March 1992 Chem. Pharm. Bull. 40(3) 639—643 (1992)

Synthesis of Metabolites and Related Compounds of 3-Isobutyryl-2-isopropylpyrazolo[1,5-*a*]pyridine (Ibudilast). II. Metabolites of Pyridine Ring

Katsuya AWANO,* Kazuhiko IWASE, Yoshio NAGATSU and Seigo SUZUE

Central Research Laboratories, Kyorin Pharmaceutical Co., Ltd., Nogi-machi, Shimotsuga-gun, Tochigi 329-01, Japan. *Received July 9, 1991*

Novel 6-hydroxylated or methanesulfonylated pyrazolo[1,5-*a*]pyridine derivatives as an authentic reference of metabolites for 3-isobutyryl-2-isopropylpyrazolo[1,5-*a*]pyridine (ibudilast) were prepared by the method of substitution with Br^+ on the pyridine ring and subsequent displacement of Br with MeO^- or MeS^-. For this reason, we investigated the orientation of halogenation on the pyridine ring of pyrazolo[1,5-*a*]pyridine. The reactivity of the pyridine ring was at the 6-position, followed by the 4-position. We supposed that this finding comes from the electron-donating resonance effect of bridge-head nitrogen. These experimental results were in good agreement with the results of atomic electron densities, but a clear difference was not obtained in those of the Frontier orbitals.

Keywords pyrazolo[1,5-*a*]pyridine; ibudilast; hydroxylated metabolite; methanesulfonylated metabolite; Frontier orbital; halogenation orientation; bridge-head nitrogen

In the preceding paper,[1] we reported the synthesis of novel pyrazolo[1,5-*a*]pyridine derivatives with mono and dihydroxylated alkyl side chains as an authentic reference of metabolites for 3-isobutyryl-2-isopropylpyrazolo[1,5-*a*]pyridine (ibudilast). Ibudilast is also metabolized principally by ring oxidation[2] (Chart 1). For this reason we prepared novel pyrazolo[1,5-*a*]pyridine derivatives as a series of authentic reference compounds. In order to introduce substituents on the pyridine ring directly, we investigated the orientation of halogenation on the pyridine ring and considered these results using the molecular orbital method. There has been no detailed systematic study of a substitution reaction on the pyridine ring of pyrazolo[1,5-*a*]pyridine. This report demonstrates a synthesis of novel 6-hydroxylated or 6-methanesulfonylated pyrazolo[1,5-*a*]pyridine derivatives which are metabolites of ibudilast.

Synthesis of 6-Hydroxylated and 6-Methanesulfonylated Pyrazolo[1,5-*a*]pyridine It is known that pyrazolo[1,5-*a*]pyridines are prepared by the reaction of pyridine *N*-imine and 1,3-dipolarophiles.[3,4] However, the orientation in the reaction between 3-substituted pyridine *N*-imines and 1,3-dipolarophiles has two possible cyclization directions, C-2 and C-6 of the pyridine ring.[5] On the other hand, it is also known that pyrazolo[1,5-*a*]pyridines can be prepared from α-picoline *N*-imine and electrophiles[6] such as anhydride, acyl or aroyl chloride. Only desired 6-substituted compounds can be obtained by this route. Hydroxylated or methanesulfonylated derivatives were prepared first as shown in Chart 2. 5-Acetyloxy-2-methylpyridine or 5-methylthio-2-methylpyridine was treated with *O*-mesitylenesulfonylhydroxylamine or hydroxylamine *O*-sulfonic acid to provide the corresponding *N*-amino compound (**1**). These crude products in turn were treated with isobutyric anhydride to afford the corresponding 6-substituted pyrazolo[1,5-*a*]pyridine derivatives (**2** and M-20). The obtained 6-methylthio compound (**2**) was treated with *m*-chloroperbenzoic acid (*m*-CPBA) to give a 6-methanesulfonyl compound (**3**). Compound **3** was refluxed with 50% H_2SO_4 to provide the deacylated compound (**4**), and this in turn was reacted with propionic anhydride to afford M-16 which had a propionyl group inserted at the 3-position.

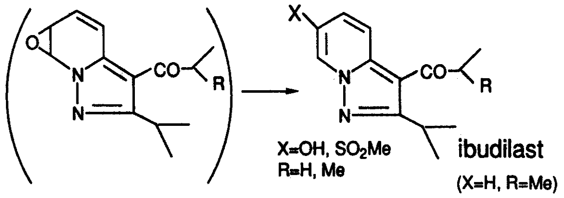


Chart 1. Metabolites of Pyridine Ring on Ibudilast

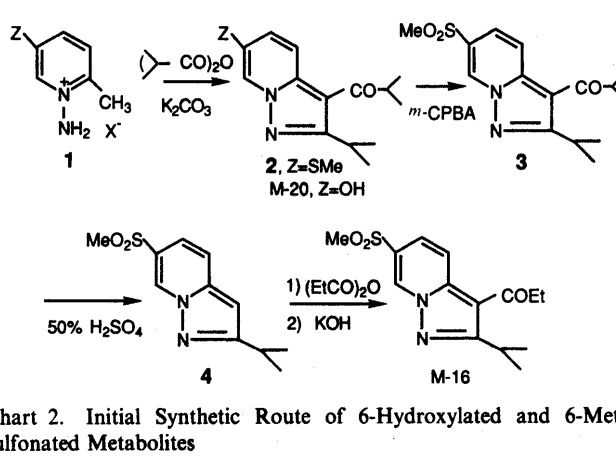
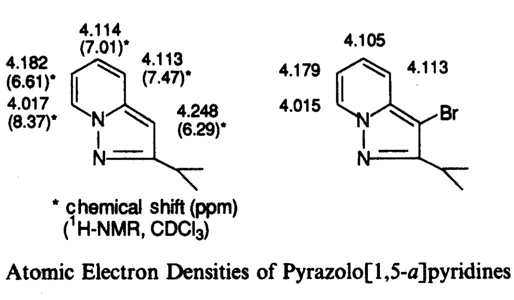


Chart 2. Initial Synthetic Route of 6-Hydroxylated and 6-Methylsulfonated Metabolites

Investigation of the Substituent Introduction on Pyrazolo[1,5-*a*]pyridine In the above synthetic method, the yield was poor and the isolation was troublesome. For this reason we investigated the direct introduction of substituents on the pyridine ring of pyrazolo[1,5-*a*]pyridine. We designed that 6-hydroxylated and 6-methanesulfonylated compounds prepared by substitution with an electrophile (Br^+) at the 6-position of the pyrazolo[1,5-*a*]pyridine ring, and subsequently displaced the halogen group with nucleophiles such as MeO^- and MeS^-, respectively.

We researched the orientation of halogenation first.



* chemical shift (ppm)
(^{1}H-NMR, $CDCl_3$)

Chart 3. Atomic Electron Densities of Pyrazolo[1,5-*a*]pyridines

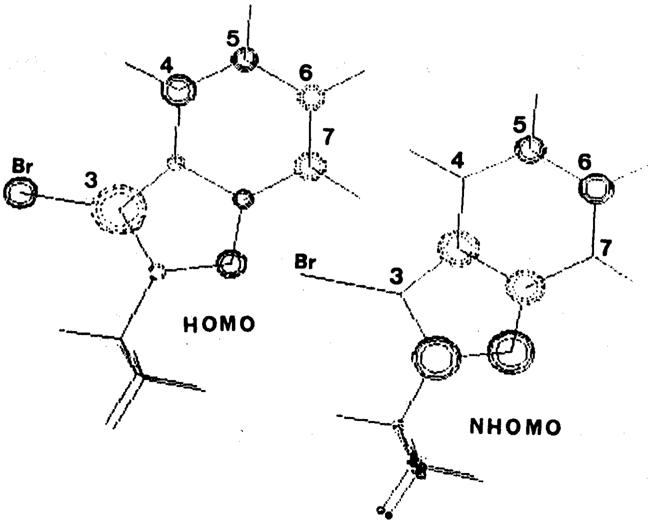


Chart 4. HOMO and NHOMO of 3-Bromo-2-isopropylpyrazolo[1,5-*a*]pyridine

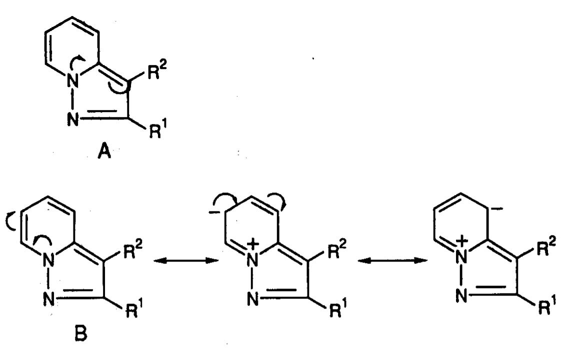
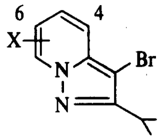


Chart 5. Electron-Donating Effects of Bridge-Head Nitrogen

Table I. Halogenation of 3-Bromo-2-isopropylpyrazolo[1,5-*a*]pyridine



Reagent	Mol. ratio	React. time (h)	React. temp. (°C)	Yield (%)[a]		
				4-X	6-X	4,6-DiX
NCS	1	2	50 (DMF)	—	47	—
NBS	1.3	3	70 (DMF)	18	24	16
NBS	1	2	50 (DMF)	—	45	7
Br_2	1	3	Reflux ($CHCl_3$)	—	67	5

a) Isolated yield, — not isolated.

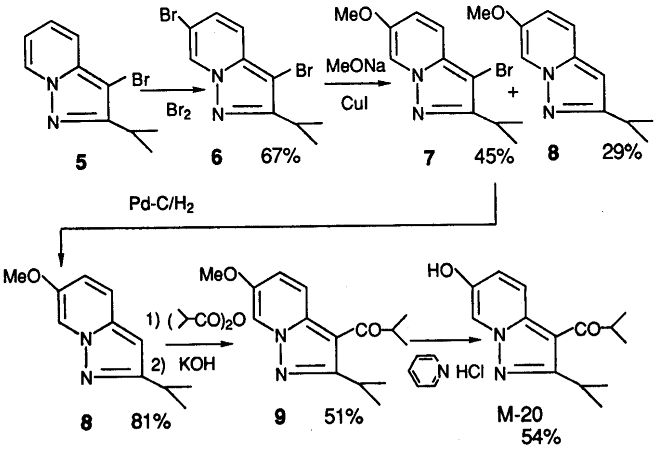


Chart 6. Improved Synthetic Route of 6-Hydroxylated Metabolite

Pyrazolo[1,5-*a*]pyridine, which differs from normal aromatic compounds, has a high electrophilic substitution activity at the 3-position.[6] It is thought that this phenomenon results from a very high electron density at the 3-position which arises from the strong electron-donating effect of the bridge-head nitrogen as shown in Chart 5, A. This is confirmed by calculated atomic electron densities and the chemical shifts (Chart 3). This calculation also suggests that the most reactive position next to the 3-position is the 6-position, followed by the 4-position on the pyridine ring. We actually researched the orientation of halogenation as shown in Table I. These results lead to the conclusion that the halogenation of 3-bromo-2-isopropylpyrazolo[1,5-*a*]pyridine (**5**) occured at the 6-position first, followed by the 4-position. However, at a higher reaction temperature (70 °C) and by the use of excess *N*-bromosuccinimide (NBS) (1.3 eq), the selectivity of the orientation disappeared and 4-bromo, 6-bromo and 4,6-dibromo compounds were produced. It is known that reactions with NBS and *N*-chlorosuccinimide (NCS) involve two kinds of mechanisms, a radical mechanism and a polar mechanism. However, in these reactions, the halogenations with NBS and NCS were actually an electrophilic substitution reaction because a 2-isopropyl group halogenated product was not obtained. These results suggest that the 4- and 6-position, as well as 3-position, are governed by the electron-donating effect of bridge-head nitrogen (Chart 5, B).

We calculated the Frontier orbital (highest occupied molecular orbital (HOMO) and NHOMO (next HOMO)) of the 3-bromo-2-isopropylpyrazolo[1,5-*a*]pyridine (**5**). Chart 4 shows that the 4-position has a large HOMO and very small NHOMO, and the 6-position has a relatively small HOMO and large NHOMO. Thus, a clear difference between the 4- and 6-positions was not obtained using this method. We supposed that the result of bromination came from the contribution of NHOMO.

Improved Synthetic Route of 6-Hydroxylated Metabolite (M-20) Table I shows that we can produce the 6-bromo compound (**6**) by the bromination of compound **5**. For this reason, 6-hydroxylated metabolite was prepared by substitution with Br^+ on the pyridine ring and by subsequent displacement of the bromo group with MeO^- as follows.

The 6-bromo compound (**6**) which was obtained by bromination with bromine, was reacted with sodium methoxide in the presence of cuprous iodide to yield the 6-methoxy compound (**7**), and debrominated compound (**8**), produced at the same time as a reduction product by using copper. The 3-bromo group of **6** was not reacted with nucleophile (MeO^-) because the 3-position of **6** has a very high electron density as shown in Chart 5, A. Compound **7** was reduced with palladium–carbon in a hydrogen atmosphere to provide the debrominated compound (**8**). The compound **8** was reacted with isobutyric anhydride in the presence of an acid catalyst to provide the 3-isobutyryl compound (**9**), and this in turn was treated with pyridine hydrochloride to give the 6-hydroxy

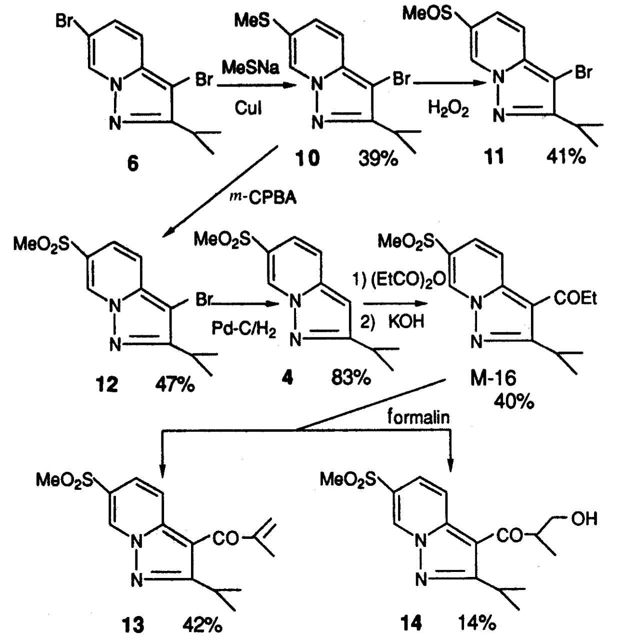


Chart 7. Improved Synthetic Route of 6-Methylsulfonated Metabolite and Related Derivatives

metabolite (M-20).

Synthesis of 6-Methanesulfonylated Metabolite (M-16) and Related Compounds The 6-bromo compound was also reacted with a methylthiolate anion under the same condition to provide the methylthio compound (**10**), followed by oxidation with *m*-CPBA to form the methanesulfonyl compound (**12**). On the other hand, oxidation using 35% H_2O_2 in acetic acid produced only a methanesulfinyl compound (**11**). Compound **12** was reduced with palladium–carbon to give **4**, followed by propionylation with propionic anhydride to yield M-16. Next, compound M-16 was treated with formalin to provide a 3-β-hydroxylated compound (**14**) through the introduction of a hydroxymethyl group into the α-position of a 3-propionyl group. At this time, a considerable amount of dehydrated compound (**13**) was obtained as a by-product. Compound **14** was as yet undetected as a metabolite.

In conclusion, novel 6-hydroxylated or 6-methanesulfonylated pyrazolo[1,5-*a*]pyridine derivatives were prepared by the method of substitution with an electrophile (Br^+) on the pyridine ring, and by subsequent displacement of the bromo group with two nucleophiles (MeO^-, MeS^-), respectively. We investigated the orientation of halogenation on the pyridine ring of pyrazolo[1,5-*a*]pyridine at the same time. The orientation was at the 6-position, followed by the 4-position. We concluded that this result came from the electron-donating resonance effect of bridge-head nitrogen and was in good agreement with the atomic electron densities, but a clear difference between the 4- and 6-positions was not obtained in that of the Frontier orbitals.

Experimental

Apparatus and Method Melting points were measured with a Yanagimoto melting point apparatus and were uncorrected. Nuclear magnetic resonance (NMR) spectra were measured with a JNM-FX 90Q FT NMR spectrometer using tetramethylsilane as an internal standard. Column chromatography was carried out on silica gel (Wakogel C-200). Atomic electron densities and Frontier orbitals were calculated using the AM1 method (QCPE program no. 527).

The structure of metabolites was identified in comparison with authentic samples (gas chromatography-mass spectrometry (GC/MS) and thin layer chromatography (TLC)) obtained by the following procedures.[2]

6-Hydroxy-3-isobutyryl-2-isopropylpyrazolo[1,5-*a*]pyridine (M-20) Initial Method: 5-Acetyloxy-1-amino-2-methylpyridinium mesitylenesulphonate (**1**: Z=OAc, 12.7 g) which was prepared[5] from 5-acetyloxy-2-methylpyridine (6.0 g) was dissolved in 50 g of isobutyric anhydride and heated at 40—60 °C for 3 h. To the mixture was added 7.0 g of K_2CO_3 and 15 ml of pyridine. The mixture was refluxed for 10 h. After cooling, the reaction mixture was filtered and the filtrate was concentrated *in vacuo*. To the residue was added 50 ml of conc. HCl, the mixture was refluxed for 1 h, and after cooling was extracted with CH_2Cl_2. The organic layer was concentrated to give a residue which was dissolved in 10% aq. KOH solution. The solution was acidified with AcOH after treatment with active carbon and extracted with CH_2Cl_2. The organic layer was dried over anhyd. Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed over silica gel employing diethyl ether and then CH_2Cl_2 as the eluent. The obtained material was purified by silica gel, this time employing diethyl ether as an eluent. Recrystallization from benzene–hexane gave 2.5 g of M-20 as colorless needles, mp 89—90 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.32, 1.40 (6H × 2, d, $J=6.8$ Hz, $CH(C\underline{H}_3)_2$, $COCH(C\underline{H}_3)_2$), 3.34, 3.76 (1H, m, $J=6.8$ Hz, $C\underline{H}(CH_3)_2$, $COC\underline{H}(CH_3)_2$), 5.60 (1H, br, OH), 6.96 (1H, dd, $J=9.0$, 1.2 Hz, pyrazolopyridine-5-H), 7.76 (1H, d, $J=9.0$ Hz, pyrazolopyridine-4-H), 8.02 (1H, d, $J=1.2$ Hz, pyrazolopyridine-7-H). MS *m/z*: 246 (M^+). Infrared (IR) (KBr): 1618 cm^{-1} (C=O). *Anal.* Calcd for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.22; H, 7.29; N, 11.41.

Improved Method: To a solution of 3-bromo-2-isopropylpyrazolo[1,5-*a*]pyridine (**5**; 14.0 g) in $CHCl_3$ (50 ml) was slowly added bromine (10.0 g). The mixture was heated to reflux for 2 h. After cooling, the reaction mixture was poured into an aqueous $NaHSO_3$ solution and extracted with $CHCl_3$. The organic layer was washed with aqueous 10% NaOH solution and then dried over anhyd. Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography and eluted with hexane–CH_2Cl_2 (1 : 1) to give 12.5 g (67%) of 3,6-dibromo-2-isopropylpyrazolo[1,5-*a*]pyridine (**6**), mp 53—54 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.37 (6H, d, $J=6.8$ Hz, $CH(C\underline{H}_3)_2$), 3.24 (1H, m, $J=6.8$ Hz, $C\underline{H}(CH_3)_2$), 7.14 (1H, dd, $J=9.2$, 1.5 Hz, pyrazolopyridine-5-H), 7.29 (1H, d, $J=9.2$ Hz, pyrazolopyridine-4-H), 8.50 (1H, d, $J=1.5$ Hz, pyrazolopyridine-7-H). MS *m/z*: 316 (M^+). IR (KBr): 2970, 1500, 1310, 825 cm^{-1}. *Anal.* Calcd for $C_{10}H_{10}Br_2N_2$: C, 37.77; H, 3.17; N, 8.84. Found: C, 37.64; H, 3.19; N, 8.88. The dibromo compound (**6**; 6.3 g) and CuI (0.63 g) were added to the solution of dimethylformamide (DMF) (15 ml) and MeONa prepared from MeOH (82 ml) and Na (8.7 g), and refluxed for 3 h. After cooling, the insoluble materials were filtered off and to the filtrate was added 30 ml of water, followed by extraction with benzene. The organic layer, after being dried over anhyd. Na_2SO_4, was concentrated to dryness. The residue was subjected to silica gel chromatography and eluted with hexane–CH_2Cl_2 (1 : 1). First fraction: Recrystallization from hexane gave 2.4 g (45%) of **7** as white plates, mp 49—51 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.38 (6H, d, $J=6.8$ Hz, $CH(C\underline{H}_3)_2$), 3.23 (1H, m, $J=6.8$ Hz, $C\underline{H}(CH_3)_2$), 3.80 (3H, s, OCH_3), 6.93 (1H, dd, $J=9.5$, 2.0 Hz, pyrazolopyridine-5-H), 7.29 (1H, d, $J=9.5$ Hz, pyrazolopyridine-4-H), 7.98 (1H, d, $J=2.0$ Hz, pyrazolopyridine-7-H). MS *m/z*: 268 (M^+). Second fraction: Concentration *in vacuo* gave 1.1 g (29%) of 2-isopropyl-6-methoxypyrazolo[1,5-*a*]pyridine (**8**) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.34 (6H, d, $J=7.0$ Hz, $CH(C\underline{H}_3)_2$), 3.14 (1H, m, $J=7.0$ Hz, $C\underline{H}(CH_3)_2$), 3.78 (3H, s, OCH_3), 6.22 (1H, s, pyrazolopyridine-3-H), 6.85 (1H, dd, $J=9.6$, 2.0 Hz, pyrazolopyridine-5-H), 7.31 (1H, d, $J=9.6$ Hz, pyrazolopyridine-4-H), 8.02 (1H, d, $J=2.0$ Hz, pyrazolopyridine-7-H). MS *m/z*: 190 (M^+). A solution of **7** in ethanol (30 ml) was agitated in a hydrogen atmosphere under atmospheric pressure at room temperature in the presence of 10% palladium–carbon (0.1 g). After absorption ceased, the solution was filtered and concentrated to dryness. The residue was purified by column chromatography on silica gel employing hexane–CH_2Cl_2 (1 : 4) as an eluent to give 0.57 g (81%) of **8**. Compound **8** (0.3 g) was refluxed with isobutyric anhydride (5 ml) and conc. H_2SO_4 (2 drops) for 7 h, then cooled to room temperature. A solution of 10% aq. KOH solution (10 ml) was added to the reaction mixture and stirred at 70 °C for 1 h. The mixture was extracted with $CHCl_3$ and washed with water. The organic layer, after being dried over anhyd. Na_2SO_4, was concentrated to dryness. The residue was subjected to silica gel column chromatography and eluted with CH_2Cl_2–AcOEt (9 : 1) to afford 0.21 g (51%)

of 3-isobutyryl-2-isopropyl-6-methoxypyrazolo[1,5-*a*]pyridine (**9**) as a blackish oil. ^{1}H-NMR ($CDCl_3$) δ: 1.24, 1.40 (6H × 2, d, *J*=6.8 Hz, $CH(C\underline{H}_3)_2$, $COCH(C\underline{H}_3)_2$), 3.31, 3.74 (1H × 2, m, *J*=6.8 Hz, $C\underline{H}(CH_3)_2$, $COC\underline{H}(CH_3)_2$), 3.84 (3H, s, OCH_3), 7.17 (1H, dd, *J*=9.7, 2.2 Hz, pyrazolopyridine-5-H), 7.94 (1H, d, *J*=9.7 Hz, pyrazolopyridine-4-H), 8.08 (1H, d, *J*=2.0 Hz, pyrazolopyridine-7-H). MS *m/z*: 260 (M^+). A mixture of **9** (0.10 g) and pyridine hydrochloride (4.0 g) was heated at 160 °C for 2 h under stirring, then poured into ice-cold water and extracted with $CHCl_3$. The organic layer was separated, washed with successively with water, dil. HCl solution and water again, dried over anhyd. Na_2SO_4 and concentrated to dryness. The residue was chromatographed over silica gel employing CH_2Cl_2–MeOH (9:1) as the eluent. The eluate was evaporated to dryness and the residue was recrystallized from benzene–hexane to afford the title compound (M-20) in a yield of 51 mg (54%), mp 87—90 °C. *Anal.* Calcd for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.31; H, 7.35; N, 11.39. The spectroscopic data was identical with that of the sample obtained by the foregoing procedure.

2-Isopropyl-6-methanesulfonyl-3-propionylpyrazolo[1,5-*a*]pyridine (M-16) Initial Method: 1-Amino-2-methyl-5-methylthiopyridinium iodide (**1**: Z=SMe, X=I^-, 26.6 g) prepared[7] from 2-methyl-5-methylthiopyridine[8] (19.0 g), NH_2OSO_3H (28.0 g) and 57% HI (50 ml), was added to a solution of 50 ml of isobutyric anhydride and refluxed for 3 h. The reaction mixture was concentrated *in vacuo* and to the residue was added water, followed by extraction with CH_2Cl_2. The organic layer was washed with water and concentrated to dryness. The residue was purified by column chromatography on silica gel employing CH_2Cl_2 as an eluent to give 0.51 g (2%) of **2**. But this compound was impure. *m*-CPBA (1.0 g) was added to the solution of crude **2** (0.51 g) in CH_2Cl_2 (16 ml) under cooling and left at room temperature for 1 h. The reaction mixture was washed with a water solution of $Na_2S_2O_4$ and K_2CO_3, dried over anhyd. Na_2SO_4, and concentrated. The residue was recrystallized from AcOEt after treatment with active carbon to give 0.30 g (53%) of 3-isobutyryl-2-isopropyl-6-methanesulfonylpyrazolo[1,5-*a*]pyridine (**3**) as colorless needles, mp 175—176 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.76, 0.89 (6H × 2, d, *J*=7.0 Hz, $CH(C\underline{H}_3)_2$, $COCH(C\underline{H}_3)_2$), 2.59 (3H, s, SO_2CH_3), 2.80, 3.20 (1H × 2, m, *J*=7.0 Hz, $C\underline{H}(CH_3)_2$, $COC\underline{H}(CH_3)_2$), 7.20 (1H, dd, *J*=9.0, 1.2 Hz, pyrazolopyridine-5-H), 7.67 (1H, d, *J*=9.0 Hz, pyrazolopyridine-4-H), 8.62 (1H, d, *J*=1.2 Hz, pyrazolopyridine-7-H). *Anal.* Calcd for $C_{15}H_{20}N_2O_5$: C, 58.43; H, 6.54; N, 9.09. Found: C, 58.40; H, 6.62; N, 8.92. The compound (**3**; 0.30 g) was added to 50% H_2SO_4 (40 ml) and refluxed for 5 h. The mixture was poured into ice-cold water and extracted with $CHCl_3$. The organic layer was dried over anhyd. Na_2SO_4 and evaporated to dryness. The obtained crystals were washed with hexane to give 0.19 g (82%) of 2-isopropyl-6-methanesulfonylpyrazolo[1,5-*a*]pyridine (**4**), mp 115—116 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (6H, d, *J*=7.0 Hz, $CH(C\underline{H}_3)_2$), 3.04 (3H, s, SO_2CH_3), 3.13 (1H, m, *J*=7.0 Hz, $C\underline{H}(CH_3)_2$), 6.39 (1H, s, pyrazolopyridine-3-H), 7.23 (1H, dd, *J*=9.3, 1.6 Hz, pyrazolopyridine-5-H), 7.48 (1H, d, *J*=9.3 Hz, pyrazolopyridine-4-H), 8.96 (1H, s, pyrazolopyridine-7-H). IR (KBr): 1305, 1125 cm^{-1} (SO_2). *Anal.* Calcd for $C_{11}H_{14}N_2O_2S$: C, 55.44; H, 5.92; N, 11.75. Found: C, 55.50; H, 5.95; N, 11.65. The mixture of **4** (0.19 g), propionic anhydride (30 ml) and conc. H_2SO_4 (3 drops) was refluxed for 6 h and poured into ice-cold water. The mixture was extracted with CH_2Cl_2 and concentrated to dryness. Ten percent aq. KOH (200 ml) was added to the residue and stirred at 70 °C for 2 h. Ice-cold water was added to the reaction mixture, followed by extraction with $CHCl_3$. The organic layer was washed with water, dried over anhyd. Na_2SO_4, and concentrated to dryness. The crude crystals were recrystallized from hexane–benzene to give 60 mg (26%) of the title compound (M-16), mp 170—171 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.29 (3H, t, *J*=7.1 Hz, $CH_2C\underline{H}_3$), 1.40 (6H, d, *J*=7.0 Hz, $CH(C\underline{H}_3)_2$), 2.91 (2H, q, *J*=7.1 Hz, $C\underline{H}_2CH_3$), 3.11 (3H, s, SO_2CH_3), 3.67 (1H, m, *J*=7.0 Hz, $C\underline{H}(CH_3)_2$), 6.69 (1H, dd, *J*=8.9, 1.1 Hz, pyrazolopyridine-5-H), 7.31 (1H, d, *J*=8.9 Hz, pyrazolopyridine-4-H), 8.12 (1H, d, *J*=1.1 Hz, pyrazolopyridine-7-H). MS *m/z*: 294 (M^+). IR (KBr): 1664 (C=O), 1296, 1124 cm^{-1} (SO_2). *Anal.* Calcd for $C_{14}H_{18}N_2O_3S$: C, 57.13; H, 6.17; N, 9.52. Found: C, 57.34; H, 6.24; N, 9.35.

Improved Method: A solution of **6** (8.2 g) in DMF (30 ml) was added to the solution of MeSNa in MeOH which was obtained from *ca.* 15% aq. MeSNa (121.4 ml), *conc.* HCl (21.9 ml) and Na (3.0 g) in MeOH (40 ml). CuI (0.99 g) was added to the mixture and refluxed for 20 h under a nitrogen atmosphere. The insoluble materials were filtered off. The filtrate was concentrated *in vacuo*, then 50 ml of water was added. The water solution was extracted with hexane, dried over anhyd. Na_2SO_4 and concentrated to give 2.9 g (39%) of 3-bromo-2-isopropyl-6-methylthiopyrazolo[1,5-*a*]pyridine (**10**). ^{1}H-NMR ($CDCl_3$) δ: 1.36 (6H, d, *J*=7.0 Hz, $CH(C\underline{H}_3)_2$), 2.45 (3H, s, SCH_3), 3.25 (1H, m, *J*=7.0 Hz, $C\underline{H}(CH_3)_2$), 7.07 (1H, d, *J*=8.2 Hz, pyrazolopyridine-5-H), 7.30 (1H, d, *J*=8.2 Hz, pyrazolopyridine-4-H), 8.25 (1H, s, pyrazolopyridine-7-H). MS *m/z*: 284 (M^+). The compound **10** (2.9 g) was dissolved in CH_2Cl_2 (30 ml), *m*-CPBA (4.0 g) was added, and the mixture was stirred at room temperature for 2 h. The reaction mixture was washed with aq. K_2CO_3 solution, dried over anhyd. Na_2SO_4, and concentrated to dryness. The residue was recrystallized from MeOH to give 1.5 g (47%) of 3-bromo-2-isopropyl-6-methanesulfonylpyrazolo[1,5-*a*]pyridine (**12**) as colorless needles, mp 156—157 °C. MS *m/z*: 316 (M^+). IR (KBr): 1302, 1123 cm^{-1} (SO_2). *Anal.* Calcd for $C_{11}H_{13}BrN_2O_2S$: C, 41.65; H, 4.13; N, 8.83. Found: C, 41.76; H, 3.91; N, 8.96. However, compound **10** was oxidized by 35% H_2O_2 at room temperature in AcOH, but only a 6-methanesulfinyl compound (**11**) was obtained as colorless needles (41%), mp 77—78 °C. MS *m/z*: 300 (M^+). IR (KBr): 1044 cm^{-1} (SO). *Anal.* Calcd for $C_{11}H_{13}BrN_2OS$: C, 43.86; H, 4.35; N, 9.30. Found: C, 44.02; H, 4.16; N, 9.46. A solution of **12** (1.14 g) and KOH (1.00 g) in EtOH (50 ml) was agitated in a hydrogen atmosphere under atmospheric pressure at 50 °C in the presence of 10% palladium–carbon (0.40 g) for 3 h. The solution was filtered, washed with hot EtOH, and the filtrate was concentrated to dryness. To the residue was added water (50 ml), followed by extraction with AcOEt. The organic layer was dried over anhyd. Na_2SO_4 and concentrated *in vacuo* to give colorless needles. The crystals were recrystallized from AcOEt to give 0.71 g (83%) of 2-isopropyl-6-methanesulfonylpyrazolo[1,5-*a*]pyridine (**4**), mp 115—116 °C. *Anal.* Calcd for $C_{11}H_{14}N_2O_2S$: C, 55.44; H, 5.92; N, 11.75. Found: C, 55.55; H, 5.95; N, 11.66. The spectroscopic data was identical with that of the sample obtained by the foregoing procedure. Compound **13** was treated with propionic anhydride in a manner similar to that described in the initial method to give M-16 as colorless needles (40%), mp 170—171 °C. *Anal.* Calcd for $C_{14}H_{18}N_2O_3S$: C, 57.13; H, 6.17; N, 9.52. Found: C, 56.90; H, 6.19; N, 9.25. The spectroscopic data was identical with that of the sample obtained by the foregoing procedure.

3-(3-Hydroxy-2-methylpropionyl)-2-isopropyl-6-methanesulfonylpyrazolo[1,5-*a*]pyridine (14) To the solution of M-16 (0.34 g) and KOH (0.10 g) in water (2 ml) and dioxane (4 ml) was added dropwise 37% formalin (0.4 ml) in dioxane (2 ml). The mixture was stirred at 55—60 °C for 1 h and evaporated to dryness. To the residue was added water (30 ml), followed by extraction with $CHCl_3$. The organic layer was dried over anhyd. Na_2SO_4 and concentrated to give a pale yellow oil. This oil was subjected to silica gel column chromatography and eluted with $CHCl_3$–MeOH (20:1). First fraction: Recrystallization from *iso*-PrOH gave 0.15 g (42%) of a dehydrated compound (**13**) as colorless needles, mp 120—121 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.34 (6H, d, *J*=6.8 Hz, $CH(C\underline{H}_3)_2$), 2.12 (3H, s, $COC(C\underline{H}_3)=CH_2$), 3.13 (3H, s, SO_2CH_3), 3.60 (1H, m, *J*=6.8 Hz, $C\underline{H}(CH_3)_2$), 5.61, 5.82 (2H, s, $C(CH_3)=C\underline{H}_2$), 7.58 (1H, d, *J*=9.0 Hz, pyrazolopyridine-5-H), 7.90 (1H, d, *J*=9.9 Hz, pyrazolopyridine-4-H), 9.12 (1H, s, pyrazolopyridine-7-H). MS *m/z*: 306 (M^+). IR (KBr): 1635 (C=O), 1301, 1122 cm^{-1} (SO_2). *Anal.* Calcd for $C_{15}H_{18}N_2O_3S$: C, 58.80; H, 5.92; N, 9.14. Found: C, 58.58; H, 5.91; N, 9.10. Second fraction: Drying *in vacuo* gave 52 mg (14%) of the title compound (**14**) as hydrate crystals, mp 104—106 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.22 (3H, d, *J*=6.8 Hz, $CH(C\underline{H}_3)CH_2OH$), 1.35 (6H, d, *J*=7.0 Hz, $CH(C\underline{H}_3)_2$), 3.18 (3H, s, SO_2CH_3), 2.90—4.05 (5H, m, $C\underline{H}(CH_3)C\underline{H}_2O\underline{H}$, $C\underline{H}(CH_3)_2$), 7.28 (1H, d, *J*=9.0 Hz, pyrazolopyridine-5-H), 7.89 (1H, d, *J*=9.0 Hz, pyrazolopyridine-4-H), 8.95 (1H, s, pyrazolopyridine-7-H). MS *m/z*: 324 (M^+). IR (KBr): 3200—3650 (OH), 1625 (C=O), 1300, 1140 cm^{-1} (SO_2). *Anal.* Calcd for $C_{15}H_{20}N_2O_4S \cdot H_2O$: C, 52.62; H, 6.48; N, 8.18. Found: C, 52.46; H, 6.74; N, 7.86.

Halogenation of 3-Bromo-2-isopropylpyrazolo[1,5-*a*]pyridine (5) The mixture of **5** (10.0 g) and NBS (10.0 g) in DMF (100 ml) was stirred at 70 °C for 3 h. The reaction mixture was poured into ice-cold water and extracted with benzene. The extract was washed with water, dried over anhyd. Na_2SO_4, and concentrated to dryness. The residue was subjected to silica gel column chromatography and eluted with hexane–CH_2Cl_2 (1:1). The obtained mixture fractions were purified by column chromatography again. First fraction: The eluate was evaporated to dryness to give 2.60 g (16%) of 3,4,6-tribromo-2-isopropylpyrazolo[1,5-*a*]pyridine as white needles, mp 102—104 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (6H, d, *J*=6.8 Hz, $CH(C\underline{H}_3)_2$), 3.25 (1H, m, *J*=6.8 Hz, $C\underline{H}(CH_3)_2$), 7.39 (1H, d, *J*=1.5 Hz, pyrazolopyridine-5-H), 8.47 (1H, d, *J*=1.5 Hz, pyrazolopyridine-7-H). MS *m/z*: 394 (M^+). IR (KBr): 2970, 1500, 1485, 1310, 830 cm^{-1}. *Anal.* Calcd for $C_{10}H_9Br_3N_2$: C, 30.26; H, 2.29; N, 7.06. Found: C, 30.55; H, 2.23; N, 7.14. Second fraction: The eluate was evaporated to dryness to give 3.20 g (24%) of 3,6-dibromo-2-isopropylpyrazolo[1,5-*a*]pyridine as white needles, mp 53—54 °C. *Anal.* Calcd for $C_{10}H_{10}Br_2N_2$: C, 37.77; H, 3.17; N, 8.84. Found: C, 37.82; H, 3.13; N, 8.81. The spectroscopic data was identical with that of the sample obtained by the foregoing procedure. Third fraction: The eluate was evaporated to dryness to give 2.40 g (18%) of 3,4-dibromo-2-isopropylpyrazolo[1,5-*a*]pyridine as white needles, mp 89—90 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.37 (6H, d, J=6.8 Hz, CH(C$\underline{H}_3$)$_2$), 3.29 (1H, m, J=6.8 Hz, C$\underline{H}$(CH$_3$)$_2$), 6.53 (1H, dd, J=7.3, 7.0 Hz, pyrazolopyridine-6-H), 7.32 (1H, dd, J=7.3, 1.1 Hz, pyrazolopyridine-5-H), 8.34 (1H, dd, J=7.0, 1.1 Hz, pyrazolopyridine-7-H). MS m/z: 316 (M^+). IR (KBr): 2970, 1510, 1395, 767 cm^{-1}. *Anal.* Calcd for $C_{10}H_{10}Br_2N_2$: C, 37.77; H, 3.17; N, 8.84. Found: C, 37.56; H, 3.10; N, 8.85. Additional halogenation of **5** was carried out in a similar manner as described above and these results are summarized in Table I. 3-Bromo-6-chloro-2-isopropylpyrazolo-[1,5-*a*]pyridine was obtained as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.37 (6H, d, J=6.8 Hz, CH(C$\underline{H}_3$)$_2$), 3.27 (1H, m, J=6.8 Hz, C$\underline{H}$(CH$_3$)$_2$), 7.14 (1H, dd, J=9.5, 1.2 Hz, pyrazolopyridine-5-H), 7.32 (1H, dd, J=9.5, 0.9 Hz, pyrazolopyridine-4-H), 8.47 (1H, dd, J=1.2, 0.9 Hz, pyrazolopyridine-7-H). MS m/z: 272 (M^+). IR (NaCl): 2975, 1485, 1300, 1090, 1041, 785 cm^{-1}. *Anal.* Calcd for $C_{10}H_{10}BrClN_2$: C, 43.91; H, 3.68; N, 10.24. Found: C, 43.99; H, 3.53; N, 10.08.

Acknowledgment The authors are grateful to the staff of the Analytical Center and the Drug Metabolism.

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