hr and hydrolyzed with 2.3 ml of water, 2.3 ml of a 15% solution of NaOH, and 7 ml of water. The precipitate formed was filtered and thoroughly washed with ether. After drying and evaporation of the ether, the amine was obtained as an oily residue. The **hydrochloride,** formed with an alcoholic solution of HCl, was recrystallized from absolute ethanol yielding 1.95 g (50%), mp 188–189°.

Anal. Calcd for $C_{15}H_{18}ClNO$: C, 68.31; H, 6.88; N, 5.31. Found: C, 68.08; H, 6.88; N, 5.11.

2-(5-Hydroxy-2-biphenylyl)ethylamine (8).—The hydrochloride (2.2 g) of **7** was refluxed with 33 ml of 48% HBr for 5 hr. After concentration under vacuum, the red oily residue was dissolved in a small amount of water and treated with a saturated solution of $NaHCO_3$. Continuous extraction with ether gave a solid material which was converted into the hydrochloride with an ethereal solution of HCl. After recrystallization from absolute ethanol–anhydrous ether, the **hydrochloride** presented mp 209° dec, yield 1.55 g (74%).

Anal. Calcd for $C_{14}H_{16}ClNO$: C, 67.34; H, 6.46; Cl, 14.20; N, 5.60. Found: C, 67.22; H, 6.30; Cl, 14.50; N, 5.40.

Ethyl 5-Methoxy-2-biphenylacetate.—Acid **1** (11.4 g) was transformed into the chloride by reaction with 10 g of oxalyl chloride in 30 ml of benzene. After the usual treatment, the acid chloride was dissolved in 30 ml of anhydrous benzene, and the solution was added dropwise with stirring in a cooled ethereal solution of excess diazomethane. The mixture was left overnight at room temperature and the solvents were evaporated under vacuum. The **diazo ketone** thus obtained, a yellow solid of mp 72–75°, was dissolved in 150 ml of absolute ethanol, the solution was heated at 55–60°, and an alcoholic suspension of Ag_2O (prepared from 2.5 g of $AgNO_3$ and 2 *N* NaOH) was added in portions. The mixture was then refluxed for 15 min, treated with charcoal, and filtered, and the solvent was evaporated. Distillation of the residue yielded 7.8 g of the **ester** (58% yield, based on the acid), bp 184° (2 mm).

Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.39; H, 6.60.

Saponification of the ester with alcoholic NaOH afforded the corresponding **acid,** mp 114° (lit.[10] mp 115–116°).

2-(5-Methoxy-2-biphenylyl)ethanol.—The above ester (12.7 g) was reduced in 150 ml of anhydrous ether with 4.8 g of $LiAlH_4$. After decomposition of the complex with water and 3% H_2SO_4, the organic phase was separated, the solvent was evaporated and the residue was distilled under reduced pressure yielding 8.95 g (84%) of the alcohol, bp 160° (1 mm).

Anal. Calcd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.02. Found: C, 78.88; H, 7.20.

2-(5-Methoxy-2-biphenylyl)ethyl Bromide.—A solution of 1.4 ml of PBr_3 in 6 ml of benzene was added dropwise in a cooled solution of 8.9 g of 2-(5-methoxy-2-biphenylyl)ethanol in 8 ml of anhydrous benzene. The mixture was kept in an ice bath for 3 hr, then warmed at 60° for 3 hr, cooled, and poured into crushed ice. The organic layer was separated, washed successively with 10% NaOH, 10% HCl, and water, and dried, and the solvent was evaporated. The residue yielded on distillation 7 g (61%) of the bromide, bp 166° (1 mm).

Anal. Calcd for $C_{15}H_{15}BrO$: C, 61.86; H, 5.20; Br, 27.44. Found: C, 62.06; H, 5.09; Br, 27.10.

The method used to prepare the amines **9–12** (see Table I) is illustrated by the following procedure.

N,N-Diethyl-2-(5-methoxy-2-biphenylyl)ethylamine (9).—2-(5-Methoxy-2-biphenylyl)ethyl bromide (3 g) in 20 ml of absolute ethanol was refluxed with 3.7 g of diethylamine for 4 hr. The ethanol was distilled, and the residue was taken up with saturated $NaHCO_3$ and extracted with ether. After washing, drying, and evaporating the ether, the yellow oil was converted into the **hydrochloride** with alcoholic HCl. The salt was recrystallized from absolute ethanol–anhydrous ether; yield 1.3 g of white needles (see Table I).

Acknowledgments.—The authors gratefully acknowledge support of this investigation by a research grant from the Scientific Committee of NATO. The authors are indebted to Professor P. Lechat, of the Pharmacology Institute of the University of Paris, for carrying out the pharmacological tests, and to the Microanalytical Laboratory of CIBA, Basel (Switzerland), for performing the microanalyses.

Analogs of 2,6-Pyridinedimethanol Bis(N-methylcarbamate)

P. F. JUBY, R. B. BABEL, G. E. BOCIAN, N. M. CLADEL, J. C. GODFREY, B. A. HALL, T. W. HUDYMA, G. M. LUKE, J. D. MATISKELLA, W. F. MINOR, T. A. MONTZKA, R. A. PARTYKA, R. T. STANDRIDGE, AND L. C. CHENEY

Research Division, Bristol Laboratories, Division of Bristol-Myers Company, Syracuse, New York 13201

Received January 27, 1967

Recently, Shimamoto and co-workers have described the pharmacology of a new bradykinin antagonist, 2,6-pyridinedimethanol bis(N-methylcarbamate) ($R_1 = R_2 = CH_3NHCO_2CH_2$ in the general structure of Table I), which exhibited powerful antiatherosclerotic properties when fed orally to rabbits.[1,2] Further studies[3,4] have led to the claim that the compound has beneficial effects on human vascular occlusive diseases associated with atherosclerosis, and that it is useful in the treatment of inflammatory disorders such as rheumatic fever and rheumatoid arthritis.

It should be noted that 2,6-pyridinedimethanol bis(N-methylcarbamate) and related compounds[5] show structural resemblances to a series of substituted-propanol carbamates with antiinflammatory properties.[6] Other pyridinemethanol carbamates have been tested for sedative and anticonvulsive activities.[7]

We have now prepared additional carbamate and urea analogs of 2,6-pyridinedimethanol bis(N-methylcarbamate) and these are listed in Tables I–VI. All the compounds were prepared by standard procedures.

Pharmacology.—All the compounds were found to be inactive when tested orally in rats for possible antiinflammatory activity, using the carrageenin-induced edema technique.[8] Representative compounds of the various structural types were also tested for an inhibitory effect on the reversed passive cutaneous anaphylactic reaction in guinea pigs,[9] with only compounds **29, 50,** and **123** showing activity.

Experimental Section[10]

Unless indicated otherwise, the alcohols, thiols, amines, isocyanates, isothiocyanates, and carbamoyl chlorides used to prepare the carbamates and ureas in Tables I–VI were obtained from commercial sources.

Acyl Isocyanates.—Acetyl isocyanate was prepared from acetyl chloride and silver cyanate.[11] Chloroacetyl isocyanate, butyryl

(1) T. Shimamoto, *Asian Med. J.*, **6**, 12 (1963).

(2) T. Shimamoto, F. Numano, and T. Fujita, *Am. Heart J.*, **71**, 216 (1966).

(3) T. Shimamoto and T. Atsumi, *Japan. Heart J.*, **6**, 407 (1965).

(4) T. Shimamoto, H. Maezawa, H. Yamazaki, T. Atsumi, T. Fujita, T. Ishioka, and T. Sunaga, *Am. Heart J.*, **71**, 297 (1966).

(5) M. Inoue, M. Ishikawa, H. Ishikawa, and T. Shimamoto, South African Patent 64/1679 (Oct 20, 1964).

(6) (a) O. Büch, *Arch. Intern. Pharmacodyn.*, **123**, 140 (1959); (b) O. Büch, *Arch. Exptl. Pathol. Pharmakol.*, **238**, 92 (1960).

(7) J.-C. Billiotte and A. Debay, *Chim. Therap.*, 164 (1966).

(8) C. A. Winter, E. A. Risley, and G. W. Nuss, *Proc. Soc. Exptl. Biol. Med.*, **111**, 544 (1962).

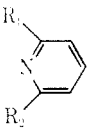
(9) D. H. Campbell, J. S. Garvey, N. E. Cremer, and D. H. Sussdorf, "Methods in Immunology," W. A. Benjamin, Inc., New York, N. Y., 1963, p 216.

(10) Melting points were determined with a variety of equipment and are uncorrected.

(11) O. C. Billeter, *Ber.*, **36**, 3213 (1903).

TABLE I

PYRIDINE DERIVATIVES



No.	R_1	R_2	Mp or bp (mm), °C	Cryst solvent[a]	Method[b]	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
Simple Substituted Carbamates												
1	H	$CH_3NHCO_2CH_2$	77–78	A–B	1	$C_8H_{10}N_2O_2 \cdot \frac{1}{4}H_2O$[d]	53.24	5.86	8.28	53.40	5.57	8.42
2	H	$(CH_3)_2NCO_2CH_2$	74–75 (0.01)		1	$C_9H_{12}N_2O_2$	59.98	6.71	15.55	59.70	6.65	15.80
3	H	3-$C_5H_4NNHCO_2CH_2$[c]	130.5–132.5	C	3	$C_{12}H_{11}N_3O_2$	62.87	4.84	18.33	63.09	5.00	18.68
4	CH_3	$CH_3NHCO_2CH_2$	139–141	D–C	1	$C_9H_{13}N_2O_2 \cdot HCl$	49.89	6.05		49.79	6.02	
5	CH_3	$(CH_3)_2NCO_2CH_2$	108–112 (0.5)		1	$C_{10}H_{14}N_2O_2$	61.83	7.27		61.80	7.10	
6	CH_3	$C_5H_5NHCO_2CH_2$	123–124.5	A	1	$C_{10}H_{14}N_2O_2 \cdot HCl$	52.06	6.55	12.15	52.25	6.75	12.35
7	CH_3	$(C_2H_5)_2NCO_2CH_2$	101–102 (0.05)		1	$C_{12}H_{18}N_2O_2$	64.84	8.16		64.51	8.28	
8	CH_3	$C_5H_5NHCO_2CH_2$	108–109.5	E	1	$C_{14}H_{14}N_2O_2$	69.40	5.83	11.56	69.50	5.82	11.78
9	CH_3	$CH_3NHC(S)OCH_2$	108–109.5	F	2	$C_9H_{11}NOS$	55.07	6.16	14.28	55.40	6.42	14.48
10	CH_3	$C_5H_5NHC(S)OCH_2$	201–201.5	G	2	$C_{13}H_{14}N_2OS \cdot HCl$	48.67	6.13	11.36	48.75	6.20	11.52
11	CH_3	$C_5H_5NHC(S)OCH_2$	106.5–108	D–H	2	$C_{14}H_{14}N_2OS$			10.85			10.60
12	$C_5H_5NHCO_2CH_2$[c]	$C_5H_5NHCO_2CH_2$[c]	126–127	C	3	$C_{18}H_{18}N_4O_4$	59.00	6.27	13.76	59.18	6.36	13.87
13	$C_5H_5O_2CCH_2NHCO_2CH_2$	$C_5H_5O_2CCH_2NHCO_2CH_2$	85–86.5	C	1	$C_{12}H_{16}N_2O_6$	51.38	5.83		51.40	6.11	
14	$CH_3(CH_2)_3O_2CCH_2NHCO_2CH_2$	$CH_3(CH_2)_3O_2CCH_2NHCO_2CH_2$	101–104	A–B	1	$C_{12}H_{26}N_2O_6 \cdot HCl$	51.46	6.59	8.57	51.50	6.49	8.73
15	m-$ClC_6H_4NHCO_2CH_2$	m-$ClC_6H_4NHCO_2CH_2$	111–112	D	1	$C_{20}H_{17}Cl_2N_3O_4$			9.42			9.32
16	p-$ClC_6H_4NHCO_2CH_2$	p-$ClC_6H_4NHCO_2CH_2$	175–176.5	G	1	$C_{20}H_{17}Cl_2N_3O_4$	56.51	3.84	9.42	56.23	4.16	9.64
17	5-$C_4H_3N_2NHCO_2CH_2$[f]	5-$C_4H_3N_2NHCO_2CH_2$[f]	234–235 dec	I–H	3	$C_{12}H_{10}N_4O_4$	53.56	3.97	25.72	53.80	4.12	25.90
18	2-$C_4H_3N_2NHCO_2CH_2$[g]	2-$C_4H_3N_2NHCO_2CH_2$[g]	235–237	I–D	3	$C_{12}H_{10}N_4O_4$	53.56	3.97	25.72	53.55	4.18	25.73
19	$HOCH_2$	$CH_3NHCO_2CH_2$	91–92	E	1[h]	$C_9H_{12}N_2O_3$	55.09	6.17	14.28	55.30	6.27	14.15
20	$(CH_3)_2NCO_2CH_2$	$CH_3NHCO_2CH_2$	114–115.5	E–J	1′	$C_{12}H_{17}N_3O_4$	53.92	6.41	15.72	54.05	6.44	15.81
21	$C_6H_5NHCO_2CH_2$	$CH_3NHCO_2CH_2$	88–90	E	1′	$C_{16}H_{17}N_3O_4$	60.94	5.43	13.33	61.26	5.42	13.50
22	$C_6H_{11}NHCO_2CH_2$[i]	$CH_3NHCO_2CH_2$	136–137	D–H	1′	$C_{16}H_{23}N_3O_4$	59.79	7.21	13.08	59.80	7.23	13.32
23	3-$C_5H_4NNHCO_2CH_2$[c]	$CH_3NHCO_2CH_2$	170–172	D	3′	$C_{18}H_{16}N_4O_4$	56.96	5.10	17.71	56.70	5.25	17.71
24	5-$C_4H_3N_2NHCO_2CH_2$[f]	$CH_3NHCO_2CH_2$	167–169	G	3′	$C_{14}H_{14}N_4O_4$	52.99	4.77	22.07	53.15	4.79	21.97
25	2-$C_4H_3N_2NHCO_2CH_2$[g]	$CH_3NHCO_2CH_2$	156–157	G	3′	$C_{14}H_{14}N_4O_4$	52.99	4.77	22.07	53.25	4.88	22.02
Acyl Carbamates												
26	H	$C_6H_5CONHCO_2CH_2$	98.5–101	E	1	$C_{18}H_{17}N_3O_3$	65.62	4.72	10.93	65.35	4.77	10.90
27	$CH_3CONHCO_2CH_2$	$CH_3CONHCO_2CH_2$	180–181	G	1	$C_{10}H_{18}N_4O_4$	50.48	4.89	13.59	50.30	4.84	13.65
28	$ClCH_2CONHCO_2CH_2$	$ClCH_2CONHCO_2CH_2$	215–216 dec	I–H	1	$C_8H_{10}Cl_2N_4O_6$	41.28	3.46	11.11	41.26	3.66	11.20
29	$CH_3(CH_2)_2CONH-CO_2CH_2$	$CH_3(CH_2)_2CONH-CO_2CH_2$	196–198	D	1	$C_{12}H_{20}N_4O_6$	55.38	6.35	11.50	56.00	6.43	11.60
30	$C_6H_5CONHCO_2CH_2$	$C_6H_5CONHCO_2CH_2$	168.5–170.5	C–D	1	$C_{28}H_{18}N_4O_6$	63.73	3.42	9.70	64.09	4.68	10.00
31	$C_6H_5CH_2CONHCO_2-CH_2$	$C_6H_5CH_2CONHCO_2-CH_2$	225–227	I–H	1	$C_{30}H_{26}N_4O_6$	65.07	5.02	9.11	65.30	5.07	9.00
32	$CH_3CONHCO_2CH_2$	$CH_3NHCO_2CH_2$	130–131	D	1′	$C_{12}H_{18}N_4O_6$	51.24	5.38	14.94	51.33	5.36	15.03
33	$ClCH_2CONHCO_2CH_2$	$CH_3NHCO_2CH_2$	154.5–155.5	D	1′	$C_{12}H_{17}ClN_4O_6$	45.64	1.47	13.30	45.75	4.47	13.32
34	$CH_3(CH_2)_2CONH-CO_2CH_2$	$CH_3NHCO_2CH_2$	133–134	D	1′	$C_{14}H_{24}N_4O_6$	51.36	6.19	13.59	54.40	6.20	13.72
35	$C_6H_5CONHCO_2CH_2$	$CH_3NHCO_2CH_2$	119–121	E	1′	$C_{23}H_{22}N_4O_6$	59.47	4.99	12.24	59.46	5.13	11.95
36	$C_6H_5CH_2CONHCO_2-CH_2$	$CH_3NHCO_2CH_2$	155.5–156.5	D	1′	$C_{25}H_{26}N_4O_6$	60.49	5.36	11.76	60.75	5.45	11.78
Sulfonyl Carbamates												
37	$C_6H_5SO_2NHCO_2CH_2$	$CH_3NHCO_2CH_2$	78–80	H	1′	$C_{18}H_{22}N_4O_8S$			11.08			10.94
38	$CH_3SO_2NHCO_2CH_2$	$CH_3SO_2NHCO_2CH_2$	182–184.5	D–H	4	$C_{14}H_{18}N_4O_8S_2$	34.64	3.97	11.02	34.78	4.12	11.29
39	$C_6H_5SO_2NHCO_2CH_2$	$C_6H_5SO_2NHCO_2CH_2$	169–171	G–B	1	$C_{24}H_{19}N_4O_8S_2 \cdot HCl$	46.54	3.72	7.75	46.77	4.07	7.92
Thiol Carbamates												
40	H	$CH_2NHCS_2CH_2$	70–71	K	1	$C_5H_{10}N_2S_2$	48.45	5.08	14.13	48.70	5.30	14.15
41	H	$CH_2NHC(O)SCH_2$	148–150 dec	D–B	1	$C_{14}H_{16}N_2OS \cdot HCl$	43.92	5.07	14.67[b]	43.95	4.97	14.85[b]
42	H	$C_6H_5NHCS_2CH_2$	113–114.5	C	1	$C_{18}H_{18}N_2S_2$	59.96	4.65		59.80	4.73	
43	H	$C_6H_5NHC(O)SCH_2$	130–132	C	1	$C_{28}H_{26}N_2O_2S$	63.90	4.95		64.05	4.97	
44	CH_3	$NH_2C(O)SCH_2$	126–129	H	4	$C_4H_{10}N_2OS$	52.72	5.53	15.38	52.75	5.16	15.38
45	CH_3	$CH_3NHCS_2CH_2$	133–135	D	1	$C_{10}H_{22}N_2S_2$	50.91	5.70	13.19	51.03	5.62	13.33
46	CH_3	$CH_3NHC(O)SCH_2$	120–122.5	D	1	$C_9H_{12}N_2OS$	55.07	6.16	14.28	55.25	6.27	14.18
47	CH_3	$C_6H_5NHC(O)SCH_2$	104–106	K	1	$C_{14}H_{14}N_2OS$	65.09	5.46	10.85	64.99	5.52	10.95
48	$CH_3NHCS_2CH_2$	$CH_3NHCS_2CH_2$	116–117	C–J	1	$C_{11}H_{18}N_2S_4$	41.61	4.76	13.23	41.81	4.90	13.40
49	$C_6H_5NHC(O)SCH_2$[f]	$C_6H_5NHC(O)SCH_2$[f]	146–148	D	3	$C_{18}H_{16}N_4O_2S_2$	53.38	5.68	19.00[b]	53.45	5.68	18.82[b]
50	$CH_3NHC(O)SCH_2$	$CH_3NHC(O)SCH_2$	120.5–122	C	1	$C_{14}H_{18}N_4O_2S_2$	46.29	5.30	14.72	46.54	5.35	14.95
51	$C_6H_5NHC(O)SCH_2$	$C_6H_5NHC(O)SCH_2$	106–107	K–J	1	$C_{28}H_{26}N_4O_2S_2$	49.81	6.41	13.41	49.95	6.10	13.70
52	$C_6H_5NHC(O)SCH_2$	$C_6H_5NHC(O)SCH_2$	177–179	D	1	$C_{30}H_{30}N_4O_2S_2$	61.59	4.68	10.26	61.70	4.87	10.12
53	$C_6H_5CONHC(O)-SCH_2$	$C_6H_5CONHC(O)-SCH_2$	186–188.5	I–H	1	$C_{28}H_{18}N_2O_4S_2$	59.33	4.11	9.03	59.27	4.40	8.85
Pyridineethanol Carbamates												
54	H	$CH_2NHCO_2CH_2CH_2$	105–105.5	L	1	$C_9H_{12}N_2O_2 \cdot 0.5Y$[d]	55.45	5.92	11.76	55.65	6.06	11.90
55	H	$C_6H_5NHCO_2CH_2CH_2$[j]	121–122.5	M	1	$C_{14}H_{14}N_2O_2$	69.40	5.83	11.56	69.50	5.88	11.55
56	H	$CH_2NHCO_2CH-(CCl_3)CH_2$	152.5–153	M	1	$C_{10}H_{11}Cl_3N_2O_2$	40.36	3.73	9.42	40.25	3.64	9.55
57	CH_3	$CH_3NHCO_2CH_2CH_2CH_2$	116–124	K–A	1	$C_{20}H_{14}N_2O_2 \cdot HBr$	43.65	5.50	10.18	43.60	5.43	10.30
58	CH_3	$C_5H_5NHCO_2CH_2CH_2$	125–128	A	1	$C_{21}H_{16}N_2O_2 \cdot HBr$	45.68	5.93	9.67	45.80	6.18	9.42
59	CH_3	$C_5H_5NHCO_2CH_2CH_2$	121–131 dec	A	1	$C_{28}H_{28}N_2O_2 \cdot HBr$	53.42	5.08	8.31	53.40	5.17	8.29

TABLE I (*Continued*)

No.	R_1	R_2	Mp or bp (mm), °C	Crystn solvent[a]	Method[b]	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
				Pyridinepropanol Carbamates								
60	H	$CH_3NHCO_2(CH_2)_3$	67.5–69.5	C	1	$C_{16}H_{14}N_2O_2 \cdot 0.5Y$[d]	57.13	6.39	11.11	57.20	6.40	11.22
61	H	$C_6H_5NHCO_2(CH_2)_3$[m]	79.5–80.5	G	1	$C_{15}H_{16}N_2O_2$	70.29	6.29	10.93	70.25	6.48	10.90
62	H	$C_6H_5NHCO_2(CH_2)_3$[n]	150–151	K		$C_{23}H_{26}N_2O_6S$	62.42	5.92	6.33	62.44	6.08	6.12
				α-Substituted Derivatives								
63	H	$CH_3NHCO_2CH(CH_2C_6H_5)$	110–111	C–J	1	$C_{15}H_{16}N_2O_2$	70.29	6.29		70.30	6.26	
64	H	$C_6H_5NHCO_2CH(CH_2C_6H_5)$	84–85	C–J	1	$C_{20}H_{18}N_2O_2$	75.45	5.69	8.80	75.16	5.78	8.99
65	H	$C_2H_5O_2CCH_2NHCO_2CH(C_6H_5CH_2)$	*o*		1	$C_{18}H_{20}N_2O_4$	65.84	6.14		66.00	6.37	
66	H	$C_6H_5NHCO_2CH(C_6H_5NHCO_2CH_2)$	59–62	C–J	1	$C_{21}H_{19}N_3O_4$	66.83	5.07		67.10	5.21	
67	H	$C_2H_5O_2CCH_2NHCO_2CH(C_2H_5O_2CCH_2NHCO_2CH_2)$	*o*		1	$C_{17}H_{23}N_3O_8$	51.38	5.83	10.57	51.03	6.00	10.76
68	CH_3	$(C_6H_5NHCO_2CH_2)_2CH$	146.5–147	C	1	$C_{23}H_{23}N_3O_4$	68.13	5.72	10.37	68.40	5.82	10.45
69	$CH_3NHCO_2CH(CH_3)$	$CH_3NHCO_2CH(CH_3)$	*o*		1	$C_{13}H_{19}N_3O_4 \cdot 0.5H_2O$	53.78	6.94		53.45	7.27	
70	$CH_3NHCO_2C(CH_3)_2$	$CH_3NHCO_2C(CH_3)_2$	163–164	C–J	1	$C_{15}H_{23}N_3O_4$	58.23	7.49	13.59	58.30	7.53	13.55
71	$C_6H_5NHCO_2C(CH_3)_2$	$C_6H_5NHCO_2C(CH_3)_2$	181–182	C–J	1	$C_{25}H_{27}N_3O_4$	69.26	6.28	9.70	69.30	6.31	9.52
72	$C_2H_5O_2CCH_2NHCO_2C(CH_3)_2$	$C_2H_5O_2CCH_2NHCO_2C(CH_3)_2$	130–132	C–J	1	$C_{21}H_{31}N_3O_8$	55.62	6.89	9.09	55.35	7.02	9.34
				Ureas								
73	H	$CH_3NHCON(CH_3)CH_2$	132–135 (0.2)		1	$C_9H_{13}N_3O$			23.45			23.70
74	H	$CH_3NHCON(CH_3)CH_2$[p]	127.5–130	F		$C_{10}H_{16}IN_3O$	37.39	5.02		37.70	5.23	
75	CH_3	$C_6H_5NHCONHCH_2$	152–153	M	1	$C_{14}H_{15}N_3O$	69.69	6.27	17.42	69.83	6.42	17.75
76	CH_3	*o*-$ClC_6H_4NHCONHCH_2$	162–163	A	1	$C_{14}H_{14}ClN_3O$	60.98	5.12		61.32	5.23	
77	CH_3	*m*-$ClC_6H_4NHCONHCH_2$	179–180	F	1	$C_{14}H_{14}ClN_3O$			15.24			15.20
78	CH_3	*p*-$ClC_6H_4NHCONHCH_2$	177–178.5	D	1	$C_{14}H_{14}ClN_3O$	60.98	5.12	15.24	61.10	5.17	15.55
79	CH_3	2,5-$Cl_2C_6H_3NHCONHCH_2$	189.5–190	A	1	$C_{14}H_{13}Cl_2N_3O$	54.21	4.22		54.51	4.28	
80	$NH_2CONHCH_2$	$NH_2CONHCH_2$	238.5–240	H	5	$C_9H_{13}N_5O_2$			31.38			31.37
81	$CH_3NHCONHCH_2$	$CH_3NHCONHCH_2$	212.5–213.5	H	1	$C_{11}H_{17}N_5O_2$	52.57	6.82	27.87	52.50	6.88	28.00
82	$CH_3NHCSNHCH_2$	$CH_3NHCSNHCH_2$	182.5–184	G	1	$C_{11}H_{17}N_5S_2$	46.63	6.05	24.72	46.61	6.38	24.80
83	$C_2H_5NHCONHCH_2$	$C_2H_5NHCONHCH_2$	224.5–225	D–H	1	$C_{13}H_{21}N_5O_2$	55.89	7.58		56.00	7.55	
84	$C_2H_5NHCSNHCH_2$	$C_2H_5NHCSNHCH_2$	96.5–98.5	C	1	$C_{13}H_{21}N_5S_2$	50.16	6.75	22.51	50.00	6.67	22.64
85	$C_6H_5NHCONHCH_2$	$C_6H_5NHCONHCH_2$	240–240.5	I–H	1	$C_{21}H_{21}N_5O_2$	67.18	5.64	18.66	67.50	5.57	18.95
86	$C_6H_5NHCSNHCH_2$	$C_6H_5NHCSNHCH_2$	192.5–194	I–H	1	$C_{21}H_{21}N_5S_2$	61.91	5.16	17.19	61.56	5.46	17.50
87	$CH_3(CH_2)_2CONHCONHCH_2$	$CH_3(CH_2)_2CONHCONHCH_2$	211–213	G	1	$C_{17}H_{25}N_5O_4$	56.19	6.88	19.28	56.20	6.95	19.60
88	$C_6H_5CONHCONHCH_2$	$C_6H_5CONHCONHCH_2$	241–243.5	I–H	1	$C_{23}H_{21}N_5O_4$	64.03	4.87	16.24	63.80	4.92	16.43
				Reverse Carbamates								
89	CH_3	$CH_3O_2CNHCH_2$	167–168	F	6	$C_9H_{12}N_2O_2 \cdot HCl$			12.93			13.05
90	CH_3	$C_2H_5O_2CNHCH_2$	95–101 (0.15)		6	$C_{10}H_{14}N_2O_2$	61.83	7.27	14.42	61.70	7.36	14.61
91	$CH_3O_2CNHCH_2$	$CH_3O_2CNHCH_2$	118.5–119.5	E–N	6	$C_{11}H_{16}N_2O_4$	52.17	5.97	16.59	52.00	5.90	16.83
92	$C_2H_5O_2CNHCH_2$	$C_2H_5O_2CNHCH_2$	85–86.5	E–N	6	$C_{13}H_{19}N_2O_4$	55.50	6.81	14.94	55.20	6.77	15.25
93	$C_6H_5O_2CNHCH_2$	$C_6H_5O_2CNHCH_2$	135–136	G–H	6	$C_{21}H_{19}N_2O_4$	66.84	5.04	11.14	67.05	5.01	10.90

[a] A = acetone, B = diethyl ether, C = ethyl acetate, D = ethanol, E = benzene, F = acetonitrile, G = methanol, H = water, I = dimethylformamide, J = Skellysolve B (bp 60–80°), K = 2-propanol, L = 95% ethanol, M = toluene, N = cyclohexane, O = 1-butanol. [b] See Experimental Section. [c] C_5H_4N = pyridyl. [d] X = *p*-toluenesulfonic acid, $C_7H_8O_3S$; Y = fumaric acid, $0.5C_4H_4O_4$. [e] C_3H_5 = cyclopropyl. [f] $C_4H_3N_2$ = pyrimidinyl. [g] $C_4H_3N_2$ = pyrazinyl. [h] Product obtained from a reaction between 2,6-pyridinedimethanol in pyridine and insufficient methyl isocyanate for dicarbamate formation. [i] Product obtained by treatment of **19** with the appropriate isocyanate, carbamoyl chloride, or acid azide. [j] C_6H_{11} = cyclohexyl. [k] Sulfur analysis. [l] E. Profft and R. Schmuck, *Arch. Pharm.*, **296,** 209 (1963). [m] K. Winterfeld and E. Müller, *ibid.*, **284,** 269 (1951). [n] Methyl *p*-toluenesulfonate of **61**. [o] Noncrystalline product. [p] Methiodide of **73**.

isocyanate,[12] bp 109–114° (760 mm), benzoyl isocyanate, and phenylacetyl isocyanate were prepared from the reaction of oxalyl chloride with the corresponding primary amides.[13]

Acid Azides.—Nicotinic acid azide, pyrimidine-5-carboxylic acid azide (mp 48–53°, characterized as the carbamates **17** and **24**), pyrazine-2-carboxylic acid azide[14] (characterized as the carbamates **18** and **25**), and cyclopropanecarboxylic acid azide (not isolated, but characterized as the carbamates **12** and **49**) were prepared by the general procedure of Weinstock.[15]

Sulfonyl Isocyanates.—Methanesulfonyl isocyanate,[16] bp 83–84° (16 mm), and benzenesulfonyl isocyanate,[17] bp 110° (3.7 mm), were both prepared from the reaction of oxalyl chloride with methanesulfonamide and benzenesulfonamide, respectively, by methods similar to those described by Franz and Osuch.[18]

6-Methyl-2-pyridinemethanethiol, bp 49° (0.5 mm), was prepared from 2-chloromethyl-6-methylpyridine in a yield of 44.7%

(12) This product has not been reported previously but was too reactive toward atmospheric moisture for satisfactory elemental analyses. The product was characterized as the carbamates **29** and **34** and the urea **87**.

(13) A. J. Speziale and L. R. Smith, *J. Org. Chem.*, **28,** 1805 (1963).

(14) The crude pyrazine-2-carboxylic acid azide was a semisolid material which could not be purified for satisfactory elemental analyses.

(15) J. Weinstock, *J. Org. Chem.*, **26,** 3511 (1961).

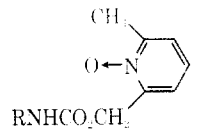
(16) O. C. Billeter, *Ber.*, **38,** 2013 (1905).

(17) O. C. Billeter, *ibid.*, **37,** 690 (1904).

(18) J. E. Franz and C. Osuch, *J. Org. Chem.*, **29,** 2592 (1964).

TABLE II

PYRIDINE N-OXIDE DERIVATIVES

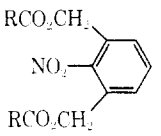


No.	R	Mp, °C	Crysin solvent[a]	Method[b]	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
94	CH_3	129.5–130.5	E	1	$C_9H_{12}N_2O_3$	55.09	6.17	14.28	55.15	6.14	14.49
95	C_6H_5	167–168	G–H	1	$C_{14}H_{14}N_2O_3$	65.10	5.46	10.85	65.25	5.52	11.03
96	3-C_5H_4N[c]	184–185	H	3	$C_{13}H_{13}N_3O_3$	60.22	5.05	16.21	60.40	5.07	16.35

[a–c] See footnotes in Table I.

TABLE III

NITROBENZENE DERIVATIVES

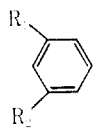


No.	R	Mp, °C	Crysin solvent[a]	Method[b]	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
97	NH_2	199.5–200.5	G	4	$C_{12}H_{11}N_3O_6$	44.61	4.12	15.61	44.65	4.18	15.75
98	CH_3NH	144–145.5	H	1	$C_{13}H_{13}N_3O_6$	48.48	5.09	14.14	48.75	5.18	14.30
99	$(CH_3)_2N$	111–113	D–H	1	$C_{14}H_{15}N_3O_6$	51.68	5.89	12.92	51.60	5.94	12.80
100	3-C_5H_4NNH[c]	195–196 dec	O	3	$C_{20}H_{17}N_5O_6$	56.73	4.05	16.54	57.00	4.28	16.55

[a–c] See footnotes in Table I.

TABLE IV

BENZENE DERIVATIVES



No.	R_1	R_2	Mp or bp (mm), °C	Crysin solvent[a]	Method[b]	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
101	CH_3	$NHCO_2CH_3$	84–86	N	1	$C_9H_{11}NO_2$	65.44	6.71	8.48	65.38	6.85	8.56
102	CH_3	$CH_3NHCO_2CH_3$	92–97 (0.02)		1	$C_{10}H_{13}NO_2$	67.02	7.31	7.82	66.90	7.52	7.87
103	CH_3	$(CH_3)_2NCO_2CH_3$	70–75 (0.01)		1	$C_{11}H_{15}NO_2$	68.37	7.82	7.25	68.30	7.78	6.98
104	CH_3	$C_6H_5NHCO_2CH_2$	64–65.5	N	1	$C_{15}H_{15}NO_2$	74.66	6.27	5.81	74.41	6.28	5.97
105	CH_3	3-$C_5H_4NNHCO_2CH_2$[c]	139–140	G–H	3	$C_{14}H_{14}N_2O_2$	69.40	5.83	11.56	69.41	6.05	11.77
106	$NH_2CO_2CH_2$	$NH_2CO_2CH_3$	150–152	G–H	4	$C_{10}H_{12}N_2O_4$	53.57	5.39	12.50	53.70	5.37	12.58
107	$CH_3NHCO_2CH_2$	$CH_3NHCO_2CH_3$	139–140	G	1	$C_{12}H_{16}N_2O_4$	57.13	6.39	11.11	57.00	6.56	11.36
108	$C_2H_5NHCO_2CH_2$	$C_2H_5NHCO_2CH_3$	134.5–135.5	G–H	1	$C_{14}H_{20}N_2O_4$	59.98	7.19	9.99	59.98	7.30	10.19
109	$C_6H_5NHCO_2CH_2$	$C_6H_5NHCO_2CH_3$	132.5–134.5	G	1	$C_{22}H_{20}N_2O_4$	70.20	5.36	7.44	70.25	5.15	7.45
110	$(CH_3)_2NCO_2CH_2$	$(CH_3)_2NCO_2CH_3$	192–194 (0.02)		1	$C_{14}H_{20}N_2O_4$	59.98	7.19	9.99	60.20	7.40	10.18
111	3-$C_5H_4NNHCO_2CH_2$[c]	3-$C_5H_4NNHCO_2CH_2$[c]	163–165	G–H	3	$C_{20}H_{18}N_4O_4$	63.48	4.80	14.81	63.55	4.95	15.04
112	$C_6H_5NHC(S)OCH_2$	$C_6H_5NHC(S)OCH_2$	136.5–137.5	E	2	$C_{28}H_{20}N_2O_2S_2$	64.69	4.93	6.86	64.90	4.88	7.05
113	$CH_3NHC(O)SCH_2$	$CH_3NHC(O)SCH_2$	150–152	D	1	$C_{12}H_{16}N_2O_2S_2$	50.67	5.67	9.85	50.50	5.67	9.65
114	$C_6H_5NHC(O)SCH_2$	$C_6H_5NHC(O)SCH_2$	183–185	I–H	1	$C_{28}H_{20}N_2O_2S_2$	64.69	4.93	6.86	64.65	5.05	6.88
115	$CH_3NHCONHCH_2$	$CH_3NHCONHCH_2$	201.5–202.5	G	1	$C_{19}H_{18}N_4O_2$	57.58	7.25	22.39	57.65	7.34	22.25
116	$(CH_3)_2NCONHCH_2$	$(CH_3)_2NCONHCH_2$	147–149	C	1	$C_{14}H_{22}N_4O_2$	60.43	7.91	20.15	60.13	7.87	19.90
117	$C_2H_5NHCONHCH_2$	$C_2H_5NHCONHCH_2$	195–196.5	G–B	1	$C_{14}H_{22}N_4O_2$	60.43	7.91	20.15	60.50	7.99	20.20
118	$C_2H_5O_2CCH_2$-NHCONHCH$_2$	$C_2H_5O_2CCH_2$-NHCONHCH$_2$	200.5–202.5	D	1	$C_{15}H_{20}N_4O_6$	54.81	6.64	14.21	54.80	6.86	14.52
119	$CH_3NHCSNHCH_2$	$CH_3NHCSNHCH_2$	134.5–137	G	1	$C_{19}H_{18}N_4S_2$	51.05	6.43		51.20	6.42	
120	$C_2H_5NHCSNHCH_2$	$C_2H_5NHCSNHCH_2$	163–165	G	1	$C_{14}H_{22}N_4S_2$	54.18	7.15	18.05	54.50	7.27	18.32
121	$C_2H_5O_2CNHCH_2$	$C_2H_5O_2CNHCH_2$	103.5–105	D–H	6	$C_{18}H_{20}N_2O_4$	59.98	7.19	9.99	59.80	7.03	10.18
122	$C_6H_5O_2CNHCH_2$	$C_6H_5O_2CNHCH_2$	154.5–155	G	6	$C_{28}H_{20}N_2O_4$	70.21	5.32	7.45	70.42	5.52	7.47

[a–c] See footnotes in Table I.

by the general procedure of Urquhart, *et al.*[19] The thiol was characterized as the carbamates **44–47**.

2,6-Pyridinedimethanethiol, bp 94–96° (0.35 mm), was prepared in 65.3% yield from 2,6-pyridinedimethanol by the general method of Frank and Smith.[20] The dithiol was characterized as the carbamates **48–53**.

2-[2-(6-Methylpyridyl)]ethanol,[21] **2-[2-(6-methylpyridyl)]-1,3-propanediol,**[21] **and 1-(2-pyridyl)-3,3,3-trichloro-2-propanol**[22] were prepared according to known procedures.

2,6-Bis(aminomethyl)pyridine,[23] bp 89–91° (0.15–0.2 mm),

(19) G. G. Urquhart, J. W. Gates, Jr., and R. Connor, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p 363.

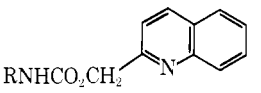
(20) R. L. Frank and P. V. Smith, *J. Am. Chem. Soc.*, **68**, 2103 (1946).

(21) R. Bodalski, J. Michalski, and K. Studniarski, *Roczniki Chem.*, **38**, 1337 (1964); *Chem. Abstr.*, **62**, 1627*d* (1965).

(22) C. W. Tullock and S. M. McElvain, *J. Am. Chem. Soc.*, **61**, 961 (1939).

(23) F. Lions and K. V. Martin, *ibid.*, **79**, 2733 (1957).

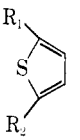
TABLE V
QUINOLINE DERIVATIVES



No.	R	Mp, °C	Crystn solvent[a]	Method[b]	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
123	CH_3	94.5–95	B–J	1	$C_{12}H_{12}N_2O_2$	66.65	5.60		66.75	5.70	
124	C_6H_5	129.5–130.5	C–J	1	$C_{17}H_{14}N_2O_2$	73.36	5.07	10.07	73.11	5.13	10.25

[a,b] See footnotes in Table I.

TABLE VI
THIOPHENE DERIVATIVES



No.	R_1	R_2	Mp, °C	Crystn solvent[a]	Method[b]	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
125	H	$CH_3NHCONHCH_2$	96.5–97.5	E	1	$C_7H_{10}N_2OS$	49.40	5.92	16.46	49.36	6.00	16.60
126	$CH_3NHCO_2CH_2$	$CH_3NHCO_2CH_2$	89–91	G–B	1	$C_8H_{14}N_2O_4S$	46.51	5.42	10.85	46.75	5.54	10.88
127	$C_2H_5NHCO_2CH_2$	$C_2H_5NHCO_2CH_2$	98–100	A–J	1	$C_{12}H_{18}N_2O_4S$	50.35	6.28	9.79	50.40	6.37	9.58

[a,b] See footnotes in Table I.

was prepared from 2,6-bis(chloromethyl)pyridine[24] in 56% yield by the Gabriel method.[25]

6-Methyl-2-pyridinemethanol N-oxide, mp 111–113°, was prepared from 6-methyl-2-pyridinemethanol by the method of Furukawa.[26]

2-Nitro-1,3-benzenedimethanol.—1,3-Dimethoxycarbonyl-2-nitrobenzene[27] was reduced with $NaBH_4$ and $AlCl_3$ in diethyleneglycol dimethyl ether by a general method for the reduction of esters to alcohols in the presence of nitro groups.[28] The light-sensitive 2-nitro-1,3-benzenedimethanol was recrystallized from water to give yellow needles, mp 101.5–102° (32.5% yield).

Anal. Calcd for $C_8H_9NO_4$: C, 52.46; H, 4.95; N, 7.65. Found: C, 52.30; H, 5.05; N, 7.74.

3-Methylbenzyl alcohol[29] and 1,3-benzenedimethanol[30] were prepared by the reductions of methyl *m*-toluate and dimethyl isophthalate, respectively, with $LiAlH_4$ in tetrahydrofuran solutions.

1,3-Benzenedimethanethiol[31] was prepared from 1,3-benzenedimethanol according to the general procedure of Frank and Smith.[20]

2,5-Thiophenedimethanol, bp 123–125° (0.05 mm), was prepared from thiophene by the method of Griffing and Salisbury.[32]

General Methods for the Preparation of Carbamates and Ureas. Method 1.—A solution of an alcohol, thiol, or amine in an appropriate solvent such as pyridine, benzene, toluene, acetone, or ether was treated with an isocyanate, acyl isocyanate, sulfonyl isocyanate, isothiocyanate, or carbamoyl chloride at temperatures ranging from room temperature to the reflux temperature of the solution for 0.5–108 hr. Reactions using the more volatile isocyanates, such as methyl isocyanate, were conducted in glass pressure bottles.

Method 2.—A solution of an alcohol and potassium *t*-butoxide in *t*-butyl alcohol was treated with an isothiocyanate at room temperature.[33]

Method 3.—A solution of an alcohol in benzene or pyridine was heated under reflux with an acid azide.

Method 4.—Primary carbamates were prepared from the reaction of an alcohol with sodium cyanate and trifluoroacetic acid in methylene chloride.[34]

Method 5.—A monosubstituted urea was prepared by heating an aqueous solution of an amine hydrochloride and KCNO on a steam bath for 45 minutes.[35]

Method 6.—A solution of an amine in a solvent such as benzene or ether was treated with an alkyl or aryl chloroformate in the presence of a base such as pyridine or triethylamine.

Acknowledgment.—The authors are particularly grateful to Dr. Max E. Bierwagen and his staff for all of the pharmacological test results and for helpful comments during the preparation of this manuscript. Thanks are also due to Mr. J. C. Heffernan for technical assistance and to the analytical and spectroscopic departments for their services.

(24) W. Baker, K. M. Buggle, J. F. W. McOmie, and D. A. M. Watkins, *J. Chem. Soc.*, 3594 (1958).
(25) J. C. Sheehan and W. A. Bolhofer, *ibid.*, **72**, 2786 (1950).
(26) S. Furukawa, *Yakugaku Zasshi*, **78**, 957 (1958); *Chem. Abstr.*, **53**, 3219*h* (1959).
(27) A. Wohl, *Ber.*, **43**, 3474 (1910).
(28) H. C. Brown and B. C. Subba Rao, *J. Am. Chem. Soc.*, **77**, 3164 (1955).
(29) Br. Radziszewski and P. Wispek, *Ber.*, **15**, 1743 (1882).
(30) C. Mettler, *ibid.*, **39**, 2933 (1906).
(31) A. Kötz, *ibid.*, **33**, 729 (1900).
(32) J. M. Griffing and L. F. Salisbury, *J. Am. Chem. Soc.*, **70**, 3416 (1948).
(33) A. Streitwieser, Jr., and J. R. Wolfe, Jr., *ibid.*, **79**, 903 (1957).
(34) B. Loev and M. F. Kormendy, *J. Org. Chem.*, **28**, 3421 (1963).
(35) P. Ruggli and B. Prijs, *Helv. Chim. Acta*, **28**, 674 (1945).

2-Acylimino-1,1-dimethylphenethylamines and Related Compounds. Anorectic Agents

JOHN KRAPCHO AND JOHN P. HIGH

The Squibb Institute for Medical Research, New Brunswick, New Jersey

Received December 8, 1966

Numerous substituted phenethylamines exhibit central nervous system stimulation and anorectic activity.[1] We found that 1-(2-imino-1,1-dimethyl-2-phenylethyl)-piperidine (I), when administered to mice by the oral route caused significant CNS stimulation and depres-

I, R = H
II, R = $COCH_3$

(1) R. A. McLean in "Medicinal Chemistry," A. Burger Ed., Interscience Publishers, Inc., New York, N. Y., 1960, Chapter 29, p 592.