Synthesis of Metabolites and Related Compounds of 3-Isobutyryl-2-isopropylpyrazolo[1,5-*a*]pyridine (Ibudilast). I. Metabolites of Alkyl Side Chains

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3-Isobutyryl-2-isopropylpyrazolo[1,5-*a*]pyridine (ibudilast) has a large number of metabolites. In order to unequivocally establish the true identity of these metabolites, we prepared a series of authentic reference compounds, namely novel pyrazolo[1,5-*a*]pyridine derivatives with mono- and dihydroxylated alkyl side chains and carboxylated alkyl side chains. These results lead to the conclusion that reactions at the 3-position of pyrazolo[1,5-*a*]pyridine are governed by the electron-donating effect and the weak basicity of bridge-head nitrogen. On the basis of these results we were able to establish a method of functional group introduction to the alkyl side chains of pyrazolo[1,5-*a*]pyridine.

Keywords ibudilast; pyrazolo[1,5-*a*]pyridine; hydroxylated metabolite; carboxylated metabolite; bridge-head nitrogen; functional group introduction

3-Isobutyryl-2-isopropylpyrazolo[1,5-*a*]pyridine (ibudilast) is a newly developed antiallergic and cerebroactive agent which differs structurally from other medicines.

Previous studies[1] on the metabolism of ibudilast showed that it had a large number of metabolites in laboratory animals and man and was metabolized principally by ring oxidation and alkyl side chain hydroxylation. In order to unequivocally establish the true identity of these metabolites, we prepared a series of authentic reference compounds. On the basis of the characteristics of pyrazolo[1,5-*a*]-pyridine we established a method of functional group introduction. Despite the large number of investigations[2] there has never been a detailed, systematic study on pyrazolo[1,5-*a*]pyridine. This paper presents the synthesis of novel pyrazolo[1,5-*a*]pyridine derivatives with mono- and dihydroxylated and carboxylated alkyl side chains as an authentic reference of metabolites for ibudilast, as shown in Chart 1.

Synthesis of the Hydroxylated Side Chains on Ibudilast α-Hydroxylated Side Chains Chart 3(A) shows the synthesis of dihydroxylated metabolite M-4 on ibudilast and this compound was prepared as follows. Dimethyl pyrazolo[1,5-*a*]pyridine-2,3-dicarboxylate (**1**) was obtained by the reaction of 1-aminopyridinium iodide with acetylene dicarboxylic acid dimethyl ester in the presence of a base.[3] This dimethyl ester was hydrolyzed by 10% aq. NaOH to a dicarboxylic acid (**2**). The dicarboxylic acid (**2**) was refluxed with ethanol in the presence of conc. H_2SO_4 with the evolution of carbon dioxide at the 3-position to afford the mono ester (**3**).

Pyrazolo[1,5-*a*]pyridine is characterized by a strong electron-donating effect and by weak basicity of bridge-head nitrogen. Decarboxylation at the 3-position of pyrazolo[1,5-*a*]pyridine easily occured in the presence of acid. It is considered that a resonance stabilized form (Chart 2, a) is formed by proton addition and performs a role as an electron pool which accepts the electron pair generated by the C–C bond fission at the time of decarboxylation. A clear difference between the 3-carboxy group and 2-carboxy group of pyrazolo[1,5-*a*]pyridine was confirmed in this reaction.

The mono ester (**3**) was then reacted with isobutyric anhydride in the presence of conc. H_2SO_4. 3-Carbonyl group enol ester (**3'**) was hydrolyzed by aq. NaOH, and the product was esterified again to afford the isobutyryl compound (**4**).

3-Acylation of pyrazolo[1,5-*a*]pyridine proceeded in satisfactory yields when treated with acid anhydride in the presence of acid (Chart 2, c). However, good yields were not obtained in Friedel–Crafts acylation because the bridge-head nitrogen of pyrazolo[1,5-*a*]pyridine has weak basicity and its electron-donating effect was inhibited by complexation with Lewis acid.

Compound **4** was changed into 2-(1-hydroxy-1-methyl-ethyl)-3-isobutyrylpyrazolo[1,5-*a*]pyridine (M-1) by means of the Grignard reaction with methyl magnesium iodide. The 3-carbonyl group of **4** was unreactive with the Grignard

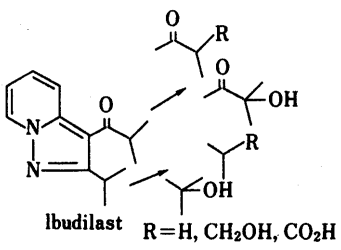

Chart 1. Alkyl Side Chain Metabolites of Ibudilast

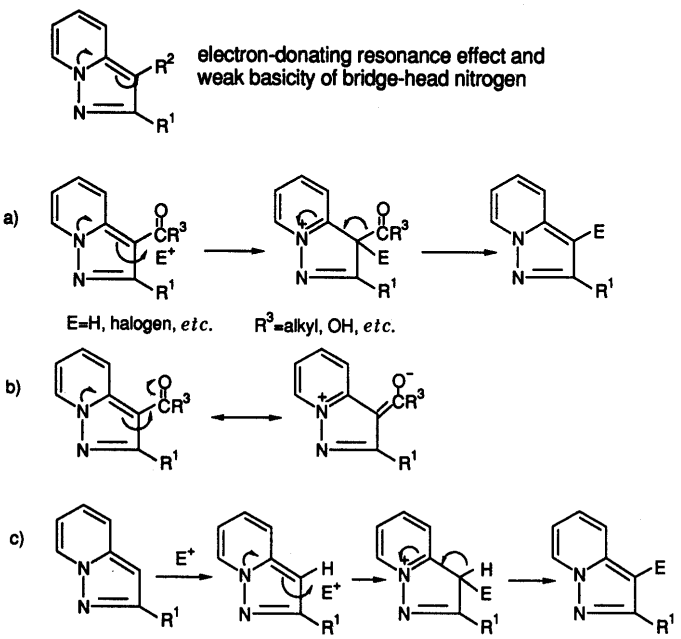

Chart 2. Characteristics of Pyrazolo[1,5-*a*]pyridine Derivatives

reagent because the carbonyl group is resonant with the bridge-head nitrogen and its electron density increased as shown in Chart 2, b. Next, **4** was treated with a catalytic amount of dimethylformamide (DMF) and phosphorus oxychloride to afford the chloroethylene compound (**5**) along with a small amount of formyl compound (**5′**) as a Vilsmeier reaction product. Compound **5** was heated with a methanol solution of sodium methoxide in a pressure vessel at 100 °C, which would not react at atmospheric pressure, to provide the methoxide (**6**). This in turn was treated with *m*-chloroperbenzoic acid (*m*-CPBA) to afford the epoxide (**7**). Subsequent treatment of the epoxide with sodium methoxide afforded the acetal (**8**). A small amount of carbonyl compound (**8′**) was produced at the same time. It is considered that **8′** might result from hydrolysis of the acetal. The acetal (**8**) led to **9** by the Grignard reaction with methylmagnesium iodide, and this was treated with acid to provide 2-(1-hydroxy-1-methylethyl)-3-(2-hydroxy-2-methylpropionyl)pyrazolo[1,5-*a*]pyridine (M-4).

A monohydroxylated compound (M-2) of the 3-isobutyryl group on ibudilast was prepared by the synthetic route shown in Chart 3 (B).

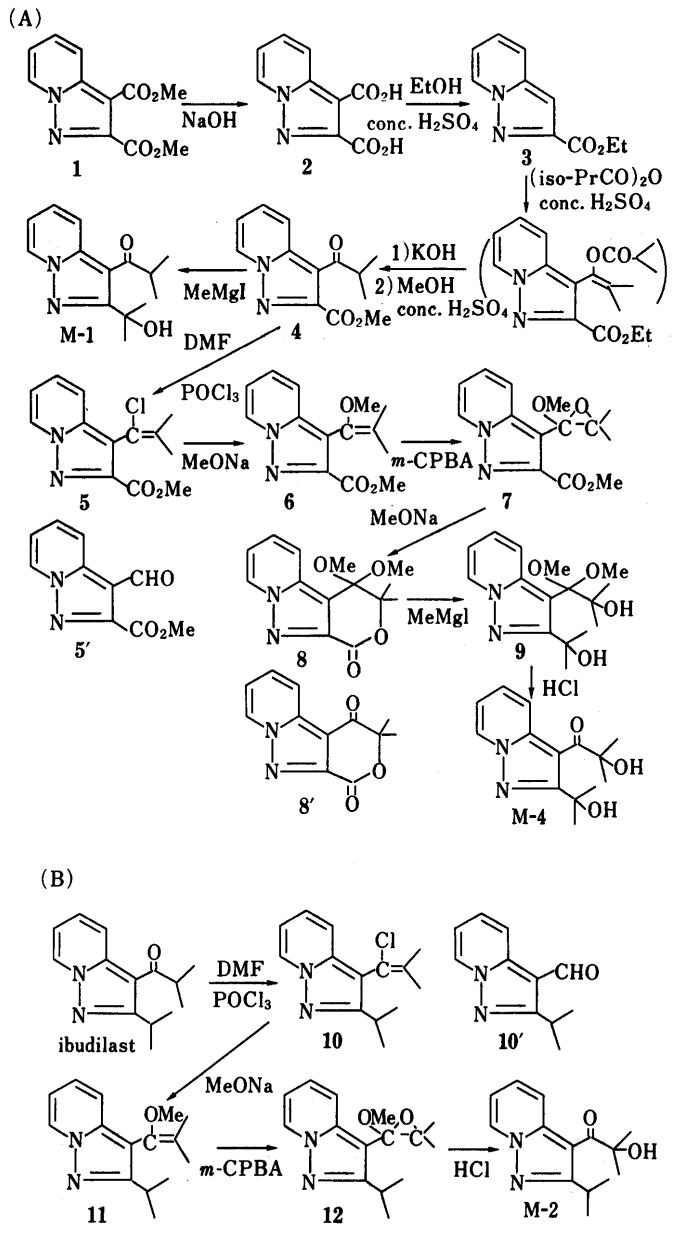

Chart 3. Synthesis of α-Hydroxylated Side Chains

Ibudilast was treated with a catalytic amount of DMF and phosphorus oxychloride to afford the chloroethylene compound (**10**), and a small amount of formyl compound (**10′**) produced at the same time as a by-product. The chloroethylene compound (**10**) was heated under reflux with a methanol solution of sodium methoxide. Subsequent treatment of the methoxide compound (**11**) with *m*-CPBA gave the epoxide (**12**), which in turn was treated with acid to provide 3-(2-hydroxy-2-methylpropionyl)-2-isopropylpyrazolo[1,5-*a*]pyridine (M-2) in good yields.

Synthesis of β-Hydroxylated Side Chains β-Hydroxylated metabolites of the 2-isopropyl group on ibudilast were synthesized by the method shown in Charts 4(A) and 4(B). It is known that pyrazolo[1,5-*a*]pyridines are prepared by using pyridine *N*-imine as the 1,3-dipolar compound.[4] In view of this, acetonedicarboxylic acid dimethyl ester was used as a 1,3-dipolarophile to obtain the 2-acetate type pyrazolo[1,5-*a*]pyridine which was a key starting material for the synthesis of 2-β-hydroxylated or carboxylated metabolites.

Treatment of *N*-aminopyridinium iodide with acetonedicarboxylic acid dimethyl ester in an alkaline water solution at room temperature afforded methyl (3-methoxycarbonylpyrazolo[1,5-*a*]pyridine-2-yl)acetate (**13**) in relatively good yield. This was converted to the propionate (**14**) by the reaction with methyl iodide in the presence of tetrabutylammonium hydrogen sulfate, as shown in Chart 4(A). However, when methylation was carried out after the decarboxylation at the 3-position (**18**), a mixture of mono (**16**) and dimethylated compound (**16′**) was obtained and it was difficult to separate them. It is considered that these results stem from the steric effect of the 3-methoxycarbonyl group (**13**). This propionate (**14**) was hydrolyzed with aq. NaOH to the dicarboxylic acid (**15**), which in turn was refluxed with ethanol in the presence of conc. H_2SO_4 to afford the mono ester (**16**). This was reduced with excess sodium borohydride to the alcohol compound (**17**). This compound **17** was a key intermediate for the synthesis of 2-β-hydroxylated metabolites (Chart 4(B)). Reaction of **17** with isobutyric anhydride or propionic anhydride in the presence of conc. H_2SO_4 as a catalyst afforded 2-(2-hydroxy-1-methylethyl)-3-isobutyryl compound (**20**) or 2-(2-hydroxy-1-methylethyl)-3-propionyl compound (**19**), respectively. The isobutyryl compound (**20**) was further oxidized by lead tetraacetate to afford the 3-α-acetyloxy compound (**21**), which in turn was hydrolyzed to the 2-β,3-α-dihydroxylated compound (M-18). The propionyl compound (**19**) was treated with formalin to provide the 2-β,3-β-dihydroxylated compound (M-17) through the introduction of the hydroxylmethyl group into the α-position of the 3-propionyl group. In addition, compound **20** was treated with thionyl chloride to afford the β-chloro compound (**22**). This was refluxed with a sodium methoxide solution to provide the vinyl compound (**24**). This vinyl compound (**24**) could also be prepared by an alternate route. Compound **17** was dehydrated with potassium hydrogen sulfate to **23**, which in turn was reacted with isobutyric anhydride in the presence of acid to afford **24**. Compound **24** was oxidized with potassium permanganate in an aqueous acetone solution to the 2-α,2-β-dihydroxylated compound (M-19) which as yet had been undetected as

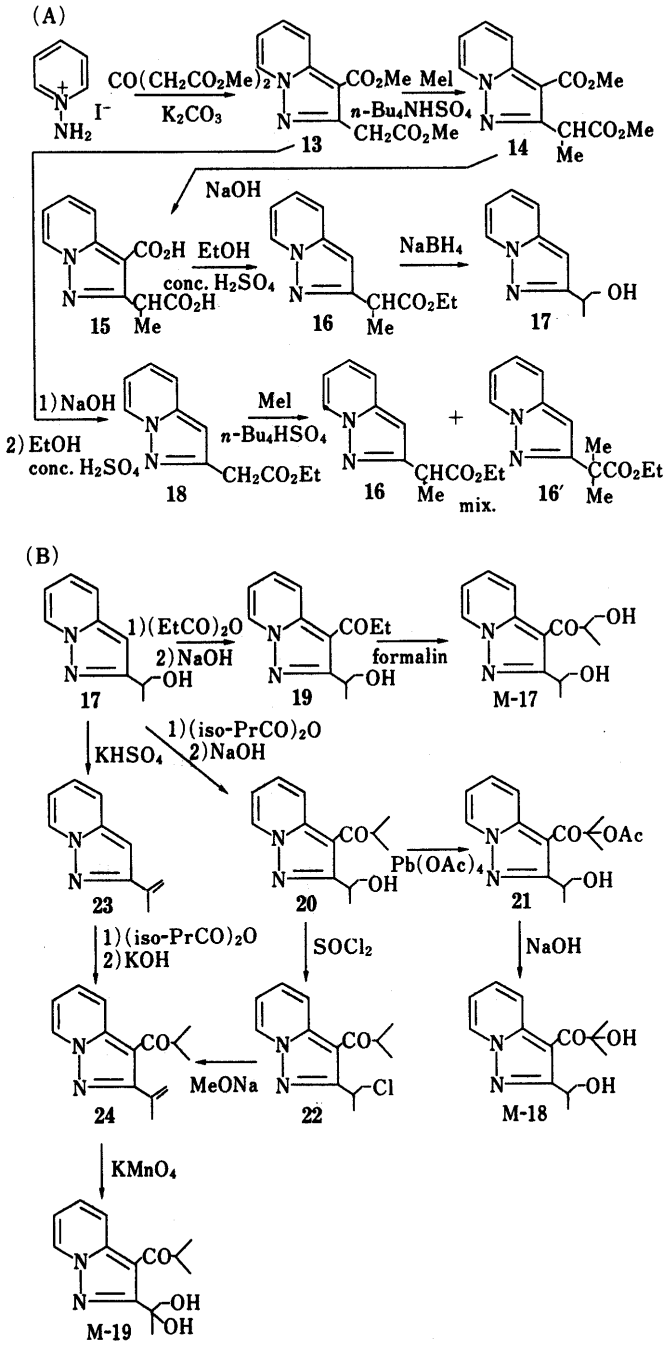

Chart 4. Synthesis of β-Hydroxylated Side Chain

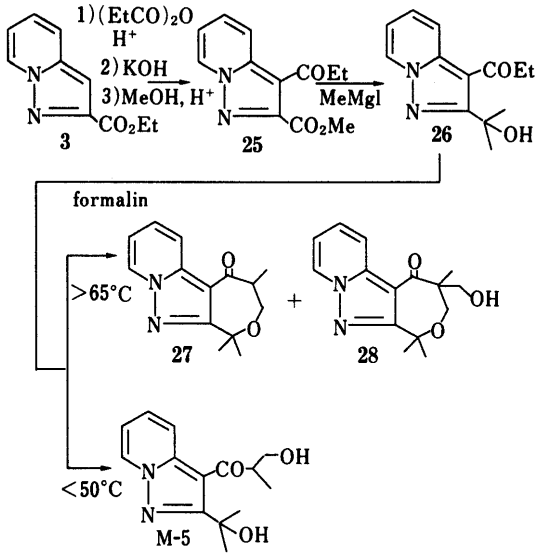

Chart 5. Synthesis of α,β-Dihydroxylated Side Chain

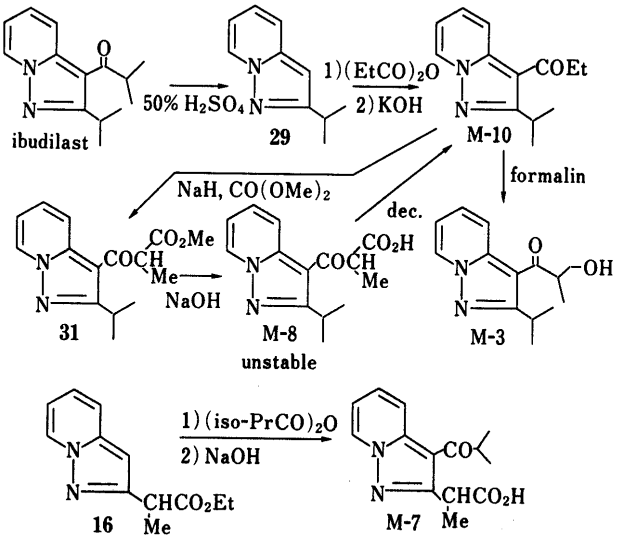

Chart 6. Synthesis of Carboxylated Side Chains

metabolite.

Ibudilast was refluxed with 50% conc. H_2SO_4 to afford the deacylated compound (**29**). Deacylation of the 3-position occurred easily in the presence of acid for the reason mentioned previously (Chart 2, a). This compound **29** was treated with propionic anhydride to provide the 3-propionyl compound (M-10). This was reacted with formalin in the presence of a base to afford the 3-(3-hydroxy-2-methylpropionyl)-2-isopropylpyrazolo[1,5-*a*]-pyridine (M-3) which was introduced to the hydroxy group into the β-position of the 3-isobutyl group (Chart 6). Furthermore, the compound **3** was treated with propionic anhydride to provide the propionyl compound (**25**) as shown in Chart 5. This was converted to 2-α-hydroxyisopropyl compound (**26**) by a reaction with methyl magnesium iodide. The selective reactivity of the 2-carbonyl group in this reaction appeared for the previously described reason (Chart 2, b). The compound **26** was treated with formalin to afford 2-(1-hydroxy-1-methylethyl)-3-(3-hydroxy-2-methylpropionyl)pyrazolo[1,5-*a*]pyridine (M-5) in a way similar to that shown in the case of compound M-3. However, at a higher reaction temperature (above 65 °C) cyclized ethers (compounds **27** and **28**) were produced. These compounds resulted from dehydration and dihydroxymethylation, respectively.

Synthesis of the Carboxylated Side Chains on Ibudilast Side chain carboxylated compounds were prepared from intermediate products of the previously described hydroxylated side chains and synthesized as follows (Chart 6).

Compound M-10 was treated with sodium hydride and the resulting anion was reacted with dimethylcarbonate to afford the 3-position side chain methoxycarbonylated compound (**31**). This ester was hydrolyzed with an alkaline solution to the carboxylic acid (M-8), but this carboxyl group was unstable because of β-keto acid and decomposed gradually into the initial propionyl compound (M-10) with the evolution of carbon dioxide (Chart 6). Compound **16** was refluxed with isobutyric anhydride in the pesence of

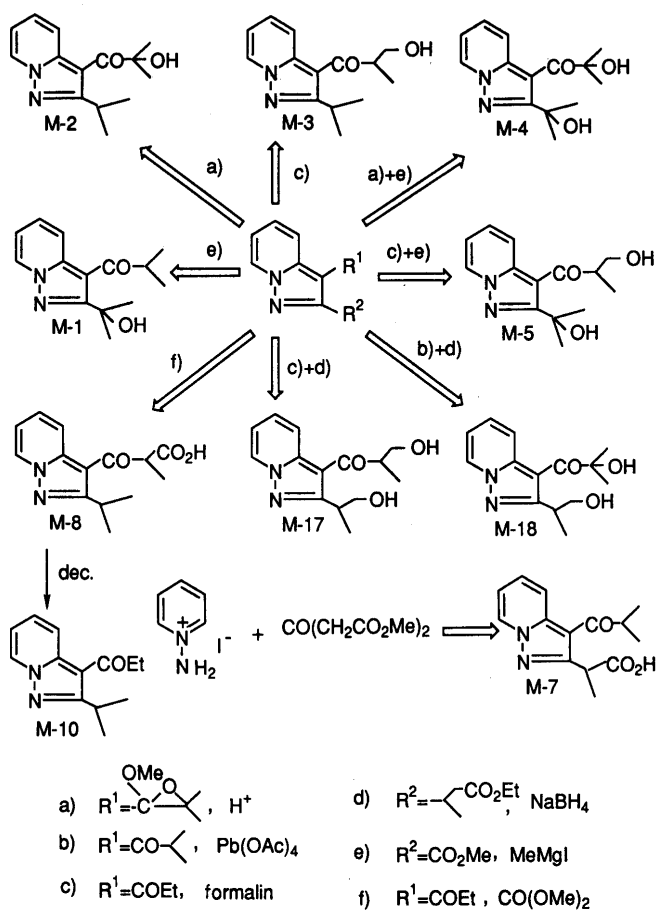

Chart 7. Synthetic Methods of Metabolites

acid and hydrolyzed with alkali to the 2-(3-isobutyryl-pyrazolo[1,5-*a*]pyridine-2-yl)propionic acid (M-7).

The results are summarized as follows: Miscellaneous novel pyrazolo[1,5-*a*]pyridine derivatives of mono- and dihydroxylated alkyl side chains and carboxylated alkyl side chains could be synthesized as shown in Chart 7. A 3-α-hydroxylated side chain was synthesized by oxidation with lead tetraacetate or *via* the epoxide. A 2-α-hydroxylated side chain was synthesized using the Grignard reaction. A 3-β-hydroxylated side chain was synthesized by hydroxymethylation of ethyl ketone with formalin. A 2-β-hydroxylated side chain was synthesized by the reduction of propionate with sodium borohydride. 2,3-Dihydroxylated side chains were synthesized by a combination of the previously described methods. Whereas, the 2-carboxylated side chain was prepared by the reaction of pyridine *N*-imine with acetonedicarboxylic acid dimethyl ester and the 3-carboxylated side chain was prepared by carboxylation with dimethylcarbonate.

Thus, it was proved that reactions at the 3-position of pyrazolo[1,5-*a*]pyridine ring are governed by the electron-donating effect and the weak basicity of bridge-head nitrogen. On the basis of these characteristics, it was able to establish synthetic fundamentals of an alkyl side chains functional group introducted on pyrazolo[1,5-*a*]pyridine.

Experimental

Apparatus and Method Melting points were measured with a Yanagimoto melting point apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectra were measured with a JNM-FX 90Q FT NMR spectrometer using tetramethylsilane as an internal standard. Mass spectra (MS) were recorded using a JEOL JMS-D300 spectrometer; in all cases direct sample insertion was carried out into the ion source. Column chromatography was carried out on silica gel (Wakogel C-200) and alumina gel (Aluminumoxide 90, Art. 1097, Merck).

The structure of the metabolites was identified in comparison with authentic samples (gas chromatography-mass spectrometry (GC/MS) and thin layer chromatography (TLC)) obtained by the following procedures.[1)]

3-Isobutyryl-2-methoxycarbonylpyrazolo[1,5-*a*]pyridine (4) A solution of 2-ethoxycarbonylpyrazolo[1,5-*a*]pyridine (**3**; 4.2 g), isobutyric anhydride (42 ml) and conc. H_2SO_4 (5 drops) was refluxed for 8 h. This reaction mixture was poured into an ice-water solution, and was alkalized with potassium carbonate. The aqueous layer was extracted with $CHCl_3$, the extract was dried over anhyd. Na_2SO_4, and then concentrated under reduced pressure. A 10% KOH water solution and a small amount of ethanol were added to the residue, and this mixture was heated at 60 °C for 1 h with stirring, then poured into ice-cold water and acidified with acetic acid. The mixture was extracted with $CHCl_3$, the extract was dried over anhyd. Na_2SO_4, and after removal of the solvent, the residue was washed with a small amount of ether and collected by filtration. About 2 g of the obtained crystals were added to the solution of methanol (50 ml) and conc. H_2SO_4 (4 ml), and then refluxed for 1 h and left overnight at room temperature. The reaction mixture was poured into ice-cold water, and extracted with $CHCl_3$. The extract was dried over anhyd. Na_2SO_4 and after removal of the solvent, the residue was chromatographed over silica gel employing a CH_2Cl_2–AcOEt (9 : 1) mixture as the eluent. The eluate was evaporated to dryness to afford the title compound as an oily product in a yield of 3.8 g (70%). ^{1}H-NMR ($CDCl_3$) δ: 1.21 (6H, d, J=6.8 Hz, $CH(C\underline{H}_3)_2$), 3.56 (1H, m, J=6.8 Hz, $C\underline{H}(CH_3)_2$), 4.06 (3H, s, $CO_2C\underline{H}_3$), 7.06 (1H, ddd, J=7.0, 6.8, 1.5 Hz, pyrazolopyridine-6-H), 7.46 (1H, dd, J=9.0, 6.8 Hz, pyrazolopyridine-5-H), 8.23 (1H, dd, J=9.0, 1.5 Hz, pyrazolopyridine-4-H), 8.53 (1H, d, J=7.0 Hz, pyrazolopyridine-7-H). MS *m/z*: 246 (M^+). Infrared (IR) (KBr): 1738, 1641 cm^{-1} (C=O). *Anal.* Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.38; H, 5.68; N, 11.33.

2-(1-Hydroxy-1-methylethyl)-3-isobutyrylpyrazolo[1,5-*a*]pyridine (M-1) Grignard reagent was prepared by adding a solution of methyl iodide (2.3 g) in diethyl ether (30 ml) to a mixture of magnesium (0.4 g) in diethyl ether (30 ml). A solution of **4** (2.3 g) in diethyl ether (20 ml) was added to this reagent with stirring. The stirring was continued at room temperature for 2 h, then the mixture was poured into a water solution of ammonium hydrochloride. After separation of the ether layer, the aqueous layer was extracted with $CHCl_3$. The combined extracted layer was dried over anhyd. Na_2SO_4, and after removal of the solvent, the residue was chromatographed over silica gel employing CH_2Cl_2–AcOEt (9 : 1) mixture as the eluent. The eluate was evaporated to dryness and the residue was recrystallized from benzene–hexane to afford the title compound as colorless needles, mp 92—93 °C, in a yield of 1.1 g (48%). ^{1}H-NMR ($CDCl_3$) δ: 1.29 (6H, d, J=6.8 Hz, $CH(C\underline{H}_3)_2$), 1.66 (6H, s, $C(OH)(C\underline{H}_3)_2$), 3.46 (1H, m, J=6.8 Hz, $C\underline{H}(CH_3)_2$), 6.97 (1H, td, J=6.8, 1.3 Hz, pyrazolopyridine-6-H), 7.03 (1H, s, OH), 7.49 (1H, td, J=6.8, 1.1 Hz, pyrazolopyridine-5-H), 7.83 (1H, d, J=9.0 Hz, pyrazolopyridine-4-H), 8.52 (1H, dd, J=6.8, 1.1 Hz, pyrazolopyridine-7-H). MS *m/z*: 264 (M^+). IR (KBr): 3210—3380 (OH), 1623 cm^{-1} (C=O). *Anal.* Calcd for $C_{14}H_{18}N_2O_3$: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.26; H, 7.40; N, 11.35.

2-(1-Hydroxy-1-methylethyl)-3-(2-hydroxy-2-methylpropionyl)pyrazolo-[1,5-*a*]pyridine (M-4) A solution of compound **4** (0.6 g), phosphorus oxychloride (1.2 ml) and DMF (two drops) was refluxed for 6 h, then poured into ice-cold water and made slightly basic to litmus with conc. NH_4OH. The resulting solution was extracted with CH_2Cl_2, dried over anhyd. Na_2SO_4 and then concentrated. The residue was purified by column chromatography on alumina gel employing CH_2Cl_2 as an eluent to give 0.5 g (77%) of **5** in the form of white prisms, mp 81—82 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.64, 2.10 (3H × 2, s, $=C(CH_3)_2$), 4.00 (3H, s, CH_3), 6.93 (1H, td, J=6.8, 1.5 Hz, pyrazolopyridine-6-H), 7.23 (1H, dd, J=9.0, 6.8 Hz, pyrazolopyridine-5-H), 7.53 (1H, dd, J=9.0, 1.5 Hz, pyrazolopyridine-4-H), 8.50 (1H, d, J=6.8 Hz, pyrazolopyridine-7-H). MS *m/z*: 264 (M^+). IR (KBr): 1732 cm^{-1} (C=O). *Anal.* Calcd for $C_{13}H_{13}ClN_2O_2$: C, 58.99; H, 4.95; N, 10.58. Found: C, 58.97; H, 4.95; N, 10.51. Further elution with CH_2Cl_2 gave 45 mg (9%) of **5′** as a by-product, mp 148—149 °C (white needles). ^{1}H-NMR ($CDCl_3$) δ: 4.08 (3H, s, CO_2CH_3), 6.88 (1H, td, J=7.0, 1.5 Hz, pyrazolopyridine-6-H), 7.18 (1H, dd, J=8.8, 6.8 Hz, pyrazolopyridine-5-H), 7.54 (1H, dd, J=8.8, 1.5 Hz, pyrazolopyridine-4-H), 8.51 (1H, d, J=7.0 Hz, pyrazolopyridine-7-H), 10.60 (1H, s, CHO). MS *m/z*: 204. IR (KBr): 1729, 1648 cm^{-1} (C=O). *Anal.* Calcd for $C_{10}H_8N_2O_3$: C, 58.82; H, 3.95; N, 13.72. Found: C 58.67; H, 3.96; N,

13.63. Compound **5** (0.5 g) was added to sodium methoxide prepared from methanol (1.2 ml) and sodium (50 mg). The mixture was heated at 100 °C in a pressure bottle for 3 h, then poured into water and extracted with CH_2Cl_2. The extract was dried over anhyd. Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on a column of silica gel, and eluted with CH_2Cl_2 to give 0.25 g (51%) of **6** as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.46, 1.92 (3H × 2, s, $=C(CH_3)_2$), 3.28 (3H, s, OCH_3), 3.99 (3H, s, CO_2CH_3), 6.94 (1H, ddd, J=6.8, 6.6, 1.3 Hz, pyrazolopyridine-6-H), 7.20 (1H, dd, J=8.7, 6.6 Hz, pyrazolopyridine-5-H), 7.54 (1H, dd, J=8.7, 1.3 Hz, pyrazolopyridine-4-H), 8.51 (1H, d, J=6.8 Hz, pyrazolopyridine-7-H). MS m/z: 260 (M^+). *m*-CPBA (0.18 g) was added to a solution of **6** (0.20 g) in CH_2Cl_2 (1 ml) and methanol (0.8 ml) under cooling with cold water. After the addition was completed, the mixture was stirred for 1 h, then made alkaline with aq. K_2CO_3 and extracted with CH_2Cl_2. The extract was dried over anhyd. Na_2SO_4, and concentrated *in vacuo* to give 0.20 g (94%) of **7** as an oil. Compound **7** (0.20 g) was added to a sodium methoxide solution prepared from methanol (3 ml) and sodium (0.20 g). The mixture was allowed to stand at room temperature for 20 min and then concentrated. Water was added to the residue and extracted with CH_2Cl_2. The extract was dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to afford **8** as a semi-solid (0.15 g). ^{1}H-NMR ($CDCl_3$) δ: 1.55 (6H, s, $>C(CH_3)_2$), 3.32 (6H, s, OCH_3 × 2), 7.01 (1H, ddd, J=7.0, 6.8 Hz, pyrazolopyridine-6-H), 7.32 (1H, dd, J=9.0, 1.3 Hz, pyrazolopyridine-5-H), 7.84 (1H, dd, J=9.0, 1.3 Hz, pyrazolopyridine-4-H), 8.57 (1H, d, J=7.0 Hz, pyrazolopyridine-7-H). The water layer was made acidic to litmus with conc. HCl and extracted with $CHCl_3$. The extract was dried over anhyd. Na_2SO_4 and evaporated to dryness. The residue was recrystallized from methanol to give **8′** as a by-product, mp 196—198 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.73 (6H, s, $>C(CH_3)_2$), 7.31 (1H, ddd, J=7.0, 6.8, 1.3 Hz, pyrazolopyridine-6-H), 7.72 (1H, dd, J=8.8, 1.3 Hz, pyrazolopyridine-5-H), 8.29 (1H, dd, J=8.8, 1.3 Hz, pyrazolopyridine-4-H), 8.79 (1H, d, J=6.8 Hz, pyrazolopyridine-7-H). MS m/z: 230 (M^+). IR (KBr): 1740, 1662 cm^{-1} (C=O). *Anal.* Calcd for $C_{12}H_{10}N_2O_3$: C, 62.60; H, 4.38; N, 12.17. Found: C, 62.35; H, 4.40; N, 11.89. A stirred solution of **8** (0.15 g) in ether (4 ml) was treated dropwise with the Grignard reagent prepared from methyl iodide (0.70 g) and magnesium (0.10 g) in ether (20 ml). The mixture was stirred at room temperature for 3 h, then refluxed for 2 h and cooled in an ice bath. The mixture was poured into a water solution of NH_4Cl and extracted with CH_2Cl_2. The extract was dried over anhyd. Na_2SO_4 and concentrated *in vacuo* to give **9** (0.16 g, 98%). ^{1}H-NMR ($CDCl_3$) δ: 1.28 (6H, d, J=4.8 Hz, $C(CH_3)_2(OH)$), 1.66 (6H, d, J=9.1 Hz, $C(CH_3)_2(OH)$), 3.20 (3H, s, OCH_3), 3.66 (3H, s, OCH_3), 6.69 (1H, dd, J=6.8, 1.3 Hz, pyrazolopyridine-6-H), 7.09 (1H, ddd, J=9.0, 6.8, 1.3 Hz, pyrazolopyridine-5-H), 7.66 (1H, dd, J=9.0, 1.3 Hz, pyrazolopyridine-4-H), 8.31 (1H, d, J=6.8 Hz, pyrazolopyridine-7-H). Compound **9** was dissolved in a solution of methanol (2 ml) and water (1 ml), then one drop of conc. HCl was added. The mixture was stirred at room temperature for 30 min, made alkaline with K_2CO_3, and extracted with CH_2Cl_2. The extract was dried over anhyd. Na_2SO_4 and concentrated. The residue was recrystallized from AcOEt to give 21 mg (12%) of M-4 as colorless needles, mp 139—140 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.57 (6H, s, $C(CH_3)_2(OH)$), 1.62 (6H, s, $COC(CH_3)_2(OH)$), 3.44, 6.43 (1H × 2, s, OH), 6.88 (1H, td, J=7.8, 1.3 Hz, pyrazolopyridine-6-H), 7.36 (1H, t, J=7.8 Hz, pyrazolopyridine-5-H), 8.36 (2H, d, J=7.8 Hz, pyrazolopyridine-4-H, 7-H). MS m/z: 262 (M^+). IR (KBr): 3240—3400 (OH), 1623 cm^{-1} (C=O). *Anal.* Calcd for $C_{14}H_{18}N_2O_3$: C, 64.10; H, 6.92; N, 10.68. Found: C, 64.12; H, 6.78; N, 10.61.

3-(1-Chloro-2-methyl-1-propenyl)-2-isopropylpyrazolo[1,5-*a*]pyridine (10) To a solution of ibudilast (4.6 g) in DMF (20 ml) was added phosphorous oxychloride (10 ml) under cooling in an ice bath. The resulting solution was heated gradually to 140—150 °C and this was maintained for 2 h. The mixture was allowed to cool to room temperature, then it was poured into ice-cold water. The solution was made basic to litmus with Na_2CO_3 and extracted with CH_2Cl_2. The extract was dried over anhyd. Na_2SO_4 and then concentrated. The residue was purified by column chromatography on silica gel employing benzene as an eluent. First fraction: Distillation under reduced pressure, bp 138 °C (4 mmHg), gave 3.5 g (74%) of **10**. ^{1}H-NMR ($CDCl_3$) δ: 1.37 (6H, d, J=6.8 Hz, $CH(CH_3)_2$), 1.60, 2.03 (3H × 2, s, $=C(CH_3)_2$), 3.22 (1H, m, J=6.8 Hz, $CH(CH_3)_2$), 6.65 (1H, td, J=6.8, 1.1 Hz, pyrazolopyridine-6-H), 7.05 (1H, td, J=9.0, 1.1 Hz, pyrazolopyridine-5-H), 7.30 (1H, dd, J=9.0, 1.1 Hz, pyrazolopyridine-4-H), 8.38 (1H, dd, J=6.8, 1.1 Hz, pyrazolopyridine-7-H). MS m/z: 248 (M^+). *Anal.* Calcd for $C_{14}H_{17}ClN_2$: C, 67.60; H, 6.89; N, 11.26. Found: C, 67.57; H, 6.89; N, 11.27. Second fraction: 3-Formyl-2-isopropylpyrazolo[1,5-*a*]pyridine (**10′**; 0.60 g, (17%)) was obtained as a by-product, mp 84 °C (recryst. from hexane). ^{1}H-NMR ($CDCl_3$) δ: 1.46 (6H, d, J=6.8 Hz, $CH(CH_3)_2$), 3.60 (1H, m, J=6.8 Hz, $CH(CH_3)_2$), 6.99 (1H, t, J=6.8 Hz, pyrazolopyridine-6-H), 7.47 (1H, dd, J=8.8, 6.8 Hz, pyrazolopyridine-5-H), 8.22 (1H, d, J=8.8 Hz, pyrazolopyridine-4-H), 8.49 (1H, d, J=6.8 Hz, pyrazolopyridine-7-H), 10.15 (1H, s, CHO). MS m/z: 188 (M^+). IR (KBr): 1651 cm^{-1} (C=O). *Anal.* Calcd for $C_{11}H_{12}N_2O$: C, 70.18; H, 6.43; N, 14.88. Found: C, 70.14; H, 6.46; N, 14.79.

2-Isopropyl-3-(1-methoxy-2-methyl-1-propenyl)pyrazolo[1,5-*a*]pyridine (11) Metallic sodium (0.25 g) was dissolved in methanol (10 ml), then **10** (2.5 g) was added. The mixture was refluxed for 30 min and then concentrated under reduced pressure. Water was added to the residue, then the mixture was extracted with CH_2Cl_2. The extract was dried over anhyd. Na_2SO_4 and distilled under reduced pressure (bp 118 °C (3 mmHg)) to give 1.6 g (65%) of **11**. ^{1}H-NMR ($CDCl_3$) δ: 1.34 (6H, d, J=6.8 Hz, $CH(CH_3)_2$), 1.45, 1.86 (3H × 2, s, $=C(CH_3)_2$), 3.20 (1H, m, J=6.8 Hz, $CH(CH_3)_2$), 3.21 (3H, s, OCH_3), 6.67 (1H, td, J=6.8, 1.1 Hz, pyrazolopyridine-6-H), 7.06 (1H, td, J=9.0, 1.1 Hz, pyrazolopyridine-5-H), 7.30 (1H, dd, J=9.0, 1.1 Hz, pyrazolopyridine-4-H), 8.40 (1H, d, J=6.8 Hz, pyrazolopyridine-7-H). *Anal.* Calcd for $C_{15}H_{20}N_2O$: C, 73.75; H, 8.25; N, 11.47. Found: C, 73.53; H, 8.28; N, 11.42.

3-(2-Hydroxy-2-methylpropionyl)-2-isopropylpyrazolo[1,5-*a*]pyridine (M-2) A solution of **11** (1.5 g) in CH_2Cl_2 (10 ml) was treated portion-wise with a solution of *m*-CPBA (1.35 g) in CH_2Cl_2 (20 ml) at 5—10 °C, and then left overnight at room temperature. The precipitate was filtered off and washed with CH_2Cl_2. The filtrate was evaporated *in vacuo* and purified by column chromatography on alumina gel employing benzene as an eluent to give **12**. The compound thus obtained was dissolved in water–isopropanol (1 : 2, 10 ml), to which was added five drops of conc. HCl. This mixture was left at room temperature for 30 min, and then extracted with CH_2Cl_2. The extract was dried over anhyd. Na_2SO_4 and evaporated to dryness. The residue was recrystallized from hexane to afford 1.1 g (73%) of M-2, mp 129.5—130 °C (colorless needles). ^{1}H-NMR ($CDCl_3$) δ: 1.37 (6H, d, J=6.8 Hz, $CH(CH_3)_2$), 1.60 (6H, s, $C(CH_3)_2OH$), 2.98 (1H, s, OH), 3.74 (1H, m, J=6.8 Hz, $CH(CH_3)_2$), 6.88 (1H, td, J=6.8, 1.1 Hz, pyrazolopyridine-6-H), 7.34 (1H, td, J=9.0, 6.8 Hz, pyrazolopyridine-5-H), 8.21 (1H, dd, J=9.0, 1.1 Hz, pyrazolopyridine-4-H), 8.46 (1H, dd, J=6.8, 1.1 Hz, pyrazolopyridine-7-H). MS m/z: 246 (M^+). IR (KBr): 3348—3560 (OH), 1621 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, 68.38; H, 7.49; N, 11.37.

2-Isopropyl-3-propionylpyrazolo[1,5-*a*]pyridine (M-10) A mixture consisting of 2-isopropylpyrazolo[1,5-*a*]pyridine[5] (**29**; 50 g), propionic anhydride (100 ml) and seven drops of conc. H_2SO_4 was refluxed for 6 h. The mixture was poured into 4 N of a KOH water solution (**11**), stirred for 2 h at room temperature, and extracted with CH_2Cl_2. The extract was dried over anhyd. Na_2SO_4 and purified by column chromatography on alumina gel employing benzene as an eluent. The obtained material was distilled under reduced pressure, bp 143—146 °C (3 mmHg) to give 46 g (68%) of oil, which solidified on standing, mp 43—45 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.19 (3H, t, J=7.5 Hz, CH_2CH_3), 1.37 (6H, d, J=7.0 Hz, $CH(CH_3)_2$), 2.89 (2H, q, J=7.5 Hz, CH_2CH_3), 3.40 (1H, m, J=7.0 Hz, $CH(CH_3)_2$), 6.77 (1H, dd, J=7.1, 6.8 Hz, pyrazolopyridine-6-H), 7.23 (1H, dd, J=9.0, 6.8 Hz, pyrazolopyridine-5-H), 7.97 (1H, d, J=9.0 Hz, pyrazolopyridine-4-H), 8.33 (1H, d, J=7.1 Hz, pyrazolopyridine-7-H). MS m/z: 216 (M^+). IR (KBr): 1640 cm^{-1} (C=O). *Anal.* Calcd for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95. Found: C, 72.36; H, 7.49; N, 13.12.

3-(3-Hydroxy-2-methylpropionyl)-2-isopropylpyrazolo[1,5-*a*]pyridine (M-3) Thirty seven percent formalin (3.3 ml) in 1,4-dioxane (11.8 ml) was added to a solution of M-10 (5.0 g), KOH (0.20 g) in water (13.7 ml) with stirring. The resulting solution was heated at 55—57 °C for 20 min and concentrated to dryness. The residue was chromatographed over silica gel employing $CHCl_3$ as the eluent. The eluate was evaporated to dryness and the residue was recrystallized from petroleum ether to afford the title compound in a yield of 3.2 g (56%) as white needles, mp 60—62 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.29 (3H, t, J=7.0 Hz, $CH(CH_3)CH_2OH$), 1.46 (6H, d, J=7.0 Hz, $CH(CH_3)_2$), 2.63 (1H, br, OH), 3.10—3.80 (2H, m, $CH(CH_3)_2$, $CH(CH_3)CH_2OH$), 3.90 (2H, br, CH_2OH), 6.77 (1H, dd, J=7.0, 6.8 Hz, pyrazolopyridine-6-H), 7.29 (1H, dd, J=9.0, 6.8 Hz, pyrazolopyridine-5-H), 7.93 (1H, d, J=9.0 Hz, pyrazolopyridine-4H), 8.37 (1H, d, J=7.0 Hz, pyrazolopyridine-7-H). MS m/z: 246 (M^+). IR (KBr): 3210—3490 (OH), 1641 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, 68.10; H, 7.32; N, 11.20.

Methyl (3-Methoxycarbonylpyrazolo[1,5-*a*]pyridine-2-yl)acetate (13) A mixture of 1-aminopyridinium iodide (30 g), K_2CO_3 (15 g) and β-ketoglutaric acid dimethyl ester (25 g) in DMF (150 ml) was stirred at room temperature for 2 h. The solution was extracted with diethyl ether

and washed with water. The extract was concentrated under reduced pressure and recrystallized from hexane to give 16.1 g (48%) of **13** as white needles, mp 82—85 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.73, 3.89 (3H × 2, s, CH_3), 4.14 (2H, s, $CH_2CO_2CH_3$), 6.94 (1H, td, J=6.8, 1.1 Hz, pyrazolopyridine-6-H), 7.45 (1H, td, J=9.0, 1.1 Hz, pyrazolopyridine-5-H), 8.12 (1H, dd, J=9.0, 1.1 Hz, pyrazolopyridine-4-H), 8.48 (1H, dd, J=6.8, 1.1 Hz, pyrazolopyridine-7-H). MS m/z: 248 (M^+), IR (KBr): 1725, 1640 cm^{-1} (C=O). *Anal.* Calcd for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.28. Found: C, 58.01; H, 4.59; N, 11.27.

Methyl 2-(3-Methoxycarbonylpyrazolo[1,5-*a*]pyridine-2-yl)propionate (14) A solution of **13** (6.0 g) and methyl iodide (12.4 g) in CH_2Cl_2 (40 ml) was added dropwise to a stirred solution of NaOH (3.5 g) and tetrabutylammonium hydrogen sulfate (15.0 g) in water (36 ml). Stirring was continued for an additional 4 h at room temperature, and the reaction mixture was extracted with CH_2Cl_2. The extract was dried over anhyd. Na_2SO_4, and concentrated. The residue was dissolved in diethyl ether and the insoluble material filtered off, then the filtrate was evaporated to dryness to give 5.5 g (87%) of **14** as pale yellow needles, mp 65—67 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.66 (3H, d, J=7.5 Hz, $CH(CH_3)CO_2CH_3$), 3.70, 3.89 (3H × 2, s, CO_2CH_3), 4.57 (1H, q, J=7.5 Hz, $CH(CH_3)CO_2CH_3$), 6.91 (1H, dd, J=7.9, 7.0 Hz, pyrazolopyridine-6-H), 7.39 (1H, dd, J=8.8, 7.9 Hz, pyrazolopyridine-5-H), 8.10 (1H, d, J=8.8 Hz, pyrazolopyridine-4-H), 8.45 (1H, d, J=7.0 Hz, pyrazolopyridine-7-H). MS m/z: 262 (M^+). IR (KBr): 1722, 1638 cm^{-1} (C=O). *Anal.* Calcd for $C_{13}H_{14}N_2O_4$: C, 59.54; H, 5.38; N, 10.68. Found: C, 59.57; H, 5.36; N, 10.71.

2-(3-Carboxypyrazolo[1,5-*a*]pyridine-2-yl)propionic Acid (15) Compound **14** (5.5 g) was added to a solution of NaOH (10 g) in water (100 ml), and stirred at 70 °C for 4 h. After cooling, the solution was acidified with conc. HCl, and the resulting precipitate was filtered and washed with water. The obtained solid was dried under vacuum to give 4.0 g (81%) of **15** as a white powder, mp 194—197 °C. ^{1}H-NMR (d_6-DMSO) δ: 1.51 (3H, d, J=7.0 Hz, $CH(CH_3)CO_2H$), 4.49 (1H, q, J=7.0 Hz, $CH(CH_3)CO_2H$), 7.08 (1H, dd, J=7.0, 6.8 Hz, pyrazolopyridine-6-H), 7.52 (1H, dd, J=8.8, 6.8 Hz, pyrazolopyridine-5-H), 8.04 (1H, d, J=8.8 Hz, pyrazolopyridine-4-H), 8.77 (1H, d, J=7.0 Hz, pyrazolopyridine-7-H), 12.37 (2H, br, CO_2H). MS m/z: 234 (M^+). IR (KBr): 1733, 1645 cm^{-1} (C=O).

Ethyl 2-(Pyrazolo[1,5-*a*]pyridine-2-yl)propionate (16) Compound **15** (4.0 g) was added to a solution of ethanol (60 ml) and conc. H_2SO_4 (4 ml), and refluxed for 4 h. The reaction mixture was evaporated to dryness and dissolved in $CHCl_3$. The organic layer was washed with water, dried over anhyd. Na_2SO_4, and thoroughly evaporated to dryness to give 3.5 g (94%) of **16** as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, J=7.0 Hz, $CH(CH_3)CO_2CH_2CH_3$), 1.62 (3H, d, J=7.3 Hz, $CH(CH_3)CO_2Et$), 4.03 (1H, q, J=7.3 Hz, $CH(CH_3)CO_2Et$), 4.18 (2H, q, J=7.0 Hz, $CH(CH_3)CO_2CH_2CH_3$), 6.43 (1H, s, pyrazolopyridine-3-H), 6.68 (1H, ddd, J=6.8, 6.6, 1.5 Hz, pyrazolopyridine-6-H), 7.04 (1H, ddd, J=8.8, 6.6, 1.1 Hz, pyrazolopyridine-5-H), 7.44 (1H, dd, J=8.8, 1.5 Hz, pyrazolopyridine-4-H), 8.39 (1H, dd, J=6.8, 1.1 Hz, pyrazolopyridine-7-H). MS m/z: 218 (M^+). IR (NaCl): 1722 cm^{-1} (C=O).

Ethyl (Pyrazolo[1,5-*a*]pyridine-2-yl)acetate (18) Compound **18** was obtained from **13** was methylated in the same manner as that of **14**. The mixture of the mono (**16**) and dimethylated compound (**16'**) was produced and the two were difficult to separate.

Compound **18**: ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, J=7.0 Hz, CH_2CH_3), 3.86 (2H, s, CH_2CO_2Et), 4.18 (2H, q, J=7.0 Hz, CH_2CH_3), 6.45 (1H, s, pyrazolopyridine-3-H), 6.63 (1H, ddd, J=7.0, 6.8, 1.2 Hz, pyrazolopyridine-6-H), 7.05 (1H, ddd, J=9.0, 6.8, 1.0 Hz, pyrazolopyridine-5-H), 7.41 (1H, dd, J=9.0, 1.2 Hz, pyrazolopyridine-4-H), 8.37 (1H, dd, J=7.0, 1.0 Hz, pyrazolopyridine-7-H).

Compound **16**: The NMR spectroscopic data was identical with that of sample (**16**) obtained by the foregoing procedure.

Compound **16'**: ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, t, J=7.0 Hz, CH_2CH_3), 1.70 (6H, s, $C(CH_3)_2CO_2Et$), 4.23 (2H, q, J=7.0 Hz, CH_2CH_3), 6.45 (1H, s, pyrazolopyridine-3-H), 6.68 (1H, ddd, J=6.8, 6.6, 1.5 Hz, pyrazolopyridine-6-H), 7.04 (1H, ddd, J=8.8, 6.6, 1.1 Hz, pyrazolopyridine-5-H), 7.44 (1H, dd, J=8.8, 1.5 Hz, pyrazolopyridine-4-H), 8.39 (1H, dd, J=6.8, 1.1 Hz, pyrazolopyridine-7-H).

2-(2-Hydroxyl-1-methylethyl)pyrazolo[1,5-*a*]pyridine (17) Sodiumborohydride (7.0 g) was added into a solution of **16** (3.5 g) in methanol (50 ml) by portions. The mixture was refluxed for 3 h, then concentrated under reduced pressure, diluted with water and extracted with $CHCl_3$. The extract was dried over anhyd. Na_2SO_4 and then concentrated. The residue was purified by column chromatography on silica gel employing CH_2Cl_2–AcOEt (9 : 1) as an eluent to give 2.8 g (99%) of **17** in the form of a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.37 (3H, d, J=7.0 Hz, $CH(CH_3)CH_2OH$), 3.00—3.40 (2H, m, $CH(CH_3)CH_2OH$), 3.82 (2H, br, $CH(CH_3)CH_2OH$), 6.34 (1H, s, pyrazolopyridine-3-H), 6.67 (1H, ddd, J=6.8, 6.6, 1.3 Hz, pyrazolopyridine-6-H), 7.06 (1H, ddd, J=8.8, 1.3, 0.9 Hz, pyrazolopyridine-5-H), 7.45 (1H, dd, J=8.8, 1.3 Hz, pyrazolopyridine-4-H), 8.35 (1H, dd, J=6.8, 0.9 Hz, pyrazolopyridine-7-H). MS m/z: 176 (M^+). IR (NaCl): 3360—3580 (OH), 1505, 1320 cm^{-1}. *Anal.* Calcd for $C_{10}H_{12}N_2O$: C, 68.16; H, 6.86; N, 15.90. Found: C, 68.02, H, 6.69; N, 15.92.

2-(2-Hydroxy-1-methylethyl)-3-propionylpyrazolo[1,5-*a*]pyridine (19) Three drops of conc. H_2SO_4 were added to a solution of **17** (5.8 g) in propionic anhydride (30 ml) and refluxed for 8 h. The mixture was poured into 10% NaOH (150 ml) and stirred at 60 °C for 3 h, then extracted with $CHCl_3$. The extract was dried over anhyd. Na_2SO_4 and evaporated to dryness. The residue obtained was chromatographed on silica gel employing CH_2Cl_2–AcOEt (5 : 1) as an eluent to give 3.8 g (50%) of **19**, mp 74—76 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.26 (3H, t, J=7.0 Hz, $COCH_2CH_3$), 1.40 (3H, d, J=7.0 Hz, $CH(CH_3)CH_2OH$), 2.96 (2H, q, J=7.0 Hz, $COCH_2CH_3$), 3.22 (1H, m, $CH(CH_3)CH_2OH$), 3.94 (3H, br, $CH(CH_3)CH_2OH$), 6.93 (1H, td, J=7.0, 1.3 Hz, pyrazolopyridine-6-H), 7.42 (1H, td, J=9.0, 1.1 Hz, pyrazolopyridine-5-H), 8.04 (1H, dd, J=9.0, 1.3 Hz, pyrazolopyridine-4-H), 8.47 (1H, dd, J=7.0, 1.1 Hz, pyrazolopyridine-7-H). *Anal.* Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.18; H, 6.90; N, 11.93.

2-(2-Hydroxy-1-methylethyl)-3-(3-hydroxy-2-methylpropionyl)pyrazolo[1,5-*a*]pyridine (M-17) Thirty seven percent formalin (3.8 ml) was added dropwise to a stirred solution of **19** (3.8 g), KOH (0.38 g) in 1,4-dioxane (100 ml). Sitrring was continued at 45—50 °C for 1 h, and then the mixture was poured into ice-cold water. The mixture was extracted with $CHCl_3$, dried over anhyd. Na_2SO_4, and evaporated to dryness. The residue thus obtained was chromatographed on a silica gel employing CH_2Cl_2–AcOEt–MeOH (10 : 2 : 1) as an eluent to give 2.1 g (49%) of the title compound, mp 68—70 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.28 (3H, d, J=7.0 Hz, $CH(CH_3)CH_2OH$), 1.39 (3H, m, $COCH(CH_3)CH_2OH$), 2.78 (1H, br, $COCH(CH_3)CH_2OH$), 3.19 (1H, br, $CH(CH_3)CH_2OH$), 3.50 (1H, m, $COCH(CH_3)CH_2OH$), 3.93 (5H, m, $COCH(CH_3)CH_2OH$, $CH(CH_3)CH_2OH$), 6.96 (1H, dd, J=6.8, 6.6 Hz, pyrazolopyridine-6-H), 7.43 (1H, dd, J=8.8, 6.6 Hz, pyrazolopyridine-5-H), 8.02 (1H, d, J=8.8 Hz, pyrazolopyridine-4-H), 8.49 (1H, d, J=6.8 Hz, pyrazolopyridine-7-H). MS m/z: 262 (M^+). IR (KBr) 3150—3480 (OH), 1637 cm^{-1} (C=O). *Anal.* Calcd for $C_{14}H_{18}N_2O_3$: C, 64.10; H, 6.92; N, 10.68. Found: C, 64.08; H, 6.90; N, 10.67.

2-(2-Hydroxy-1-methylethyl)-3-isobutyrylpyrazolo[1,5-*a*]pyridine (20) Three drops of conc. H_2SO_4 were added to a solution of **17** (18.0 g) in isobutyric anhydride (30 ml), refluxed for 8 h, and then concentrated. The residue was treated with 10% aq. NaOH (150 ml) and a small amount of ethanol at 60 °C for 3 h, and extracted with CH_2Cl_2. The extract was dried over anhyd. Na_2SO_4 and evaporated to dryness. The residue was chromatographed on a silica gel employing CH_2Cl_2–AcOEt–MeOH (7 : 2 : 1) as an eluent to give 16.0 g (64%) of **20**. ^{1}H-NMR ($CDCl_3$) δ: 1.33 (6H, d, J=6.8 Hz, $COCH(CH_3)_2$), 1.40 (3H, d, J=6.6 Hz, $CH(CH_3)CH_2OH$), 3.10—3.50 (2H, m, $COCH(CH_3)_2$, $CH(CH_3)CH_2OH$), 3.95 (3H, br, $CH(CH_3)CH_2OH$), 6.93 (1H, ddd, J=6.8, 6.6, 1.3 Hz, pyrazolopyridine-6-H), 7.43 (1H, ddd, J=9.0, 6.6, 1.1 Hz, pyrazolopyridine-5-H), 7.97 (1H, dd, J=9.0, 1.3 Hz, pyrazolopyridine-4-H), 8.48 (1H, dd, J=6.8, 1.1 Hz, pyrazolopyridine-7-H). MS m/z: 246 (M^+). IR (NaCl): 3360—3590 (OH), 1619 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, 68.31; H, 7.36; N, 11.31.

3-(2-Acetyloxy-2-methylpropionyl)-2-(2-hydroxy-1-methylethyl)pyrazolo[1,5-*a*]pyridine (21) Lead tetraacetate (5.4 g) was added to a stirred solution of **20** (3.0 g) in acetic acid (20 ml). Stirring was continued for an additional 2 h at room temperature, and the reaction mixture was poured into ice-cold water and then extracted with ether. The extract was washed with water and dried over anhyd. Na_2SO_4, and then concentrated. The residue was subjected to silica gel column chromatography and eluted with CH_2Cl_2–AcOEt (9 : 1) to give 1.1 g (30%) of **21** as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.38 (3H, d, J=6.6 Hz, $CH(CH_3)CH_2OH$), 1.74 (6H, s, $COC(CH_3)_2OAc$), 1.82 (3H, s, $COCH_3$), 3.30 (1H, br, OH), 3.90 (1H, br, $CH(CH_3)CH_2OH$), 3.93 (2H, br, $CH(CH_3)CH_2OH$), 6.89 (1H, ddd, J=6.8, 6.6, 1.3 Hz, pyrazolopyridine-6-H), 7.40 (1H, ddd, J=9.0, 6.6, 1.1 Hz, pyrazolopyridine-5-H), 8.19 (1H, dd, J=9.0, 1.3 Hz, pyrazolopyridine-4-H), 8.46 (1H, dd, J=6.8, 1.1 Hz, pyrazolopyridine-7-H). MS m/z: 304 (M^+).

2-(2-Hydroxy-1-methylethyl)-3-(2-hydroxy-2-methylpropionyl)pyrazolo[1,5-*a*]pyridine (M-18) A mixture of **21** (1.1 g), 10% NaOH water solution (50 ml) and a small amount of ethanol was stirred at 60 °C for

2 h, and then poured into ice-cold water. The reaction mixture was made slightly acidic with conc. HCl and was extracted with $CHCl_3$. The extract was washed with water, dried over anhyd. Na_2SO_4, and concentrated. The residue was chromatographed on silica gel employing CH_2Cl_2–AcOEt (5:1) and then CH_2Cl_2–AcOEt–MeOH (7:2:1) as an eluent to give 0.3 g (32%) of M-18. ^{1}H-NMR ($CDCl_3$) δ: 1.32 (3H, d, J=6.0 Hz, $CH(CH_3)CH_2OH$), 1.56 (6H, s, $COC(CH_3)_2OH$), 3.81 (2H, br, $CH(CH_3)CH_2OH$), 4.11 (1H, m, $CH(CH_3)CH_2OH$), 6.90 (1H, ddd, J=6.8, 6.6, 1.2 Hz, pyrazolopyridine-6-H), 7.36 (1H, ddd, J=9.0, 6.6, 1.1 Hz, pyrazolopyridine-5-H), 8.31 (1H, dd, J=9.0, 1.2 Hz, pyrazolopyridine-4-H), 8.43 (1H, dd, J=6.8, 1.1 Hz, pyrazolopyridine-7-H). MS m/z: 262 (M^+). IR (KBr): 1633 (C=O), 3200—3690 cm^{-1} (OH). *Anal.* Calcd for $C_{14}H_{18}N_2O_3$: C, 64.10; H, 6.92; N, 10.68. Found: C, 64.39; H, 6.73, N, 10.43.

2-(2-Chloro-1-methylethyl)-3-isobutyrylpyrazolo[1,5-*a*]pyridine (22) A solution of thionyl chloride (2 ml) in $CHCl_3$ (3 ml) was added to a solution of **20** (3.0 g) and pyridine (1 ml) in $CHCl_3$ (5 ml) under stirring, and then refluxed for 1 h. The reaction mixture was poured into ice-cold water and extracted with $CHCl_3$. The organic layer was washed with water and dried over anhyd. Na_2SO_4, and then concentrated. The residue was purified by column chromatography on silica gel employing CH_2Cl_2–AcOEt (9:1) as an eluent to give 2.5 g (78%) of **22** in the form of a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.26 (6H, d, J=6.8 Hz, $CH(CH_3)_2$), 1.50 (3H, d, J=6.8 Hz, $CH(CH_3)CH_2Cl$), 3.33 (1H, m, J=6.8 Hz, $CH(CH_3)_2$), 3.80—4.10 (3H, m, $CH(CH_3)CH_2Cl$), 6.92 (1H, ddd, J=6.8, 6.6, 1.1 Hz, pyrazolopyridine-6-H), 7.43 (1H, ddd, J=9.0, 6.6, 1.1 Hz, pyrazolopyridine-5-H), 7.95 (1H, dd, J=9.0, 1.3 Hz, pyrazolopyridine-4-H), 8.49 (1H, dd, J=6.8, 1.1 Hz, pyrazolopyridine-7-H). MS m/z: 264 (M^+).

2-(1-Methylvinyl)-3-isobutyrylpyrazolo[1,5-*a*]pyridine (24) Compound **22** (2.5 g) was added to the reagent prepared from 1.0 g of sodium and 20 ml of methanol with stirring, and then refluxed for 2 h. The reaction mixture was poured into ice-cold water and extracted with $CHCl_3$. The extract was dried over anhyd. Na_2SO_4 and then concentrated. The residue was chromatographed twice over silica gel employing CH_2Cl_2–AcOEt (9:1) as an eluent. The eluate was evaporated to dryness to afford the title compound in a yield of 0.80 g (37%). ^{1}H-NMR ($CDCl_3$) δ: 1.16 (6H, d, J=6.8 Hz, $CH(CH_3)_2$), 2.26 (3H, s, $C(CH_3)=CH_2$), 3.49 (1H, m, J=6.8 Hz, $CH(CH_3)_2$, 5.28, 5.49 (2H, s, $=CH_2$), 6.95 (1H, ddd, J=6.8, 6.6, 1.1 Hz, pyrazolopyridine-6-H), 7.42 (1H, ddd, J=9.0, 6.6, 1.1 Hz, pyrazolopyridine-5-H), 8.26 (1H, dd, J=9.0, 1.3 Hz, pyrazolopyridine-4-H), 8.45 (1H, dd, J=6.8, 1.1 Hz, pyrazolopyridine-7-H). MS m/z: 228 (M^+).

This compound could also be synthesized in the following manner. A mixture of **17** (1.0 g) and potassium hydrogensulfate (10.0 g) in toluene (100 ml) was refluxed for 7 h, and then evaporated to dryness. To the residue was added water, followed by extraction with $CHCl_3$. The extract was dried over anhyd. Na_2SO_4 and purified by column chromatography on silica gel employing benzene–hexane (4:1) as an eluent to give 0.65 g (72%) of **23** in the form of colorless needles, mp 34—36 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.24 (3H, d, J=0.9 Hz, $C(CH_3)=CH_2$), 5.20 and 5.76 (2H, d, J=0.9 Hz, $=CH_2$), 6.56 (1H, d, J=0.9 Hz, pyrazolopyridine-3-H), 6.67 (1H, td, J=6.8, 1.3 Hz, pyrazolopyridine-6-H), 7.04 (1H, td, J=9.0, 1.1 Hz, pyrazolopyridine-5-H), 7.43 (1H, dt, J=9.0, 1.1 Hz, pyrazolopyridine-4-H), 8.39 (1H, dq, J=6.8, 1.3, 0.9 Hz, pyrazolopyridine-7-H). Compound **23** was treated with isobutyric anhydride and conc. H_2SO_4 and was worked up in the previously mentioned manner to afford **24** in a 53% yield.

2-(1,2-Dihydroxy-1-methylethyl)-3-isobutyrylpyrazolo[1,5-*a*]pyridine (M-19) A solution of potassium permanganate (1.0 g) in water (2 ml) and acetone (20 ml) was added dropwise to the solution of **24** (0.70 g) in acetone (3 ml) at −5 °C with stirring. Stirring was continued for an additional 30 min, then the mixture was left for 1 h. The precipitated MnO_2 was filtered off, and the filtrate was extracted with $CHCl_3$. The extract was dried over anhyd. Na_2SO_4, and then concentrated. The residue was chromatographed over silica gel employing CH_2Cl_2–AcOEt–MeOH (8:1.5:0.5) as the eluent. The eluate was evaporated to dryness and the residue was recrystallized from benzene–hexane to afford the title compound in a yield of 0.12 g (15%) as white needles, mp 122—124 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (6H, d, J=6.8 Hz, $CH(CH_3)_2$), 1.58 (3H, s, CH_3), 2.92 (1H, br, OH), 3.46 (1H, m, J=6.8 Hz, $CH(CH_3)_2$), 3.93 (2H, br, CH_2OH), 7.02 (1H, ddd, J=6.8, 6.6, 1.1 Hz, pyrazolopyridine-6-H), 7.24 (1H, s, OH), 7.54 (1H, dd, J=9.0, 6.6 Hz, pyrazolopyridine-5-H), 7.86 (1H, d, J=9.0 Hz, pyrazolopyridine-4-H), 8.53 (1H, dd, J=6.8, 1.1 Hz, pyrazolopyridine-7-H). MS m/z: 262 (M^+). IR (KBr): 3300—3680 (OH), 1621 cm^{-1} (C=O). *Anal.* Calcd for $C_{14}H_{18}N_2O_3$: C, 64.10; H, 6.92; N, 10.68. Found: C, 63.83; H, 6.87; N, 10.56.

2-Methoxycarbonyl-3-propionylpyrazolo[1,5-*a*]pyridine (25) The title compound was prepared by following the same procedure as described for **4**. The yield is 63% and the characteristics of the product are mp 93—94 °C (recryst. from hexane–benzene) and colorless needles. ^{1}H-NMR ($CDCl_3$) δ: 1.21 (3H, t, J=7.0 Hz, $COCH_2CH_3$), 3.04 (2H, q, J=7.0 Hz, $COCH_2CH_3$), 4.06 (3H, s, CO_2CH_3), 7.05 (1H, td, J=7.0, 1.0 Hz, pyrazolopyridine-6-H), 7.48 (1H, td, J=9.2, 7.0, 1.0 Hz, pyrazolopyridine-5-H), 8.34 (1H, d, J=7.2 Hz, pyrazolopyridine-4-H), 8.51 (1H, d, J=7.0 Hz, pyrazolopyridine-7-H). MS m/z: 232 (M^+). IR (KBr): 1735, 1650 cm^{-1} (C=O). *Anal.* Calcd for $C_{12}H_{12}N_2O_3$: C, 62.02; H, 5.21; N, 12.06. Found: C, 61.90; H; 5.16; N, 12.00.

2-(1-Hydroxy-1-methylethyl)-3-propionylpyrazolo[1,5-*a*]pyridine (26) Compound **25** was treated with the Grignard reagent in the same manner as described for M-1 and was obtained in a 38% yield. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (3H, t, J=7.0 Hz, $COCH_2CH_3$), 1.66 (6H, s, $C(CH_3)_2OH$), 3.04 (2H, q, $COCH_2CH_3$), 6.98 (1H, td, J=7.0, 1.0 Hz, pyrazolopyridine-6-H), 7.50 (1H, td, J=9.2, 7.0, 1.0 Hz, pyrazolopyridine-5-H), 7.89 (1H, d, J=9.2 Hz, pyrazolopyridine-4-H), 8.51 (1H, d, J=7.0 Hz, pyrazolopyridine-7-H). MS m/z: 232 (M^+).

1,2,3,5-Tetrahydro-2-hydroxymethyl-2,5,5-trimethyl-1-oxooxepino-[3,4-*c*]pyrazolo[1,5-*a*]pyridine (28) and 1,2,3,5-Tetrahydro-2,5,5-trimethyl-1-oxooxepino[3,4-*c*]pyrazolo[1,5-*a*]pyridine (27) A solution of formalin (0.15 ml) in 1,4-dioxane (0.6 ml) was added dropwise to a solution of **26** (0.20 g), KOH (10 mg) in water (0.6 ml) and 1,4-dioxane (2 ml) with stirring. The mixture was stirred at a temperature 55 to 65 °C for 3 h, then poured into ice-cold water and extracted with $CHCl_3$. The extract was washed with water, dried over anhyd. Na_2SO_4, and after removal of the solvent, the residue was chromatographed over silica gel employing a CH_2Cl_2–AcOEt (9:1) mixture as the eluent. First fraction: Recrystallization from benzene–hexane gave **28** (0.10 g, 42%) as white leaflets, mp 130—134 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.18 (3H, s, CH_3), 1.70 (6H, s, $C(CH_3)_2O$–), 3.00 (1H, br, CH_2OH), 3.80—4.00 (4H, CH_2OH, $-CH_2O$–), 7.01 (1H, td, J=7.0, 1.0 Hz, pyrazolopyridine-6-H), 7.47 (1H, td, J=7.0, 1.0 Hz, pyrazolopyridine-5-H), 8.44 (2H, dd, J=7.0, 1.0 Hz, pyrazolopyridine-4-, 7-H). MS m/z: 274 (M^+). IR (KBr): 3300—3600 (OH), 1638 cm^{-1} (C=O). *Anal.* Calcd for $C_{15}H_{18}N_2O_3$: C, 65.67; H, 6.61; N, 10.21. Found: C, 65.55; H, 6.62; N, 10.30. Second fraction: Recrystallization from benzene–hexane gave 20 mg of **27** as white prisms, mp 136—139 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.28 (3H, d, J=7.5 Hz, $CH(CH_3)CH_2O$–), 1.70 (6H, s, $C(CH_3)_2O$–), 1.68 (1H, m, $CH(CH_3)CH_2$–), 3.88—4.01 (2H, CH_2O–), 6.98 (1H, td, J=7.0, 1.3 Hz, pyrazolopyridine-6-H), 7.44 (1H, t, J=7.0 Hz, pyrazolopyridine-5-H), 8.42 (2H, d, J=7.5 Hz, pyrazolopyridine-4, 7-H). MS m/z: 244 (M^+). IR (KBr): 1640 (C=O), 1500 cm^{-1}. *Anal.* Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.86; H, 6.61; N, 11.43.

2-(1-Hydroxy-1-methylethyl)-3-(3-hydroxy-2-methylpropionyl)pyrazolo-[1,5-*a*]pyridine (M-5) Thirty seven percent formalin (0.1 ml) was added dropwise to a solution of **26** (0.10 g) and KOH (10 mg) in 1,4-dioxane (3 ml) was stirring. The mixture was stirred at about 50 °C for 1 h then poured into ice-water and extracted with $CHCl_3$. The extract was dried over anhyd. Na_2SO_4 and after removal of the solvent, the residue was chromatographed over silica gel employing a CH_2Cl_2–AcOEt (9:1) mixture and then a MeOH containing solvent as the eluent. The eluate was evaporated to dryness and the residue was recrystallized from hexane–benzene to afford the title compound in a yield of 48 mg (43%) as white plates, mp 130—133 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.31 (3H, d, J=7.0 Hz, $CH(CH_3)CH_2OH$), 1.66 (6H, sd, J=2.2 Hz, $C(CH_3)_2OH$), 2.40 (1H, br, CH_2OH), 3.60 (1H, m, $CH(CH_3)CH_2OH$), 3.89 (2H, dd, J=9.7, 7.0 Hz, CH_2OH), 6.87 (1H, s, $C(CH_3)_2OH$), 6.97 (1H, td, J=7.0, 1.3 Hz, pyrazolopyridine-6-H), 7.50 (1H, td, J=9.0, 6.6, 1.3 Hz, pyrazolopyridine-5-H), 7.89 (1H, d, J=9.0 Hz, pyrazolopyridine-4-H), 8.51 (1H, dd, J=7.0, 1.3 Hz, pyrazolopyridine-7-H). MS m/z: 262 (M^+). IR (KBr): 3500—3600 (OH), 1625 cm^{-1} (C=O). *Anal.* Calcd for $C_{14}H_{18}N_2O_3$: C, 64.10; H, 6.92; N, 10.68. Found: C, 63.80; H, 7.01; N, 10.65.

2-Isopropyl-3-(2-methoxycarbonylpropionyl)pyrazolo[1,5-*a*]pyridine (31) Sodium hydride (55%, 6.0 g) was added in a small portion to a solution of M-10 (9.0 g) in dimethyl carbonate (60 ml) with stirring. After the addition was completed, the mixture was refluxed for 1 h, then poured into ice-cold water and extracted with $CHCl_3$. The extract was dried over anhyd. Na_2SO_4, and after removal of the solvent, the residue was chromatographed over silica gel employing a $CHCl_3$–AcOEt (20:1) mixture as an eluent. The eluate was evaporated to dryness and the residue was recrystallized from hexane to afford the title compound in a yield of 11.0 g (96%), as white needles mp 64—65 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.41 (6H, d, J=6.8 Hz, $CH(CH_3)_2$), 1.53 (3H, d, J=7.0 Hz, COCH-

($C\underline{H}_3$)CO_2CH_3), 3.71 (1H, m, J=6.8 Hz, $C\underline{H}(CH_3)_2$), 3.71 (3H, s, $COCH(CH_3)CO_2C\underline{H}_3$), 4.28 (1H, q, J=7.0 Hz, $COC\underline{H}(CH_3)CO_2CH_3$), 6.93 (1H, td, J=6.8, 1.3 Hz, pyrazolopyridine-6-H), 7.43 (1H, td, J=9.0, 6.8, 1.3 Hz, pyrazolopyridine-5-H), 8.09 (1H, d, J=9.0 Hz, pyrazolopyridine-4-H), 8.49 (1H, d, J=7.0 Hz, pyrazolopyridine-7-H). MS m/z: 274 (M^+). IR (KBr): 1741, 1632 cm^{-1} (C=O). *Anal.* Calcd for $C_{15}H_{18}N_2O_3$: C, 65.67; H, 6.61; N, 10.21. Found: C, 65.77; H, 6.68; N, 10.25.

3-(2-Carboxypropionyl)-2-isopropylpyrazolo[1,5-*a*]pyridine (M-8) A mixture of **31** (0.5 g), methanol (5 ml), KOH (0.5 g) and water (0.5 ml) was stirred under cooling in an ice-water bath and the temperature of the solution was raised to room temperature, where it was maintained for 23 h. The solvent was removed *in vacuo* by the use of a water aspirator (bath temp. below 35 °C). Water was added to the residue followed by washing with $CHCl_3$. The aqueous layer was made acidic with dil. HCl under cooling. The extract was washed with water, dried over anhyd. Na_2SO_4, and after removal of the solvent at the temperature below 20 °C the residue was washed with hexane to afford the title compound in a yield of 0.31 g (65%), mp 82—84 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.40 (6H, d, J=7.0 Hz, $CH(C\underline{H}_3)_2$), 1.62 (3H, d, J=7.0 Hz, $CH(C\underline{H}_3)CO_2H$), 3.73 (1H, m, J=7.0 Hz, $C\underline{H}(CH_3)_2$), 4.25 (1H, q, J=7.0 Hz, $C\underline{H}(CH_3)CO_2H$), 7.01 (1H, td, J=6.8, 1.0 Hz, pyrazolopyridine-6-H), 7.52 (1H, td, J=9.0, 1.0 Hz, pyrazolopyridine-5-H). 8.10 (1H, d, J=9.0 Hz, pyrazolopyridine-4-H), 8.56 (1H, dd, J=6.8, 1.0 Hz, pyrazolopyridine-7-H), 8.82 (1H, br, CO_2H). *Anal.* Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.83; H, 6.25; N, 10.76. Compound M-8 was unstable and decomposed gradually into M-10 at room temperature.

2-(3-Isobutyrylpyrazolo[1,5-*a*]pyridine-2-yl)propionic Acid (M-7) Three drops of conc. H_2SO_4 were added to a solution of **16** (1.2 g) in isobutyric anhydride (20 ml) and refluxed for 8 h. The mixture was poured into 10% aq. NaOH (300 ml) and stirred at 60 °C for 2 h. The mixture was made acidic with conc. HCl and then extracted with $CHCl_3$. The extract was dried over anhyd. Na_2SO_4 and evaporated to dryness. The residue obtained was chromatographed on a silica gel employing CH_2Cl_2–AcOEt–MeOH (8:1.5:0.5) as an eluent to give 1.1 g (74%) of the title compound, mp 80—82 °C (recryst. from hexane–CH_2Cl_2). ^{1}H-NMR ($CDCl_3$) δ: 1.25 (6H, d, J=7.0 Hz, $CH(C\underline{H}_3)_2$), 1.68 (3H, d, J=7.5 Hz, $CH(C\underline{H}_3)CO_2H$), 3.35 (1H, m, J=7.0 Hz, $C\underline{H}(CH_3)_2$), 4.52 (1H, q, J=7.5 Hz, $C\underline{H}(CH_3)CO_2H$), 6.97 (1H, dd, J=7.0, 6.8 Hz, pyrazolopyridine-6-H), 7.45 (1H, dd, J=9.0, 6.8 Hz, pyrazolopyridine-5-H), 7.85 (1H, d, J=9.0 Hz, pyrazolopyridine-4-H), 8.58 (1H, d, J=7.0 Hz, pyrazolopyridine-7-H), 10.05 (1H, br, CO_2H). MS m/z: 260 (M^+). IR (KBr): 1731, 1639 cm^{-1} (C=O). *Anal.* Calcd for $C_{14}H_{16}N_2O_3 \cdot 1/2H_2O$: C, 62.44; H, 6.36; N, 10.40. Found: C, 62.69; H, 6.28; N, 10.34.

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