measurement was determined on 15 and was found to be consistent with the formula $C_{19}H_{16}{}^{16}O_2{}^{18}O$ within 4 ppm. The location of the ^{18}O in warfarin was checked by the ratio of *m/e* 267/*m/e* 265 fragment ions (Table II).[2a]

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Naphthylalkyl Lactamimides as Inhibitors of Blood Platelet Aggregation

Edward M. Roberts, J. Martin Grisar,* Robert D. MacKenzie, George P. Claxton, and Thomas R. Blohm

Merrell-National Laboratories, Division of Richardson-Merrell Inc., Cincinnati, Ohio 45215.

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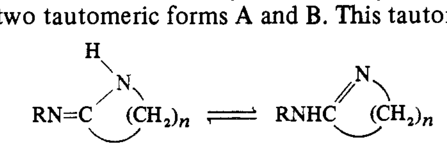
Hexahydro-2-[1-(1-naphthyl)ethylimino]azepine·HCl (2) (RMI 7822) was found to inhibit human blood platelet aggregation induced by ADP and other agents with minimal release of procoagulant platelet factor 3. The compound was selected after careful modification of structural parameters, such as α-substitution, lactam ring size, aromatic substitution, as well as evaluation of its optical isomers.

Arterial thrombosis, especially in arteries supplying heart muscle and brain, is a leading cause of death and disability.[1] The blood platelets play a dominant role in such thromboses, both in the initial event and at the occlusive stage.[2] The so-called white thrombus that develops before fibrin clot formation is composed primarily of aggregated platelets. A number of tissue constituents can initiate platelet aggregation.[3] Among these substances adenosine diphosphate (ADP) seems to be especially important, since it not only can initiate aggregation, but appears to mediate aggregation due to other agents as well.[4] Physiologic functions of platelets include hemostasis and possible repair of vascular endothelium.[5] In performing these functions platelets must undergo controlled adhesion and aggregation. Agents that would normalize abnormal platelet functions in the thrombosis-prone individual would have great therapeutic value. For these reasons we have adopted and developed techniques to evaluate large numbers of compounds available to us from earlier synthetic programs in our laboratories. Using human platelet-rich plasma (PRP) we measured *in vitro* inhibition of platelet aggregation induced by ADP, collagen, and several other agents.[6] Compounds that showed activity were then checked for release of platelet factor 3 (PF3) or PF3-like activity by measuring Stypven time. PF3 is a phospholipoprotein that acts as a cofactor in the coagulation process. Since we had established earlier that a normal breakfast causes PF3-like activity of from 0.1 to 0.3%, we adopted this as our limit of acceptability.[7] Selected compounds were then evaluated further. We reported earlier our findings on certain piperidineethanols of benzyl- and benzylidenefluorene,[8,9] and on a member of a series of anilines,[10] obtained from Zellner.[11] We now wish to report our findings on certain lactamimides.

An exploratory series of lactamimides was prepared by one of us (E.M.R.) as potential antihypertensive agents. Later one of these, compound 2† in Table I, was found to inhibit ADP-induced platelet aggregation. We then explored systematically the effect of structural modifications on this activity by preparing and evaluating the compounds listed in Table I. This study revealed that activity is distributed broadly throughout the series. The structural parameter that most affects inhibition of platelet aggregation in this series was found to be the substituent R on the carbon atom adjacent to the lactamimide function (compounds **1-6**). The unsubstituted congener **1** was found to be less active than several of the alkyl-substituted congeners, and of these the methyl-substituted compound **2** showed least effect on PF3 release. The sterically hindered *tert*-butyl congener **5** and the phenyl-substituted congeners **16-19** were less active. Exploration of the influence of the lactam ring size (compounds **2, 7-10**) showed that the 5- and 6-membered lactam ring congeners are less active (*cf.* also **14** *vs.* **13** and **16** *vs.* **17**), while the larger 8- and 13-membered ring congeners showed enhanced PF3 release. Several examples of aromatic substitution (compounds **11-14, 16, 17**) revealed no trends, nor did the structural changes represented by compounds **15** and **20**. No significant differences were found between the *d* and *l* isomers of **2**.

Compound 2† also inhibited aggregation induced by thrombin, epinephrine, and serotonin. It did not inhibit clot retraction and this property may be advantageous. More detail on these and additional evaluations will be reported elsewhere.

Lactamimides, also named cyclic or semicyclic amidines,[19] exist in two tautomeric forms A and B. This tautomerism

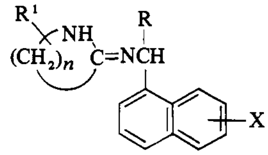


A B

has been studied by Kwok and Pranc.[20] It is not known, however, which tautomer prevails in the crystalline monohydrochloride salts, not to mention solutions under physio-

†Also named RMI 7822.

Table I. Naphthylalkyl Lactamimides. Effects on Human Blood Platelets



No.	R	R¹	*n*	X	Mp,[a] °C	Recrystn solvent[b]	% yield	Formula[c]	Effects on human blood platelets[d]: Concn, µg/ml	% inhibition of aggregation *vs.* ADP	% inhibition of aggregation *vs.* Collagen	Release of PF3
1	H	H	5	H	214–215	A	51[e]	$C_{17}H_{20}N_2 \cdot HCl$	300			0.004 (2)
									100	46 (2)	89 (2)	0.002 (2)
									30	15 (2)	33 (2)	
									10	8	13 (2)	
dl-2	CH_3	H	5	H	224–232	A	56[e]	$C_{18}H_{22}N_2 \cdot HCl$	300			0.037
									100	70 (2)	100 (2)	0.003
									30[f]	46 (2)	54 (2)	
									10	0 (2)	36 (2)	
d-2					252–253	B	38[e,g]		300			0.063
									100	83 (4)	91 (3)	0.022
									30	20 (5)	72 (3)	
									10	15 (2)	42 (3)	
l-2					252–253	B	36[e,h]		300			0.150
									100	56 (8)	87	0.013
									30	14 (9)		
									10	11 (4)		
3	CH_2CH_3	H	5	H	283–284 dec	A	76[i]	$C_{19}H_{24}N_2 \cdot HCl$	100	61		
									30	18		
4	$CH(CH_3)_2$	H	5	H	290–291 dec	A	62[j]	$C_{20}H_{26}N_2 \cdot HCl$	300			0.46
									100	91	100	0.014
									30	14	94	
									10		63	
5	$C(CH_3)_3$	H	5	H	>300	A	56[k]	$C_{21}H_{28}N_2 \cdot HCl$	100	71		
									30	10		
									10	0		
6	C_4H_9-*n*	H	5	H	200–201	C	74[l]	$C_{21}H_{28}N_2 \cdot HCl$	300			3.0
									100	79 (3)	100	0.12
									30	31 (3)	97	
									10	18	22	
7	CH_3	H	3	H	300–301 dec	A	37[h]	$C_{16}H_{18}N_2 \cdot HCl$	300			<0.001
									100	55 (2)	88	<0.001
									30	29 (2)	81	
8	CH_3	H	4	H	258–259	A	28[h]	$C_{17}H_{20}N_2 \cdot HCl$	300			0.002
									100	55 (2)	70	<0.001
									30	9	27	
9	CH_3	H	6	H	234–236	A	59[h]	$C_{19}H_{24}N_2 \cdot HCl$	300			0.30
									100	87	100	0.037
									30	16	86	
10	CH_3	H	11	H	217–219	A	28[h]	$C_{24}H_{34}N_2 \cdot HCl$	300			2.60
									100	100	100	0.50
									30	50	100	
									10	15	0	
11	CH_3	H	5	4-Cl	263–265	D	50[m]	$C_{18}H_{21}ClN_2 \cdot HCl$	300			0.75
									100	91 (3)	98 (2)	0.10
									30	22 (3)	80 (2)	
									10	10	43 (2)	
12	H	H	5	2-CH_3	223–228	A	82[e]	$C_{18}H_{22}N_2 \cdot HCl$	300			0.021 (2)
									100	52 (2)		0.004 (2)
									30	29 (2)		
13	CH_3	H	5	5,8-Me_2	265–267 dec	A	5[n]	$C_{20}H_{26}N_2 \cdot HCl$	300			2.30
									100	96 (4)	100 (2)	0.088
									30	37 (4)	89 (2)	
									10	8 (2)	21 (2)	
14	CH_3	H	4	5,8-Me_2	205–207 dec	E	66[n]	$C_{19}H_{24}N_2 \cdot HCl$	300			0.3
									100	96	100	0.032
									30	16	89	
									10		22	
15	CH_3	5-*tert*-Bu	5	H	>300	A	19[e]	$C_{22}H_{30}N_2 \cdot HCl$	100	93		
									30	0		
16	C_6H_5	H	4	4-F	197–199	A	69[o]	$C_{22}H_{21}FN_2 \cdot HCl$	100	87		
									30	11		
17	C_6H_5	H	5	4-F	278–279	A	73[o]	$C_{23}H_{23}FN_2 \cdot HCl$	100	90		
									30	20		
18	$C_6H_4CH_3$-*o*	H	5	H	290–292	A	64[p]	$C_{24}H_{26}N_2 \cdot HCl$	100	85		
									30	36		
19	$C_6H_4CH_3$-*o*	H	5	H[q]	308–309 dec	A	46[r]	$C_{24}H_{26}N_2 \cdot HCl$	100	66		
									30	18		
20	CH_3	H	5	H[q]	251–252	D	23[e]	$C_{18}H_{22}N_2 \cdot HCl$	300			0.15
									100	80 (2)		0.057
									30	32 (2)		
									10	5 (2)		

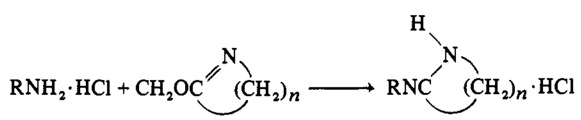
Table I *(Continued)*

Compound	Effects on human blood platelets[d]			
	Concn, μg/ml	% inhibition of aggregation *vs.* ADP	Collagen	Release of PF3
α-[*p*-(Fluoren-9-ylidenemethyl)phenyl]-2-piperidineethanol glycolate (RMI 10,393)[s]	300			0.747 (6)
	100	99 (4)	100 (2)	0.162 (6)
	30	28 (6)	39 (2)	0.003 (7)
	10	1 (6)	0 (2)	
N-(2-(Diethylaminoethyl)-*N*-(2-hydroxy-2-phenylethyl)-2,5-dichloroaniline (AN162)[t]	300			0.52 (42)
	100	62 (118)	75 (35)	0.10 (47)
	30	10 (104)	11 (35)	
2,4,6-Trimorpholinopyrimido[5,4-*d*]pyrimidine (RA 433 BS)[u]	300			
	100	47 (2)		<0.001
	30	25		<0.001
	10	15		
2-(5,10-Dihydrothiazolo[3,2-*b*][2,4]benzodiazepin-3-yl)phenol·HBr[v]	300			<0.001
	100	85		<0.001
	30	45		

[a]Melting points were detd on a Hoover capillary melting point apparatus and are corrected. [b]A = MeOH-Me_2CO, B = anhyd EtOH, C = MeCN, D = MeOH-MeCN, E = MeOH-Me_2CO-Et_2O. [c]All compds were analyzed for C, H and one other element. Analytical results obtained for these elements were within ±0.4% of calcd values. [d]See Experimental Section for method of biological evaluation. Values in parentheses refer to number of determinations. [e]From commercially available starting material as HCl salt. [f]This corresponds to 1×10^{-4} *M*. [g]From dextrorotatory amine; for *d*-2, $[\alpha]^{25}D$ +14.4°. [h]From levorotatory amine; for *l*-2, $[\alpha]^{25}D$ −9.6°. [i]From α-ethyl-1-naphthalenemethylamine·HCl, mp 269–270°, lit.[12] mp 281–282°. [j]Described in the Experimental Section. [k]From α-*tert*-butyl-1-naphthalenemethylamine·HCl, mp 276–278° dec, obtained in 9% yield from *tert*-butyl cyanide; the presence of the *tert*-butyl group was confirmed by nmr; the main product (41%) was *tert*-butyl α-naphthyl ketone, mp 78–81, lit.[13] mp 73–74°. [l]From α-*n*-butyl-1-naphthalenemethylamine·HCl, mp 246–247° dec; for free base *cf.* Schultz, *et al.*[14] [m]See Experimental Section. [n]From α,5,8-trimethyl-1-naphthalenemethylamine·HCl, mp 270–271°, obtained by Leuckart reaction in 63% from 4,8-dimethyl-1-acetonaphthone, mp 49–51°. [o]From α-(4-fluoro-1-naphthyl)benzylamine·HCl, mp 290–292° dec, obtained in 52% yield from benzonitrile. [p]From α-*o*-tolyl-1-naphthalenemethylamine·HCl, mp 302–306°; for free base see Cervinka, *et al.*[15] [q]β-Naphthyl derivative. [r]From α-*o*-tolyl-2-naphthalenemethylamine·HCl, mp 306–309° dec, obtained in 49% yield from *o*-tolunitrile. [s]Ref 8 and 9. [t]Ref 10. [u]Ref 16 and 17. [v]Ref 18.

logic conditions. For the sake of convenience we have represented and named all compounds in the tautomeric form A.

The compounds listed in Table I were prepared, with one exception, from the appropriate primary amine hydrochloride C, and the appropriate *O*-methyl lactim D by the method



C D A

first described by Benson and Cairns.[21] Yields were generally good (Table I).

Two examples are described in the Experimental Section. We preferred the method using no, or very little, solvent particularly for reactions with sterically hindered amines. Compound **10** was prepared by the procedure of Bredereck[22,23] in which the complex formed from a lactam and $POCl_3$ was used with a primary amine as the free base *or the hydrochloride salt.* No effort was made to improve the low yield obtained with this procedure.

The primary amines were prepared either by Leuckart reaction from the corresponding ketones or by *in situ* $LiAlH_4$ reduction of the addition products of Grignard reagents to nitriles. An example of each of these reactions is given in the Experimental Section and the footnotes to Table I give appropriate detail and references.

The ir spectra of lactamimides show C=N stretching vibrations that vary with ring size: 7 (1675 cm^{-1}), 8 (1650), 2 (1640), 9 (1645), and **10** (1650), as expected.

Experimental Section‡

dl-**Hexahydro-2-[1-(1-naphthyl)ethylimino]azepine · HCl (2).** A mixt of 176.4 g (0.85 mole) of *dl*-α-(1-naphthyl)ethylamine·HCl and 118.5 g (0.932 mole) of *O*-methylcaprolactim in 950 ml of MeOH was refluxed for 3 hr. The solvent was evapd and the residue crystd and recrystd from MeOH-Me_2CO to give 143.1 g (56%) of *dl*-2 (Table I).

2-[1-(1-Naphthyl)ethylimino]azacyclotridecane · HCl (10). To 21.7 g (0.11 mole) of 2-azacyclotridecanone in 200 ml of C_6H_6 was added dropwise 15.3 g (0.10 mole) of $POCl_3$, and the mixt was stirred at room temp for 4 hr under exclusion of moisture. Then 17.1 g (0.10 mole) of *l*-α-(1-naphthyl)ethylamine was added and the mixt was stirred at room temp for 1 hr and at reflux temp for 4 hr. The mixt was allowed to stand overnight, 2 *N* HCl was added, and the organic phase, after addn of some CH_2Cl_2, was dried (Na_2SO_4) and evapd to dryness. The residue was crystd and recrystd from MeOH-Me_2CO to give 10.8 g (28%) of **10** (Table I).

2-{[2,2-Dimethyl-1-(1-naphthyl)propyl]imino}hexahydroazepine · HCl (5). A slurry of 7.5 g (0.03 mole) of powdered α-*tert*-butyl-1-naphthalenemethylamine · HCl in 8 ml of *O*-methylcaprolactim was allowed to stand at room temp for 5 days with occasional stirring. The mixt became nearly homogeneous and then solidified. Small portions of anhyd EtOH were added to keep the mixt stirrable. When the mixt ceased to further solidify, it was cooled and the product was collected and recrystd (Table I). This method is particularly suited for reactions with sterically hindered amines.

2-Methyl-1-(1-naphthyl)propylamine · HCl. To Grignard reagent, prepd from 161.0 g (1.31 mole) of $BrCHMe_2$ and 31.8 g of Mg turnings in 300 ml of Et_2O, was added 800 ml of PhMe, Et_2O was distd off, 50.0 g (0.327 mole) of 1-cyanonaphthalene was added, and the mixt was refluxed overnight. (In some analogous prepns, this soln was added directly to $LiAlH_4$ in Et_2O to obtain the amine.) This mixt was decompd with hot 6 *N* HCl, sepd, washed (H_2O), and dried (Na_2SO_4), solvent was distd off from the PhMe layer, and the residue was distd to obtain 2-methyl-1-propionaphthone, 44.6 g (69%), bp 160–170° (0.6 mm), $n^{25}D$ 1.5925.

This material (30.3 g, 0.153 mole) was mixed with 30.7 g (0.486 mole) of $HCOONH_4$ and was slowly heated to 150° with stirring. After the initial foaming had subsided, the temp of the heating bath was raised to 185–190° and stirring was continued for 3 hr. Upon cooling, the mixt was washed with H_2O, the washes were extd with a small amt of C_6H_6 and the ext was added to the residue along with 150 ml of concd HCl. This mixt was refluxed for 6 hr, and on cooling the product pptd and was collected, 34.6 g (85%), mp 287–288°. Recrystn from H_2O raised the mp by 1°. *Anal.* ($C_{14}H_{17}N$ · HCl) C, H, N.

4-Chloro-α-methyl-1-naphthalenemethylamine · HCl. A mixt of 50.0 g (0.24 mole) of 4′-chloro-1′-acetonaphthone[24] and 49.0 g

‡See footnotes *a* and *b* to Table I.

(0.78 mole) of $HCOONH_4$ was treated as described in the preceding paragraph, 43.1 g (73%), recrystd from MeCN-MeOH, mp 293-294°. *Anal.* ($C_{12}H_{12}ClN \cdot HCl$) C, H; N: calcd, 5.79; found, 5.22.

Biological Methods. Blood Collection and Isolation of Plasma. Whole blood was obtained from voluntary, experienced donors before breakfast. Donors were instructed to take no drugs, specifically aspirin, for 5 days before giving blood. If the plasma was lipidemic or, in a preliminary aggregation experiment, showed no second phase aggregation (aspirin-like effect), this plasma was not used. Blood was collected by the 2-syringe technique. It was decalcified with 3.8% sodium citrate soln (1:9 with blood). The citrated blood was centrifuged at 100*g* for 10 min and citrated platelet-rich plasma (PRP) was isolated. Platelet-poor plasma (PPP) was isolated by recentrifuging the blood residue at 1500*g* for 15 min.

Inhibition of Platelet Aggregation. Compounds were tested for inhibition of ADP- and collagen-induced aggregation in a Bryston platelet aggregometer by the procedure of Mustard, *et al.*[6] Human platelet-rich plasma (PRP) was diluted with autologous platelet-poor plasma to 400,000 platelets/mm^3. Solns of test compd were prepd and added to obtain the indicated concs. Saline was added to another sample of the same plasma to serve as control. After incubation for 20 min at 37°, ADP (2 μg/ml of final concentration) was added to induce aggregation. Platelet aggregation produces an increase in light transmittance (ΔT) through the plasma sample in the aggregometer and this response was recorded on a Bausch and Lomb VOM-5 chart recorder. The maxima of the ΔT responses for control and test sample were then used to calculate per cent inhibition of platelet aggregation by the test compound.

Collagen was prepared by the method of Hovig[25] and was standardized.[9] The values given in Table I refer to inhibition of the initial slope of the aggregation curve, as discussed elsewhere.[10]

Platelet Factor 3 Activation. A soln of the test compd was added to human citrated PRP and incubated at 37° for 20 min, and a modified Stypven test was performed. The plasma was diluted 1:10 for this modified test.[7]

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Treloxinate and Related Hypolipidemic 12*H*-Dibenzo[*d*,*g*][1,3]dioxocin-6-carboxylate Derivatives[1]

J. Martin Grisar,* Roger A. Parker, Takashi Kariya, Thomas R. Blohm, Robert W. Fleming, Vladimir Petrow,

Merrell-National Laboratories, Division of Richardson-Merrell Inc., Cincinnati, Ohio 45215,

David L. Wenstrup, and Robert G. Johnson

Department of Chemistry, Xavier University, Cincinnati, Ohio 45207. *Received June 5, 1972*

Synthetic studies on *o*-phenylenedioxyacetic acids led to preparation of 2,10-dichloro-12*H*-dibenzo[*d*,*g*]-[1,3]dioxocin-6-carboxylic acid, and its methyl ester, treloxinate, was found to be a potent hypolipidemic agent. Structural modifications of treloxinate and the effect of these on hypocholesterolemic and hypotriglyceridemic activity were explored in rats (Wistar strain). Variation of aromatic substitution patterns and the size of the central heterocyclic ring resulted in decrease or loss of activity. A general synthetic method was developed to prepare analogous tricyclic acids from bisphenols and excess potassium dichloroacetate in hydroxylic solvents. Yields were affected by the size of the central ring and by aromatic substitution but surprisingly little by steric hindrance.

A large number of alkylcarboxylic acids with aryl or aryloxy substituents have been reported to have hypolipidemic activity.[2] Clofibrate, ethyl 2-(*p*-chlorophenoxy)-2-methylpropionate, is one of the more effective of these agents, and is the most widely used for control of hyperlipidemias associated with atherosclerotic cardiovascular diseases. This