(12) G. A. Omura, W. R. Vogler, R. V. Smalley, N. Maldonado, G. O. Broun, W. H. Knospe, Y. S. Ahn, and G. B. Faguet, *Cancer Treat. Rep.*, **61**, 1379 (1977).
(13) G. A. LePage and A. Khaliq, *Cancer Treat. Rep.*, submitted (1978).
(14) T. Tamaoki and G. A. LePage, *Cancer Res.*, **35**, 1015 (1975).
(15) The nucleoside antibiotic aristeromycin offers a precedent for replacement of the furanose O of adenosine with CH_2 in an active molecule; R. J. Suhadolnik, "Nucleoside Antibiotics", Wiley-Interscience, New York, 1970, p 236.
(16) This concept has been advanced independently for an α-nucleoside which had a 2′ substituent; D. Horton and M. Sakata, *Carbohydr. Res.*, **48**, 41 (1976).
(17) A. Rosenthal and C. M. Richards, *Carbohydr. Res.*, **32**, 67 (1974).
(18) D. H. R. Barton and R. Subramanian, *J. Chem. Soc., Perkin Trans. 1*, 1718 (1977).
(19) D. H. R. Barton and S. W. McCombie, *J. Chem. Soc., Perkin Trans. 1*, 1574 (1975).
(20) J. Hildesheim, J. Clêophax, A.-M. Sepulchre, and S. D. Gero, *Carbohydr. Res.*, **9**, 315 (1969).
(21) Unreactivity of the C-2 sulfonyloxy group on pyranose rings was recently attributed to torsional strain and dipolar effects owing to use of the unfavored anomer in the attempted nucleophilic displacements that have been reported; M. Miljkovic, M. Gligorijevic, and D. Glisin, *J. Org. Chem.*, **39**, 3223 (1974).
(22) R. Ranganathan, *Tetrahedron Lett.*, 1291 (1977); this is a promising approach to 2′-deoxynucleosides if the 2′-thioacetate that is produced can be successfully desulfurized.
(23) A. Rosenthal and M. Sprinzl, *Can. J. Chem.*, **47**, 4477 (1969).
(24) A. Rosenthal and D. A. Baker, *J. Org. Chem.*, **38**, 198 (1973).
(25) D. C. Baker, D. Horton, and C. G. Tindall, Jr., *Carbohydr. Res.*, **24**, 192 (1972).
(26) J. S. Jewell and W. A. Szarek, *Tetrahedron Lett.*, **43** (1969).
(27) D. C. Baker, D. K. Brown, D. Horton, and R. G. Nickol, *Carbohydr. Res.*, **32**, 299 (1974).
(28) M. Funabashi, H. Sato, J. Yoshimura, *Bull. Chem. Soc. Jpn.*, **49**, 788 (1976).
(29) B. Fleming and H. I. Bolker, *Can. J. Chem.*, **52**, 888 (1974).
(30) D. H. Hollenberg, K. A. Watanabe, and J. J. Fox, *Carbohydr. Res.*, **42**, 241 (1975).
(31) W. W. Lee, A. P. Martinez, L. Goodman, and D. W. Henry, *J. Org. Chem.*, **37**, 2923 (1972).
(32) L. B. Townsend, *Synth. Proced. Nucleic Acid Chem., 1968-1973*, **2**, 299–301, 336–338 (1973). The exceptions noted in this review were nearly always with 8-substituted purine nucleosides.
(33) S. David and J. C. Fischer, *Carbohydr. Res.*, 18, 39 (1971).
(34) T. Huynh-Dinh, A. Kolb, C. Gouyette, J. Igolen, and S. Tran-Dinh, *J. Org. Chem.*, **40**, 2825 (1975).
(35) J. S. Ingwall, *J. Am. Chem. Soc.*, **94**, 5487 (1972).
(36) G. A. LePage, *Can. J. Biochem.*, **46**, 655 (1968).
(37) W. A. Szarek, J. S. Jewell, I. Szczerek, and J. K. N. Jones, *Can. J. Chem.*, **47**, 4473 (1969).
(38) A. Rosenthal and M. Sprinzl, *Can. J. Chem.*, **47**, 3941 (1969).

Synthesis and Platelet Aggregation Inhibitory Activity of 6-Isobutyl-α-methyl-3-pyridineacetic Acid

Ronald H. Rynbrandt,* Burris D. Tiffany, Doris P. Balgoyen, Edward E. Nishizawa, and A. Rene Mendoza

Research Laboratories, The Upjohn Company, Kalamazoo, Michigan 49001. *Received August 31, 1978*

2-(4′-Isobutylphenyl)propionic acid, ibuprofen, is an antiinflammatory agent which possesses moderate platelet aggregation inhibitory activity. It was therefore of interest to determine what effect the replacement of the phenyl group of ibuprofen by a 3-pyridyl ring would have on platelet aggregation inhibitory activity. As a result, 6-isobutyl-α-methyl-3-pyridineacetic acid (**7**) and its 2-chloro analogue **13** were synthesized. The key step in the synthesis of **7** and **13** involved the oxidative rearrangement of enol ether **11** to the carboxylic ester **12** with thallium trinitrate. The entire sequences of reactions for the synthesis of compounds **7** and **13** are described in detail. Platelet aggregation inhibitory evaluation of **7** and **13** showed **7** to possess activity equivalent to ibuprofen; however, **13** was devoid of platelet aggregation inhibitory activity at an equivalent dose.

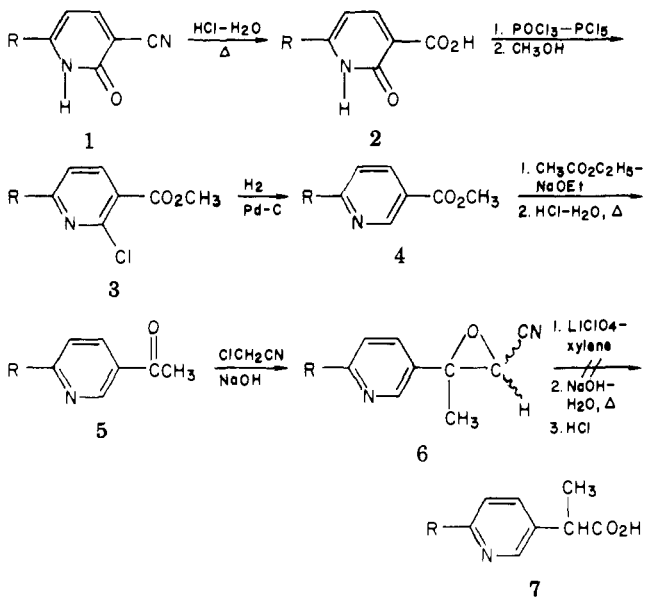
2-(4′-Isobutylphenyl)propionic acid, ibuprofen, is an antiinflammatory agent which possesses moderate platelet aggregation inhibitory activity.[1] It was therefore of interest to determine what effect the replacement of the phenyl group of ibuprofen by a 3-pyridyl ring would have on platelet aggregation inhibitory activity. As a result, 6-isobutyl-α-methyl-3-pyridineacetic acid (**7**) and its 2-chloro analogue, 2-chloro-6-isobutyl-α-methyl-3-pyridineacetic acid (**13**), were prepared and tested for platelet aggregation inhibitory activity.

Chemistry. The initial attempt to prepare **7** (Scheme I) was patterned to afford 3-acetyl-6-isobutylpyridine (**5**), which we anticipated could be converted to **7** by the method recently described by White and Wu.[2] This conversion failed; however, it is presented here in order to illustrate a limitation of this method for the preparation of carboxylic acids. 1,2-Dihydro-6-isobutyl-2-oxonicotinic acid (**2**)[3] was converted to methyl 2-chloro-6-isobutylnicotinate (**3**) by treatment with phosphorus oxychloride and phosphorus pentachloride, followed by absolute methanol. Dehalogenation of **3** with hydrogen and 5% palladium on charcoal catalyst afforded **4** in 68% yield. Conversion of **4** to the desired ketone **5** was accomplished by condensation with ethyl acetate followed by decarboxylation.

White and Wu[2] have recently described the conversion of 4-isobutylacetophenone to 2-(4′-isobutylphenyl)-propionic acid by treatment of the ketone with chloroacetonitrile to afford the glycidylnitrile, which was subsequently opened with lithium perchlorate followed by basic hydrolysis to afford the acid. Treatment of ketone **5** with chloroacetonitrile and sodium hydroxide in dimethylformamide afforded the glycidylnitrile **6** as a 50:50 mixture of isomers (NMR) in 57% yield. When **6** was treated with lithium perchlorate in xylene at 110 °C, the desired acid **7** was not obtained. NMR analyses of the reaction products showed the acidic component to be isobutyric acid and the neutral material to be a pyridineglycidylnitrile devoid of an isobutyl group. When the glycidylnitrile of 3-acetylpyridine was treated in a similar manner, the reaction afforded α-methyl-3-pyridineacetic acid in good yield. The apparent reason for the failure of this method with **6** is that the pyridyl nucleus activates the methylene carbon atom of the 6-isobutyl group such that it is oxidized and subsequently cleaved by lithium perchlorate.

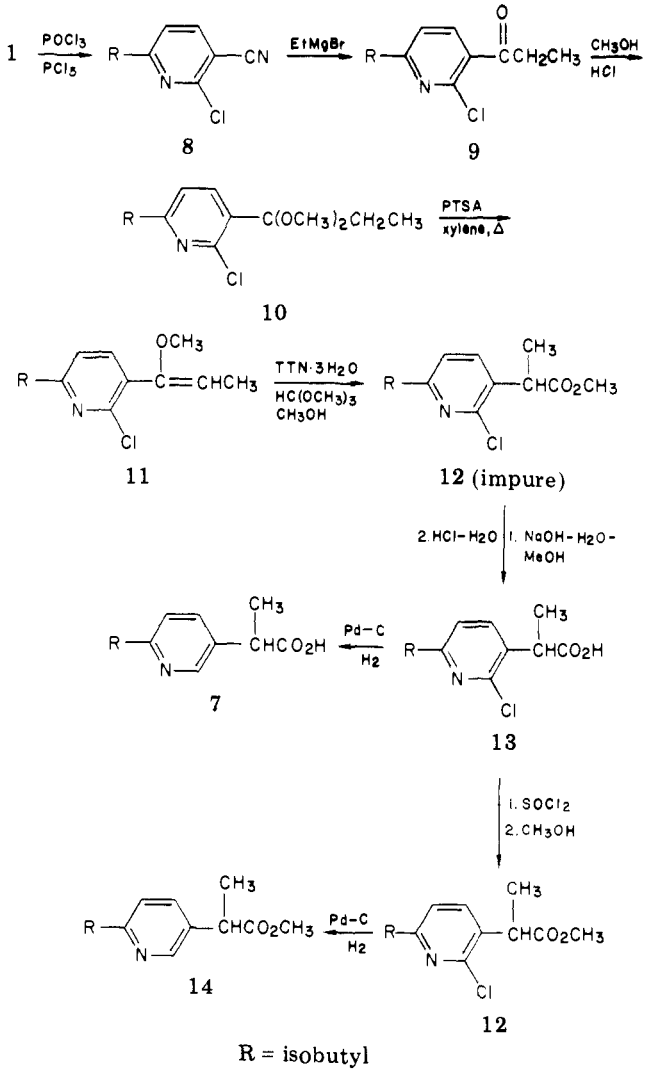
0022-2623/79/1822-0525$01.00/0

Scheme I



R = isobutyl

Scheme II



R = isobutyl

The desired acid 7 and its 2-chloro analogue 13 were successfully prepared by the reaction sequence outlined in Scheme II. This reaction sequence was designed to utilize the method recently reported by Walker and Pillai for the conversion of 4-isobutylpropiophenone to 2-(4'-isobutylphenyl)propionic acid by treatment of the enol ether of the ketone with thallium trinitrate.[4] 1,2-Dihydro-6-isobutyl-2-oxonicotinonitrile (1)[3] was converted to compound 8 by treatment with phosphorus oxychloride and phosphorus pentachloride. Treatment of 8 with ethylmagnesium bromide in benzene afforded the ethyl ketone 9 in 50% yield. Ketone 9 was converted into the dimethyl ketal 10 in 87% yield by treatment with a large excess of hydrogen chloride in a mixture of absolute methanol and trimethyl orthoformate. Ketal 10 was transformed into the enol ether 11 by heating at reflux in xylene with 4-methylbenzenesulfonic acid as the catalyst. When 11 was treated with thallium trinitrate in methanol, it underwent an oxidative rearrangement almost instantaneously to afford the desired propionic ester 12 in 65% yield. The only significant byproduct was the ketone 9. Basic hydrolysis of crude 12 afforded a 60% yield of acid 13. Dehalogenation of 13 with hydrogen and 10% palladium on charcoal catalyst afforded the desired acid 7. Pure 12 was obtained by conversion of 13 to the acid chloride and subsequent treatment with absolute methanol. Dehalogenation of 12 afforded the methyl ester of 7, compound 14.

Table I. Modified ex Vivo Rat Assay. Comparison of Platelet Inhibition Activity (Collagen-Induced) of Ibuprofen and Compound 7 Using the Modified ex Vivo Rat Assay

compd	oral dose, mg/kg	extent of aggregat[a]	% inhibn
ibuprofen	0	41.0 ± 0.6[b]	
	10	36.8 ± 2.0[b]	10[c]
	40	4.8 ± 4.4[b]	88[d]
7	0	81.2 ± 2.1[b]	
	10	53.6 ± 9.6[b]	33[d]
	50	28.4 ± 9.6[b]	65[d]

[a] Aggregation units or peak heights. [b] Group standard plus or minus standard deviation of mean, five animals/group. [c] Statistically different from control, $p = 0.052$. [d] Statistically different from control, $p < 0.0005$.

Pharmacology. 6-Isobutyl-α-methyl-3-pyridineacetic acid (7), 2-chloro-6-isobutyl-α-methyl-3-pyridineacetic acid (13), and ibuprofen were evaluated for antithrombotic activity using the mouse pulmonary thromboembolism screen at 50 mg/kg previously described by Nishizawa and co-workers.[5] Compound 7 and ibuprofen were active; however, the 2-chloro analogue 13 was inactive and, as a result, was not further evaluated. Compound 7 and ibuprofen were evaluated for oral platelet aggregation inhibitory activity in the rat using a modified ex vivo assay (see Experimental Section). Data in Table I show compound 7 inhibited collagen-induced platelet aggregation by 65% at 50 mg/kg ($p < 0.0005$) and 33% at 10 mg/kg ($p < 0.0005$). In comparison, ibuprofen inhibited aggregation by 88% at 40 mg/kg ($p < 0.0005$) and 10% at 10 mg/kg ($p = 0.052$). These data show that compound 7 and ibuprofen are essentially equipotent in inhibiting collagen-induced platelet aggregation in the rat. It is of interest that the 2-chloro analogue of 7, compound 13, displayed no platelet aggregation inhibitory activity at an equivalent dose.

Experimental Section

All melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The structures of all compounds were supported by IR, NMR, and mass spectra. IR spectra were obtained on a Perkin-Elmer Model 421 recording spectrometer in Nujol mulls, the NMR spectra were recorded on a Varian A-60D spectrometer, and the mass spectra were determined on an Atlas CH-4 spectrometer. All elemental

analyses were within ±0.4% of the theoretical values, except where noted.

Methyl 2-Chloro-6-isobutylnicotinate (3). The following procedure is a major modification of the method described by Sperber and co-workers[6] for the preparation of the ethyl ester. To a stirred mixture of **2**[3] (29.94 g, 0.15 mol) and $POCl_3$ (49.1 mL) maintained at 100 °C there was added PCl_5 (92.1 g, 0.44 mol) over a period of 1 h. The mixture was then heated at reflux for an additional 2 h and concentrated in vacuo. The residue was poured into ice–water, extracted with CH_2Cl_2 (3 × 250 mL), and dried (Na_2SO_4). Solvent was removed in vacuo and the residue was heated at reflux with MeOH (200 mL) for 1.5 h. Excess MeOH was removed in vacuo and the residue was distilled to afford 15 g (44%) of **3**: bp 125–130 °C (0.5 mm). Anal. ($C_{11}H_{14}ClNO_2$) C, H, Cl; N: calcd, 6.15; found, 6.60.

Methyl 6-Isobutylnicotinate (4). A solution of **3** (7.0 g, 0.030 mol) in absolute EtOH (115 mL) and concentrated HCl (2 mL) was dehalogenated with H_2 using 5% palladium on charcoal (2.0 g) at an initial pressure of 3.5 kg/cm^2. The catalyst was removed by filtration and the solvent was removed in vacuo. The residue was dissolved in H_2O (60 mL), made basic with saturated $NaHCO_3$ solution, and extracted with CH_2Cl_2 (3 × 100 mL). The combined extracts were dried (Na_2SO_4) and the solvent was removed in vacuo. The residue was distilled to afford 3.92 g (68%) of **4**: bp 85–90 °C (0.5 mm). Anal. ($C_{11}H_{15}NO_2$) C, H, N.

3-Acetyl-6-isobutylpyridine (5). A solution of **4** (2.68 g, 0.013 mol) and ethyl acetate (2.33 g, 0.029 mol) was added by syringe over a 10-min period to a solution of sodium ethoxide prepared from Na (0.46 g) and absolute EtOH (11 mL). The mixture was stirred at ambient temperature for 1 h and then heated at reflux for 10 h. The cooled reaction mixture was diluted with H_2O (7 mL) and then neutralized with concentrated HCl. Additional concentrated HCl (2.88 mL) was added, and the mixture was heated at reflux for 2.5 h and cooled. The mixture was made basic with saturated K_2CO_3 solution and extracted with CH_2Cl_2 (2 × 50 mL). The combined extracts were dried (Na_2SO_4) and the solvent was removed in vacuo to afford a colorless oil. The oil was chromatographed on silica gel to afford 2.14 g (93%) of **5**. Anal. ($C_{11}H_{15}NO$) C, H, N.

Preparation of the Glycidylnitrile of 5. A mixture of **5** (0.50 g, 2.8 mmol), pulverized NaOH flakes (0.64 g, 16 mmol), and DMF (5 mL) was stirred at ambient temperature for 1.5 h. Chloroacetonitrile (0.45 g, 6.0 mmol) in toluene (1.2 mL) was added dropwise with stirring to the above mixture, which was maintained at 10–15 °C. The mixture was then allowed to warm to ambient temperature and Et_2O (10 mL) and H_2O (5 mL) were added. The mixture was filtered through Celite, and the organic layer was separated, washed with H_2O (2 × 10 mL), and dried (Na_2SO_4). The solvent was removed in vacuo to afford 0.33 g (57%) of the glycidylnitrile **6**. The NMR spectrum showed the ratio of cis and trans isomers to be ca. 1:1.

Reaction of 6 with $LiClO_4$. A mixture of **6** (0.33 g, 1.5 mmol), $LiClO_4$ (0.10 g, 0.90 mmol), and xylene (15 mL) was heated at 110 °C with stirring for 20 h. The reaction mixture was cooled, H_2O (2.3 mL) and 50% NaOH (2.3 mL) were added, and the mixture was heated at 70–75 °C for 6 h. The cooled mixture was treated with H_2O (10 mL) and extracted with Et_2O (2 × 20 mL). The aqueous layer was acidified to pH 1 with concentrated HCl and evaporated to dryness. The dry residue was triturated with hot absolute EtOH (3 × 50 mL) and filtered. The filtrate was concentrated in vacuo to afford an oil (0.092 g). NMR analysis showed the material to be isobutyric acid. The combined above Et_2O extracts were dried (Na_2SO_4) and concentrated in vacuo to afford an oil (0.19 g). NMR analysis showed the presence of the glycidylnitrile group and the pyridine ring system.

6-Isobutyl-2-chloronicotinonitrile (8). To stirred $POCl_3$ (400 mL) there was added portionwise **1**[3] (265 g, 1.50 mol). The resulting suspension was heated to 80 °C and PCl_5 (345 g, 1.65 mol) was added in small portions over a 35-min period. The mixture was heated at 80–85 °C for an additional 40 min and cooled, and excess $POCl_3$ was removed in vacuo. The residue was distilled, bp 104–105 °C (0.2 mm), to afford 262 g (90%) of a colorless oil which crystallized upon cooling.

A 209-g portion of the crystalline product was dissolved in MeOH (800 mL) at 35 °C and ice was gradually added with stirring to a total volume of 2 L. The mixture was cooled in ice–acetone, and the precipitate was removed by filtration, washed with cold 50% aqueous methanol, and dried to afford 207 g of large colorless crystals, mp 46.5–49 °C. The analytical sample was obtained by recrystallization from Skellysolve B (SSB):[7] mp 48–48.5 °C. Anal. ($C_{10}H_{11}ClN_2$) C, H, N, Cl.

6-Isobutyl-2-chloro-3-propionylpiperidine (9). A solution of **8** (39.0 g, 0.20 mol) in benzene (450 mL) was partially distilled (ca. 50 mL) to remove traces of H_2O. The solution was cooled to 20 °C and 3 M ethylmagnesium bromide (110 mL, 0.33 mol) in Et_2O was added, causing an exotherm to 50 °C. The solution was heated at reflux under N_2 for 2.5 h and cooled. A solution of concentrated HCl (70 mL) in H_2O (350 mL) was added; the layers were separated, and the organic portion was washed with H_2O (200 mL), saturated $NaHCO_3$ solution (100 mL), and H_2O (200 mL). The organic portion was dried (Na_2SO_4) and concentrated in vacuo to afford 39 g of oil. The oil was subjected to adsorption chromatography on silica gel. The column was eluted with 2 L each of 5, 10, and 15% acetone in SSB, collecting 500-mL fractions. The product (27.8 g), contaminated with 10–20% impurity, was in fractions 8–11. It was absorbed on 2 kg of silica gel packed in CH_2Cl_2 and eluted with 6% acetone in SSB, collecting 500-mL fractions. The product appeared in fractions 15–17 and amounted to 22.6 g (50%) of an orange oil. The analytical sample was obtained by short-path distillation at 105 °C (0.05 mm), to give a clear colorless oil. Anal. ($C_{12}H_{16}ClNO$) C, H, N, Cl.

6-Isobutyl-2-chloro-3-propionylpyridine Dimethyl Ketal (10). To a solution of **9** (18.76 g, 0.083 mol) in trimethyl orthoformate (18.76 g, 0.177 mol) there was added 40 mL of a solution of HCl in absolute MeOH (0.188 g of HCl/g of solution). The reaction mixture was stored at 5 °C for 16 h, made basic by addition of 25% $NaOCH_3$ in MeOH (25 mL), and treated with dry ice to bring the pH to 8. The pasty mixture was diluted with E_2O (100 mL), and the precipitate was removed by filtration. The filtrate was concentrated in vacuo and the residue was diluted with SSB (100 mL), filtered to clarify, and concentrated in vacuo to afford 19.5 g (87%) of light brown oil. GC analysis showed the product to be >95% pure. The analytical samples was obtained by short-path distillation at 100 °C (0.5 mm) to afford a clear viscuous oil. Anal. ($C_{14}H_{22}Cl_2NO$) C, H, N, Cl.

6-Isobutyl-2-chloro-3-(1-methoxy-1-propenyl)pyridine (11). To a solution of **10** (9.42 g, 35.0 mmol) in xylene (94 mL) there was added 4-methylbenzenesulfonic acid (0.95 g), and the mixture was slowly distilled so that 20 mL of distillate was collected in 2 h. The reaction mixture was made alkaline with 25% $NaOCH_3$ in CH_3OH (2 mL), washed with H_2O (2 × 50 mL), and back-extracted with xylene (20 mL). The combined organic fractions were dried (Na_2SO_4), filtered, and concentrated in vacuo to afford 10.4 g of an orange oil. This was dissolved in SSB (20 mL) and subjected to adsorption chromatography on 500 g of silica gel packed in SSB. This was eluted with 2 L each of 4, 6, and 8% acetone in SSB, collecting 500-mL fractions. Fraction 4 afforded 5.74 g (68%) of product. GC analysis showed the material to be 96% pure: NMR ($CDCl_3$) δ 1.48 (d, 2.25 H, J = 7 Hz), 1.78 (d, 0.75 H, J = 7 Hz), 3.63 (s, 3 H), 4.9 (q, 1 H, J = 7 Hz). A satisfactory elemental analysis could not be obtained on this very sensitive compound.

Methyl 2-Chloro-6-isobutyl-α-methyl-3-pyridineacetate (12). A solution of $Tl(NO_3)_3 \cdot 3H_2O$[8] (16.0 g, 36 mmol) in trimethyl orthoformate (12.0 g, 113 mmol) was covered with hexane (60 mL). A solution of **11** (8.0 g, 33 mmol) in hexane (60 mL) was added dropwise with stirring over a 20-min period to the above mixture maintained at 25 °C. The mixture was stirred for an additional 20 min at 25 °C, hexene (1 mL) was added [to reduce residual $Tl(NO_3)_3$], and the precipitate was removed by filtration and rinsed with Et_2O (50 mL). The filtrate was washed with saturated NaCl solution (25 mL) and H_2O (50 mL) and dried ($MgSO_4$). The solvent was removed in vacuo to afford 8.0 g (94%) of crude **12** as a colorless oil. The analytical sample was prepared by alkaline hydrolysis to the acid and subsequent conversion to the ester via the acid chloride (see following experiments).

2-Chloro-6-isobutyl-α-methyl-3-pyridineacetic Acid (13). A mixture of crude **12** (above) (8.0 g, 31 mmol), MeOH (180 mL), and NaOH (2.4 g, 60 mmol) was heated at reflux for 3 h. The solvent was removed in vacuo and the residue was dissolved in H_2O (150 mL). The aqueous solution was extracted with Et_2O

(2 × 50 mL) to remove neutral material, acidified to pH 3.5 with 1 N HCl, and extracted with Et_2O (2 × 250 mL). The combined extracts were washed with H_2O (50 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo to afford 4.6 g (60%) of product: NMR ($CDCl_3$) δ 0.97 (d, 6 H, J = 6.5 Hz), 1.54 (d, 3 H, J = 7.5 Hz), 2.07 (m, 1 H), 2.62 (d, 2 H, J = 6.5 Hz), 4.18 (q, 1 H, J = 7.5 Hz), 7.05 (d, 1 H, J = 8.0 Hz), 7.62 (d, 1 H, J = 8.0 Hz), 7.95 (s, 1 H, exchanges with D_2O). The analytical sample was obtained by short-path distillation at 150 °C (0.1 mm) to afford a colorless oil. Anal. ($C_{15}H_{16}ClNO_2$) C, H, N, Cl.

Methyl 2-Chloro-6-isobutyl-α-methyl-3-pyridineacetate (12). A solution of **13** (3.3 g, 13.6 mmol), CH_2Cl_2 (20 mL), and $SOCl_2$ (1.5 mL) was heated at reflux for 2.5 h. The solution was cooled, concentrated in vacuo, dissolved in CH_2Cl_2 (20 mL), and treated dropwise with absolute MeOH (2.0 mL). After stirring for 1 h at ambient temperature, the solution was concentrated in vacuo to afford 2.81 g (99%) of colorless oil. The analytical sample was obtained by short-path distillation at 140 °C (0.1 mm) to afford a colorless oil. Anal. ($C_{13}H_{18}ClNO_2$) C, H, N, Cl.

Methyl 6-Isobutyl-α-methyl-3-pyridineacetate (14). A solution of **12** (1.27 g, 5.0 mmol) in MeOH (160 mL) was dehalogenated with H_2 using 10% palladium on charcoal (1.0 g) catalyst at an initial pressure of 3.5 kg/cm^2. The catalyst was removed by filtration and the solvent was removed in vacuo. The residue was dissolved in H_2O (20 mL) and extracted with Et_2O (2 × 20 mL). The aqueous phase was made basic to pH 11 by addition of 10% NaOH solution and extracted with CH_2Cl_2 (3 × 30 mL). The combined extracts were washed with H_2O (20 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo to afford 0.78 g (74%) of oily product. The analytical sample was obtained by short-path distillation at 140 °C (0.1 mm) to afford a colorless oil. Anal. ($C_{13}H_{18}NO_2$) C, H, N.

6-Isobutyl-α-methyl-3-pyridineacetic Acid (7). A solution of **13** (1.20 g, 50 mmol) in MeOH (160 mL) was dehalogenated with H_2 using 10% palladium on charcoal (1.0 g) catalyst at an initial pressure of 3.5 kg/cm^2. The catalyst was removed by filtration and the solvent was removed in vacuo. The residue was dissolved in H_2O (5 mL) and extracted with Et_2O (30 mL) (discarded). The aqueous portion was treated with saturated $NaHCO_2$ solution to a pH of 5.9 and extracted with Et_2O (2 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent was removed to afford 0.56 g (55%) of an oil which crystallized spontaneously. The analytical sample was recrystallized from Et_2O–hexane to afford colorless crystals: mp 69–71 °C; NMR (Me_2SO-d_6) δ 0.92 (d, 6 H, J = 6.0 Hz), 1.55 (d, 3 H, J = 7.0 Hz), 2.22 (m, 1 H), 3.02 (d, 2 H), 4.29 (q, 1 H, J = 7.0 Hz), 7.8–8.8 (m, 3 H), 9.5–10.1 (s, 1 H). Anal. ($C_{12}H_{17}NO_2$) C, H, N.

Inhibition of Platelet Aggregation. Ex vivo platelet inhibitory activity was determined following oral adminstration of the drugs to five male Sprague–Dawley rats fasted overnight. The compounds were dissolved in Emulfor–ethanol (1:1) to a concentration of 62.5 mg/mL and subsequently diluted with sterile vehicle no. 122 (The Upjohn Company, Kalamazoo, MI; 0.25% methylcellulose in water) to 6.25 mg/mL. Animals were dosed with these solutions to produce the required dosage (mg/kg). The control group of rats was dosed with a vehicle containing Emulfor–ethanol (1:1). One hour after dosing, the rats were anesthetized with an intraperitoneal injection (2 mL/kg) of 5% sodium cyclopal in saline. Blood was collected from the abdominal aorta into syringes containing 0.10 volume of 2.2% sodium citrate. The blood samples were centrifuged at 700g for 30 min in an International PPJ centrifuge to obtain platelet-poor plasma (PPP). The plasma samples were refrigerated at 4 °C until assayed for platelet-aggregation activity. Pooled platelet-rich plasma (PRP) was prepared from untreated rats by centrifuging citrated blood at 250g for 10 min at 10 °C and adjusting the platelet count with homologous PPP to 10^6 platelets/mm^3. For aggregation studies, aliquots (0.45 mL) of PRP from untreated rats and 0.45 mL of PPP from treated or control rats were combined and warmed to 37 °C for 10 min. The degree of platelet aggregation was determined with the addition of a titrated amount of collagen suspension,[9] to give submaximal aggregation, and measured in a Payton Aggregometer® coupled with an Omniscribe® recorder. Heights of control aggregation peaks were compared to those of treated groups by use of the Standard Oneway Analysis of Variance Statistical Assay.

References and Notes

(1) D. J. Wynalda and C. D. Brooks, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, **34**, 873 (1975).
(2) D. R. White and D. K. Wu, *J. Chem. Soc., Chem. Commun.*, 988 (1974).
(3) R. P. Mariella, *J. Am. Chem. Soc.*, **69**, 2670 (1947).
(4) J. A. Walker and M. D. Pillai, *Tetrahedron Lett.*, 3707 (1977).
(5) E. E. Nishizawa, D. J. Wynalda, D. E. Suydam, T. R. Sawa, and J. R. Schultz, *Thromb. Res.*, 1, 233 (1972).
(6) N. Sperber, M. Sherlock, D. Papa, and D. Kinder, *J. Am. Chem. Soc.*, 81, 704 (1959).
(7) Skellysolve B is a petroleum fraction, bp 60–70 °C, sold by the Skelly Oil Co.
(8) Thallium salts are extremely toxic.
(9) Collagen suspension is prepared by homogenizing bovine tendon collagen (type I, acid insoluble) in acidic solution (pH 2.5) to 2 mg/mL. Dilution of this stock solution is prepared in Tyrodes buffer, pH 7.5.