compounds was also calculated. Each compound was studied at least in six animals.

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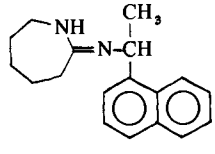
Benzhydryl and Fluorenyl Lactamimides with Hypoglycemic, Diuretic, Blood Platelet Aggregation Inhibitory, and Antiinflammatory Activities

J. Martin Grisar,* George P. Claxton, Norbert L. Wiech, Ronald W. Lucas, Robert D. MacKenzie, and Sidney Goldstein

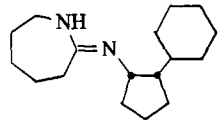
Merrell-National Laboratories, Division of Richardson-Merrell Incorporated, Cincinnati, Ohio 45215. *Received February 2, 1973*

2-[(Diphenylmethyl)imino]piperidine hydrochloride (**2**) and 2-(9-fluorenylimino)hexahydroazepine hydrochloride (**45**) were found to have hypoglycemic properties in rats at 5–10 mg/kg po. These benzhydryl lactamimides were selected after extensive exploration of structural parameters including variation of lactam ring size, N and C substitution, aromatic substituents, and preparation of tricyclic fluorenyl and dihydrodibenzocycloheptenyl analogs. These compounds also showed potent diuretic properties in rats but not in dogs. Compounds **20** and **49** were the most potent diuretics in rats. While most benzhydryl lactamimides inhibited ADP-induced aggregation of human blood platelets only weakly, compounds **34**, **39**, and **41** were comparable to the naphthylalkyl lactamimide **1**. Several benzhydryl lactamimides showed antiinflammatory activity in rats (carrageenin-induced abcess method) at 100 mg/kg po but did not protect against uv-induced erythrema in guinea pigs. Compound **2** showed antihistaminic activity. Compounds **2** and **45** were selected for pathologic-toxicologic evaluation in preparation for clinical trial as hypoglycemic agents.

We recently reported on the effects of the naphthylalkyl lactamimide I† on adenosine diphosphate (ADP) and collagen-induced aggregation of human blood platelets.[1]



I



II

Extended evaluation of I led to the discovery of its hypoglycemic activity. Evaluation of other lactamimides then led us to follow a rationale according to which lactamimides derived from sterically hindered primary amines were pursued as potential hypoglycemic agents. This led to the development of II.†,[2] At the same time we found that the benzhydryl lactamimide **3** (Table I) had strong hypoglycemic activity. We now wish to report on the synthesis and biological evaluation of related benzhydryl, fluorenyl, and dibenzocycloheptenyl lactamimides.

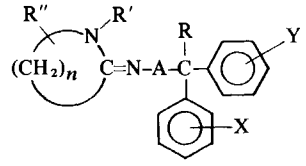
Hypoglycemic Effects. The compounds listed in Table I were prepared and evaluated for hypoglycemic activity in fasted, glucose-primed rats by the method of Gerritsen and Dulin.[3] With compounds **1–6** the effect of the lactam ring size was explored. The five- and six-membered congeners **1** and **2**† were more potent than **3** while the larger eight-, nine-, and 13-membered ring congeners were less active. In the fluorene series **43–47**, on the other hand, the seven-membered ring congener **45**† was the most active, while the smaller ring congeners were inactive. Lactam ring *N*-methyl substitution (**7–9**) showed very similar, though somewhat reduced, potency while the *N*-benzyl congener **10** was inactive. A chlorine or *tert*-butyl substituent in the lactam ring (**11, 12, 47**) gave inactive compounds.

A large number of aromatic substituents were explored (**13–35**). In respect to hypoglycemic activity, however, all of these had less or no activity with the exception of the methoxy derivatives **22–25**. Of compounds in which the two benzene rings were tied into a tricyclic fluorene moiety (**43–47**), **45** showed highest activity, but the dihydrodibenzocycloheptene derivatives **48–50** had no hypoglycemic activity. Compounds **13**, **20**,† **21**, **33**, and **49**† had a hyperglycemic effect, as shown in Table II.

Diuretic Effects. In the course of the hypoglycemic evaluation, diuresis was observed. Diuretic activity was evaluated in saline-loaded rats by a modification of the

†The following code numbers were assigned: I, RMI 7822; II, RMI 11894; **2**, RMI 11943; **20**, RMI 11842; **41**, RMI 12366; **45**, RMI 10026; **49**, RMI 11749.

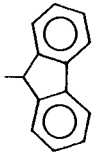
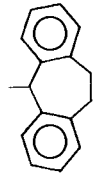
Table I. Benzhydryl-, Fluorenyl-, and Dihydrodibenzocycloheptenyl Lactamimides and Their Hypoglycemic and Diuretic Activity in Rats



No.	X	Y	R	A	R′	R″	n	Mp,[a] °C	Mol formula[b]	Yield, %	Dose (rats), mg/kg po	Plasma glucose % redn[c]	Diuresis after 5 hr[d] Vol % above control	Na+ mequiv	K+ mequiv	Cl− mequiv
1	H	H	H		H	H	3	217–219	$C_{17}H_{18}N_2 \cdot HCl$	33	100	24				
											50	33				
											25	42	341	3.84	0.47	3.51
											12.5	24				
											6	11[e]				
											3		46	1.04	0.31	1.24
2[g]	H	H	H		H	H	4	241–242	$C_{18}H_{20}N_2 \cdot HCl$	82	100	46				
											50	52				
											25	42	271	3.70	0.34	3.31
											12.5	41				
											10		177	3.20	0.50	3.60
											6	12[e]				
											3	7[f]	108	2.50	0.35	2.65
3	H	H	H		H	H	5	265–266 dec	$C_{19}H_{22}N_2 \cdot HCl$	58	100	53				
											50	52				
											25	50	293	6.12	0.54	7.63
											12.5	16[f]				
											10		248	6.59	0.74	9.05
											6	1[f]				
											3		134	4.44	1.08	6.45
											1		66	3.04	0.86	4.55
4	H	H	H		H	H	6	313–314 dec	$C_{20}H_{24}N_2 \cdot HCl$	4	100	33				
											50	0				
											25	3[f]	399	4.88	0.41	5.55
											10		314	4.20	0.51	4.65
											3		152	3.21	0.29	3.05
5	H	H	H		H	H	7	283–285 dec	$C_{21}H_{26}N_2 \cdot HCl$	5	100	34				
											25		352	4.14	0.42	4.70
6	H	H	H		H	H	11	140–165	$C_{25}H_{34}N_2 \cdot HCl$	11	100	13[e]				
											25		189	2.75	0.34	2.98
7	H	H	H		Me	H	3	194–195	$C_{18}H_{20}N_2 \cdot HCl$	42	100	29				
											50	45				
											25	50	296	3.86	0.50	3.98
											12.5	29				
											6	0				
											3		14	0.89	0.21	0.91
8	H	H	H		Me	H	4	225–228	$C_{19}H_{22}N_2 \cdot HCl$	29	100	5[f]				
											50	33				
											25	40	201	2.89	0.49	3.16
											12.5	16[e]				
											6	7[f]				
											3		63	1.05	0.22	1.05

9	H	H	H	Me	H	5	147–149 dec	$C_{20}H_{24}N_2 \cdot C_4H_4O_4$[h]	2	50	32				
										25	30				
										12.5	17[e]				
										6	10[f]				
10	H	H	H	CH_2Ph	H	3	190–191	$C_{24}H_{24}N_2 \cdot HCl$	43	100	0				
11	H	H	H	H	3-Cl	5	235–236 dec	$C_{19}H_{21}ClN_2 \cdot HCl$	30	100	0				
12	H	H	H	H	5-*t*-Bu	5	>300	$C_{23}H_{30}N_2 \cdot HCl$	13	100	13[f]				
13	*o*-Me	H	H	H	H	5	275–276	$C_{20}H_{24}N_2 \cdot HCl$	37	100	*i*				
										25		705	8.10	1.00	7.70
										10		195	6.80	1.10	6.90
										3		95	5.50	1.00	5.30
14	*p*-*i*-Pr	H	H	H	H	5	203–206	$C_{22}H_{28}N_2 \cdot HCl$	7	100	9[e]				
15	*p*-Cl	H	H	H	H	5	237–239	$C_{19}H_{21}ClN_2 \cdot HCl$	72	100	28				
										25		273	7.43	1.10	10.51
										10		242	5.99	1.01	8.01
										3		136	4.25	0.90	5.93
										1		54	2.43	0.82	4.36
16	*p*-F	H	H	H	H	5	237–238	$C_{19}H_{21}FN_2 \cdot HCl$	69	100	18[e]				
										25		305	7.30	0.65	6.00
17	*p*-F	H	H	H	H	4	211–213	$C_{18}H_{19}FN_2 \cdot HCl$	78	100	19[e]				
										25		202	5.30	0.58	4.70
18	*p*-Br	H	H	H	H	5	233–234	$C_{19}H_{21}BrN_2 \cdot HCl$	78	100	0				
										25		631	8.30	0.95	7.70
19	*p*-CF_3	H	H	H	H	5	208–209	$C_{20}H_{21}F_3N_2 \cdot HCl$	43	100	0				
										25		325	6.90	1.10	6.50
20[g]	*m*-CF_3	H	H	H	H	5	237–238	$C_{20}H_{21}F_3N_2 \cdot HCl$	69	100	*i*				
										25		796	9.80	0.75	8.45
										10		414	6.20	0.60	6.10
										3		223	3.90	0.80	4.20
21	*o*-CF_3	H	H	H	H	5	227–229	$C_{20}H_{21}F_3N_2 \cdot HCl$	60	100	*i*				
22	*p*-OMe	H	H	H	H	5	224–227	$C_{20}H_{24}N_2O \cdot HCl$	79	100	55				
										25	23	337	5.50	0.66	5.40
										12.5	4[f]				
23	*p*-OMe	H	H	H	H	4	184–186	$C_{19}H_{22}N_2O \cdot HCl$	62	100	47				
										25	24				
										12.5	23				
24	*m*-OMe	H	H	H	H	5	235–237 dec	$C_{20}H_{24}N_2O \cdot HCl$	72	100	17[e]				
25	*o*-OMe	H	H	H	H	5	235–237 dec	$C_{20}H_{24}N_2O \cdot HCl$	74	100	15[e]				
26	3,4-$(OMe)_2$	H	H	H	H	5	236–238	$C_{21}H_{26}N_2O_2 \cdot HCl$	72	100	0				
										25		305	7.30	0.65	6.00
27	3,4,5-$(OMe)_3$	H	H	H	H	5	239–241 dec	$C_{22}H_{28}N_2O_3 \cdot HCl$	50	100	0				
										25		113	3.10	0.62	3.30
28	*p*-OBu	H	H	H	H	5	165–168	$C_{23}H_{30}N_2O \cdot HCl$	64	100	9[f]				
29	*p*-OCF_3	H	H	H	H	5	190–193	$C_{20}H_{21}F_3N_2O \cdot HCl$	33	100	0				
										25		264	6.60	0.81	6.00
30	*p*-SCF_3	H	H	H	H	5	206–209	$C_{20}H_{21}F_3N_2S \cdot HCl$[i]	53	100	17[e]				
										25		293	6.90	0.93	6.50
31	*p*-Cl	*p*-Cl	H	H	H	5	255–257 dec	$C_{19}H_{20}Cl_2N_2 \cdot HCl$	46	100	0				
										25		732	8.70	1.00	10.30
32	*p*-Cl	*m*-CF_3	H	H	H	5	249–251	$C_{20}H_{20}ClF_3N_2 \cdot HCl$	25	100	0				
										25		303	6.30	1.10	6.10
33	*m*-CF_3	*m*-CF_3	H	H	H	5	260–262	$C_{21}H_{20}F_6N_2 \cdot HCl$	54	100	*i*				
										25		206	5.20	0.70	5.20
34	*p*-Ph	H	H	H	H	5	265–266	$C_{25}H_{26}N_2 \cdot HCl$	62	100	0				
35	*p*-OPh	H	H	H	H	5	201–203	$C_{25}H_{26}N_2O \cdot HCl$	46	100	23				

Table I (*Continued*)

No.	X	Y	R	A	R′	R″	*n*	Mp,[a] °C	Mol formula[b]	Yield, %	Dose (rats) mg/kg po	Plasma glucose % redn[c]	Diuresis after 5 hr[d] Vol % above control	Na^+ mequiv	K^+ mequiv	Cl^- mequiv
36	H	H	H	$-CH_2-$	H	H	5	242–244	$C_{20}H_{24}N_2 \cdot HCl$	73	100	26				
											25		217	5.58	0.62	7.86
											10		137	4.25	0.83	6.92
											3		6	2.62	0.98	4.14
37	H	H	H	$-CH_2CH_2-$	H	H	5	240–241 dec	$C_{21}H_{26}N_2 \cdot HCl$	57	100	8[f]				
											25		39	3.03	0.87	4.95
38	H	H	H	$-CH(Me)-$	H	H	5	291–292 dec	$C_{21}H_{26}N_2 \cdot HCl$	54	100	4[f]				
											25		53	1.59	0.29	1.99
39	H	H	Me	$-CH(Me)-$	H	H	5	252–254 dec	$C_{22}H_{28}N_2 \cdot HCl$	66	100	23				
40	H	H	Pr	$-CH_2-$	H	H	4	221–222	$C_{22}H_{28}N_2 \cdot HCl$	82						
41[g]	H	H	Pr	$-CH_2-$	H	H	5	238–240 dec	$C_{23}H_{30}N_2 \cdot HCl$	79	100	6[f]				
											25		223			
42	H	H	Pr	$-CH_2-$	H	H	6	179–182 dec	$C_{24}H_{32}N_2 \cdot C_4H_4O_4$[k]							
43					H	H	3	268–270 dec	$C_{17}H_{16}N_2 \cdot HCl$	20	100	0				
											25		454			
44					H	H	4	272–275 dec	$C_{18}H_{18}N_2 \cdot HCl$	12	100	6[f]				
											25		314			
45[g]					H	H	5	307–308 dec	$C_{19}H_{20}N_2 \cdot HCl$	46	100	47				
											50	44				
											25	49	237	3.10	0.40	3.40
											12.5	32				
											10		173	3.20	0.65	3.45
											6	22				
											3	0	74	1.90	0.40	2.20
46					H	H	6	287–289 dec	$C_{20}H_{22}N_2 \cdot HCl$	14	100	34				
											25		216			
47					H	5-*t*-Bu	5	296–299 dec	$C_{23}H_{28}N_2 \cdot HCl$	21	100	0				
											25		0			
48					H	H	4	262–263 dec	$C_{20}H_{22}N_2 \cdot HCl$	76	100	6[f]				
											25		238			
49					H	H	5	292–293 dec	$C_{21}H_{24}N_2 \cdot HCl$	69	100	*i*				
											25		422	6.84	0.59	3.90
											10		257	4.06	0.30	4.85
											3		211	2.17	0.36	4.10
50					H	H	6	292–293 dec	$C_{22}H_{26}N_2 \cdot HCl$	55	100	3[f]				
											25		168			
I[g,l]											100	34				
											50	20[e]				
											25		277	4.64	0.99	5.69
											10		82	3.71	0.64	4.61
											3		16	2.78	0.55	3.65
II[g,m]											100	53				
											50	49				
											25	42	219	3.10	0.40	4.00
											12.5	33				
											6	13[e]				
Tolbutamide											100	41				
											50	43				
											25	29				
											12.5	16[f]				

Saline control			2.12	0.71	3.18
Furosemide	25	634	5.68	0.88	6.76
	10 (10)[n]	146	3.08	0.79	3.68
	3	0	2.30	0.45	2.00
Amiloride	25 (2)[n]	68	2.50	0.10	2.10
Chlorothiazide	25 (20)[n]	90	2.61	0.95	3.83

[a]Melting points were determined on a Hoover capillary melting point apparatus and are corrected. [b]All compounds were analyzed for C, H, and one other element. Analytical results obtained for these elements were within ±0.4% of calculated values, unless otherwise indicated. [c]Determined by the method of Gerritsen and Dulin,[3] as described in the Experimental Section. All values over 20% were statistically significant at $p \leq 0.05$. [d]Determined by the method of Lipschitz, *et al.*,[4] as described in the Experimental Section. [e]Statistically significant at $p \leq 0.05$. [f]Statistically not significant, $p \geq 0.05$. [g]See footnote †. [h]Maleate salt. [i]Hyperglycemic, see Table II. [j]*Anal.* Calcd: C, 57.90; H, 5.34; Cl, 8.54; neut equiv, 414.94. Found: C, 58.45; H, 5.56; Cl, 8.48; neut equiv, 418.9. [k]Fumarate salt. [l]Reference 1. [m]Reference 2. [n]Number in parentheses indicates number of determinations.

Table II. Hyperglycemic Activity in Rats[a]

Compd no.	Dose (rats), mg/kg po	Plasma glucose % of control
13	100	144
20[b]	100	127
21	100	133
33	100	139
49[b]	100	143
Theophyllin	100	140

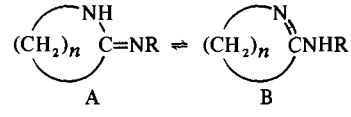
[a]See footnote *c*, Table I. [b]See footnote †.

method of Lipschitz, *et al.*,[4] and the results are listed in Table I. Comparison with known diuretic agents, listed at the end of Table I, showed that the lactamimides are potent diuretics in rats, particularly compounds **20**† and **49**.† A favorable Na^+:K^+ excretion ratio was found with only slight kaluresis. Several compounds were evaluated in mannitol phosphate infused dogs by the method of Beyer,[5] as shown in Table III. In this animal model, that with few exceptions[6] is generally believed to more closely resemble man, the lactamimides caused considerably less excretion of Na^+ and Cl^- than known agents. One compound (**3**) showed slight K^+ retention.

Effects on Platelet Aggregation. We reported earlier on the inhibition of ADP- and collagen-induced aggregation of human blood platelets by I.†,[1] Benzhydryl lactamimides were also evaluated for this property by the method of Mustard, *et al.*,[7] and for release of platelet factor 3 (PF3) by the method of MacKenzie, *et al.*;[8] see Table IV. Most benzhydryl lactamimides were less effective in inhibiting aggregation than I. One exception was the 13-membered lactam ring congener **6** that, however, also caused high PF3 release (as did the 13-membered naphthylalkyl lactamimide),[1] and another was the chlorine-substituted congeners **15**, **31**, and **32** that are highly diuretic. Of potential interest are compounds **34**, **39**, and **41**† because they are about as effective as I† without having hypoglycemic and/or diuretic activity.

Antiinflammatory Activity. The benzhydryl lactamimides were evaluated in rats by the carrageenin-induced abcess assay of Goldstein and Schnall,[9] and the results are listed in Table V. Several compounds were active at 100 mg/kg and a few at 30 mg/kg. Compounds **41**† and **49**† were inactive when evaluated by the ultraviolet-induced erythrema assay[10] in intact male guinea pigs using aspirin (270 mg/kg po) as a standard. Since the animals were not protected, it was concluded that these compounds may act by a different mechanism than aspirin.

Antihistaminic Activity. It was found that **2** protects guinea pigs against fatal anaphylaxis by antigen aerosol at 100 mg/kg po. Histamine- and acetylcholine-induced spasms of isolated guinea pig ileum were inhibited by 50% at a concentration of **2** of $2 \times 10^{-5} M$.



Chemistry. Lactamimides, also named cyclic or semicyclic amidines,[11] occur in two tautomeric forms A and B. This tautomerism has been studied by Kwok and Pranc.[12] It is not known, however, which tautomer prevails in the crystalline monohydrochloride salts, much less in solutions under physiologic conditions. For the sake of convenience we have represented and named all compounds in the tautomeric form A.

Table III. Electrolyte Excretion in Mannitol Phosphate Infused Dogs[a]

Compd no.	Dose, mg/kg po	Na^+, μequiv/min		K^+, μequiv/min		Cl^-, μequiv/min	
		pre	post	pre	post	pre	post
1	25	5.9	70.5	5.5	23.8	29.2	35.7
2[b]	25	3.3	24.9	2.8	6.0	23.5	34.8
	25	36.7	96.8	12.2	20.0	29.2	88.0
3	25	32.6	110.5	9.7	5.8	44.9	111.4
	25	10.3	273.0	11.1	8.1	24.8	266.8
	25	27.4	195.3	17.1	4.8	36.7	160.1
	25	10.2	40.9	4.1	9.5	13.8	101.3
4	25	26.9	200.1	13.1	30.4	32.0	274.1
20[b]	25	4.1	135.3	2.7	14.9	10.5	112.5
	25	12.7	83.7	16.3	19.7	8.2	25.6
	10	5.8	58.9	6.7	16.1	9.4	35.3
	10	2.2	22.8	3.1	12.8	11.0	21.5
	5	6.0	62.4	5.7	12.5	7.2	58.5
	5	1.6	21.0	4.3	14.2	5.7	15.9
31	25	6.2	84.4	5.7	16.9	15.2	56.1
	25	3.5	168.1	10.4	21.2	33.8	170.6
36	25	17.3	58.8	6.1	10.8	29.0	22.8
45[b]	25	1.7	47.4	3.7	12.8	11.0	44.0
	25	60.9	198.9	7.6	18.1	54.4	186.6
	25	10.6	23.1	2.8	7.3	15.3	34.3
	25	2.5	78.4	2.2	10.5	3.4	67.1
49[b]	25	54.7	205.0	19.7	11.1	83.4	212.9
	25	10.5	270.0	3.1	13.8	11.5	130.2
	25	4.3	55.8	4.9	7.0	4.3	47.7
Furosemide	25	5.0	342.0	1.6	35.0	24.5	731.6
	25	6.6	2812.0	7.3	121.4	19.5	1385.3
Amiloride	10	10.6	172.8	5.9	1.8	6.0	1.5
	10	3.4	110.5	6.3	2.7	15.3	1.1
	1	72.4	148.4	10.6	2.9	57.3	2.1
Chlorothiazide	25	13.1	309.4	17.1	82.6	18.9	444.7
	25	103.9	295.2	12.6	43.9	148.8	401.8
Theophylline	50	4.6	202.1	5.3	29.1	29.0	320.1
	50	4.8	120.0	4.0	18.1	6.2	146.6
I[b,c]	25	2.8	4.8	1.7	0.8	14.2	22.1
II[b,d]	25	13.4	40.7	12.0	15.1	25.8	32.6
	25	28.5	156.4	7.0	25.4	24.6	65.5

[a] By the procedure of Beyer;[5] see Experimental Section. Values for the average of three 10-min periods before and the 10-min period with maximal excretion after oral administration of test compound are given. [b] See footnote †. [c] Reference 1. [d] Reference 2.

Of the various methods available for synthesizing lactamimides,[11] we used only two. One, first used by Benson and Cairns,[13] consists of reaction of *O*-methyllactims with primary amine hydrochlorides. The other, extensively explored by Bredereck and coworkers,[14,15] consists of reaction of the complex obtained from a lactam with $POCl_3$ and a primary amine base *or hydrochloride salt.* Examples of these reactions are given in the Experimental Section.

The primary amine hydrochlorides employed are listed in Table VI, excepting those that are commercially available. Most of the substituted benzhydrylamines were prepared by *in situ* $LiAlH_4$ reduction of the addition products of phenylmagnesium halides with benzonitriles.

The ir spectra of lactamimides show C=N stretching vibrations that vary with ring size: **1** (1675 cm^{-1}), **2** (1660 cm^{-1}), **3** (1640 cm^{-1}), **4-6** (1645-1650 cm^{-1}), **43** (1675 cm^{-1}), **44** (1660-1670 cm^{-1}), **45** (1640-1650 cm^{-1}), **46** (1650 cm^{-1}).

Conclusion

Careful evaluation of structural features required for optimal hypoglycemic activity of benzhydryl and fluorenyl lactamimides led to the selection of compounds **2**† and **45**† for pathologic-toxicologic evaluation. These compounds also showed diuretic properties but it is difficult to project the relative strength of this effect in respect to hypoglycemic activity in man from data in rats and dogs. Compounds **20**† and **49**† were found to be the most potent diuretic agents of this series in rats. While these effects were seen at a level of 5-10 mg/kg, a number of other activities were observed at around 100 mg/kg. These include hyperglycemic, platelet aggregation inhibitory, antiinflammatory, and antihistaminic effects. Compound **41**† is typical of this type. With this many activities, efforts will be directed next toward elucidation of the biological mechanism of these compounds.

Experimental Section

Biological Methods. Plasma Glucose. Hypoglycemic activity was determined by the method of Gerritsen and Dulin.[3] Young male rats of body weight 145–155 g (Sprague-Dawley strain) were fasted overnight. Six animals were given a glucose load of 100 mg sc after dosing of the test compound by a stomach tube. Later (2 hr) blood was withdrawn and plasma glucose was determined by the glucose oxidase procedure.[16]

Diuresis. In rats a modification of the procedure of Lipschitz, *et al.*,[4] was used. Two groups of three male Sprague-Dawley rats weighing 200–400 g were deprived of food and water for 17 hr and were dosed by a stomach tube with 25 ml/kg of 0.85% saline solution containing the desired amount of test compound. Compounds that were insoluble in saline were suspended in 0.5% methocel solution at 0.3% concentration of the compound. The suspensions were given orally followed by a supplementary oral dose of saline, calculated so that the total volume of liquid administered equaled 25 ml/kg.

Electrolyte excretion in dogs was determined by the method of Beyer.[5] Female dogs (both mongrels and beagles), weighing 6–14 kg, were trained to lie quietly on their backs with as little restraint as possible. After fasting for 24 hr they were given 25 ml/kg of H_2O orally 60 and 30 min prior to the beginning of the study. The dogs were then restrained on their backs and a urinary catheter was inserted into the bladder. After the last water load (10 min), 25 mg/kg iv of 0.14 *M* mannitol was started at a rate of 3 ml/min and was maintained throughout the experiment. After 20 min of infusion,

Table IV. Inhibition of ADP-Induced Aggregation of Human Blood Platelets[a]

	Effects on human blood platelets					
	% inhibn of ADP-ind aggregation at μg/ml			% release of PF3 at μg/ml		
No.	100	30	10	300	100	30
1	40					
2[b]	49					
3	43					
4	75					
6	100	46	11	2.0	0.16	
7	19 (2)					
8	22					
11	62 (2)					
12	57 (2)					
13	61					
15	100	61	2	0.12	0.044	
16	54					
17	49					
20[b]	68					
21	49	19				
22	52					
25	45	12				
26	14					
27	0					
28	76 (2)	7				
29	93	0		0.62	<0.001	
30	83	17		0.92	0.090	
31	91 (2)	36 (2)				
32	90	46				
33	14					
34	88 (2)	37 (2)	20	0.68	0.056	
35	95					
36	85	25		0.20	0.001	<0.001
37	91	27		0.36	0.010	<0.001
38	80					
39	100	33				
40	91	53	12			
41[b]	100	57	1	0.13	0.004	
42	97 (2)	23 (2)	1			
45[b]	48	0				
47	93	20				
48	63					
49[b]	80 (2)	40		0.005	<0.001	
50	34			0.058	<0.001	
I[b,c]	70 (2)	46 (2)	0 (2)	0.037	0.003	

[a]The methods described in ref 1 were used. Values in parentheses refer to number of determinations. [b]See footnote †. [c]Reference 1.

Table V. Antiinflammatory Activity by the Carrageenin-Induced Abcess Method[a]

	Abcess wt, % control at oral dose, mg/kg			
Compd no.	250[b]	100[b]	50	30
2[d]	62 (3)[c]	78[c]		
10	44[c]	60 (3)[c]	62 (3)[c]	
12	66 (2)[c]			
13	50 (3)[c]	64[c]		93 (2)
15	40 (2)[c]	58 (2)[c]		80
16	62[c]	60[c]		
17	60 (3)[c]	69[c]		
18	49[c]	92		
19	52 (2)[c]	68[c]		
20[d]	34 (2)[c]	49 (2)[c]		
22	68 (2)[c]	98 (2)		
26		121		
27		113		
31	36 (2)[c]	55 (2)[c]		67[c]
32	46 (3)[c]	58 (3)[c]		69 (2)[c]
33	48 (2)[c]	61 (2)[c]		64[c]
34	62[c]	106		
36	72[c]			
37	76			
38	111			
41[d]	54 (4)[c]	76 (2)[c]		80
45[d]	65[c]	95 (2)		
48	61 (2)[c]	87		
49[d]	50 (3)[c]	57 (3)[c]		76[c]
50	37 (3)[c]	48[c]	66[c]	74[c]
Aspirin[b]	70 (17)[c]	90 (17)		
Phenylbutazone		54 (25)[c]	65 (33)[c]	

[a]By the method described in ref 9. Values in parentheses indicate the number of determinations; each determination was carried out in groups of five rats. [b]The values given for aspirin were carried out at 270 and 90 mg/kg; similarly, some of the determinations that were carried out at 270 and 90 mg/kg were pooled with values obtained at 250 and 100 mg/kg. [c]Statistically significant at $p \leq 0.05$. [d]See footnote †.

the control phase of the experiment was started. After rinsing the bladder with distilled water, three urine collections over 10-min periods were obtained for control values. Test compound was administered in aqueous solution (30 ml) by a stomach tube and, after a 20-min waiting period, urine collection was resumed in 10-min periods.

Na^+ and K^+ were analyzed on a Model 21 Coleman flame photometer and were recorded on a recorder as mequiv/min. Cl^- was analyzed by the method of Schales and Schales.[17]

Results are expressed in milliequivalents per minute pre- and postadministration of the test compound (Table III). The control values (pre) are an average of three 10-min determinations. The post values are those of the highest 10-min period after treatment with the test compound.

2-[(Diphenylmethyl)imino]piperidine Hydrochloride (2).† A mixture of 17 g of powdered $Ph_2CHNH_2 \cdot HCl$ and 15 ml of *O*-methylvalerolactim was allowed to stand at room temperature for 7 days with occasional stirring. Several 5-ml portions of EtOH were added to keep the mixture that solidifies stirrable before cooling (−20°) and collecting the product. Two recrystallizations (from MeOH–Me_2CO and from EtOH) gave 19.0 g (82%) of **2** (Table I). All compounds listed in Table I, except compounds **4–12**, were prepared by this procedure.

Hexahydro-2-[[*m*-(trifluoromethyl)-α-phenylbenzyl]imino]-azepine Hydrochloride (20).† A mixture of 17.0 g (0.059 mol) of powdered α-phenyl-*m*-(trifluoromethyl)benzylamine hydrochloride (**56**) and 25 ml (0.18 mol) of *O*-methylcaprolactim was allowed to stand at room temperature for 6 days with occasional stirring. Several small portions of EtOH were added to maintain a stirrable slurry. The mixture was cooled (−20°) and the precipitate was collected, washed with Et_2O, and recrystallized twice from MeOH–Me_2CO to give 15.5 g (69%) of **20** (Table I).

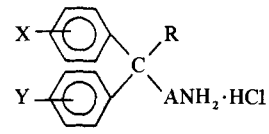
2-[(2,2-Diphenylpentyl)imino]hexahydroazepine Hydrochloride (41).† A mixture of 17 g (0.062 mol) of powdered $PrC(Ph)_2CH_2NH_2 \cdot HCl$ and 17 ml (0.12 mol) of *O*-methylcaprolactim was allowed to stand at room temperature for 4 days with occasional stirring. Several 5-ml portions of EtOH were added to maintain a stirrable suspension. The mixture was cooled, the precipitate was collected, washed with Et_2O, and recrystallized from MeOH–Me_2CO, and 18.1 g (79%) of **41** was obtained (Table I).

2-(9-Fluorenylimino)hexahydroazepine Hydrochloride (45).† A mixture of 58.5 g (0.27 mol) of 9-aminofluorene, 40 g (0.31 mol) of *O*-methylcaprolactim, and 900 ml of MeOH was refluxed for 1 hr. About half the solvent was evaporated and product crystallized. A second crop was obtained on further concentrating the mother liquor. The two crops were combined and recrystallized once from MeOH–Me_2CO and once from EtOH to give 66.5 g (79%) of **45** (Table I).

2-[10,11-Dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5-yl)imino]-hexahydroazepine Hydrochloride (49).† A mixture of 5.6 g (0.023 mol) of 10,11-dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5-amine hydrochloride and 8 ml (0.057 mol) of *O*-methylcaprolactim was allowed to stand for 2 days with occasional stirring and addition of a few drops of EtOH to keep the mixture in a stirrable state. After cooling, the product was collected, washed with Et_2O, and recrystallized from MeOH–Me_2CO to give 5.6 g (69%) of **49** (Table I).

1-Benzyl-2-[(diphenylmethyl)imino]pyrrolidine Hydrochloride (10). To 47.1 g (0.27 mol) of 1-benzylpyrrolid-2-one in C_6H_6 was added dropwise 38.5 g (0.25 mol) of $POCl_3$ and the mixture was stirred at room temperature for 4 hr. Then 48.8 g (0.25 mol) of Ph_2CHNH_2 was added, and the mixture was stirred for 1 hr at room temperature and for 4 hr at reflux temperature. It was allowed to stand overnight, decomposed by addition of 2 *N* HCl, made basic with 2 *N* NaOH, separated organic phase, dried (Na_2SO_4), and evaporated to dryness. The resulting oil crystallized after trituration with Et_2O and the product was recrystallized twice from MeOH–Me_2CO to give 40.5 g (43%) of **10** (Table I). Compounds **4–12** were

Table VI. Benzhydrylamines



No.	X	Y	A	R	Mp,[a] °C	Lit. mp, °C	Yield, % (method)[b]	Mol formula	Analyses[c]
51	*o*-Me	H		H	310–312 dec	220–249[d]	86 (B)	$C_{14}H_{15}N\cdot HCl$	
52	*p*-*i*-Pr	H		H	240–243 dec		20 (A)	$C_{16}H_{19}N\cdot HCl$	C, H, N
53	*p*-F	H		H	306–307 dec		41 (A)	$C_{13}H_{12}FN\cdot HCl$	C, H, Cl
54	*p*-Br	H		H	292–294	246[e]	56 (B)	$C_{13}H_{12}BrN\cdot HCl$	C, H, N
55	*p*-CF_3	H		H	>305		42 (A)	$C_{14}H_{12}F_3N\cdot HCl$	C, H, Cl, N
56	*m*-CF_3	H		H	278–279		81 (A)	$C_{14}H_{12}F_3N\cdot HCl$	C, H, Cl
57	*o*-CF_3	H		H	191–202		21 (B)[f]	$C_{14}H_{12}F_3N\cdot HCl$	*g*
58	*p*-OMe	H		H	224–226	191[h]	52 (A)	$C_{14}H_{15}NO\cdot HCl$	C, H, N
59	*m*-OMe	H		H	265–266 dec		45 (A)	$C_{14}H_{15}NO\cdot HCl$	C, H, N
60	*o*-OMe	H		H	260–261 dec	250[i]	20 (A)	$C_{14}H_{15}NO\cdot HCl$	C, H, N
61	3,4-$(OMe)_2$	H		H	246–248 dec	229–230[j]	13 (B)	$C_{15}H_{17}NO_2\cdot HCl$	C, H, N
62	3,4,5-$(OMe)_3$	H		H	227–229		31 (B)	$C_{16}H_{19}NO_3\cdot HCl$	N[k]
63	*p*-OBu	H		H	209–211	213–214[l]	73 (B)	$C_{17}H_{21}NO\cdot HCl$	C, H, N
64	*p*-OCF_3	H		H	269–270 dec		45 (B)	$C_{14}H_{12}F_3NO\cdot HCl$	C, H, Cl
65	*p*-SCF_3	H		H	248–254 dec		29 (B)	$C_{14}H_{12}F_3NS\cdot HCl$	*g*
66	*p*-Cl	*p*-Cl		H	294–297 dec	292[m]	88	$C_{13}H_{11}Cl_2N\cdot HCl$	
67	*p*-Cl	*m*-CF_3		H	279–283		39 (A)	$C_{14}H_{11}ClF_3N\cdot HCl$	C, H
68	*m*-CF_3	*m*-CF_3		H	293–294 dec		43	$C_{15}H_{11}F_6N\cdot HCl$	C, H, Cl
69	*p*-Ph	H		H	274–276 dec	252 dec[n]	27 (A)	$C_{19}H_{17}N\cdot HCl$	
70	*p*-O-Ph	H		H	222–223	218–219[n]	57 (A)	$C_{19}H_{17}NO\cdot HCl$	C, H, Cl
71	H	H	-CHMe-	H	281–283 dec	280–282[o]	27 (C)	$C_{15}H_{17}N\cdot HCl$	
72	H	H	-CHMe-	Me	230–231 dec	224–225[p]	41 (C)	$C_{16}H_{19}N\cdot HCl$	
73	H	H	$-CH_2-$	Pr	208–210	190[q]	59 (D)	$C_{17}H_{21}N\cdot HCl$	C, H, Cl

[a] Melting points were determined on a Hoover capillary melting point apparatus and are corrected. [b] Method: A, from X-C_6H_4MgBr + Y-C_6H_4-CN, followed by $LiAlH_4$ reduction; B, from Y-C_6H_4MgBr + X-C_6H_4-CN, followed by $LiAlH_4$ reduction; C, by Leuckart reaction; D, by $LiAlH_4$ reduction of nitrile. [c] Where elemental analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. [d] H. Goldschmidt and H. Stocker, *Ber.*, **24**, 2806 (1891). [e] J. Kalamar and B. Ryban, *Chem. Zvesti*, **20**, 79 (1966); *Chem. Abstr.*, **64**, 17453 (1966). [f] An attempt to prepare this compound by method A failed. [g] Material was impure as judged by the melting point. [h] A. Hantzsch and F. Kraft, *Ber.*, **24**, 3512 (1891). [i] P. Billon, *Ann. Chim. (Paris)*, 7, 314 (1927). [j] A. H. Bhatkhande and B. V. Bhide, *J. Univ. Bombay, A*, **24**, 11 (1955); *Chem. Abstr.*, **51**, 11324 (1957). [k] *Anal.* Calcd: C, 62.03; H, 6.51; N, 4.52. Found: C, 62.59; N, 4.57. [l] C. Torres y Gonzales, *Bull. Soc. Chim. Fr.*, **37**, 1591 (1925). [m] M. V. Patwardhan, N. L. Phalnikar, and B. V. Bhide, *J. Univ. Bombay*, 18, 22 (1950); *Chem. Abstr.*, **45**, 1986 (1951). [n] G. Koller, *Monatsh. Chem.*, **12**, 508 (1891). [o] J. Levy, P. Gallais, and D. Abragam, *Bull. Soc. Chim. Fr.*, **43**, 872 (1928). [p] H. E. Zaugg, M. Freidfelder, and B. W. Horrom, *J. Org. Chem.*, **15**, 1191 (1950). [q] French patent 1,209,836 (1960) [*Chem. Abstr.*, **55**, 17584 (1961)]; E. M. Schultz, C. M. Robb, and J. M. Sprague, *J. Amer. Chem. Soc.*, 69, 188, 2454 (1947).

all prepared by this method; no efforts were made to optimize yields.

5-*tert*-Butyl-2-(9-fluorenylimino)hexahydroazepine Hydrochloride (47). A mixture of 15.0 g (0.069 mol) of 9-aminofluorene hydrochloride and 20 ml of 5-*tert*-butyl-2-methoxy-4,5,6,7-tetrahydro-3*H*-azepine was allowed to stand at room temperature for 6 days with occasional stirring and addition of small portions of EtOH. After cooling, the product was collected, washed with Et_2O, and recrystallized once from MeOH–Me_2CO and once from EtOH to give 8.3 g (33%) of **47** (Table I).

α-Phenyl-*m*-(trifluoromethyl)benzylamine Hydrochloride (56). To *m*-CF_3-C_6H_4MgBr, prepared from 0.19 mol each of Mg turnings and *m*-CF_3-C_6H_4Br in 200 ml of anhydrous Et_2O, was added a solution of 16.5 g (0.16 mol) of PhCN in 30 ml of Et_2O over 15 min. The mixture was refluxed for 2 hr and allowed to stand overnight. It was then added over 30 min to a stirred suspension of $LiAlH_4$ in anhydrous Et_2O. The mixture was refluxed for 20 hr and decomposed by addition of 7 ml of H_2O, 7 ml of 15% NaOH, followed by 22 ml of H_2O, and the Et_2O phase obtained after filtering off and washing the inorganic material with Et_2O was treated with 500 ml of 2 *N* HCl. A precipitate resulted that was collected and washed throughly with Et_2O: 37.0 g (81%); mp 267–270°. A sample was recrystallized twice from *i*-PrOH–H_2O to mp 278–279° (**56**, Table VI).

3,3-Diphenyl-2-butylamine Hydrochloride (72). MeMgI was prepared from 137 g (0.966 mol) of MeI and Mg turnings in Et_2O, Et_2O was replaced by C_6H_6, and 100 g (0.483 mol) of $MeC(Ph)_2CN$ in C_6H_6 was added. The mixture was refluxed overnight and decomposed with 2 *N* HCl (heated for 1 hr to assure hydrolysis), and the product was extracted into C_6H_6; the extract was dried (Na_2SO_4) and the solvent evaporated to give 104.7 g of oil [$MeC(Ph)_2COMe$]. This material (78.5 g, 0.349 mol) was mixed with 88 g (1.4 mol) of $HCOONH_4$ and was heated slowly to 183–185° and was stirred at that temperature for 6.5 hr. Upon cooling, the mixture was washed with H_2O, the washes were extracted with a small amount of C_6H_6, and the extract was added to the residue along with 150 ml of concentrated HCl. This mixture was heated on a steam bath for 6 hr, and on cooling the product precipitated and was collected. Recrystallization from *i*-PrOH–H_2O gave 37.2 g (41%) of **72** (Table VI).

5-*tert*-Butyl-2-methoxy-4,5,6,7-tetrahydro-3*H*-azepine. To a stirred, refluxing solution of 394 g (2.33 mol) of 5-*tert*-butylcaprolactam in 2 l. of C_6H_6 was added dropwise over 6 hr 290 g (2.30 mol) of Me_2SO_4. Refluxing was continued overnight. The mixture was cooled in an ice bath and excess 50% K_2CO_3 solution was added cautiously. The C_6H_6 phase was separated, washed (saturated NaCl solution), and dried (Na_2SO_4) and the solvent was evaporated. The residue was distilled: bp 69–79° (0.5 mm); 354 g (84%); $n^{26}D$ 1.4677; ir (neat) 1690 cm^{-1}. *Anal.* ($C_{11}H_{21}NO$) C, H, N.

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Synthesis of α,β-Poly[(2-hydroxyethyl)-DL-aspartamide], a New Plasma Expander

Paolo Neri,* Guido Antoni, Franco Benvenuti, Francesco Cocola, and Guido Gazzei

Research Centre, I.S.V.T. Sclavo, Siena, Italy. *Received October 24, 1972*

Poly(amino acids) are of potential interest for use as plasma expanders, owing to their protein-like nature and the possibility of preparation by synthesis. High molecular weight poly-DL-succinimide was synthesized by thermal polyermization of aspartic acid in the presence of phosphoric acid, under reduced pressure, with some modifications of earlier methods. Reaction of this polymer with ethanolamine in controlled conditions afforded α,β-poly[(2-hydroxyethyl)-DL-aspartamide], with a molecular weight between 10,000 and 90,000. The poly(amino acid) is water-soluble, nontoxic, and nonantigenic in animals; moreover, the effect on the clotting time is less than in the case of dextran and the clearance rate lower than that of gelatin. For these reasons its use as a plasma expander is proposed. The difficulties of scaling up the method for the practical preparation of a plasma expander are considerably less than those involved in the preparation of an analogous compound [poly[N^5-(2-hydroxyethyl)-L-glutamine]] previously proposed by us.

The use of poly(amino acids) as plasma substitutes has been proposed by various authors in the past.[1-6] Poly(amino acids) would seem to have definite advantages over the other polymers generally used for this purpose; in fact, these compounds are similar to proteins and therefore one could assume that they will be cleaved in the body to amino acids or small peptides, which would be easily eliminated and nontoxic, and also able to contribute to the patient's nutrition. In order to be used as a plasma substitute, a poly(amino acid) must satisfy some fundamental requirements, *e.g.*, lack of toxicity and immunogenicity. Moreover, the molecular weight of a product to be used as a plasma expander should be low enough to ensure a maximum of oncotic pressure per weight unit and at the same time be sufficiently high to be retained in the blood to exert a steady pharmacological effect. However, other factors such as the shape of the molecules and the chemical nature of the compound can affect both the magnitude and the duration of the activity.

The first poly(amino acid) proposed as a possible plasma expander was poly(glutamic acid).[3-6] However, the results were not encouraging, because this compound proved to be either inefficient[3,4] or toxic.[5,6] One can speculate that this inconvenience was related to the high net charge exhibited by this compound at physiological pH,[5,6] since the copolymers of glutamic acid and lysine, for instance, were found to have a lower toxicity.[7] Consequently, we decided to prepare poly(amino acids) with no charge for use as plasma expanders. This can be achieved easily by blocking the side carboxyl groups in an amide linkage with an amino alcohol. The hydroxyl would render the polymer soluble in water, at the same time eliminating the electric interaction with cells and other components of the organism.

We have previously shown[8] that poly[N^5-(2-hydroxyethyl)-L-glutamine (PHEG)[†] has proved efficient, nontoxic, and nonimmunogenic when tested in animals. However, the large-scale preparation of this product raises complex technical and economic problems. This is a serious disadvantage for a plasma expander, one of the fundamental requirements for this kind of product being easy, low-cost production.[9] A plasma expander with better characteristics than those of existing products would hardly be of importance if it could not be easily produced at a reasonable cost and in large quantities. In this respect, the synthesis of analogous derivatives of poly(aspartic acid) is of particular interest. In fact, these compounds are easily obtained by polymerization of aspartic acid simply by heating[10-13] to yield a polysuccinimide [anhydropoly(aspartic acid)] reactive with amines.[14] Thus, compounds similar to poly(hydroxyalkylglutamines) are obtained after reaction with amino alcohols.

The methods described in the literature for the polymerization of aspartic acid provide polymers of low molecular weight, however, which are unsuitable for the synthesis of a plasma substitute.

By polymerizing aspartic acid in the presence of phosphoric acid in thin layer under reduced pressure, we obtained a polysuccinimide which gave α,β-poly[(2-hydroxyethyl)-DL-aspartamide] with a molecular weight of about 50,000 when reacted with ethanolamine, as shown in Scheme I.

While the synthesis of PHEG involves at least four steps (synthesis of γ-methylglutamate, *N*-carboxy anhydride formation, polymerization, and reaction with ethanolamine) the preparation of PHEA requires only two, simpler reactions. In addition, the management of large amounts of phosgene, a reagent widely used for the synthesis of *N*-carboxy anhydride, raises complex problems as regards safety in a large-scale plant. On the contrary, experience so far gained in a pilot plant has shown that the preparation of PHEA can be scaled up economically.

Results and Discussion

Polymerization of Aspartic Acid. Thermal polymerization of DL-aspartic acid in the presence of H_3PO_4 and in

[†] Abbreviations: PHEA, α,β-poly[(2-hydroxyethyl)-DL-aspartamide]; PHEG, poly[N^5-(2-hydroxyethyl)-L-glutamine]; DCC, *N,N'*-dicyclohexylcarbodiimide; DMF, *N,N*-dimethylformamide.