Acid-Catalyzed Reactions of 3-(Hydroxymethyl)- and 3-(1-Hydroxyethyl)pyrazolo[1,5-*a*]pyridines

Yasuyoshi Miki*, Noriko Nakamura, Hiroko Hachiken and Shoji Takemura

Faculty of Pharmaceutical Sciences, Kinki University,
3-4-1, Kowakae, Higashi-Osaka 577, Japan

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Treatment of 3-(hydroxymethyl)pyrazolo[1,5-*a*]pyridines with trifluoroacetic acid in refluxing dichloromethane led to the formation of bis(pyrazolo[1,5-*a*]pyrid-3-yl)methanes or bis[(pyrazolo[1,5-*a*]pyrid-3-yl)]-methyl ethers depending upon the concentration of trifluoroacetic acid. In contrast, similar treatment of 3-(1-hydroxyethyl)pyrazolo[1,5-*a*]pyridines gave a mixture of 3-vinylpyrazolo[1,5-*a*]pyridines and 1,3-bis(pyrazolo-[1,5-*a*]pyrid-3-yl)-1-butenes.

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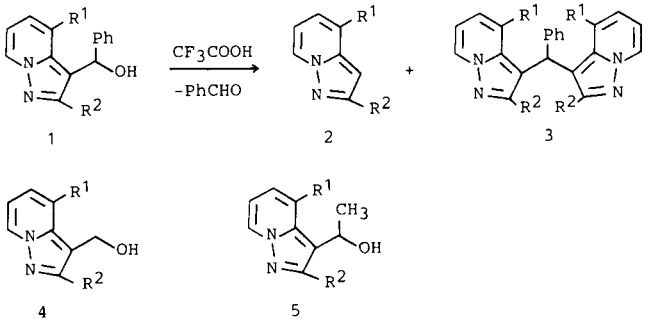
Although pyrazolo[1,5-*a*]pyridines [1] are regarded as the aza-analogue of indoles, but the chemical properties of this interesting heterocycles have not as yet been fully defined. Recently, we reported that the reaction of 3-(α-hydroxybenzyl)pyrazolo[1,5-*a*]pyridines **1** with trifluoroacetic acid gave 3-unsubstituted pyrazolo[1,5-*a*]pyridines **2**, phenylbis(pyrazolo[1,5-*a*]pyrid-3-yl)methanes **3**, or bis[α-(pyrazolo[1,5-*a*]pyrid-3-yl)benzyl] ethers, depending upon the presence or absence of the 2- and/or 4-substituents of pyrazolo[1,5-*a*]pyridine [2]. We were then led to examine the behavior of 3-(hydroxymethyl)- **4** and 3-(1-hydroxyethyl)-pyrazolo[1,5-*a*]pyridines **5** toward acid, in order to see how the acid-catalyzed reactions observed with the α-hydroxybenzyl derivatives **1** would be influenced by substituents both on the ring and at the side chain.

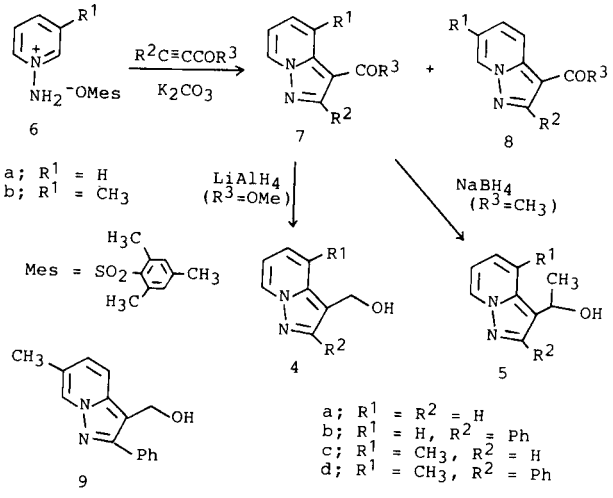
Scheme 1



The 3-(hydroxymethyl)- **4** and 3-(1-hydroxyethyl)pyrazolo[1,5-*a*]pyridines **5** were prepared according to the synthetic method similar to that of 3-(α-hydroxybenzyl)pyrazolo[1,5-*a*]pyridines **1** [2] as outlined in Scheme 2.

Treatment of 3-(hydroxymethyl)pyrazolo[1,5-*a*]pyridine **4a** with trifluoroacetic acid (2.5 equivalents) in refluxing chloroform gave only the bis(pyrazolo[1,5-*a*]pyrid-3-yl)-methane **10a** [3], whereas similar reaction of **4a** with trifluoroacetic acid (0.01 equivalent) in refluxing dichloromethane yielded the bis[(pyrazolo[1,5-*a*]pyrid-3-yl)methyl] ether **11a** as a major product. Similar results were obtained with **4b-d** on the reaction of trifluoroacetic acid (Table 1). When treated with 2.5 equivalents of trifluoroacetic acid in refluxing dichloromethane, the ether **11b** was completely transformed into the bis(2-phenylpyrazolo[1,5-*a*]-pyrid-3-yl)methane **10b** in 96% yield. These behavior of **4** is essentially the same as that of the 3-(α-hydroxybenzyl)-pyrazolo[1,5-*a*]pyridines **1** [2].

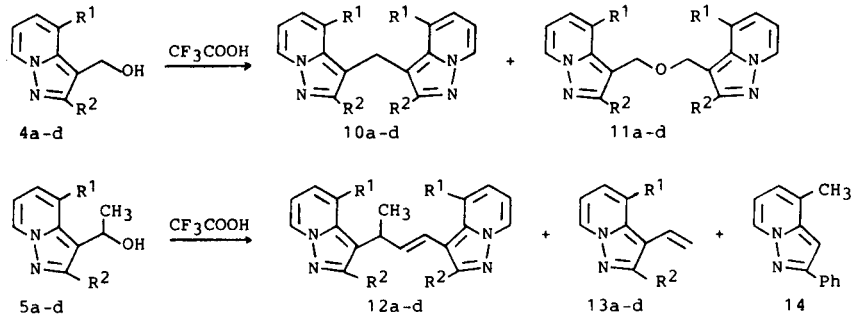
Scheme 2



In contrast, treatment of 3-(1-hydroxyethyl)pyrazolo-[1,5-*a*]pyridine **5a** with trifluoroacetic acid (2.5 equivalents) gave only 1,3-bis(pyrazolo[1,5-*a*]pyrid-3-yl)-1-butene **12a** in 80% yield. On the other hand, similar reaction of **5a** with trifluoroacetic acid (0.01 equivalent) yielded a mixture of **12a** and 3-vinylpyrazolo[1,5-*a*]pyridine **13a** in 10% and 32% yields, respectively. Treatment of **5b-d** with trifluoroacetic acid (0.01 and 2.5 equivalents) afforded similar products but **5d** gave an additional product, 4-methyl-2-phenylpyrazolo[1,5-*a*]pyridine **14**, along with **12d** and **13d** (Table 2).

The structures of these products were assigned on the basis of elemental analyses and the spectroscopic evidence (see Experimental). The elemental analyses of the oily 3-vinylpyrazolo[1,5-*a*]pyridines **13a,c** were performed after reduction of vinyl group to ethyl group. The *trans*-stereo-

Scheme 3



a; $R^1 = R^2 = H$, b; $R^1 = H$, $R^2 = Ph$,

c; $R^1 = CH_3$, $R^2 = H$, d; $R^1 = CH_3$, $R^2 = Ph$

Table 1

Reaction of 3-(Hydroxymethyl)pyrazolo[1,5-*a*]pyridines **4a-d** with Trifluoroacetic Acid

4	R^1	R^2	CF_3COOH (equivalents)	Reaction Conditions [a] Solvents	Time (hours)	Yield (%) 10	11
a	H	H	2.5	chloroform	5	88	—
			0.01	dichloromethane	6	14	73
b	H	Ph	2.5	dichloromethane	2 [b]	86	—
			0.01	dichloromethane	5	18	73
c	CH_3	H	2.5	chloroform	5	72	—
			0.01	chloroform	5	13	67
d	CH_3	Ph	2.5	dichloromethane	7	93	—
			0.01	dichloromethane	4	5	61

[a] All reactions were carried out in refluxing solvent.
[b] At room temperature.

Table 2

Reaction of 3-(1-Hydroxyethyl)pyrazolo[1,5-*a*]pyridines **5a-d** with Trifluoroacetic Acid

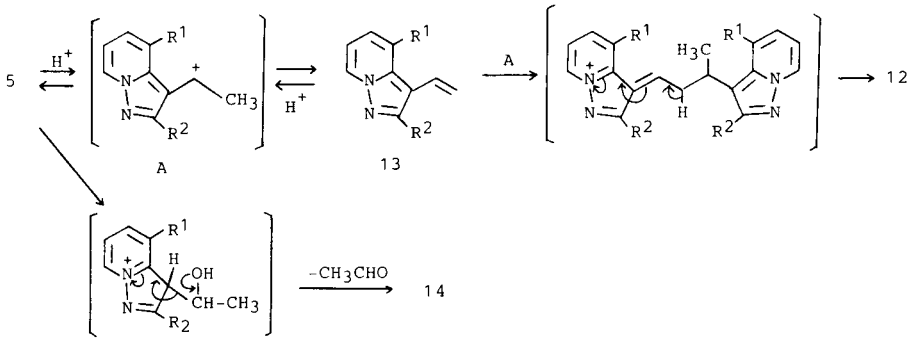
5	R^1	R^2	CF_3COOH (equivalents)	Reaction Conditions [a] Temperature	Time (hours)	Yield (%) 12	13	14
a	H	H	2.5	rt	0.25	80	—	—
			0.01	reflux	8	10	32	—
b	H	Ph	2.5	rt	0.75	82	—	—
			0.01	reflux	4	17	44	—
c	CH_3	H	2.5	rt	0.25	81	—	—
			0.01	reflux	7	38	46	—
d	CH_3	Ph	2.5	rt	0.25	63	—	22
			0.01	reflux	8	9	46	34

[a] All reactions were carried out in dichloromethane.

chemistry of **12** was assigned on the basis of the large coupling constants (J = 16-17 Hz) between the two olefinic protons in the nmr spectra.

The formation of 1,3-bis(pyrazolo[1,5-*a*]pyrid-3-yl)-1-butenes **12** is straightforward and outlined in Scheme 4. 3-(1-Hydroxyethyl)pyrazolo[1,5-*a*]pyridines **5** undergo acid-cat-

Scheme 4



alyzed dehydration to give 3-vinylpyrazolo[1,5-*a*]pyridines **13**. In the presence of 2.5 equivalents of trifluoroacetic acid, the 3-vinylpyrazolo[1,5-*a*]pyridines **13** dimerise *via* the carbenium ion intermediate **A** to afford ultimately 1,3-bis(pyrazolo[1,5-*a*]pyrid-3-yl)-1-butenes **12**. In the case of **5d**, the presence of two bulky substitutents at 2- and 4-positions may retard the rate of dimerisation, so that the loss of acetaldehyde can compete to give 4-methyl-2-phenylpyrazolo[1,5-*a*]pyridine **14** [2].

EXPERIMENTAL

All mps are uncorrected. The ^{1}H-nmr spectra were determined on a JEOL FX200 spectrometer using tetramethylsilane as an internal standard. The ir spectra were recorded with a Hitachi EPI-G2 spectrophotometer.

Methyl Pyrazolo[1,5-*a*]pyridine-3-carboxylates and 3-Acetylpyrazolo[1,5-*a*]pyridines (**7**) and (**8**).

General Procedure.

To a suspension of the *N*-aminopyridinium mesitylenesulfonate **6a,b** (10 mmoles) and potassium carbonate (12 mmoles) in tetrahydrofuran (100 ml) was added methyl propiolate (12 mmoles), methyl phenylpropiolate (10 mmoles), 3-butyn-2-one (12 mmoles), or 4-phenyl-3-butyn-2-one (10 mmoles). The reaction mixture was stirred at room temperature for a few days. The insoluble material was filtered off and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel.

Methyl Pyrazolo[1,5-*a*]pyridine-3-carboxylate (**7a**).

Compound **7a** was obtained in 52% yield in *N*,*N*-dimethylformamide instead of tetrahydrofuran as solvent, mp 88° (*n*-hexane); ir (Nujol): 1685 (C=O) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 3.91 (s, 3H, $COOCH_3$), 6.92 (dt, 1H, J = 7, 1 Hz, H-6), 7.38 (ddd, 1H, 9, 7, 1 Hz, H-5), 8.12 (dt, 1H, J = 9, 1 Hz, H-4), 8.36 (s, 1H, H-2), and 8.48 (dt, 1H, J = 7, 1 Hz, H-7).

Anal. Calcd. for $C_9H_8N_2O_2$: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.41; H, 4.56; N, 16.00.

Methyl 2-Phenylpyrazolo[1,5-*a*]pyridine-3-carboxylate (**7b**).

Compound **7b** was obtained in 51% yield, mp 112-113° (*n*-hexane); ir (Nujol): 1665 (C=O) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 3.82 (s, 3H, $COOCH_3$), 6.93 (dt, 1H, J = 7, 1 Hz, H-6), 7.39 (ddd, 1H, J = 9, 7, 1 Hz, H-5), 7.3-7.8 (m, 5H, Ph), 8.17 (dt, 1H, J = 9, 1 Hz, H-4), and 8.49 (dt, 1H, J = 7, 1 Hz, H-7).

Anal. Calcd. for $C_{15}H_{12}N_2O_2$: C, 71.42; H, 4.79; N, 11.10. Found: C, 71.59; H, 4.77; N, 10.96.

Methyl 4-Methyl- (**7c**) and 6-Methylpyrazolo[1,5-*a*]pyridine-3-carboxylates (**8c**).

Reaction of **6b** (616 mg, 2 mmoles) and methyl propiolate (202 mg, 2.4 mmoles) as described in General Procedure afforded a mixture of **7c** and **8c**, which was separated by column chromatogrphy on silica gel. Elution with *n*-hexane/ether (5:1) gave **7c** (129 mg, 34%) and **8c** (67 mg, 18%).

Compound **7c** had mp 108-109° (*n*-hexane); ir (Nujol): 1715 (C=O) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 2.82 (s, 3H, CH_3), 3.86 (s, 3H, $COOCH_3$), 6.81 (t, 1H, J = 7 Hz, H-6), 7.09 (d quintet, 1H, J = 7, 1 Hz, H-5), 8.35 (br d, 1H, J = 7 Hz, H-7), and 8.37 (s, 1H, H-2).

Anal. Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.31; H, 5.27; N, 14.65.

Compound **8c** had mp 100-101° (*n*-hexane); ir (Nujol): 1685 (C=O) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 2.38 (s, 3H, CH_3), 3.90 (s, 3H, $COOCH_3$), 7.24 (dd, 1H, J = 9, 1.5 Hz, H-5), 8.02 (d, 1H, J = 9 Hz, H-4), 8.29 (s, 1H, H-2), and 8.31 (m, 1H, W/2 = 5 Hz, H-7).

Anal. Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.23; H, 5.36; N, 14.71.

Methyl 4-Methyl- (**7d**) and 6-Methyl-2-phenylpyrazolo[1,5-*a*]-pyridine-3-carboxylates (**8d**).

Reaction of **6b** (616 mg, 2 mmoles) and methyl phenylpropiolate (320 mg, 2 mmoles) as described in the General Procedure gave a mixture of **7d** and **8d** (197 mg, 37%), which could not be separated by column chromatography on silica gel. A mixture of **7d** and **8d** was used for the next reduction without separation.

3-Acetylpyrazolo[1,5-*a*]pyridine (**7e**).

Compound **7e** was obtained in 66% yield, mp 102-103° (*n*-hexane); ir (Nujol): 1630 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 2.56 (s, 3H, CH_3), 7.03 (dt, 1H, J = 7, 1 Hz, H-6), 7.50 (ddd, 1H, J = 9, 7, 1 Hz, H-5), 8.37 (s, 1H, H-2), 8.42 (dt, 1H, J = 9, 1 Hz, H-4), and 8.56 (dt, 1H, J = 7, 1 Hz, H-7).

Anal. Calcd. for $C_9H_8N_2O$: C, 67.49; H, 5.03; N, 17.49. Found: C, 67.74; H, 4.78; N, 17.49.

3-Acetyl-2-phenylpyrazolo[1,5-*a*]pyridine (**7f**).

Compound **7f** was obtained in 58% yield, mp 94-95° (*n*-hexane); ir (Nujol): 1630 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 2.12 (s, 3H, CH_3), 6.99 (dt, 1H, J = 7, 1 Hz, H-6), 7.4-7.6 (m, 6H, H-5 and Ph), 8.40 (dt, 1H, J = 9 , 1 Hz, H-4), and 8.49 (dt, 1H, J =

7, 1 Hz, H-7).

Anal. Calcd. for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.33; H, 5.00; N, 12.00.

3-Acetyl-4-methyl- (**7g**) and 3-Acetyl-6-methylpyrazolo[1,5-*a*]pyridines (**8g**).

Reaction of **6b** (616 mg, 2 mmoles) and 2-butyn-2-one (163 mg, 2.4 mmoles) as described in the General Procedure afforded a mixture of **7g** and **8g**, which was separated by column chromatography on silica gel. Elution with *n*-hexane/ether (1:1) gave **7g** (168 mg, 48%) and **8g** (64 mg, 18%).

Compound **7g** had mp 61-62° (*n*-hexane); ir (Nujol): 1650 (C=O) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 2.58 (s, 3H, $COCH_3$), 2.80 (s, 3H, CH_3), 6.86 (t, 1H, J = 7 Hz, H-6), 7.13 (d quintet, 1H, J = 7, 1 Hz, H-5), 8.31 (s, 1H, H-2), and 8.34 (br d, 1H, J = 7 Hz, H-7).

Anal. Calcd. for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.85; H, 5.77; N, 15.90.

Compound **8g** had mp 122-124° (*n*-hexane); ir (Nujol): 1645 (C=O) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 2.38 (d, 3H, J = 1 Hz, CH_3), 2.53 (s, 3H, $COCH_3$), 7.29 (dd, 1H, J = 9, 2 Hz, H-5), 8.23 (br d, 1H, J = 9 Hz, H-4), 8.25 (s, 1H, H-2), and 8.29 (m, 1H, W/2 = 4 Hz, H-7).

Anal. Calcd. for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.86; H, 5.81; N, 15.97.

3-Acetyl-4-methyl- (**7h**) and 3-Acetyl-6-methyl-2-phenylpyrazolo-[1,5-*a*]pyridines (**8h**).

Reaction of **6b** (616 mg, 2 mmoles) and 4-phenyl-3-butyn-2-one (288 mg, 2 mmoles) as described in General Procedure yielded a mixture of **7h** and **8h**, which was separated by column chromatography on silica gel. Elution with *n*-hexane containing gradually increasing amounts of ethyl acetate afforded **7h** (261 mg, 52%) and **8h** (120 mg, 24%).

Compound **7h** had mp 109-110° (*n*-hexane); ir (Nujol): 1655 (C=O) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 2.22 (s, 3H, CH_3), 2.51 (s, 3H, $COCH_3$), 6.81 (t, 1H, J = 7 Hz, H-6), 7.05 (d quintet 1H, J = 7, 1 Hz, H-5), 7.4-7.6 (m, 5H, Ph), and 8.35 (br d, 1H, J = 7 Hz, H-7).

Anal. Calcd. for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 77.08; H, 5.65; N, 11.14.

Compound **8h** had mp 129-131° (*n*-hexane); ir (Nujol): 1625 (C=O) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 2.13 (s, 3H, $COCH_3$), 2.41 (s, 3H, CH_3), 7.32 (dd, 1H, J = 9, 1 Hz, H-5), 7.4-7.6 (m, 5H, Ph), 8.28 (s, 1H, H-7), and 8.31 (dd, 1H, J = 9, 1 Hz, H-4).

Anal. Calcd. for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.97; H, 5.63; N, 11.16.

3-(Hydroxymethyl)pyrazolo[1,5-*a*]pyridines (**4a-d**).

General Procedure.

A suspension of **7a-d** (1 mmole) and lithium aluminium hydride (4 mmoles) in tetrahydrofuran (10 ml) was stirred at room temperature for 0.5-1 hour. After an excess of lithium aluminium hydride was destroyed by addition of a saturated Rochelle salt solution, the precipitate was filtered off and the filtrate was extracted with dichloromethane. The extract was dried over sodium sulfate and concentrated. The residue was purified by column chromatography [silica gel: *n*-hexane/ethyl acetate (10:1)].

3-(Hydroxymethyl)pyrazolo[1,5-*a*]pyridine (**4a**).

Compound **7a** was obtained in 82% yield, mp 44-46° (dichloromethane-*n*-hexane) (lit [4] mp 48°).

3-(Hydroxymethyl)-2-phenylpyrazolo[1,5-*a*]pyridine (**4b**).

Compound **4b** was obtained in 93% yield, mp 128-133° (benzene-*n*-hexane); ir (Nujol): 3200 (OH) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.6-2.0 (br s, 1H, OH), 4.90 (s, 2H, CH_2OH), 6.73 (dt, 1H, J = 7, 1 Hz, H-6), 7.11 (ddd, 1H, J = 9, 7, 1 Hz, H-5), 7.3-7.9 (m, 5H, Ph), 7.57 (dt, 1H, J = 9, 1 Hz, H-4), and 8.41 (dt, 1H, J = 7, 1 Hz, H-7).

Anal. Calcd. for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49. Found: C, 75.09; H, 5.70; N, 12.45.

3-(Hydroxymethyl)-4-methylpyrazolo[1,5-*a*]pyridine (**4c**).

Compound **4c** was obtained in 88% yield, mp 80-81° (ether); ir (Nujol): 3300 (OH) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.98 (br s, 1H, OH), 2.68 (s, 3H, CH_3), 4.86 (s, 2H, CH_2OH), 6.63 (t, 1H, J = 7 Hz, H-6), 6.85 (d quintet, 1H, J = 7, 1 Hz, H-5), 7.81 (s, 1H, H-2) and 8.25 (br d, 1H, J = 7 Hz, H-7).

Anal. Calcd. for $C_9H_{10}N_2O$: C, 66.65; H, 6.22; N, 17.27. Found: C, 66.63; H, 6.31; N, 17.18.

3-(Hydroxymethyl)-4-methyl- (**4e**) and 3-(Hydroxymethyl)-6-methyl-2-phenylpyrazolo[1,5-*a*]pyridine (**9**).

A mixture of **7d** and **8d** (158 mg, 0.6 mmole) as described in the General Procedure afforded a mixture of **4e** and **9**, which was separated by column chromatography on silica gel. Elution with *n*-hexane/ethyl acetate (2:1) afforded **4e** (63 mg) and **9** (34 mg).

Compound **7d** had mp 139-140° (dichloromethane); ir (Nujol): 3250 (C=O) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.66 (br s, 1H, OH), 2.73 (s, 3H, CH_3), 4.92 (s, 2H, CH_2OH), 6.67 (t, 1H, J = 7 Hz, H-6), 6.90 (d quintet, 1H, J = 7, 1 Hz, H-5), 7.35-7.7 (m, 5H, Ph), and 8.32 (br d, 1H, J = 7 Hz, H-7).

Anal. Calcd. for $C_{15}H_{14}N_2O$: C, 75.60; H, 5.92; N, 11.76. Found: C, 75.61; H, 5.95; N, 11.68.

Compound **9** had mp 173-174° (dichloromethane); ir (Nujol): 3250 (C=O) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.66 (br s, 1H, OH), 2.34 (s, 3H, CH_3), 4.90 (s, 2H, CH_2OH), 7.00 (dd, 1H, J = 9, 1 Hz, H-5), 7.3-7.9 (m, 5H, Ph), 7.50 (br d, 1H, J = 9 Hz, H-4), and 8.24 (d, 1H, J = 1 Hz, H-7).

Anal. Calcd. for $C_{15}H_{14}N_2O$: C, 75.60; H, 5.92; N, 11.76. Found: C, 75.51; H, 6.00; N, 11.86.

3-(1-Hydroxyethyl)pyrazolo[1,5-*a*]pyridines (**5a-d**).

To a solution of the 3-acetylpyrazolo[1,5-*a*]pyridines **7e-h** (2 mmoles) in methanol (10 ml) was added sodium borohydride (4 mmoles) and the reaction mixture was stirred at room temperature for 0.5-1 hour. The mixture was diluted with water and extracted with chloroform. The extract was dried over sodium sulfate and concentrated. The residue was purified with column chromatography on silica gel. Elution with *n*-hexane containing gradually increasing amounts of ethyl acetate gave the corresponding alcohols **5a-d**.

3-(1-Hydroxyethyl)pyrazolo[1,5-*a*]pyridine (**5a**).

Compound **5a** was obtained in 100% yield as an oil, which was used for the further reaction without purification; ir (Neat): 3350 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.64 (d, 3H, J = 7 Hz, CH_3), 1.9-2.1 (br s, 1H, OH), 5.18 (q, 1H, J = 7 Hz, C*H*-OH), 7.09 (ddd, 1H, J = 9, 7, 1 Hz, H-5), 7.49 (dt, 1H, J = 7, 1 Hz, H-6), 7.52 (dt, 1H, J = 9, 1 Hz, H-4), 7.92 (s, 1H, H-2), and 8.34 (dt, 1H, J = 7, 1 Hz, H-7).

3-(1-Hydroxyethyl)-2-phenylpyrazolo[1,5-*a*]pyridine (**5b**).

Compound **5b** was obtained in 88% yield, mp 130-132° (benzene); ir (Nujol): 3250 (OH) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.68 (d, 3H, J = 7 Hz, CH_3), 2.00 (s, 1H, OH), 5.32 (q, 1H, J = 7 Hz, C*H*-OH), 6.73 (dt, 1H, J = 7, 1 Hz, H-6), 7.08 (ddd, 1H, J = 9, 7, 1 Hz, H-5), 7.15-7.7 (m, 5H, Ph), 7.82 (dt, 1H, J = 9, 1 Hz, H-4), and 8.41 (dt, 1H, J = 7, 1 Hz, H-7).

Anal. Calcd. for $C_{15}H_{14}N_2O$: C, 75.61; H, 5.92; N, 11.76. Found: C, 75.44; H, 5.95; N, 11.93.

3-(1-Hydroxyethyl)-4-methylpyrazolo[1,5-*a*]pyridine (**5c**).

Compound **5c** was obtained in 91% yield, mp 84-85° (ether-*n*-hexane); ir (Nujol): 3300 (OH) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.70 (d, 3H, J = 7 Hz, CH_3), 2.01 (br s, 1H, OH), 2.66 (s, 3H, CH_3), 5.25-5.4 (m, 1H, C*H*-OH), 6.61 (t, 1H, J = 7 Hz, H-6), 6.81 (d quintet, 1H, J = 7, 1 Hz, H-5), 7.91 (s, 1H, H-2), and 8.24 (br d, 1H, J = 7 Hz, H-7).

Anal. Calcd. for $C_{10}H_{12}N_2O$: C, 68.16; H, 6.86; N, 15.90. Found: C, 68.18; H, 6.91; N, 15.76.

3-(1-Hydroxyethyl)-4-methyl-2-phenylpyrazolo[1,5-*a*]pyridine (**5d**).

Compound **5d** was obtained in 94% yield, mp 150-153° (ether); ir (Nujol): 3250 (OH) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.58 (d, 3H, J = 7 Hz, CH_3), 1.97 (s, 1H, OH), 2.74 (s, 3H, CH_3), 5.45 (q, 1H, J = 7 Hz, C*H*-OH), 6.63 (t, 1H, J = 7 Hz, H-6), 6.88 (d quintet, 1H, J = 7, 1 Hz, H-5), 7.3-7.6 (m, 5H, Ph), and 8.28 (br d, 1H, J = 7 Hz, H-7).

Anal. Calcd. for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found: C, 76.15; H, 6.39; N, 10.95.

Reaction of 3-(Hydroxymethyl)- (**4**) and 3-(1-Hydroxyethyl)pyrazolo[1,5-*a*]pyridines (**5**) with Trifluoroacetic Acid.

General Procedure.

A solution of the 3-hydroxymethyl- (**4**) and 3-(1-hydroxyethyl)-pyrazolo[1,5-*a*]pyridines (**5**) (1 mmole) and trifluoroacetic acid (0.01 mmole or 2.5 mmoles) in dichloromethane (10 ml) was stirred at room temperature or refluxed. After the reaction mixture was neutralized with 5% sodium hydrogen carbonate solution, the organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic extract was washed with water, dried over sodium sulfate, and concentrated. The crude products were separated by column chromatography or preparative thin layer chromatography on silica gel (*n*-hexane or dichloromethane/ethyl acetate). These results are summarized in Table 1.

Bis(pyrazolo[1,5-*a*]pyrid-3-yl)methane (**10a**).

Compound **10a** was had mp 75-76° (*n*-hexane) (lit [3] mp 72°).

Bis[(pyrazolo[1,5-*a*]pyrid-3-yl)methyl] Ether (**11a**).

Compound **11a** had mp 85-86° (*n*-hexane); ^{1}H-nmr (deuteriochloroform): δ 4.71 (s, 4H, 2 x CH_2), 6.73 (dt, 2H, J = 7, 1.5 Hz, 2 x H-6), 7.07 (ddd, 2H, J = 9, 7, 1 Hz, 2 x H-5), 7.50 (ddd, 2H, J = 9, 1.5, 1 Hz, 2 x H-4), 7.90 (s, 2H, 2 x H-2), and 8.42 (dt, 2H, J = 7, 1 Hz, 2 x H-7).

Anal. Calcd. for $C_{16}H_{14}N_4O$: C, 69.05; H, 5.07; N, 20.13. Found: C, 69.12; H, 5.15; N, 20.01.

Bis(2-phenylpyrazolo[1,5-*a*]pyrid-3-yl)methane (**10b**).

Compound **10b** had mp 169-173° (methanol); ^{1}H-nmr (deuteriochloroform): δ 4.50 (s, 2H, CH_2), 6.55-6.7 (m, 2H, 2 x H-6), 6.75-6.9 (m, 4H, 2 x H-4 and 2 x H-5), 7.3-7.8 (m, 10H, 2 x Ph), and 8.37 (dt, 2H, J = 7, 1 Hz, 2 x H-7).

Anal. Calcd. for $C_{27}H_{20}N_4$: C, 80.98; H, 5.03; N, 13.99. Found: C, 80.98; H, 4.95; N, 14.00.

Bis[(2-phenylpyrazolo[1,5-*a*]pyrid-3-yl)methyl] Ether (**11b**).

Compound **11b** had mp 156-158° (methanol); ^{1}H-nmr (deuteriochloroform): δ 4.82 (s, 4H, 2 x CH_2), 6.72 (dt, 2H, J = 7, 1.5 Hz, 2 x H-6), 7.08 (ddd, 2H, J = 9, 7, 1 Hz, 2 x H-5), 7.3-7.9 (m, 10H, 2 x Ph), 7.49 (dt, 2H, J = 9, 1.5 Hz, 2 x H-4), and 8.44 (dt, 2H, J = 7, 1 Hz, 2 x H-7).

Anal. Calcd. for $C_{28}H_{22}N_4O$: C, 78.12; H, 5.15; N, 13.01. Found: C, 78.15; H, 5.26; N, 13.08.

Bis(4-methylpyrazolo[1,5-*a*]pyrid-3-yl)methane (**10c**).

Compound **10c** had mp 189-190° (ethyl acetate); ^{1}H-nmr (deuteriochloroform): δ 2.56 (s, 6H, 2 x CH_3), 4.56 (s, 2H, CH_2), 6.58 (t, 2H, J = 7 Hz, 2 x H-6), 6.75 (br d, 2H, J = 7 Hz, 2 x H-5), 7.48 (s, 2H, 2 x H-2), and 8.26 (br d, 2H, J = 7 Hz, 2 x H-7).

Anal. Calcd. for $C_{17}H_{16}N_4$: C, 73.89; H, 5.84; N, 20.28. Found: C, 73.80; H, 5.91; N, 20.22.

Bis[(4-methylpyrazolo[1,5-*a*]pyrid-3-yl)methyl] Ether (**11c**).

Compound **11c** had mp 137-138° (ether-dichloromethane); ^{1}H-nmr (deuteriochloroform): δ 2.57 (s, 6H, 2 x CH_3), 4.76 (s, 4H, 2 x CH_2), 6.63 (t, 2H, J = 7 Hz, 2 x H-6), 6.82 (d, quintet, 2H, J = 7, 1 Hz, 2 x H-5), 7.87 (s, 2H, 2 x H-2), and 8.27 (br d, 2H, J = 7 Hz, 2 x H-7).

Anal. Calcd. for $C_{18}H_{18}N_4O$: C, 70.56; H, 5.92; N, 18.29. Found: C, 70.50; H, 5.89; N, 18.28.

Bis(4-methyl-2-phenylpyrazolo[1,5-*a*]pyrid-3-yl)methane (**10d**).

Compound **10d** had mp 179-180° (methanol); ^{1}H-nmr (deuteriochloroform): δ 2.48 (s, 6H, 2 x CH_3), 4.82 (s, 2H, CH_2), 6.50 (t, 2H, J = 7 Hz, 2 x H-6), 6.65 (br d, 2H, J = 7 Hz, 2 x H-5), 7.0-7.2 (m, 10H, 2 x Ph), and 8.10 (br d, 2H, J = 7 Hz, 2 x H-7).

Anal. Calcd. for $C_{29}H_{24}N_4$: C, 81.28; H, 5.65; N, 13.08. Found: C, 81.19; H, 5.73; N, 13.11.

Bis[(4-methyl-2-phenylpyrazolo[1,5-*a*]pyrid-3-yl)methyl] Ether (**11d**).

Compound **11d** had mp 242-243° (ether-dichloromethane); ^{1}H-nmr (deuteriochloroform): δ 2.59 (s, 6H, 2 x CH_3), 4.68 (s, 4H, 2 x CH_2), 6.63 (t, 2H, J = 7 Hz, 2 x H-6), 6.84 (br d, 2H, J = 7 Hz, 2 x H-5), 7.3-7.7 (m, 10H, 2 x Ph), and 8.29 (br d, 2H, J = 7 Hz, 2 x H-7).

Anal. Calcd. for $C_{30}H_{26}N_4O$: C, 78.58; H, 5.72; N, 12.22. Found: C, 78.60; H, 5.82; N, 12.09.

1,3-Bis(pyrazolo[1,5-*a*]pyrid-3-yl)-1-butene (**12a**).

Compound **12a** had mp 105-106° (ether); ^{1}H-nmr (deuteriochloroform): δ 1.57 (d, 3H, J = 7 Hz, CH_3), 3.89 (d quintet, 1H, J = 7, 1 Hz, C*H*CH=CH), 6.22 (dd, 1H, J = 17, 7 Hz, CHC*H*=CH), 6.47 (dd, 1H, J = 17, 1 Hz, CHCH=C*H*), 6.65 (dt, 2H, J = 7, 1 Hz, 2 x H-6), 6.98 and 7.03 (ddd each, 2 x 1H, J = 9, 7, 1 Hz, 2 x H-5), 7.47 and 7.52 (dt each, 2 x 1H, J = 9, 1 Hz, 2 x H-4), 7.82 and 7.93 (s each, 2 x 1H, 2 x H-2), and 8.33 and 8.38 (dt each, 2 x 1H, J = 7, 1 Hz, 2 x H-7).

Anal. Calcd. for $C_{18}H_{16}N_4$: C, 74.97; H, 5.59; N, 19.43. Found: C, 75.12; H, 5.64; N, 19.34.

3-Vinylpyrazolo[1,5-*a*]pyridine (**13a**).

Compound **13a** was obtained as an oil; ^{1}H-nmr (deuteriochloro-

form): δ 5.16 (dd, 1H, J = 11, 1.5 Hz, one of -CH=CH_2), 5.50 (dd, 1H, J = 18, 1.5 Hz, one of -CH=CH_2), 6.71 (dt, 1H, J = 7, 1 Hz, H-6), 6.78 (dd, 1H, J = 18, 11 Hz, -CH=CH$_2$), 7.10 (ddd, 1H, J = 9, 7, 1 Hz, H-5), 7.58 (dt, 1H, J = 9, 1 Hz, H-4), 8.00 (s, 1H, H-2), and 8.38 (dt, 1H, J = 7, 1 Hz, H-7).

It was identified after transformation to 3-ethylpyrazolo[1,5-*a*]-pyridine (**15a**) by catalytic hydrogenation.

1,3-Bis(2-phenylpyrazolo[1,5-*a*]pyridy-3-yl)-1-butene (**12b**).

Compound **12b** had mp 140-141° (methanol); ^{1}H-nmr (deuteriochloroform): δ 1.59 (d, 3H, J = 7 Hz, CH$_3$), 4.1-4.2 (m, 1H, CHCH=CH), 6.36 (dd, 1H, J = 16, 5 Hz, CHCH=CH), 6.52 (dd, 1H, J = 16, 1.5 Hz, CHCH=CH), 6.71 and 6.73 (dt each, 2 x 1H, J = 7, 1 Hz, 2 x H-6), 7.02 and 7.07 (ddd each, 2 x 1H, J = 9, 7, 1 Hz, 2 x H-5), 7.3-7.7 (m, 12H, 2 x H-4 and 2 x Ph), and 8.40 and 8.44 (dt each, 2 x 1H, J = 7, 1 Hz, 2 x H-7).

Anal. Calcd. for $C_{30}H_{24}N_4$: C, 81.79; H, 5.49; N, 12.72. Found: C, 81.93; H, 5.36; N, 12.78.

2-Phenyl-3-vinylpyrazolo[1,5-*a*]pyridine (**13b**).

Compound **13b** had mp 77-79° (*n*-hexane); ^{1}H-nmr (deuteriochloroform): δ 5.28 (dd, 1H, J = 12, 2 Hz, one of CH=CH_2), 5.58 (dd, 1H, J = 18, 2 Hz, one of CH=CH_2), 6.75 (dt, 1H, J = 7, 1.5 Hz, H-6), 6.86 (dd, 1H, J = 18, 12 Hz, CH=CH$_2$), 7.14 (ddd, 1H, J = 9, 7, 1 Hz, H-5), 7.3-7.8 (m, 5H, Ph), 7.65-7.8 (m, 1H, H-4), and 8.44 (dt, 1H, J = 7, 1 Hz, H-7).

Anal. Calcd. for $C_{15}H_{12}N_2$: C, 81.79; H, 5.49; N, 12.72. Found: C, 81.96; H, 5.55; N, 13.00.

1,3-Bis(4-methylpyrazolo[1,5-*a*]pyrid-3-yl)-1-butene (**12c**).

Compound **12c** had mp 104-105° (*n*-hexane); ^{1}H-nmr (deuteriochloroform): δ 1.58 (d, 3H, J = 7 Hz, CH$_3$), 2.36 and 2.64 (s each, 2 x 3H, 2 x CH$_3$), 4.1-4.25 (m, 1H, CHCH=CH), 6.24 (dd, 1H, J = 16, 6 Hz, CHCH=CH), 6.50 (dd, 1H, J = 16, 1.5 Hz, CHCH=CH), 6.52 and 6.57 (t each, 2 x 1H, J = 7 Hz, 2 x H-6), 6.72 (dt, 2H, J = 7, 1 Hz, 2 x H-5), 7.85 and 7.98 (s each, 2 x 1H, 2 x H-2), and 8.18 and 8.26 (br d each, 2 x 1H, J = 7 Hz, 2 x H-7).

Anal. Calcd. for $C_{20}H_{20}N_4$: C, 75.92; H, 6.37; N, 17.71. Found: C, 75.78; H, 6.49; N, 17.65.

4-Methyl-3-vinylpyrazolo[1,5-*a*]pyridine (**13c**).

Compound **13c** was obtained as an oil; ^{1}H-nmr (deuteriochloroform): δ 2.59 (s, 3H, CH$_3$), 5.09 (dd, 1H, J = 11, 2 Hz, one of CH=CH_2), 5.52 (dd, 1H, J = 18, 2 Hz, one of CH=CH_2), 6.56 (t, 1H, J = 7 Hz, H-6), 6.78 (d quintet, 1H, J = 7, 1 Hz, H-5), 7.06 (dd, 1H, J = 18, 11 Hz, CH=CH$_2$), 8.08 (s, 1H, H-2), and 8.21 (br d, 1H, J = 7 Hz, H-7).

It was identified after transformation to 3-ethyl-4-methylpyrazolo[1,5-*a*]pyridine (**15b**) by catalytic hydrogenation.

1,3-Bis(4-methyl-2-phenylpyrazolo[1,5-*a*]pyridy-3-yl)-1-butene (**12d**).

Compound **12d** had mp 148-149° (methanol); ^{1}H-nmr (deuteriochloroform): δ 1.27 (d, 3H, J = 7 Hz, CH$_3$), 2.36 and 2.55 (s each, 2 x 3H, 2 x CH$_3$), 4.1-4.3 (m, 1H, CHCH=CH), 5.89 (dd, 1H, J = 16, 5 Hz, CHCH=CH), 6.55 and 6.60 (t each, 2 x 1H, J = 7 Hz, 2 x H-6), 6.56 (dd, 1H, J = 16, 2 Hz, CHCH=CH), 6.73 and 6.77 (br d each, 2 x 1H, J = 7, 1 Hz, 2 x H-5), 7.2-7.7 (m, 10H, 2 x Ph), and 8.22 and 8.28 (br d each, 2 x 1H, J = 7 Hz, 2 x H-7).

Anal. Calcd. for $C_{32}H_{28}N_4$: C, 82.02; H, 6.02; N, 11.96. Found: C, 82.13; H, 6.07; N, 11.80.

4-Methyl-2-phenyl-3-vinylpyrazolo[1,5-*a*]pyridine (**13d**).

Compound **13d** had mp 58-59° (*n*-hexane); ^{1}H-nmr (deuteriochloroform): δ 2.58 (s, 3H, CH$_3$), 5.16 (dd, 1H, J = 18, 2 Hz, one of CH=CH_2), 5.26 (dd, 1H, J = 11, 2 Hz, one of CH=CH_2), 6.60 (t, 1H, J = 7 Hz, H-6), 6.80 (d, quintet, 1H, J = 7, 1 Hz, H-5) 7.04 (dd, 1H, J = 18, 11 Hz, CH=CH$_2$), 7.3-7.75 (m, 5H, Ph), and 8.26 (br d, 1H, J = 7 Hz, H-7).

Anal. Calcd. for $C_{16}H_{14}N_2$: C, 82.02; H, 6.02; N, 11.92. Found: C, 81.99; H, 6.04; N, 12.02.

4-Methyl-2-phenylpyrazolo[1,5-*a*]pyridine (**14**).

Compound **14** had mp 77-78° (*n*-hexane) (lit [5] mp 77-78°).

Transformation of 3-Vinylpyrazolo[1,5-*a*]pyridines (**13a,c**) into 3-Ethylpyrazolo[1,5-*a*]pyridines (**15a,b**).

General Procedure.

3-Ethylpyrazolo[1,5-*a*]pyridine (**15a**).

A suspension of **13a** (94 mg, 0.62 mmole) and 5% Pd/C (9 mg) in ethanol (3 ml) was stirred for 5 hours at room temperature under hydrogen. The catalyst was filtered off and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel. Elution with *n*-hexane/ethyl acetate (5:1) gave **15a** (74 mg, 77%), which was an oil [picrate, mp 158-160° (dec) (methanol)]; ^{1}H-nmr (deuteriochloroform): δ 1.31 (t, 3H, J = 7.5 Hz, CH$_3$), 2.75 (q, 2H, J = 7.5 Hz, CH$_2$), 6.70 (dt, 1H, J = 7, 1 Hz, H-6), 7.04 (ddd, 1H, J = 9, 7, 1 Hz, H-5), 7.45 (dt, 1H, J = 9, 1 Hz, H-4), 7.80 (s, 1H, H-2), and 8.43 (dt, 1H, J = 7, 1 Hz, H-7).

Anal. Calcd. for $C_{15}H_{13}N_5O_7$ (picrate): 48.01; H, 3.49; N, 18.66. Found: C, 48.05; H, 3.58; N, 18.65.

3-Ethyl-4-methylpyrazolo[1,5-*a*]pyridine (**15b**).

In a similar manner as described above, **13c** (96 mg, 0.61 mmole) afforded **15b** (77 mg, 79%), which was an oil [picrate, mp 152-155° (methanol)]; ^{1}H-nmr (deuteriochloroform): δ: 1.32 (t, 3H, J = 7.5 Hz, CH$_3$), 2.61 (s, 3H, CH$_3$), 2.94 (q, 2H, J = 7.5 Hz, CH$_2$), 6.60 (t, 1H, J = 7 Hz, H-6), 6.77 (br d, 1H, J = 7 Hz, H-5), 7.76 (s, 1H, H-2), and 8.33 (br d, 1H, J = 7 Hz, H-7).

Anal. Calcd. for $C_{16}H_{15}N_5O_7$ (picrate): C, 49.36; H, 3.88; N, 17.99. Found: C, 49.35; H, 3.87; N, 18.15.

Transformation of **11a,b** into **10a,b**.

General Procedure.

To a solution of **11a** (56 mg, 0.2 mmole) in dichloromethane (2 ml) was added trifluoroacetic acid (0.5 mmole) and the reaction mixture was refluxed for 6 hours. After the reaction mixture was neutralized with 5% sodium hydrogen carbonate solution, the mixture was extracted with dichloromethane. The extract was washed with water, dried over sodium sulfate, and concentrated. The residue was purified by column chromatography (silica gel, dichloromethane-ethyl acetate) to give **10a** (33 mg, 67%) and **4a** (4 mg, 7%).

Similar treatment of **11b** (65 mg) with trifluoroacetic acid for 4 hours gave **10b** (58 mg, 96%) and **4b** (2 mg, 3%).

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