymethylpyridine (XIXb), which was obtained from Ia and benzoyl isothiocyanate, was converted into the corresponding disulfide (XXIIb) without isolation of cyclic pyridinium salt (XXb) as described in the experimental part. XXIIb was also converted into 2-benzamidopyrazolo[1,5-*a*]pyridine (XXIIIb) by Raney nickel reduction.

Thiocyanation of XXIIIa was effected by the usual method of reacting XXIIIa with ammonium thiocyanate and bromine in acetic acid to afford 3-mono and 3,4'-di-thiocyno derivatives (XXIV and XXV).

On the other hand, it was found that 2-aminopyrazolo[1,5-*a*]pyridine derivatives could be obtained from pyridine-2-acetamidoxime (XXVII) by treatment with acetic anhydride. Namely, the compound (XXVII), prepared from pyridine-2-acetonitrile (XXVI) and hydroxylamine, was treated with excess acetic anhydride at 100° for 30 min and the reaction products were separated by chromatography on alumina. 2-Acetamidopyrazolo[1,5-*a*]pyridine (XXIX), 5-methyl-3-(2-pyridylmethyl)-1,2,4-oxadiazole (XXVIII), and 2-acetamido-3-ace-

tylpyrazolo[1,5-*a*]pyridine (XXX) were obtained respectively in 29.7%, 32.9%, and 1.3% yield. Besides these products, traces of three kinds of products were separated as colorless needles having the molecular formula of $C_{11}H_{10}O_2N_3$ (mp 118–119°), pale yellow needles of $C_{11}H_{13}O_2N_3$ (mp 121°), and colorless needles of $C_{11}H_{13}O_2N_3$ (mp 149–150°), structures of which are under investigation.

Acid hydrolysis of XXIX gave 2-amino derivative (XXXII), which was converted into 2-benzamido derivative on treatment with benzoyl chloride, and it was identical with the compound (XXIIIb) obtained from XXIIb by IR spectral comparison and mixed mp determination. When the reaction time was prolonged to 24 hr in the reaction of XXVII and acetic anhydride, the yield of XXIX was increased to 42% and that of XXVIII decreased to 6.2%. This suggested a possibility for the formation of XXIX from XXVIII, and it was found that the oxadiazole derivative (XXVIII) was also convertible into pyrazolo[1,5-*a*]pyridines (XXIX and XXX) by refluxing in acetic anhydride. The structure of XXX was confirmed by the following reaction, together with its spectroscopic data and elemental analysis. The bromination of pyrazolo[1,5-*a*]pyridine derivative has been found to occur in the 3-position⁵⁾ and that of XXIX in acetic acid also took place at the 3-position to give 3-bromo derivative (XXXIa), whose structure was also evident from its NMR spectrum. On the other hand, since it has also been known that acetyl group in the 3-position of pyrazolo[1,5-*a*]pyridine derivative was easily replaced by an electrophilic reagents such as bromine,⁶⁾ the bromination of XXX was carried out and the resulting 3-bromo derivative (XXXIa) was identical with that obtained from XXIX as described above by IR spectral comparison and mixed mp determination.

Nitration and thiocyanation of XXIX were also carried out by the usual method to obtain 3-nitro and 3-thiocyano derivatives (XXXIb and XXXIc) in a good yield.

The pyrazolo[1,5-*a*]pyridines obtained in the present work are summarized in Table IV.

The concentration of these compounds inhibiting the growth of *Mycobacterium tuberculosis* Aoyama B strain was determined at 37° for 14 days in Dubos medium by Ushiyama and others of the Microbial Research Room in Kyorin Chemical Laboratory and the results are given in Table IV. Ethionamide used as the control inhibited the growth of the bacteria at 10 µg/ml, while 2-(substituted phenyl)-3-hydroxypyrazolo[1,5-*a*]pyridine derivatives (VIIIe—

Chart 6

5) W.W. Paudler and D.E. Dunham, *J. Heterocyclic Chem.*, **2**, 410 (1965).

6) M. Hirobe, Y. Minamoto, and T. Okamoto, *Abstr. 90th Annu. Meet. Pharm. Soc. Japan*, II-47 (1970).

TABLE IV. Pyrazolo[1,5-*a*]pyridine Derivatives

Compd.	R	R ₁	R ₂	Method ^(a)	Yield (%)	MIC ^(b) (μg/ml)	mp (°C)	Recryst. solvent ^(c)	Appearance ^(d)	Formula	Analysis (%)					
											Calcd.			Found		
											C	H	N	C	H	N
Vb	H	AcO	H	G (91)		>50	oil, pic. 145–146	E	yn	C ₁₅ H ₁₁ O ₉ N ₅	44.45	2.74	17.28	44.69	2.82	17.35
IIIa	Me	AcO	H	A (89)		5	oil ^(e) , pic. 152–153	E	yn	C ₁₆ H ₁₃ O ₉ N ₅	45.83	3.13	16.70	46.01	3.11	16.55
IIIb	Et	EtCOO	H	A (53)		10	43 ^(f)	H	n	C ₁₂ H ₁₄ O ₂ N ₂	66.03	6.47	12.84	66.13	6.61	12.88
IIIc	Pr	PrCOO	H	A (52)		>50	oil, pic. 106–107	E	yn	C ₁₄ H ₁₈ O ₂ N ₂	50.52	4.45	14.73	50.99	4.43	14.93
III ^g	Me	AcO	MeO	A (78)		5	oil, pic. 184	E	yn	C ₁₇ H ₁₅ O ₁₀ N ₅	45.44	3.57	15.59	45.08	3.61	15.82
Vc	Me	EtCOO	MeO	G (91)		5	73–74	H	n	C ₁₂ H ₁₄ O ₃ N ₂	61.52	6.02	11.96	61.75	5.94	11.84
IIIe	Me	AcO	EtO	A (77)		5	76–77	H	n	C ₁₂ H ₁₄ O ₃ N ₂	61.52	6.02	11.96	61.22	6.13	12.09
IVa	Me	HO	H	F (97), E (18)		5	159–160	A	n	C ₈ H ₆ ON ₂	64.85	5.44	18.91	64.68	5.38	19.01
IVb	Et	HO	H	F (97)		5	118–120	A	n	C ₉ H ₁₀ ON ₂	66.65	6.22	17.27	66.92	6.52	17.17
IVc	Pr	HO	H	F (94)		>50	100–101	A + H	r	C ₁₀ H ₁₂ ON ₂	68.16	6.86	15.90	67.85	6.74	15.95
IVd	F ₃ C	HO	H	F (25)		>50	154	C	p	C ₈ H ₆ ON ₂ F ₃	—	—	13.85	—	—	13.68
IVe	Me	HO	MeO	F (79)		5	146–148	A	n	C ₉ H ₁₀ O ₂ N ₂	60.66	5.66	15.72	60.39	5.66	15.69
IVf	Me	HO	EtO	F (91)		5	159–161	A	n	C ₁₀ H ₁₂ O ₂ N ₂	62.48	6.29	14.58	62.21	6.28	14.39
IVg	H	HO	H	B (40)		>50	117	A	n	C ₇ H ₆ ON ₂	62.68	4.51	20.89	62.45	4.50	20.71
Va	Me	MeO	H	J (86)		>50	bp 108–110/5mmHg	oil	oil	C ₉ H ₁₀ ON ₂	66.65	6.22	17.27	66.64	6.22	16.99
VIIa	Ph	HO	H	C (75), E (26), D (71)		>50	215–217	M + W	r	C ₁₃ H ₁₀ ON ₂	74.27	4.77	13.32	74.27	4.78	13.39
VIIe	<i>m</i> -F·Ph	HO	H	C (71)		1	196–197	M	n	C ₁₃ H ₉ ON ₂ F	—	—	12.28	—	—	12.38
VII ^h	<i>m</i> -Cl·Ph	HO	H	C (74)		10	210–211	M	n	C ₁₃ H ₉ ON ₂ Cl	63.78	3.69	11.48	63.45	3.65	11.13
VII ^g	<i>m</i> -Br·Ph	HO	H	C (79)		2.5	197–198	A	n	C ₁₃ H ₉ ON ₂ Br	53.98	3.13	9.68	54.27	3.01	9.35
VII ^h	<i>m</i> -I·Ph	HO	H	C (75)		1	211–212	M	n	C ₁₃ H ₉ ON ₂ I	46.50	2.68	8.34	46.09	2.74	7.68
VIIIi	<i>p</i> -Cl·Ph	HO	H	C (64)		10	188–190	M	n	C ₁₃ H ₉ ON ₂ Cl	63.78	3.69	11.44	63.71	3.44	11.09
VIIIj	<i>p</i> -MeO·Ph	HO	H	C (79)		10	174–176	M	n	C ₁₄ H ₁₃ O ₂ N ₂	69.99	5.03	11.66	69.36	4.84	11.60
VIIIk	<i>p</i> -NO ₂ ·Ph	HO	H	D (83)		>50	243–246	D + W	br	C ₁₃ H ₉ O ₃ N ₃	61.17	3.55	16.47	61.06	3.44	16.51
VIII ^l		HO	H	E (21)		10	264–266	A	n	C ₁₂ H ₉ ON ₃	68.23	4.30	19.90	68.11	4.31	19.75

XVIIe	<i>m</i> -F·Ph	AcO	H	G (93)	5	118	H	n	C ₁₅ H ₁₁ O ₂ N ₂ F	—	—	10.36	—	10.27	
XVIIf	<i>m</i> -Cl·Ph	AcO	H	G (90)	25	131—132	H	n	C ₁₅ H ₁₁ O ₂ N ₂ Cl	63.25	3.86	9.82	62.82	3.85	9.17
XVIIg	<i>m</i> -Br·Ph	AcO	H	G (94)	2.5	121—122	A + H	n	C ₁₅ H ₁₁ O ₂ N ₂ Br	54.36	3.34	8.43	54.38	3.34	8.77
XVIIh	<i>m</i> -I·Ph	AcO	H	G (96)	10	109—110	H	n	C ₁₅ H ₁₁ O ₂ N ₂ I	47.65	2.93	7.42	47.90	2.81	7.81
XVIIi	<i>p</i> -Cl·Ph	AcO	H	G (94)	5	166	A + H	n	C ₁₅ H ₁₁ O ₂ N ₂ Cl	63.25	3.86	9.82	62.93	3.90	9.56
XVIIj	<i>p</i> -MeO·Ph	AcO	H	G (91)	25	142—143	B + H	n	C ₁₆ H ₁₄ O ₃ N ₂	68.07	5.00	9.92	68.11	4.98	9.90
XVIIk	<i>p</i> -NO ₂ ·Ph	AcO	H	G (97)	>50	221—222	A	yn	C ₁₅ H ₁₁ O ₄ N ₃	60.60	3.73	14.14	60.48	3.98	13.97
XVIIl		AcO	H	G (88)	>50	140—141	M	n	C ₁₄ H ₁₁ O ₂ N ₃	66.39	4.38	16.59	66.27	4.30	16.69
XVIIIm	<i>p</i> -Br·Ph	AcO	H	G (91)	5	168	M	n	C ₁₅ H ₁₁ O ₂ N ₂ Br	54.36	3.34	8.43	54.60	3.49	8.22
IXa	Ph	PhCOO	H	H (28)	>50	125—126	M	n	C ₂₀ H ₁₄ O ₂ N ₂	76.42	4.49	8.91	76.46	4.58	8.65
IXe	<i>m</i> -F·Ph	<i>m</i> -F·PhCOO	H	H (11)	>50	177	B + H	n	C ₂₀ H ₁₃ O ₂ N ₂ F ₂	—	—	8.00	—	—	7.80
IXf	<i>m</i> -Cl·Ph	<i>m</i> -Cl·PhCOO	H	H (9)	>50	194	B	n	C ₂₀ H ₁₂ O ₂ N ₂ Cl ₂	62.68	3.15	7.31	62.39	3.14	7.22
IXg	<i>m</i> -Br·Ph	<i>m</i> -Br·PhCOO	H	H (11)	>50	207	B	n	C ₂₀ H ₁₂ O ₂ N ₂ Br ₂	50.71	2.77	5.92	50.60	2.87	5.59
IXh	<i>m</i> -I·Ph	<i>m</i> -I·PhCOO	H	H (8)	>50	246—247	O	n	C ₂₀ H ₁₂ O ₂ N ₂ I ₂	42.50	2.21	4.95	42.28	2.18	5.11
IXi	<i>p</i> -Cl·Ph	<i>p</i> -Cl·PhCOO	H	H (17)	>50	>250	B	n	C ₂₀ H ₁₂ O ₂ N ₂ Cl ₂	62.68	3.15	7.31	62.47	3.19	7.35
IXj	<i>p</i> -MeO·Ph	<i>p</i> -MeO·PhCOO	H	H (23)	>50	184	A	n	C ₂₂ H ₁₈ O ₄ N ₂	69.60	5.00	7.73	69.59	4.68	7.22
IXb	Ph	<i>p</i> -NO ₂ ·PhCOO	H	S (78)	>50	248—249	A	rn	C ₂₀ H ₁₃ O ₄ N ₃	66.85	3.65	11.70	66.71	3.69	11.53
Xa	Ph	MeO	H	I (75)	>50	80	H	n	C ₁₄ H ₁₂ ON ₂	74.99	5.38	12.49	74.77	5.21	12.41
Xb	<i>m</i> -Br·Ph	MeO	H	I (77)	>50	98—99	M	n	C ₁₄ H ₁₁ ON ₂ Br	55.45	3.66	9.24	55.22	3.80	8.89
Xc	<i>p</i> -NO ₂ ·Ph	MeO	H	I (82)	>50	166—168	A	yp	C ₁₄ H ₁₁ O ₃ N ₃	62.45	4.12	15.61	62.42	4.21	15.41
XXIIa	PhNH	-SS-	H	R (88)	>50	178	C + E	yn	C ₂₆ H ₃₀ N ₆ S ₂	64.99	4.20	17.49	64.79	4.17	17.56
XXIIb	PhCONH	-SS-	H	R (13) ^o	>50	259—261	M	yr	C ₂₃ H ₃₀ O ₂ N ₆ S ₂	62.68	3.76	15.67	62.45	3.76	15.61
XXIIa	PhNH	H	H	J (41)	>50	94—96	H	n	C ₁₃ H ₁₁ N ₃	74.62	5.30	20.08	74.64	5.37	19.98
XXIIb	PhCONH	H	H	J (26)	>50	166—167	M	r	C ₁₄ H ₁₁ ON ₃	70.87	4.67	17.71	70.60	4.55	17.78
XXIV	PhNH	NCS	H	K (62)	10	152—153	A	n	C ₁₄ H ₁₀ N ₄ S	63.15	3.79	21.04	63.86	3.64	21.14
XXV	<i>p</i> -NCS-	NCS	H	K (32)	>50	192—193	A	n	C ₁₅ H ₉ N ₃ S ₂	55.73	2.81	21.67	55.62	2.93	21.64
	PhNH														
XXXII	H ₂ N	H	H	L (90)	>50	62—63	H	n	C ₇ H ₇ N ₃	63.14	5.30	31.56	63.28	5.40	31.56
XXIX	AcNH	H	H	M (39)	>50	pic 178—179	E	yn	C ₁₃ H ₁₀ O ₇ N ₆	43.10	2.78	23.20	43.22	2.79	23.00
XXXIa	AcNH	Br	H	N (71)	>50	pic 184—185	E	yn	C ₁₅ H ₁₂ O ₈ N ₆	61.70	5.18	23.99	62.06	4.99	23.77
XXXIb	AcNH	O ₂ N	H	O (74)	>50	169—170	A	n	C ₉ H ₈ ON ₃ Br	44.56	2.99	20.79	44.67	3.04	20.58
XXXIc	AcNH	NCS	H	P (70)	>50	256—259	C + E	n	C ₉ H ₈ O ₃ N ₄	42.54	3.17	16.53	42.47	3.10	16.51
XXX	AcNH	Ac	H	M (14)	>50	197—198	M	n	C ₁₀ H ₈ ON ₄ S	49.09	3.66	25.45	48.79	3.55	25.15
XXIIIc	<i>p</i> -NO ₂ -	H	H	Q (94)	>50	>260	N	yp	C ₁₁ H ₁₁ O ₂ N ₃	51.72	3.47	24.13	51.58	3.55	24.47
	PhCONH								C ₁₄ H ₁₀ O ₃ N ₄	60.82	5.10	19.35	60.85	4.98	19.74
										59.57	3.57	19.85	59.57	3.52	19.97

a) A = I + acid anhydride, B = Ia + CH(OEt), C = pyrolysis of VII, D = VI + H₂SO₄ + K₂CO₃, E = XVIII + I₂ + pyridine, F = hydrolysis of III, G = VIII + Ac₂O, H = Ia + ArCOCl + H₂O + K₂CO₃, I = VIII + Me₂SO, J = Raney Ni + XXII, K = XXIIIa + NH₄SCN + Br₂, L = hydrolysis of XXIX, M = XXVII + Ac₂O, N = XXIX + HNO₃, P = XXIX + NH₄SCN + Br₂, Q = XXXII + p-NO₂-PhCOCl, R = XX + H₂O + K₂CO₃, S = VIIIa + p-NO₂-PhCOCl b) Minimum inhibitory concentration against *Myco. tuberculosis* Aoyama B c) A = AcOEt, B = benzene, C = chloroform, D = dimethylformamide, E = EtOH, H = hexane, M = MeOH, N = MeCN, W = H₂O, O = Ac₂O d) n = colorless needles, r = colorless rods, p = colorless plates, yn = yellow needles, yp = yellow plates, yr = yellow rods, br = brown rods e) bp 126—130° (3 mmHg) f) bp 135—140° (4 mmHg) g) Calcd. from XIXb. Ph = phenyl.

TABLE V. NMR Spectra Data for Some Pyrazolo[1,5-*a*]pyridine Derivatives

Compd.	Chemical shift, τ (ppm)						Coupling constant, J (cps)				Solv ^t . ^{a)}
	2	3	4	5	6	7	$J_{4,5}$	$J_{4,6}$	$J_{5,6}$	$J_{6,7}$	
Va	-CH ₃ 7.55	-OCH ₃ 6.10	2.51	2.99	3.39	1.19	7.0	2.0	5.0	5.0	A
Vb	1.86	-OOCCH ₃ 7.71	2.52	2.93	3.30	1.61	9.0	2.0	7.5	7.5	A
IIIa	-CH ₃ 7.63	-OOCCH ₃ 7.67	2.69	2.95	3.37	1.68	9.5	2.0		7.5	A
IIIe	-CH ₃ 7.67	-OOCCH ₃ 7.71	3.63	-OCH ₂ CH ₃ 5.99 8.58	3.66	1.95		2.5		7.5	A
Xa	Hb Ha -C ₆ H ₄ - Hb Ha Hb : 1.75	Ha: 2.25— 2.65 -OCH ₃ 6.08		2.93	3.29	1.58				7.5	A
Xc	-C ₆ H ₄ -NO ₂ 1.80	-OCH ₃ 6.05	2.50	3.00	3.32	1.75	9.0	1.5	7.0	7.0	A
XVIII	H H -C ₆ H ₄ -N H H 2.03 1.15	-OOCCH ₃ 7.57	2.53	2.77	3.11	1.52	9.0	2.0	7.0	7.5	A
XXIIa	-NH-C ₆ H ₅ 3.36	-SS-			3.60	1.92				6.0	A
XXIIIa	-NH-C ₆ H ₅ 3.90	2.73	2.95	3.15	3.48	1.81				7.0	A
XXIIb	-NHCO-C ₆ H ₅ 1.56	-SS-			3.36	1.78				5.0	A
XXIIIb	-NHCO-C ₆ H ₅ 0.32	2.81		2.95	3.52	2.15				7.5	A
XXX	-NHCOCH ₃ 7.38	-COCH ₃ 7.03	1.61	2.09	2.48	1.36	10.0		7.5	7.5	C
XXIX	-NHCOCH ₃ 0.25 7.66	2.85	2.45	2.78	3.19	1.58	9.0		7.5	7.5	A
XXXIa	-NHCOCH ₃ 2.00 7.66	-Br	2.56	2.69	3.12	1.53	10.0	2.5	7.0	7.5	A
XXXIb	-NHCOCH ₃ 7.36	-NO ₂	1.42	1.84	2.39	1.10	10.0		7.5	7.0	C
XXXIa	-NHCOCH ₃ 0.32 7.84	-SCN	2.26	2.91	2.88	1.25	10.0	2.5	7.5	7.5	B
XXXII	-NH ₂ 5.82	4.32	2.88	3.12	3.59	1.91	7.5	2.0	6.0	6.0	A

^{a)} A: Determined in CDCl₃ with TMS as internal standard, B: Determined in *d*₆-DMSO with TMS as internal standard, C: Determined in F₃CCOOH with TMS as internal standard. Data of Compd. No Xe, XXIIa, XXIIIa, XXIIb, XXIIIb, and XXXII were obtained using a 60 MHz and others were with 100 MHz.

j) were effective at equal or lower doses. Among the compounds (VIIIe—j), 2-(*m*-fluoro- or -iodophenyl)-3-hydroxy derivative was the strongest, being about 10 times stronger than Ethionamide. Among the series of 2-alkyl-3-hydroxy derivatives, 2-methyl and 2-ethyl derivatives (IVa, b, e, f) showed the same activity as that of Ethionamide. 3-Acetoxy derivatives showed activity nearly equal to that of the corresponding 3-hydroxy derivatives. 3-Thiocyano derivatives (XXIV and XXXIc) also showed potent activity.

Experimental

All melting points are uncorrected. IR spectra were taken on a Nihon Bunko Model IR-S and Model DS-301. NMR spectra were measured on a Nihon Denshi C60H and JNM-4H-100. Analytical data of the pyrazolo[1,5-*a*]pyridines are summarized in Table IV and those of VIa—j are shown in Table III.

3-Acetoxy-2-methylpyrazolo[1,5-*a*]pyridine (IIIa) and Its 5-Alkoxy Derivatives (IIIe, f)—A mixture of 3.20 g (0.02 mole) of Ia, 2.46 g (0.03 mole) of AcONa, and 50 ml of Ac₂O was refluxed for 5 hr. After removal of the excess Ac₂O under reduced pressure on a water bath using a rotary evaporator, the residual mass was treated with 30 ml of H₂O, basified with K₂CO₃, and extracted with CH₂Cl₂. The CH₂Cl₂ extract was washed with water, dried (Na₂SO₄), and distilled to give 3.38 g (89%) of IIIa as a colorless oil, bp 126—128° (3 mmHg). IR $\nu_{\text{max}}^{\text{Liq}}$ cm⁻¹: 1765 (ester). It readily formed a picrate, which was recrystallized from EtOH as yellow needles, mp 152—153°.

The same treatment of Ib or Ic as for Ia gave a crude product, which was chromatographed on silica gel using ether as eluent without distillation to give IIIe or IIIf. Experimental data are shown in Table IV.

2-Ethyl- or Propyl-3-propionyloxy- or Butyroxypyrazolo[1,5-*a*]pyridine (IIIb or IIIc)—A mixture of 1.60 g (0.01 mole) of Ia, 16 ml of propionic anhydride (or butyric anhydride), and 1.4 ml of pyridine was heated on an oil bath (140—145°) for 5 hr, and then the excess reagent were removed under a reduced pressure. The dark residue was taken up in CH₂Cl₂ and chromatographed on silica gel. The CH₂Cl₂ eluate yielded a pale brown crystal, which was recrystallized from hexane to colorless needles (IIIb), mp 43°, weighing 1.149 g (53%). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1760 (ester). When butyric anhydride was used, IIIc was obtained as a colorless oil (1.286 g, 52.3%). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1770 (ester). The picrate of IIIc was recrystallized from EtOH as yellow needles, mp 106—107°.

3-Hydroxy-2-trifluoromethylpyrazolo[1,5-*a*]pyridine (IVd)—To a cooled solution of 1.60 g Ia in 20 ml of trifluoroacetic anhydride 2 ml of pyridine was added dropwise with stirring and the mixture was refluxed for 7 hr on a water bath (60°). After removal of the excess reagents under a reduced pressure, the crude product obtained was chromatographed on silica gel using CH₂Cl₂ as eluent. IVd was obtained and recrystallized from MeOH-H₂O as colorless rods, mp 154°. Yield, 0.511 g (25%).

2-Alkyl-3-hydroxypyrazolo[1,5-*a*]pyridine (IVa—c) and Its 5-Alkoxy Derivatives (IVe, f)—A solution of III (or Vb) (0.01 mole) in 10% HCl (20 ml) was heated on a water bath for 1 hr. The solution was basified with conc. NH₄OH to give a crystalline product, which was recrystallized from the solvent shown in Table IV.

3-Acetoxy-2-methylpyrazolo[1,5-*a*]pyridine (Vb)—A mixture of 1.6 g of Ia, 25 ml of AcOH, 1.6 g of AcONa, and 2.0 g of ethyl orthoformate was refluxed for 5 hr, and the excess reagents were removed under a reduced pressure. To the resulting residue was added 20 ml of Ac₂O and the mixture was allowed to stand overnight. After removal of the excess Ac₂O under a reduced pressure, the residual dark oil was chromatographed on alumina using CH₂Cl₂ as eluent. Vb was obtained as a colorless oil (0.700 g). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1750 (ester). It gave a picrate, which was recrystallized from EtOH as yellow needles, mp 145—146°.

Reaction of Ia with BzCl in Aqueous K₂CO₃—To a solution of 1.00 g of Ia in 5 ml of H₂O containing 1.38 g of K₂CO₃, a solution of 1.40 g of BzCl in 10 ml of CH₂Cl₂ was added dropwise at 5—10° with stirring. The stirring was continued for 1 hr at the same temperature and then for further 3 hr at room temperature. The mixture was extracted with CH₂Cl₂ layer was dried over anhyd. Na₂SO₄, and evaporated to dryness. The residue was chromatographed on alumina using CH₂Cl₂ as eluent.

First Fraction: Recrystallized from MeOH gave 73 mg of 3-benzoyloxy-2-phenylpyrazolo[1,5-*a*]pyridine (IXa) as colorless needles, mp 125—126°. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1755 (ester).

Second Fraction: Recrystallization from MeOH-H₂O afford 41 mg of 3-hydroxy-2-phenylpyrazolo[1,5-*a*]pyridine (VIIIa) as colorless needles, mp 215—217° (decomp.).

Third Fraction: Recrystallization from AcOEt gave 0.184 g of 1-benzimido-2-benzoyloxymethylpyridine (VIIa) as colorless needles, mp 146°. NMR τ in CDCl₃: 4.23 (2H, singlet, -CH₂-).

Fourth Fraction: Recrystallization from MeOH-AcOEt gave 0.174 g of 1-benzimido-2-hydroxymethylpyridine (VIa) as colorless plates, mp 178—179°. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3200—2600 (OH), 1520 (-NCO-). NMR τ in D₂O: 5.39 (2H, singlet, -CH₂-). Anal. Calcd. for C₁₃H₁₂O₂N₂: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.29; H, 5.42; N, 12.36.

The data of the same reaction of Ia with another quantities of BzCl are summarized in Table I. In the same manner, Ia was allowed to react with three-fold moles of various substituted benzoyl chloride in

aq. K_2CO_3 and the results are summarized in Table II. Analytical data of VIa—j are summarized in Table III.

3-Methoxy-2-phenylpyrazolo[1,5-*a*]pyridine (Xa)—To a solution of 60 mg of VIIa in 15 ml of aq. 5% NaOH was added 1 ml of Me_2SO_4 and the mixture was stirred for 3 hr. The mixture was extracted with CH_2Cl_2 , the extract was dried over anhyd. Na_2SO_4 , and evaporated to give a crude product, which was recrystallized from hexane to 48 mg (75%) of Xa as pale grey rods, mp 80°.

By the same way, 2-(*m*-bromophenyl or *p*-nitrophenyl)-3-methoxypyrazolo[1,5-*a*]pyridine (Xb or Xc) was obtained from the corresponding 3-hydroxy derivative.

Reaction of VIa with *p*-Nitrobenzoyl Chloride in aq. K_2CO_3 —To a mixture of 366 mg of VIa and 484 mg of K_2CO_3 in 5 ml of H_2O , a solution of 650 mg of *p*-nitrobenzoyl chloride in 5 ml of $CHCl_3$ was added at room temperature with stirring. After few minutes, red needles began to separate. The stirring was continued for 6 hr and, after standing overnight, the red crystals were collected by filtration and the filtrate was extracted with $CHCl_3$. The $CHCl_3$ layer, after being dried over Na_2SO_4 , was evaporated to give a crude product, which was triturated with AcOEt. The insoluble red crystals were combined with those obtained from the reaction mixture and recrystallized from AcOEt to 94 mg of IXb as red needles, mp 248–249°.

The AcOEt layer used in the trituration was evaporated to give a crude mass, which was chromatographed over alumina with CH_2Cl_2 .

First Fraction: 45 mg of IXb.

Second Fraction: Recrystallization from MeOH- H_2O gave 4 mg of VIIa, mp 215°.

Third Fraction: Recrystallization from AcOEt gave 23 mg of 2-benzoyloxymethyl-1-(*p*-nitrobenzimidopyridine (VIIb) as pale yellow needles, mp 183–185°. IR ν_{max}^{KBr} cm^{-1} : 1730 (ester), 1580 (-NCO-). VIIb (100 mg) was treated with a solution of CH_2Cl_2 (1 ml), MeOH (1 ml), and aq. 28% NH_4OH (0.5 ml) at room temperature and gave 85 mg of 2-hydroxymethyl-1-(*p*-nitrobenzimidopyridine as colorless needles mp 205–206° (from MeOH), and methyl benzoate (58 mg). *Anal.* Calcd. for $C_{13}H_{11}O_4N_3$: C, 57.14; H, 4.06; N, 15.38. Found: C, 56.89; H, 4.20; N, 15.13. IR ν_{max}^{KBr} cm^{-1} : 3200 (broad, OH), 1570 (-NCO-).

Fourth Fraction: Recrystallized from MeOH gave 31 mg of 1-(*p*-nitrobenzimidopyridine-2-(*p*-nitrobenzoyloxymethyl)pyridine (VIIc) as colorless needles, mp 192°. IR ν_{max}^{KBr} cm^{-1} : 1740 (ester), 1580 (-NCO-).

Fifth Fraction: Recrystallization from MeOH gave 273 mg of 1-benzimidopyridine-2-(*p*-nitrobenzoyloxymethyl)pyridine (VIIId) as pale yellow needles, mp 168°. IR ν_{max}^{KBr} cm^{-1} : 1735 (ester), 1600 (-NCO-).

Pyrolysis of VIIa, e—j—The following method illustrates the general procedure for the products summarized in Table IV.

VIIa (0.337 g) was heated at 190–195° under a reduced pressure for 15 min. during which time benzoic acid (8 mg) sublimed. When cooled, the reaction mixture was triturated with CH_2Cl_2 (2 ml) and the insoluble material (VIIa, 102 mg) was collected. The CH_2Cl_2 layer was washed with 2.8% NH_4OH and evaporated to leave a crystalline mass, which was chromatographed over silica gel with CH_2Cl_2 to give 8.9 mg of IXa as the first fraction and 68 mg of VIIa as the second fraction. Total yield of VIIa, 170 mg. The aq. NH_4OH layer, on evaporation after drying over Na_2SO_4 , gave 90 mg of benzoic acid. The total yield of benzoic acid, 98 mg.

In the same way, VIIe—j were obtained as shown in Table IV.

VIIa, k from VIa, k by H_2SO_4 Treatment—Ninety-three milligrams of VIa was dissolved in 1 ml of conc. H_2SO_4 below 20° with moderate cooling and stirring. After being stirred for 2 hr at room temperature, the mixture was poured on 20 g of crushed ice. The resulting aq. solution, after being basified with K_2CO_3 , was extracted with CH_2Cl_2 . The extract was dried (Na_2SO_4) and evaporated under a reduced pressure, giving 61 mg of VIIa as colorless needles, mp 215°, on recrystallization from H_2O -MeOH. This compound was identical with the product obtained as above by mixed mp determination and IR spectral comparison. In the same way, VIIk was prepared from VIk in 86% yield.

Reaction of XVIIa—c with I_2 in Pyridine—To a suspension of 0.639 g of XVIIa in 3 ml pyridine, 760 mg of I_2 was added with stirring, refluxed for 5 hr, and the mixture was concentrated under a reduced pressure. The resulting dark mass was triturated with a small amount of $CHCl_3$ and the insoluble material was recrystallized from MeOH- H_2O to give VIIa (165 mg) as colorless needles, mp 215°. The material was identical with the sample obtained as above by admixture, thin-layer chromatography (TLC), and IR spectral comparison. In the same manner, 1-acetimido-2-picoline was reacted and the crude product was chromatographed over alumina with CH_2Cl_2 to give IVa in 11.4% yield.

1-Isonicotinoylimino-2-picoline (XVIIb), prepared as will be described later, was converted into 3-hydroxy-2-(pyridin-4-yl)pyrazolo[1,5-*a*]pyridine (VIII) in the same manner, but the isolation of VIII from the reaction mixture was as follows: The reaction mixture was concentrated under a reduced pressure, excess Ac_2O was added to the dark residue, and the mixture was allowed to stand over night, concentrated, and chromatographed over alumina with CH_2Cl_2 to give 3-acetoxy-2-(pyridin-4-yl)pyrazolo[1,5-*a*]pyridine (XVIII) which was recrystallized from AcOEt-hexane to colorless needles, mp 140–141°. IR ν_{max}^{KBr} cm^{-1} : 1760 (ester). Yield, 20.6%. XVIII thus obtained was hydrolyzed to VIII in 92% yield in the same manner as described for IVa—c.

1-Isonicotinylimino-2-picoline (XVIIb)—To a solution of 2.3 g of 1-amino-2-picolinium iodide in 10 ml of H_2O containing 3.0 g of K_2CO_3 , 1.5 g of BrCN was added with stirring at 5–10° and the mixture was stirred

for 8 hr at room temperature. Crystals which separated from the reaction mixture were collected by filtration and recrystallized from AcOEt to 0.798 g of 1-cyanimino-2-picoline as colorless needles, mp 121—122°. *Anal.* Calcd. for $C_7H_7N_3$: C, 63.14; H, 5.30; N, 31.56. Found: C, 63.02; H, 5.30; N, 31.41.

A suspension of 1.3 g of 1-cyanimino-2-picoline and 1.50 g of isonicotinic acid in 16 ml of dimethylformamide was heated on a water bath for 2 hr. The suspension became a clear solution, which was heated for further 16 hr and evaporated to dryness. The resulting crystals were extracted with CH_2Cl_2 and the extract was concentrated and chromatographed over alumina using CH_2Cl_2 containing MeOH (5%) as eluent to give 1.150 g of colorless rods, which were recrystallized from AcOEt to colorless rods, mp 146—147°. IR ν_{max}^{KBr} cm^{-1} : 1585 (—NCO—). *Anal.* Calcd. for $C_{12}H_{11}ON_3$: C, 67.59; H, 5.20; N, 19.71. Found: C, 67.51; H, 5.45; N, 19.81.

3-Acetoxy-2-substituted Phenylpyrazolo[1,5-*a*]pyridine (XVIIIe—1)—VIIIe—1 was refluxed with excess Ac_2O for 3 hr and, after removal of the excess Ac_2O , the residue was recrystallized from a suitable solvent as shown in Table IV to give XVIIIe—1.

1-Anilinothiocarbonylimino-2-hydroxymethylpyridine (XIXa)—To a solution of 1.60 g of Ia in 10 ml of H_2O containing 1.4 g of K_2CO_3 , a solution of 1.4 g of phenyl isothiocyanate in 20 ml of CH_2Cl_2 was added and the mixture was stirred for 5 hr at room temperature. The product which separated was collected and recrystallized from MeOH to colorless needles, mp 146—147°. Yield 1.855 g (71.5%). *Anal.* Calcd. for $C_{13}H_{13}ON_2S$: C, 60.22; H, 5.05; N, 16.29. Found: C, 60.12; H, 5.13; N, 16.26.

1-Benzamidothiocarbonylimino-2-hydroxymethylpyridine (XIXb)—To a solution of 1.60 g of Ia in 10 ml of H_2O containing 1.4 g of K_2CO_3 , a solution of 1.7 g of benzoyl isothiocyanate in 10 ml of CH_2Cl_2 was added and the mixture was stirred for 5 hr at room temperature and extracted with CH_2Cl_2 . The extract was dried (Na_2SO_4) and evaporated to give a crude product, which was chromatographed over alumina using CH_2Cl_2 as eluent. The title compound was obtained and recrystallized from AcOEt as colorless needles, mp 130—131°; 0.892 g (31.2%). *Anal.* Calcd. for $C_{14}H_{13}O_2N_3S$: C, 58.53; H, 4.56; N, 14.63. Found: C, 58.63; H, 4.60; N, 14.68.

2-Anilinothiopyridinium[1,2-*d*]-1,3,4-thiadiazine Hydrogen Sulfate (XXa)—To 1 ml of conc. H_2SO_4 was added 0.527 g of XIXa below 20° with moderate cooling and vigorous stirring. The resulting clear solution was stirred for 1 hr at room temperature and poured on 20 g of crushed ice. Colorless needles that separated were collected on a filter, washed with a little cooled water, and recrystallized from EtOH to pale yellow rods, mp 229—231°; 0.271 g. *Anal.* Calcd. for $C_{13}H_{12}N_3S \cdot HSO_4$: C, 46.02; H, 3.86; N, 12.39. Found: C, 46.22; H, 3.86; N, 12.35.

To aq. filtrate was basified with K_2CO_3 , followed by the same treatment as described for XXIIa, to give 213 mg of XXIIa.

2,2'-Dianilinopyrazolo[1,5-*a*]pyridine-3,3'-disulfide (XXIIa)—A solution of 200 mg of XXa in 20 ml of H_2O was basified with K_2CO_3 to give an yellow oil, which was extracted with CH_2Cl_2 . The extract was dried (Na_2SO_4) and evaporated to give a crude product, which was recrystallized from $CHCl_3$ -EtOH to 125 mg of yellow needles, mp 178°.

2,2'-Dibenzamidopyrazolo[1,5-*a*]pyridine-3,3'-disulfide (XXIIb)—Four hundred milligrams of XIXb were dissolved in 1 ml of conc. H_2SO_4 below 20° with moderate cooling and stirring. After being stirred for 30 min, the mixture was poured on 20 g of crushed ice. The resulting clear solution was basified with K_2CO_3 and extracted with CH_2Cl_2 . The extract was dried (Na_2SO_4) and evaporated to give a crude product which was recrystallized from MeOH to yellow rods, mp 259—261°; 48 mg.

2-Anilinothiopyrazolo[1,5-*a*]pyridine (XXIIIa)—To a solution of 196 mg of XXIIa in 40 ml of acetone 2.5 g of Raney Ni (W-4) was added with stirring and the stirring was continued for 10 hr, during which time the reddish yellow color of the reaction mixture disappeared. After removal of Raney Ni, the solution was evaporated to dryness under a reduced pressure to give crude crystals (70 mg), which were recrystallized from hexane to colorless needles (33 mg), mp 94—96°.

2-Benzamidopyrazolo[1,5-*a*]pyridine (XXIIIb)—The same treatment of XXIIb as for XXIIa gave XXIIIb (26.6%) as colorless needles (from MeOH), mp 166—167°.

2-Anilino-3-thiocyanopyrazolo[1,5-*a*]pyridine (XXIV) and 3-Thiocyano-2-(*p*-thiocyanoanilino)-derivative (XXV)—To a solution of 209 mg of XXIIIa and 400 mg of KSCN in 2 ml of AcOH and 1 ml of H_2O , a solution of 180 mg of Br_2 in 1 ml of AcOH was added dropwise at room temperature with stirring. After stirring for 3 hr, the mixture was poured into H_2O and the crude product separated was taken up in CH_2Cl_2 . The CH_2Cl_2 layer was washed with $NaHCO_3$ solution, dried over Na_2SO_4 , and evaporated. The resulting crystalline mass was chromatographed over alumina with CH_2Cl_2 . The first fraction gave 0.164 g (61.7%) of XXIV, which was recrystallized from AcOEt to colorless needles, mp 152—153°. The second fraction gave 0.105 g (32.5%) of XXV, recrystallized from AcOEt to colorless needles, mp 192—193°.

Pyridine-2-acetamidoxime (XXVII)—To a solution of 8.4 g (0.12 mole) of $NH_2OH \cdot HCl$ in 10 ml of H_2O a solution of 8.4 g of K_2CO_3 in 20 ml of H_2O was added gradually and then 30 ml of MeOH. Inorganic substance which precipitated was removed by filtration. To the filtrate was added 4.72 g (0.04 mole) of pyridine-2-acetonitrile and the mixture was refluxed on a water bath for 4 hr. After removal of the solvent under a reduced pressure, the residue was recrystallized from H_2O to 5.7 g (94.5%) of XXVII as colorless

needles, mp 112—114°. *Anal.* Calcd. for $C_7H_9ON_3$: C, 55.61; H, 6.00; N, 27.80. Found: C, 55.90; H, 5.92; N, 27.82.

Reaction of XXVII with Ac_2O —To 30 ml of Ac_2O , 6.0 g of XXVII was added in small portions with stirring and the mixture was heated at 100° for 30 min. After the excess reagent was removed under a reduced pressure, the residue was chromatographed over alumina with ether.

First Fraction: 51 mg of a compound, having an empirical formula $C_{11}H_{13}O_2N_3$, recrystallized from hexane as colorless needles, mp 118—119°.

Second Fraction: 2.432 g (32.9%) of 5-methyl-3-(2-pyridylmethyl)-1,2,4-oxadiazole (XXVIII) as colorless oil. Its picrate recrystallized from EtOH as yellow needles, mp 149—150°. NMR τ in $CDCl_3$: 5.65 (2H, singlet, $-CH_2-$), 7.45 (3H, singlet, CH_3). *Anal.* Calcd. for $C_9H_9ON_3 \cdot C_6H_3O_7N_3$: C, 44.56; H, 2.99; N, 20.79. Found: C, 44.81; H, 3.21; N, 20.73.

Third Fraction: 67 mg of a compound having an empirical formula $C_{11}H_{11}O_2N_3$, recrystallized from hexane as pale yellow needles, mp 121°.

Fourth Fraction: 2.200 g (29.7%) of 2-acetamidopyrazolo[1,5-*a*]pyridine (XXIX), recrystallized from $CHCl_3$ or AcOEt-hexane as colorless rods, mp 112—113°. Its picrate was recrystallized from EtOH as yellow needles, mp 184°.

Fifth Fraction: 121 mg of a compound having an empirical formula $C_{11}H_{11}O_2N_3$, recrystallized from AcOEt as colorless rods, mp 149—150°.

Sixth Fraction: 161 g of 2-acetamido-3-acetylpyrazolo[1,5-*a*]pyridine (XXX), recrystallized from MeOH as colorless needles, mp 197—198°.

Reaction of XXVIII with Ac_2O —A mixture of 0.947 g of XXVIII in 4 ml of Ac_2O was refluxed for 3 hr and then evaporated to dryness. The residue was chromatographed over alumina using ether to give 0.205 g (21.6%) of the starting material, 0.366 g (38.7%) of XXIX, and 0.176 g (13.5%) of XXX. These products were identical with those obtained as above by IR spectral comparison, TLC, and mixed mp determination.

2-Acetamido-3-bromopyrazolo[1,5-*a*]pyridine (XXXIa)—a) To a solution of 366 mg of XXIX in 2.5 ml of AcOH, 0.377 g of Br_2 in 1 ml of AcOH was added and the mixture was allowed to stand for 10 hr. The deposited crystals were collected by filtration and the filtrate was diluted with water to precipitate the same compound. Total yield, 0.377 g. It was recrystallized from AcOEt to colorless needles, mp 169—170°.

b) The same treatment of XXX as for XXIX gave XXXIa (61%), which was identified with XXXIa obtained in a) from IR spectral comparison and mixed mp determination.

2-Aminopyrazolo[1,5-*a*]pyridine (XXXII)—A solution of 0.250 g of XXIX in 17% HCl was heated on a water bath for 1.5 hr and concentrated to about one-half the original volume under a reduced pressure. The resulting solution was basified with conc. NH_4OH to give an oily product which soon solidified. The solid was separated on a filter and recrystallized from ether-hexane to colorless plates, mp 62—63°; 171 mg (90%). Its picrate was recrystallized from EtOH as yellow needles, mp 176—178°.

XXXII was allowed to react with $BzCl$ to give XXIIIb, which was identical with XXIIIb obtained from XXIIb.

2-Acetamido-3-nitropyrazolo[1,5-*a*]pyridine (XXXIb)—To a solution of 390 mg of XXIX in 2 ml of AcOH was added 0.5 ml of HNO_3 (d 1.52) with cooling in an ice-water bath. After standing for 30 min at the same temperature and then 2 hr at room temperature, the mixture was poured into water. The separated crystals were collected, washed with H_2O , dried, and recrystallized from $CHCl_3$ -EtOH to pale brown scales, mp 256—259°; 364 mg.

2-Acetamido-3-thiocyanopyrazolo[1,5-*a*]pyridine (XXXIc)—To a mixture of 0.800 g of XXIX and 1.4 g of KSCN in 6 ml of MeOH a solution of 0.8 g of Br_2 in 3 ml of MeOH saturated with KBr was added dropwise with stirring at room temperature. After the addition was completed, the mixture was allowed to stand overnight. Water was added to the mixture and the precipitated material was collected by filtration. It was recrystallized from MeOH to 0.665 g (70.5%) of pale blue needles, mp 199—200°.