by removal of the THP group, afforded 10. Treatment of the ketones 1 and 2 with 2- and 3-furyllithium gave 11, 14, 15, and 16. The acetates 12 and 13 were obtained by heating a solution of 10 or 11 in Ac_2O and pyridine at 100° for 24 hr.[2]

Compounds 17 and 18 were prepared by treating the ketones 1 and 2 with 2-thienyllithium,[20] prepared *in situ* by reacting thiophene with *n*-BuLi. A solution of freshly distilled thiophene (4.2 g), Et_2O (84 ml), and *n*-BuLi in Et_2O (1.4 *N*, 34 ml) was stirred at −10° for 1 hr. A solution of 1 (4.2 g) in toluene (168 ml) was added and the mixture was stirred overnight at room temperature. After work-up, the crude product was chromatographed on basic Al_2O_3. The fractions eluted with C_6H_6–hexane (2:1) were combined and crystallized from Me_2CO–MeOH to give pure 17 (2.0 g). The cyclopentyl ether 18 was prepared by the same method.

Acknowledgments. The authors wish to express their thanks to Dr. A. Failli for having prepared compounds 5 and 20 and Messrs. A. Legault, G. Gauthier, J. Schmid, and R. Minder for their technical help.

References

(1) (a) E. Schwenk, E. Block, and B. Whitman, U. S. Patent 2,418,603 (1947); (b) R. Ginsig. U. S. Patent 3,647,831 (1972).
(2) C. Revesz and Y. Lefebvre, *J. Med. Chem.*, preceding paper.
(3) C. Burgess, D. Burn, P. Feather, M. Howarth, and V. Petrow, *Tetrahedron*, 21, 1197 (1965).
(4) (a) Y. Lefebvre. *Tetrahedron Lett.*, 133 (1972); (b) J. M. Ferland, Y. Lefebvre, R. Deghenghi, and K. Wiesner, *ibid.*, 3617 (1966).
(5) (a) J. H. Melles and H. J. Backer, *Recl. Trav. Chim. Pays-Bas*, 72, 314 (1953); (b) *ibid.*, 72, 491 (1953).
(6) H. E. Simmons and R. D. Smith, *J. Amer. Chem. Soc.*, 80, 5323 (1958).
(7) (a) J. Furukawa, N. Kawabata, and J. Nishimura, *Tetrahedron Lett.*, 3353 (1966); (b) *Tetrahedron*, 24, 53 (1968).
(8) D. B. Miller, *J. Organometal. Chem.*, 14, 253 (1968).
(9) D. B. Miller, *Tetrahedron Lett.*, 989 (1964).
(10) C. M. Weeks and D. A. Norton, *J. Chem. Soc. B*, 1494 (1970).
(11) J. R. Parikh and W. von E. Doering, *J. Amer. Chem. Soc.*, 89, 5505 (1967).
(12) L. H. Knox, E. Velarde, S. Berger, D. Cuadriello, P. W. Landis, and A. D. Cross, *J. Amer. Chem. Soc.*, 85, 1851 (1963).
(13) (a) E. Allen and E. A. Doisy, *J. Amer. Med. Ass.*, 81, 819 (1923); (b) C. Revesz and C. I. Chappel, *J. Reprod. Fert.*, 12, 473 (1966).
(14) D. J. Finney, "Statistical Method in Biological Assay," Hafner Publishing Co., New York, N.Y., 1964, pp 468–490.
(15) B. L. Rubin, A. S. Dorfman, L. Black, and R. I. Dorfman, *Endocrinology*, 49, 429 (1951).
(16) C. Rufer, E. Schröder, and H. Gibian, *Justus Liebigs Ann. Chem.*, 705, 211 (1967).
(17) A. D. Cross, I. T. Harrison, F. A. Kincl, E. Farkas, R. Kraay, and R. I. Dorfman, *Steroids*, 4, 423 (1964).
(18) A. Ercoli and R. Gardi, *Chem. Ind. (London)*, 1037 (1961).
(19) J. A. Moede and C. Curran, *J. Amer. Chem. Soc.*, 71, 852 (1949).
(20) H. Gilman and D. A. Shirley, *J. Amer. Chem. Soc.*, 71, 1870 (1949).

Quinazolines and 1,4-Benzodiazepines. 67.[1] 5-Ferrocenyl-1,4-benzodiazepin-2-ones

Robert Kalish,* Thomas V. Steppe, and Armin Walser*

Chemical Research Department, Hoffmann-La Roche Inc., Nutley, New Jersey 07110. *Received April 1, 1974*

In a continuation of our search for medicinally useful benzodiazepines, we have prepared 1,4-benzodiazepin-2-ones containing a ferrocenyl group at the 5 position. These compounds are, to our knowledge, the first stable benzodiazepines containing an organometallic substituent. The preparation and the evaluation of the CNS activity of these 5-ferrocenylbenzodiazepinones were of particular interest because of the reported similarity of many of the physical and chemical properties of the phenyl and ferrocenyl groups.[2]

Chemistry. The key step in the synthesis of these benzodiazepinones (Scheme I) was the preparation of the alcohol 1 (83% yield) *via* the condensation of 2-lithionitrobenzene[3] with ferrocenecarboxaldehyde at −90 to −95°. Despite the known sensitivity of ferrocenes to oxidation, the conversion of 1 to 2 was effected in high yield with activated MnO_2 at 25°. Surprisingly, the reduction of 2 to 3 was more difficult to achieve. Metal reducing agents such as $SnCl_2$ and Fe–HCl were without effect. The conversion of compound 2 to 3 by catalytic hydrogenation (Pd or Pt) was slow (48–72 hr) but did give 60–70% yields of the desired amino ketone. However, the use of the Pd-catalyzed hydrogen-transfer reaction of Braude, *et al.*,[4] gave 3 in almost quantitative yield in a clean, relatively rapid (*ca.* 18 hr) reaction. The conversion of 3 to the benzodiazepinones 5 and 6 was accomplished in the standard fashion *via* bromoacetylation and then ammonolysis of the resulting α-bromoacetanilide with liquid ammonia to give the (uncharacterized) α-aminoacetanilide which was cyclized with acid to the parent benzodiazepinone 5. Finally, N-methylation of 5 gave the desired benzodiazepinone 6.

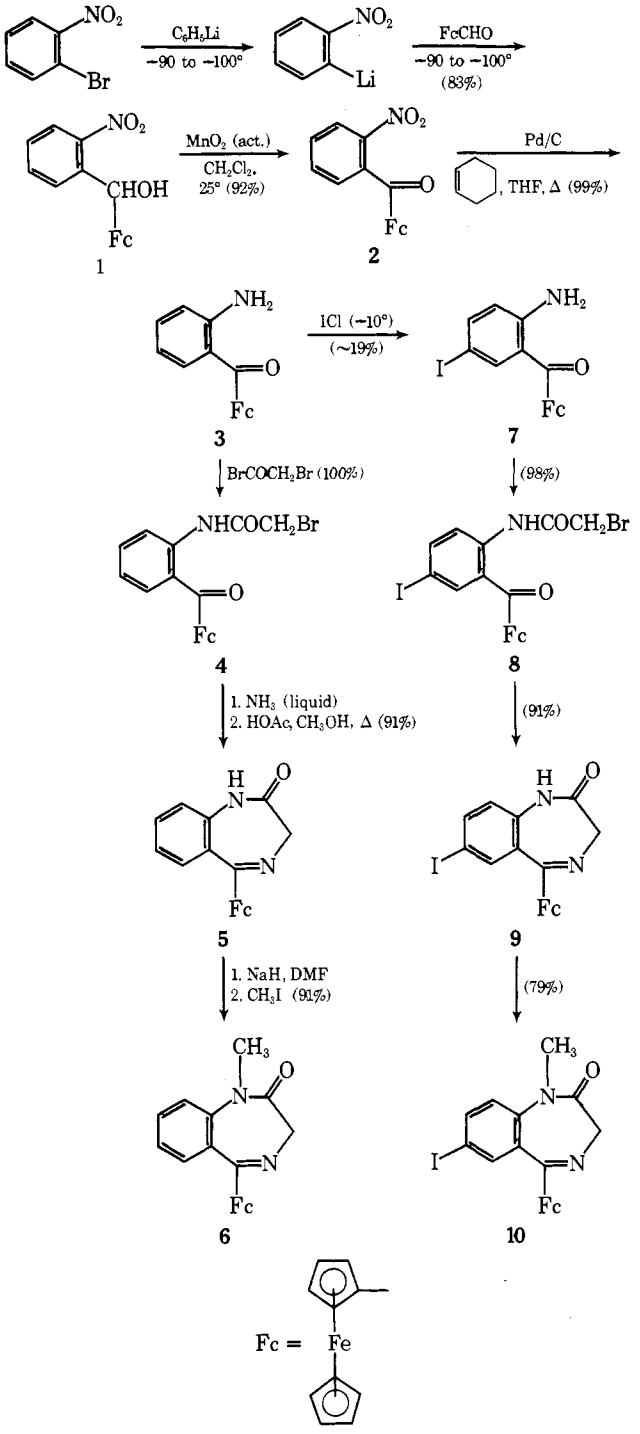
Because of the known beneficial effect of 7-halogen substituents on the activity of benzodiazepines,[5] the 7-iodobenzodiazepinones 9 and 10 were also prepared. Iodination of the amino ketone 3 with ICl was erratic but gave the desired iodoamino ketone 7 in *ca.* 19% yield. The position of the introduced iodine was established by spectral data (see Experimental Section). In particular, there was no evidence of any product resulting from either iodination ortho to the amino group or in the "less-deactivated" bottom, unsubstituted π-cyclopentadienyl ring of the ferrocenyl substituent. Conversion of 7 to the benzodiazepinones 9 and 10 was accomplished in the usual fashion.

Pharmacology. Benzodiazepines 6 and 10 are both relatively nontoxic: compound 6, LD_{50} (mice) 775 mg/kg ip and 900 mg/kg po; compound 10, LD_{50} (mice) 900 mg/kg ip and 450 mg/kg po. Both compounds were inactive at the highest doses used when screened for muscle relaxant, anticonvulsant, and taming activity in mice: muscle relaxant activity (inclined screen, po), compounds 6 and 10 ED_{50} >400 mg/kg; anticonvulsant activity (antimetrazole po), compounds 6 and 10, ED_{50} >800 mg/kg; taming activity (foot shock, po), compounds 6 and 10, ED_{50} >100 mg/kg. The methods used in these tests have been previously described.[6]

Experimental Section

Melting points were determined using a Thomas-Hoover capillary melting point apparatus and are uncorrected. All new compounds possess ir (Perkin-Elmer Model 621 and Beckman IR-9 spectrophotomers), nmr (Varian Associates A-60 and HA-100 spectrometers, TMS internal standard), uv (Cary 14 and 15 spectrophotomers), and mass spectral data (CEC 110-21B and Jeolco 01SG double-focusing spectrometers, Hitachi RMU 6L single-focusing spectrometer) in agreement with their assigned structures. Where analyses are indicated only by the symbols of the elements, the analytical results obtained for those elements were within ±0.4% of the theoretical values.

Scheme I



All reactions involving moisture- and/or oxygen-sensitive compounds were carried out in dry glassware under an argon atmosphere. THF was reagent grade (Fisher Scientific Co.) and was dried over Type 5A molecular sieves. Et_2O was Mallinckrodt analytical reagent and was used without additional drying. DMF was reagent grade (Fisher) and was dried over Type 4A molecular sieves. C_6H_5Li (2–2.5 *M* in 70:30 C_6H_6–Et_2O, Ventron Corp.) was used as received.

All solutions were dried over powdered $CaSO_4$, and solvent removal or concentration was done on a Büchi Rotavapor-R using aspirator vacuum (15–25 mm). Column chromatography was done on 70–325 mesh, neutral silica gel 50 (E. Merck). Tlc was done on precoated plates of silica gel F-254 (layer thickness 0.25 mm, E. Merck) which were equilibrated with atmospheric moisture prior to use.

2-Nitro-α-(1-ferrocenyl)benzyl Alcohol (1). A vigorously stirred, cooled (−90°) solution of 230 ml (0.55 mol) of 2.4 *M* C_6H_5Li in 2.2 l. of THF–Et_2O–hexane (2:1:1 v/v/v, henceforth referred to as TEH) was treated over a 20-min period with a solution of 101.0 g (0.50 mol) of 2-bromonitrobenzene in 200 ml of TEH; the temperature was maintained between −100 and −90° during the addition. The solution was stirred at −100 to −90° for 1 hr and then treated with a solution of 125.7 g (0.59 mol) of ferrocenecarboxaldehyde in 450 ml of TEH while maintaining the reaction temperature between −100 and −90°. After an additional 1.5 hr at −100 to −90°, the reaction mixture was poured, with stirring, into 6.5 l. of H_2O, and the solution was extracted with four 750-ml portions of CH_2Cl_2. The combined organic extracts were washed with H_2O and brine, dried, and concentrated to *ca.* 500 ml to give a suspension which was treated with 1 l. of hexane and heated to reflux. Cooling afforded 141 g (83%) of light orange product, mp 134–136°. An analytical sample, mp 134.5–136°, was obtained by recrystallization from CH_2Cl_2. *Anal.* ($C_{17}H_{15}FeNO_3$) C, H, Fe, N.

(2-Nitrobenzoyl)ferrocene (2). A solution of 245 g (0.73 mol) of 1 in 3 l. of CH_2Cl_2 was treated with 435 g (5.0 mol) of activated MnO_2 (Winthrop Laboratories), and the suspension was stirred at 25° for 65 hr and then filtered. The filter cake was washed with 4 l. of CH_2Cl_2, and the combined CH_2Cl_2 filtrates were concentrated to give 223 g (92%) of red product, mp 115–159° dec. An analytical sample, mp 159–161° dec, was prepared by recrystallization from CH_2Cl_2–hexane. *Anal.* ($C_{17}H_{13}FeNO_3$) C, H, Fe, N.

(2-Aminobenzoyl)ferrocene (3). A solution of 84.0 g (0.25 mol) of 2 in 1.8 l. of THF was treated with 202 g (2.5 mol) of cyclohexene and 16.8 g of 10% Pd/C and heated at reflux for 24 hr. Filtration followed by concentration of the filtrate afforded 75.5 g (99%) of red product, mp 91–98° dec. An analytical sample, mp 97.5–99° dec, was obtained by recrystallization from CH_2Cl_2. *Anal.* ($C_{17}H_{15}FeNO$) C, H, Fe, N.

2-Bromo-2′-ferrocenoylacetanilide (4). A stirred mixture of 3.5 g (0.012 mol) of 3 in 100 ml of CH_2Cl_2, 100 ml of saturated $NaHCO_3$, and 20 ml of 2 *N* Na_2CO_3 was cooled to 5° and treated with a solution of 4.0 g (0.02 mol) of bromoacetyl bromide in 10 ml of CH_2Cl_2. The reaction mixture was stirred at 25° for 16 hr and poured into 100 ml of H_2O. The CH_2Cl_2 layer was removed, the aqueous phase was washed with two 50-ml portions of CH_2Cl_2, and the combined CH_2Cl_2 extracts were washed with saturated $NaHCO_3$ and brine, dried, and concentrated to give 4.9 g (100%) of red product, mp 140–142.5° dec. An analytical sample, mp 141.5–142.5° dec, was obtained by recrystallization from CH_2Cl_2–hexane. *Anal.* ($C_{19}H_{16}BrFeNO_2$) C, H, Br, Fe, N.

1,3-Dihydro-5-ferrocenyl-2*H*-1,4-benzodiazepin-2-one (5). A solution of 23.3 g (0.055 mol) of 4 in 125 ml of CH_2Cl_2 was added, with stirring, to 150 ml of liquid NH_3 (maintained at −78°) over a 20-min period. The solution was stirred at reflux for 6 hr, the cooling bath was removed, and the NH_3 was allowed to evaporate overnight. The CH_2Cl_2 solution was filtered and concentrated. The red oil thus obtained was dissolved in 200 ml of MeOH containing 5 ml of glacial AcOH. The solution was heated at reflux for 5 hr, cooled, treated with 50 ml of saturated $NaHCO_3$, and poured, with stirring, into 1.2 l. of H_2O giving, after filtration, 17.3 g (91%) of red product, mp 223–227° dec. An analytical sample, mp 224.5–227° dec, was obtained by recrystallization from CH_2Cl_2. *Anal.* ($C_{19}H_{16}FeN_2O$) C, H, Fe, N.

1,3-Dihydro-5-ferrocenyl-1-methyl-2*H*-1,4-benzodiazepin-2-one (6). A stirred, cooled (5°) solution of 9.4 g (0.027 mol) of 5 in 225 ml of DMF was treated with 1.4 g (0.033 mol) of NaH (57% dispersion in mineral oil). The reaction mixture was allowed to warm to 25°, stirred for 2 hr, and treated with 5.0 ml (11.4 g, 0.08 mol) of MeI. After 1 hr at 25°, the reaction mixture was poured in 2 l. of H_2O and the red precipitate was collected giving 8.8 g (91%) of product, mp 155–160° dec. An analytical sample, mp 163–164° dec, was obtained by recrystallization from CH_2Cl_2–hexane. *Anal.* ($C_{20}H_{18}FeN_2O$) C, H, Fe, N.

2-Amino-(5-iodobenzoyl)ferrocene (7). A solution of 5.0 g (0.031 mol) of ICl in 25 ml of $CHCl_3$ was added to a vigorously stirred, cooled (−10°) solution of 3.1 g (0.01 mol) of 3 in 50 ml of THF, 75 ml of MeOH, and 40 ml of $CHCl_3$ over a period of 10 min. The dark solution was stirred at −10° for 1 hr and poured into a stirred mixture of 150 ml of $CHCl_3$ and 150 ml of H_2O containing 11 g of $NaHSO_3$. The organic layer was removed, the aqueous phase was extracted with two 50-ml portions of $CHCl_3$, and the combined organic extracts were washed with H_2O and brine and then dried. Solvent removal gave a red oil. The crude product was dissolved in C_6H_6–EtOAc (10:1 v/v), and the solution was chromatographed on 250 g of silica gel. Elution with C_6H_6–EtOAc (10:1 v/v) afforded a red oil which was crystallized from hexane to give 0.8 g (19%) of red product: mp 91.5–95° dec;

nmr (100 MHz, $CDCl_3$) δ 4.24 (5 H, s, FeC_5H_5), 4.68 (4 H, AA'BB' m, COC_5H_5Fe), 5.60 (2 H, br s, NH_2), 6.48 (1 H, d, J = 8.5 Hz, aromatic H), 7.44 (1 H, dd, J = 2.5, 8.5 Hz, aromatic H), and 8.34 (1 H, d, J = 2.5 Hz, aromatic H); ir (KBr) 3450, 3340 (NH_2), and 1610 cm^{-1} (C=O). An analytical sample, mp 94–96°, was obtained by recrystallization from hexane. *Anal.* ($C_{17}H_{14}FeINO$) C, H, Fe, I, N.

2-Bromo-4′-iodo-2′-ferrocenoylacetanilide (8). Bromoacetylation of 3.6 g (0.0083 mol) of 7 with 3.5 g (0.018 mol) of bromoacetyl bromide (in the same fashion as the bromoacetylation of 3) afforded 4.5 g (98%) of red product, mp 156–164° dec. An analytical sample, mp 172–173° dec, was obtained by recrystallization from CH_2Cl_2–hexane. *Anal.* ($C_{19}H_{15}BrFeINO_2$) C, H, Br, Fe, I, N.

1,3-Dihydro-5-ferrocenyl-7-iodo-2*H*-1,4-benzodiazepin-2-one (9). Treatment of 2.2 g (0.004 mol) of 8 with liquid NH_3 followed by cyclization in MeOH–AcOH yielded 1.7 g (91%) of orange-red product, mp 120–131° dec. An analytical sample, mp 168–171° dec, was obtained by two recrystallizations from CH_2Cl_2–hexane. *Anal.* ($C_{19}H_{15}FeIN_2O$) C, H, I, N.

1,3-Dihydro-5-ferrocenyl-7-iodo-1-methyl-2*H*-1,4-benzodiazepin-2-one (10). A stirred, cooled (5°) solution of 3.6 g (0.0077 mol) of 9 in 90 ml of DMF was treated with 0.38 g (0.0088 mol) of NaH (57% dispersion in mineral oil). The reaction mixture was allowed to warm to 25°, stirred for 2.5 hr, and treated with 2.0 ml (4.6 g, 0.032 mol) of MeI. After 1 hr at 25°, the reaction mixture was poured into 1 l. of H_2O. The brown solid thus obtained was dissolved in 200 ml of C_6H_6–EtOAc (2:1 v/v) and filtered through 10 g of silica gel to give, after removal of the solvent, 2.9 g (79%) of red-brown product, mp 144–149° dec. An analytical sample, mp 154.5–156° dec, was obtained by recrystallization from CH_2Cl_2–hexane. *Anal.* ($C_{20}H_{17}FeIN_2O$) C, H, Fe, I, N.

Acknowledgments. We are grateful to Mr. John Vermeulen for his skilled technical assistance and to Dr. L. O. Randall, Dr. W. Pool, Mrs. B. Kappell, and Ms. D. Hane for the pharmacological data. We also wish to thank the following members of our Physical Chemistry Department: Mr. S. Traiman (ir spectra), Dr. V. Toome (uv spectra), Dr. W. Benz (mass spectra), Dr. T. Williams (nmr spectra), and Dr. F. Scheidl (microanalyses).

References and Notes

(1) R. Kalish, E. Broger, G. F. Field, T. Anton, T. V. Steppe, and L. H. Sternbach, *J. Heterocycl. Chem.*, submitted for publication (paper 65).
(2) For a comprehensive review of heterocyclic ferrocenes as well as references to other aspects of ferrocene chemistry, see F. D. Popp and E. B. Moynahan, *Advan. Heterocycl. Chem.*, 13, 1 (1971).
(3) G. Köbrich and P. Buck, *Angew. Chem., Int. Ed. Engl.*, 5, 1044 (1966).
(4) E. A. Braude, R. P. Linstead, and K. R. H. Wooldridge, *J. Chem. Soc.*, 3586 (1954).
(5) L. H. Sternbach in "The Benzodiazepines," S. Garattini, E. Mussini, and L. O. Randall, Ed., Raven Press, New York, N.Y., 1973, pp 1–26.
(6) (a) L. H. Sternbach, G. A. Archer, J. V. Earley, R. I. Fryer, E. Reeder, N. Wasyliw, L. O. Randall, and R. Banziger, *J. Med. Chem.*, 8, 815 (1965); (b) L. H. Sternbach, L. O. Randall, R. Banziger, and H. Lehr in "Drugs Affecting the Central Nervous Systems," Vol. 2, A. Burger, Ed., Marcel Dekker, New York, N.Y., 1968, p 247.

Communications to the Editor

6-Methyl-1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazolin-2-one, a Potent Inhibitor of ADP-Induced Platelet Aggregation

Sir:

The role of blood platelets in thrombosis and occlusive diseases is well documented as is the effect of adenosine diphosphate (ADP) on platelet aggregation.[1] An enhanced response of platelets to ADP in diabetes mellitus[2] and myocardial infarction,[3] in addition to the inhibition of metastasis formation of blood-borne cancer cells upon a reduction of platelet aggregability,[4] suggests that compounds which inhibit ADP-induced platelet aggregation may be useful in the treatment of these disorders.

Aspirin and other nonsteroidal antiinflammatory agents (*e.g.*, phenylbutazone, indomethacin, etc.) have been shown to inhibit the release of endogenous ADP from platelet granules thereby inhibiting collagen-induced platelet aggregation.[5] Compounds of this type do not inhibit the primary wave of ADP-induced platelet aggregation nor are they very effective against the release caused by thrombin.[6]

Some drugs do inhibit the first wave of ADP-induced platelet aggregation (*e.g.*, adenosine, PGE_1, methylxanthine) but, at the concentrations required to affect platelet

Table I. Inhibition of Platelet Aggregation

	In vitro,[a] ED_{50} (μg/ml)[b]					*Ex vivo*,[a] ED_{50} (mg/kg)		
	Rabbit[c]			Dog,[c]	Human,[c]	Rabbit (ip)[d]		Dog (po),[e]
Compound	ADP[f]	Collagen[g]	Thrombin[h]	ADP[f]	ADP[f]	ADP[f]	Collagen[g]	ADP[f]
3	0.41	0.09	0.34	0.57	0.4	0.40	0.13	1.83
Aspirin	>512	7		na	na	na[i]	3	na
Phenylbutazone	>512	50		na	na	na[i]	58	na
Sulfinpyrazone	>512	62		na	na	na[i]	3	na
Dipyridamole	>512	245		na	na	na[i]	>100	na

[a] Aggregometer method of Born[15] as modified by Mustard, *et al.*[16] [b] Effective concentration required for a 50% inhibition of platelet aggregation after a 3-min incubation period (95% confidence limit). [c] Citrated platelet rich plasma (PRP). [d] Effective dose required for a 50% inhibition 2 hr after dosing (95% confidence limit). [e] Effective dose required for a 50% average inhibition of the 1- and 3-hr post-dose against ADP-induced platelet aggregation (95% confidence limit). [f] Concentration of ADP is 2.93×10^{-5} *M* (12.5 μg/ml). [g] 0.05 ml of standard suspension/0.9 ml of PRP. [h] 1 unit of bovine thrombin/ml of PRP. [i] Maximal dose tested is 100 mg/kg.