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.

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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

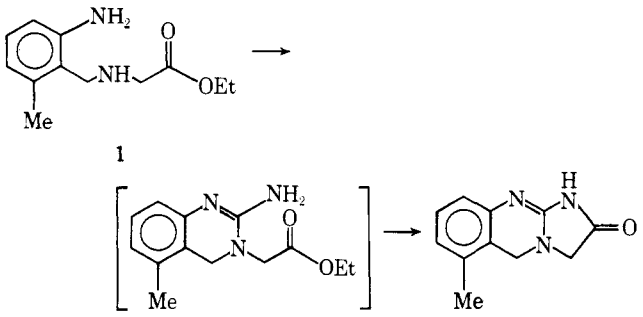
[a] Aggregometer method of Born[15] as modified by Mustard, *et al.*[16] [b] Effective concentration required for a 50% inhibition of platelet aggregation after a 3-min incubation period (95% confidence limit). [c] Citrated platelet rich plasma (PRP). [d] Effective dose required for a 50% inhibition 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.

function, significant side effects are observed, thereby limiting their clinical use as antithrombotic agents.[7]

Dipyridamole, pyrimidopyrimidines, and thienopyrimidines also inhibit ADP-induced platelet aggregation[8] and have been widely studied. At concentrations which inhibit experimentally induced platelet thrombi *in vivo*, no significant effect of platelet function has been observed clinically. Clinical studies with increasing doses of the thienopyrimidines were discontinued because of serious side effects.[9]

We wish to report that 6-methyl-1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazolin-2-one (BL-3459) exhibits potent activity against ADP-induced platelet aggregation *in vitro* in rabbit, dog, and human platelet rich plasma as well as in several *ex vivo* and *in vivo* models.

The synthesis was achieved by reaction of *N*-(2-amino-6-methylbenzyl)glycine ethyl ester (1) with cyanogen bromide presumably *via* ring closure of the 2-amino-3-(carbethoxymethyl)-3,4-dihydroquinazoline (2).



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2 3

Reduction of 2-methyl-6-nitrobenzoic acid with diborane in tetrahydrofuran resulted in 2-methyl-6-nitrobenzyl alcohol which was subsequently heated with thionyl chloride in benzene. Isolation and crystallization from cyclohexane afforded 2-methyl-6-nitrobenzyl chloride: yield 75% (based on 2-methyl-6-nitrobenzoic acid); nmr ($CDCl_3$) τ 7.45 (s, CH_3), 5.20 (s, CH_2). *Anal.* ($C_8H_8ClNO_2$) C, Cl, H, N.

Condensation of the 2-methyl-6-nitrobenzyl chloride with glycine ethyl ester in the presence of triethylamine followed by catalytic hydrogenation employing 10% Pd on carbon as catalyst afforded *N*-(2-amino-6-methylbenzyl)-glycine ethyl ester: yield 85% (based on 2-methyl-6-nitrobenzyl chloride); the material was of sufficient purity to use as such; bp 128–131° (0.07 mm); ir (film) 1745 cm^{-1} (C=O); nmr ($CDCl_3$) τ 7.70 (s, CH_3, benzyl CH_2), 6.20 (s, benzyl CH_2), 6.61 (s, glycine CH_2). *Anal.* ($C_{12}H_{18}N_2O_2$) C, H, N.

Equimolar quantities of cyanogen bromide and *N*-(2-amino-6-methylbenzyl)glycine ethyl ester were refluxed for 18 hr in ethyl alcohol and the solvent was removed *in vacuo*. Treatment of the resulting solid with aqueous base followed by crystallization from 1 *N* hydrochloric acid yielded 6-methyl-1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazolin-2-one hydrochloride: yield 55%; mp >250° dec; ir (KBr) 1805, 1690, 1605, 1590 cm^{-1}; nmr (TFA) τ 7.70 (s, CH_3), 5.45 (s, 3-CH_2), 5.10 (s, 4-CH_2). *Anal.* ($C_{11}H_{11}N_3O \cdot HCl \cdot H_2O$) C, H, N (Fischer).

Marked activity was exhibited by compound 3 on platelet function (Table I) *in vitro* and *ex vivo* in rabbits (ip) and dogs (po) with no significant increases in bleeding times at doses exceeding the ED_{50} values. Oral activity was established in several modified *in vivo* models[10] including the biolaser induced thrombosis in the rabbit ear chamber[11] (ED = 10 mg/kg), endotoxin shock in anesthetized beagle dogs[12] (ED = 10 mg/kg), hemorrhagic shock in anesthetized beagle dogs[13] (ED = 1 mg/kg), and electrically induced carotid artery thrombosis in the dog[14] (ED = 0.5 mg/kg).

These results show that 6-methyl-1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazolin-2-one significantly affects platelet function and may be of value in the treatment of platelet disorders.

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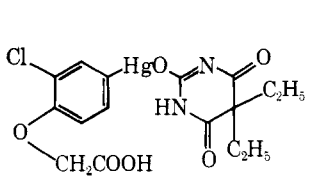
(1-Oxo-2-substituted-5-indanyloxy)acetic Acids, a New Class of Potent Renal Agents Possessing Both Uricosuric and Saluretic Activity. A Reexamination of the Role of Sulfhydryl Binding in the Mode of Action of Acylphenoxyacetic Acid Saluretics

Sir:

Because of their many desirable pharmacodynamic attributes, including potent saluresis, proper urinary Na^+/Cl^- balance, and uricosuric activity, the mercurial diuretics, particularly the phenoxyacetic acids, *e.g.*, merbaphen (1)[1] and mersalyl,[2,3] served as models which led to the discovery of the family of (acryloylphenoxy)acetic acids,[4] typified by ethacrynic acid (2a). These mercurials and ethacrynic acid exhibit biological similarities in that they induce potent saluresis in dogs[5] and in man[6] but not in rats;[7] however, they differ in that while the mercurials are



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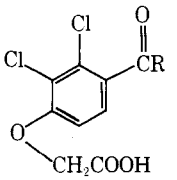

2a, R = $-C(=CH_2)C_2H_5$
b, R = $-CH(CH_3)C_2H_5$
c, R = $-C(=CHCH_3)C_2H_5$