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Synthesis of 3-Substituted Pyrazolo[1,5-*a*]pyridine Derivatives with Inhibitory Activity on Platelet Aggregation. II

KATSUYA AWANO* and SEIGO SUZUE

Central Research Laboratories, Kyorin Pharmaceutical Co., Ltd., Nogi-machi, Shimotsuga-gun, Tochigi 329-01, Japan

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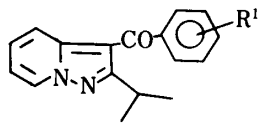
The structure–activity relationship of 3-(*p*-substituted benzoyl)pyrazolo[1,5-*a*]pyridine derivatives as inhibitors of rabbit platelet aggregation *in vitro* have been examined. The cluster analysis approach to the selection of substituents on the phenyl ring of 2-isopropyl-3-(*p*-substituted benzoyl)pyrazolo[1,5-*a*]pyridine was used, and the effect of substituents was investigated by quantitative regression analysis. The *p*-dimethylamino group was found to be the most effective *p*-substituent on the phenyl ring for antiaggregant activity.

Keywords——3-(*p*-substituted benzoyl)pyrazolo[1,5-*a*]pyridine; cluster analysis; quantitative structure–activity relationship; *p*-dimethylamino group; inhibitory activity; antiaggregant activity

In the preceding paper,[1] we reported the synthesis of 3-nicotinoyl and 3-(1,4,5,6-tetrahydronicotinoyl)pyrazolo[1,5-*a*]pyridine derivatives with inhibitory activity on platelet aggregation. We have now synthesized 3-benzoyl derivatives instead of 3-nicotinoyl derivatives, and have found that these derivatives retain the inhibitory activity. In order to find more effective substituents on the phenyl ring of the 3-benzoyl moiety, we selected substituents by using the cluster analysis approach.[2]

Thus, our interest was focused on modification of the *p*-substituents on the 3-benzoyl moiety of **1** to investigate the structure–activity relationships of these compounds as antiplatelet agents. This paper deals with the synthesis of 3-benzoylpyrazolo[1,5-*a*]pyridine derivatives and reports the structure–activity relationships for the inhibitory activities on platelet aggregation.



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Synthesis

Pyrazolo[1,5-*a*]pyridine derivatives used in this study were synthesized as shown in Chart 1. 2-Alkyl-3-(*p*-substituted benzoyl)pyrazolo[1,5-*a*]pyridines (**2**) were obtained by the reaction of 2-alkylpyrazolo[1,5-*a*]pyridine with *p*-substituted benzoyl chloride.[3] Aminobenzoyl derivatives (**3**) were obtained by the hydrogenation of the corresponding *p*-nitrobenzoyl derivatives in the presence of palladium carbon. Compound **3** readily reacted with acylating agents or alkylating agents such as acyl chloride and alkyl halide to give the corresponding *p*-substituted aminobenzoyl derivatives (**4** and **5**). The compounds obtained are summarized in Table I.

Structure–Activity Relationships

We looked for suitable *p*-substituents on the 3-benzoyl moiety of **1** by using the cluster

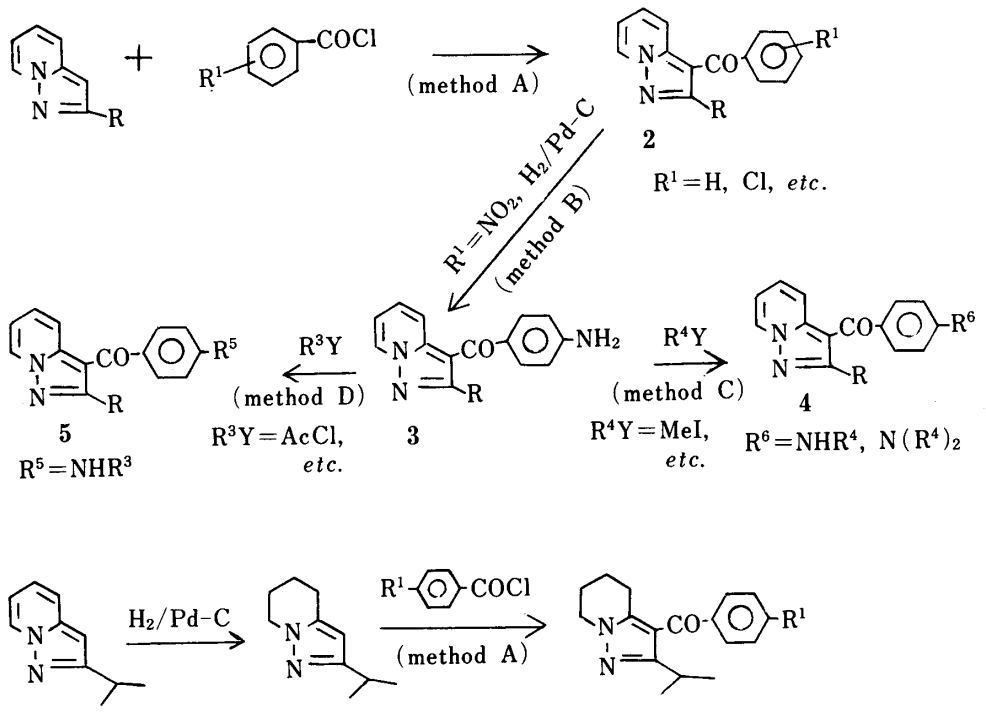


Chart 1

analysis approach, and from this 9 analogues resulted. On the basis of this result, 4 further analogues were prepared. Similarly, 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridine derivatives (6 analogues) were selected by using the cluster analysis approach. The analogues selected and prepared are listed in Tables II and III together with the biological data and physicochemical substituent constants. The correlation matrix for the parameters of substituents of **1** which resulted from cluster analysis is given in Table IV. This method leads to a series in which quantitative structure–activity relationships may be derived. The activity of tetrahydropyrazolo[1,5-*a*]pyridine derivatives was much weaker than that of pyrazolo[1,5-*a*]pyridine derivatives (Tables II and III). Firstly, Eq. 1 was derived by regression analysis using π, σ, F, R, MR and MW as single parameters (Table IV):

$$\log 1/\mathrm{ID}_{100} = -0.04\ MR\ (\pm 0.06) + 4.99\ (\pm 0.92) \qquad (1)$$

$$n=9,\quad s=0.74,\quad r=0.52,\quad F_7^1=2.58$$

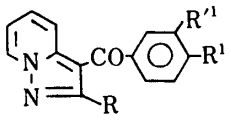
where n, s, r and F represent the number of data used for the regression analysis, standard deviation, correlation coefficient and observed F value, respectively. However the equation did not satisfy the F test at the 90% level, with an F value of 2.58 ($F^1_{7(\alpha=0.1)}=3.59$).

$$\log 1/\mathrm{ID}_{100} = -1.74\ R\ (\pm 2.17) - 0.04\ MR\ (\pm 0.05)$$
$$+4.57\ (\pm 0.92) \qquad (2)$$

$$n=9,\quad s=0.62,\quad r=0.74,\quad F_6^2=3.73$$

Equation 2 was derived in a similar manner using π, σ, F, MR and MW as double parameters; the equation satisfied the F test at the 90% level, with an F value of 3.73 ($F^2_{6(\alpha=0.1)}=3.46$). The sequential F test was used to evaluate statistically the introduction of the R term into Eq. 1. Equation 2 satisfied the sequential F test at the 90% level with an F value of 4.35 ($F^2_{6(\alpha=0.1)}=3.78$) and thus was adopted as the most appropriate equation. The coefficient of R in Eq. 2 is negative, indicating that the introduction of an electron-releasing substituent into the phenyl ring leads to an increase in activity. Similarly, the coefficient of MR is negative,

TABLE I. Physicochemical Properties of Substituted Benzoyl Derivatives



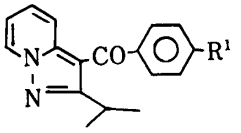
Compd. No.	R	R^1	R'^1	mp (°C)	Method (Yield (%))	Recrystn. solvent[a] (Formula)	Analysis (%) Calcd (Found) C	H	N
1	iso-Pr	H	H	69—70	A (40)	a	77.25	6.10	10.60
						($C_{17}H_{16}N_2O$)	(77.22	5.98	10.56)
2	iso-Pr	NO_2	H	134—135	A (69)	b	66.01	4.89	13.59
						($C_{17}H_{15}N_3O_3$)	(66.12	4.85	13.32)
3	iso-Pr	Cl	H	118—120	A (75)	a	68.34	5.06	9.38
						($C_{17}H_{15}ClN_2O$)	(68.09	5.02	9.30)
4	iso-Pr	$NHCOCH_3$	H	171—173	D (35)	c	71.01	5.96	13.08
						($C_{19}H_{19}N_3O_2$)	(71.02	5.92	12.96)
5	iso-Pr	OCH_3	H	95—97	A (51)	b	73.45	6.16	9.52
						($C_{18}H_{18}N_2O_2$)	(73.33	6.08	9.48)
6	iso-Pr	NH_2	H	170—172	B (92)	d	73.09	6.13	15.04
						($C_{17}H_{17}N_3O$)	(73.12	6.06	15.07)
7	iso-Pr	Br	H	118—119	A (47)	d	59.49	4.41	8.16
						($C_{17}H_{15}BrN_2O$)	(59.87	4.36	8.26)
8	iso-Pr	NHCOPh	H	211—213	D (73)	e	75.17	5.52	10.96
						($C_{24}H_{21}N_3O_2$)	(75.07	5.43	10.94)
9	iso-Pr	NH-*n*-Bu	H	114—116	C (25)	b	75.19	7.52	12.53
						($C_{21}H_{25}N_3O$)	(75.19	7.48	12.48)
10	iso-Pr	F	H	78—80	A (57)	a	72.33	5.36	9.92
						($C_{17}H_{15}FN_2O$)	(72.19	5.23	9.89)
11	iso-Pr	$NHCH_3$	H	136—138	C (25)	b	73.69	6.53	14.33
						($C_{18}H_{19}N_3O$)	(73.83	6.48	14.44)
12	iso-Pr	$N(CH_3)_2$	H	151—152	C (30)	b	74.24	6.89	13.67
						($C_{19}H_{21}N_3O$)	(74.28	6.87	13.67)
13	iso-Pr	NHEt	H	160—161	C (30)	b	74.24	6.89	13.67
						($C_{19}H_{21}N_3O$)	(74.28	6.84	13.74)
14[b]	iso-Pr	H	H	107—108	A (43)	a	76.08	7.51	10.44
						($C_{17}H_{20}N_2O$)	(75.97	7.48	10.53)
15[b]	iso-Pr	NO_2	H	150—151	A (52)	b	65.16	6.11	13.41
						($C_{17}H_{19}N_3O_3$)	(65.19	6.12	13.32)
16[b]	iso-Pr	$NHCOCH_3$	H	171—172	D (65)	d	70.13	7.12	12.91
						($C_{19}H_{23}N_3O_2$)	(70.39	7.07	12.75)
17[b]	iso-Pr	NH_2	H	216—217	B (96)	d	72.05	7.47	14.83
						($C_{17}H_{21}N_3O$)	(72.02	7.41	14.77)
18[b]	iso-Pr	NHCOPh	H	192—193	D (73)	e	74.39	6.50	10.85
						($C_{24}H_{25}N_3O_2$)	(74.46	6.43	10.83)
19[b]	iso-Pr	NH-*n*-Bu	H	139—140	C (38)	b	74.30	8.61	12.38
						($C_{21}H_{29}N_3O$)	(74.36	8.66	12.32)
20	iso-Pr	NO_2	CH_3	103—105	A (75)	f	66.86	5.30	13.00
						($C_{18}H_{17}N_3O_3$)	(67.04	5.31	12.87)
21	iso-Pr	NH_2	CH_3	80—82	B (92)	b	73.69	6.53	14.33
						($C_{18}H_{19}N_3O$)	(73.85	6.48	14.17)
22	iso-Pr	$NHCH_3$	CH_3	135—137	C (29)	b	74.24	6.89	13.67
						($C_{19}H_{21}N_3O$)	(74.48	6.87	13.55)
23	iso-Pr	$N(CH_3)_2$	CH_3	—	C (48)	b	74.74	7.21	13.07
						($C_{20}H_{23}N_3O$)	(74.50	7.20	12.82)
24	CH_3	NO_2	H	147—149	A (51)	d	64.05	3.94	14.94
						($C_{15}H_{11}N_3O_3$)	(64.33	3.85	14.77)

TABLE I. continued

Compd. No.	R	R^1	R'^1	mp (°C)	Method (Yield (%))	Recrystn. solvent [a] (Formula)	Analysis (%) Calcd (Found) C	H	N
25	CH_3	NH_2	H	194—196	B (97)	g ($C_{15}H_{13}N_3O$)	71.69 (71.49	5.21 5.14	16.72 16.50)
26	CH_3	$NHCH_3$	H	136—137	C (25)	b ($C_{16}H_{15}N_3O$)	72.43 (72.67	5.70 5.62	15.84 15.64)
27	CH_3	$N(CH_3)_2$	H	167—168	C (30)	d ($C_{17}H_{17}N_3O$)	73.09 (72.82	6.13 6.02	15.04 14.85)
28	CH_3	OCH_3	H	115—116	A (43)	h ($C_{16}H_{14}N_2O_2$)	72.16 (72.11	5.30 5.20	10.52 10.54)

a) a, hexane; b, hexane–benzene; c, ethanol–benzene; d, benzene; e, methanol; f, ethanol; g, ethyl acetate; h, ethanol–water. *b*) 4,5,6,7-Tetrahydro derivatives.

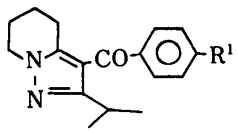
TABLE II. Biological Data and Physicochemical Constants



Compd.	R^1	ID_{100} μg/ml	σ	π	*F*	*R*	*MR*	*MW*
1	H	3.0	0.00	0.00	0.00	0.00	1.03	1.0
2	NO_2	80	−0.28	0.78	0.67	0.16	7.35	46.0
3	Cl	4.0	0.17	0.24	0.41	−0.15	6.03	35.4
4	$NHCOCH_3$	100	−0.97	0.00	0.28	−0.26	14.93	58.1
5	OCH_3	0.4	−0.02	−0.27	0.26	−0.51	7.87	31.0
6	NH_2	3.0	−1.23	−0.66	0.02	−0.68	5.43	16.0
7	Br	8.0	0.86	0.23	0.44	−0.17	8.88	79.9
8	NHCOPh	40	0.49	−0.19	0.09	−0.27	34.64	121.0
9	NH-*n*-Bu	70	1.45	−0.51	−0.28	−0.25	24.26	72.1
10	F	4.0 (1.1)	0.14	0.06	0.43	−0.34	0.92	19.0
11	$NHCH_3$	0.30 (0.87)	−0.47	−0.84	−0.11	−0.74	10.33	30.1
12	$N(CH_3)_2$	0.060 (0.048)	0.18	−0.83	0.10	−0.92	15.55	44.1
13	NHEt	5.0 (4.3)	0.08	−0.61	−0.11	−0.51	14.98	44.1

( ) ID_{100} values calculated from Eq. 2.

TABLE III. Biological Data



Compd.	R^1	ID_{100} μg/ml
14	H	10
15	NO_2	>10
16	$NHCOCH_3$	>10
17	NH_2	8
18	NHCOPh	>10
19	NH-*n*-Bu	>10

TABLE IV. Correlation Coefficient Matrix (Compounds 1—9)

	Act.	σ	π	F	R	MR	MW
Act.	1.00						
σ	−0.07	1.00					
π	−0.29	0.05	1.00				
F	−0.02	−0.20	0.85	1.00			
R	−0.48	0.31	0.84	0.43	1.00		
MR	−0.52	0.38	−0.29	−0.38	−0.10	1.00	
MW	−0.52	0.46	0.03	−0.01	0.07	0.88	1.00

indicating that small substituents enhance the activity. On the basis of this result, 4 further analogues were prepared in an attempt to obtain more active compounds. The $ID_{100}(\mu g/ml)$ values calculated from Eq 2 were in relatively good agreement with those observed in the 4 analogues (Table II).

Next, the quantitative structure–activity relationships of 13 analogues (**1**—**13**) were determined. The correlation matrix for these 13 compounds is given in Table V; Eq. 5 gave the best correlation. Equations 4 and 5 were derived by regression analysis using physicochemical parameters as double parameters (containing the square of these parameters).

$$\log 1/ID_{100} = -2.40\ R\ (\pm 1.39) + 3.94\ (\pm 0.64) \quad (3)$$

$$n=13,\ s=0.67,\ r=0.75,\ F^1_{11}=14.36$$

$$\log 1/ID_{100} = -2.53\ R\ (\pm 1.22) - 0.04\ MR\ (\pm 0.04) + 4.35\ (\pm 0.70) \quad (4)$$

$$n=13,\ s=0.57,\ r=0.84,\ F^2_{10}=12.14$$

$$\log 1/ID_{100} = -2.38\ R\ (\pm 1.15) - 0.60\pi^2\ (\pm 0.12) + 4.25\ (\pm 0.59) \quad (5)$$

$$n=13,\ s=0.55,\ r=0.86,\ F^2_{10}=14.03$$

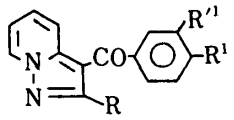
Equations 4 and 5 satisfied the F test at the 99% level, with F values of 12.14 and 14.03, respectively ($F^2_{10(\alpha=0.01)}=7.56$). Equations 4 and 5 also satisfied the sequential F test at 90% and 95%, respectively, and both showed the *p*-dimethylamino group to be the most effective substituent (compd. **12**).

To find other compounds possessing higher activity than **12**, modification of the 2-position of pyrazolo[1,5-*a*]pyridine was carried out (Table VI). The methyl group was more effective than the isopropyl group. This result is in good agreement with that for nicotinoyl derivatives.[1] 3-(*p*-Dimethylaminobenzoyl)-2-methylpyrazolo[1,5-*a*]pyridine (**27**) was the most

TABLE V. Correlation Goefficient Matrix (Compounds 1—13)

	Act.	σ	π	F	R	MR	MW
Act.	1.00						
σ	−0.11	1.00					
π	−0.58	0.12	1.00				
F	−0.20	−0.09	0.83	1.00			
R	−0.75	0.27	0.89	0.48	1.00		
MR	−0.29	0.35	−0.29	−0.41	−0.11	1.00	
MW	−0.44	0.46	0.09	−0.01	0.15	0.86	1.00

TABLE VI. Inhibitory Activities of Active Compounds on Platelet Aggregation



Compd.	R	R^1	R'^1	ID_{100} μg/ml
23	iso-Pr	$N(CH_3)_2$	CH_3	0.01
26	CH_3	$NHCH_3$	H	0.1
27	CH_3	$N(CH_3)_2$	H	0.0007
28	CH_3	OCH_3	H	0.01
Aspirin				4.0
Nictindole (L-8027)				0.1

active compound, being more potent than nictindole (L-8027).

Because of the difficulty of drug design, systematic approaches, such as cluster analysis, are attractive. This report illustrates the use of this technique in the assessment of structure–activity relationships which allow prediction of the most effective substituent with a minimum of effort.

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. Column chromatography was carried out on silica gel (Wadogel C-200). Analyses within ±0.4% of theoretical values are indicated by the symbols of the elements alone. Platelet aggregation was measured in a Sienco DP-247E aggregometer.

Materials——2-Isopropylpyrazolo[1,5-*a*]pyridine and 2-methylpyrazolo[1,5-*a*]pyridine were prepared following the reported method.[4] 2-Isopropyl-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridine was prepared by the hydrogenation of 2-isopropylpyrazolo[1,5-*a*]pyridine under pressure in the presence of palladium carbon.

Preparation of 2-Isopropyl-3-(*p*-nitrobenzoyl)pyrazolo[1,5-*a*]pyridine (2)——Method A: A mixture of 2-isopropylpyrazolo[1,5-*a*]pyridine (3g) and *p*-nitrobenzoyl chloride (5 g) was stirred for 3 h at 150—160 °C. After the mixture had been cooled with ice cold water, it was made alkaline with 10% NaOH, and triturated to afford a crude crystalline product. The precipitated crystals were collected by filtration and dried under reduced pressure to give crude crystals, which were recrystallized from benzene–hexane to give yellow needles. ^{1}H-NMR ($CDCl_3$) δ: 1.36 (6H, d, J=6.8 Hz, $CH(C\underline{H}_3)_2$), 3.44 (1H, m, J=6.8 Hz, $C\underline{H}(CH_3)_2$), 6.87 (1H, ddd, J=6.8, 6.6, 1.5 Hz, pyrazolopyridine-6-H), 7.38 (1H, dd, J=9.0, 6.6 Hz, pyrazolopyridine-5-H), 7.58 (1H, dd, J=9.0, 1.5 Hz, pyrazolopyridine-4-H), 7.81 (2H, d, J=9.0 Hz, benzoyl-3,5-H), 8.35 (2H, d, J=9.0 Hz, benzoyl-2,6-H), 8.48 (1H, d, J=6.8 Hz, pyrazolopyridine-7-H). Other *p*-substituted benzoyl derivatives were also prepared under the same conditions. The yields and characteristics of the products are listed in Table I.

Preparation of 3-(*p*-Aminobenzoyl)-2-isopropylpyrazolo[1,5-*a*]pyridine (6)——Method B: A solution of 2-isopropyl-3-(*p*-nitrobenzoyl)pyrazolo[1,5-*a*]pyridine (3 g) in ethanol (70 ml) and acetic acid (5 ml) was agitated in a hydrogen atmosphere under atmospheric pressure at room temperature in the presence of 10% palladium carbon (0.6 g) for 1 h. After absorption ceased, the solution was filtered and concentrated to dryness. The residue was recrystallized from benzene to give pale yellow leaflets, 2.5 g (Table I).

Preparation of 2-Isopropyl-3-(*p*-methyl- and *p*-dimethylaminobenzoyl)pyrazolo[1,5-*a*]pyridine (22 and 23)——Method C: A mixture of 3-(*p*-aminobenzoyl)-2-isopropylpyrazolo[1,5-*a*]pyridine (3 g), methyl iodide (1.3 g) and sodium carbonate (1.7 g) in water (36 ml) and ethanol (60 ml) was refluxed for 5 h, then concentrated to dryness. The residue was dissolved in chloroform and washed with water. The chloroform layer, after being dried over anhydrous Na_2SO_4, was concentrated to dryness. The residue was subjected to silica gel column chromatography and eluted with CH_2Cl_2–AcOEt (4:1). First fraction: Recrystallization from benzen–hexane gave 1 g of the dimethyl compound (**24**). ^{1}H-NMR ($CDCl_3$) δ: 1.37 (6H, d, J=7.0 Hz, $CH(C\underline{H}_3)_2$), 3.07 (6H, s, $N(C\underline{H}_3)_2$), 3.56 (1H, m, J=7.0 Hz, $C\underline{H}(CH_3)_2$), 6.67 (2H, d, J=8.8 Hz, benzoyl-3,5-H), 7.14 (1H, dd, J=8.8, 6.6 Hz, pyrazolopyridine-5-H), 7.44 (1H, dd, J=8.8, 1.5 Hz, pyrazolopyridine-4-H), 7.72 (2H, d, J=8.8 Hz, benzoyl-2,6-H), 8.45 (1H, d, J=7.0 Hz, pyrazolopyridine-7-H). Second fraction: Recrystallization from benzen–hexane gave 0.8 g of the

monomethyl compound (**22**). ^{1}H-NMR δ: 1.37 (6H, d, J=7.0 Hz, CH(CH$_3$)$_2$), 2.91 (3H, s, NHCH$_3$), 3.55 (1H, m, J=7.0 Hz, CH(CH$_3$)$_2$), 4.25 (1H, br, NHCH$_3$), 6.58 (2H, d, J=8.8 Hz, benzoyl-3, 5-H), 6.79 (1H, ddd, J=6.8, 6.6, 1.5 Hz, pyrazolopyridine-6-H), 7.14 (1H, dd, J=8.8, 6.6 Hz, pyrazolopyridine-5-H), 7.41 (1H, dd, J=8.8, 1.5 Hz, pyrazolopyridine-4-H), 7.67 (2H, d, J=8.8 Hz, benzoyl-2,6-H), 8.44 (1H, d, J=7.0 Hz, pyrazolopyridine-7-H).

Preparation of 3-(*p*-Benzoylaminobenzoyl)-2-isopropylpyrazolo[1,5-*a*]pyridine (8)——Method D: Benzoyl chloride (1 g in 5 ml of benzene) was added to a mixture of 3-(*p*-aminobenzoyl)-2-isopropylpyrazolo[1,5-*a*]pyridine (2 g) and triethylamine (0.7 g in 10 ml of benzene) with stirring and cooling. After 30 min at room temperature, the mixture was concentrated *in vacuo* and triturated with water. Precipitated crystals were collected by filtration and dried under reduced pressure to give crude crystals, which were recrystallized from methanol to give white needles, 2 g (Table I).

Pharmacological Test——Platelet aggregation was determined by the method using rabbit platelet-rich plasma (PRP).[5] The ID_{100} value is the concentration which gives maximum (100%) inhibition of platelet aggregation induced by arachidonic acid.

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