wave lengths. However, it is noteworthy that the oxidation–reduction potential of pheohemin a which has no formyl side chain was found to be more positive than that of spirographishemin.

Pheohemin b has been found to have a more positive oxidation–reduction potential than pheohemin a and also to be more effective as an oxidative catalyst. These results suggest that this difference in catalytic activity may be due to the presence of the formyl group which may also account for the high oxidative activity of cytochrome oxidase.

CHICAGO, ILLINOIS

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE U. S. VITAMIN AND PHARMACEUTICAL CORPORATION]

Aminocyclohexyl Esters

BY SEYMOUR L. SHAPIRO, HAROLD SOLOWAY, HARRIS J. SHAPIRO AND LOUIS FREEDMAN

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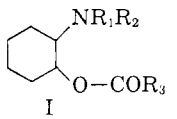
A series of *trans*-2-(substituted amino)-cyclohexyl benzoates of the type I have been synthesized and examined for pharmacological activity. Significant responses have been noted with these compounds as local anesthetics, hypotensives and central nervous system depressants.

In the course of developments leading to the elucidation of the structure[1] and total synthesis[2] of reserpine, many workers have undertaken studies[3] in the search for similar or modified pharmacological activity in simple analogs.

In our laboratories a similar objective was approached from the viewpoint that in one simple sense, reserpine in terms of its nitrogen at position 4 of ring D and its oxygen function at position 18 of ring E, might be regarded as an aromatic ester of a dialkylamino substituted cyclohexanol. In this paper, the synthesis and examination for pharmacological activity of a number of *trans*-aminocyclohexyl esters[4] of the type I are reported and the scope of the compounds is described in Table I.



I

An inspection of the literature indicates previous exploration[5,6] of analogs of I although the reported work reflects a period when careful examination for depression of central nervous system response was not being conducted.

The reaction of the secondary amine R_1R_2NH with cyclohexene oxide afforded the *trans*-substituted aminocyclohexanol[6,7] which in turn was esterified using the acid chloride R_3COCl to afford the cyclohexyl esters I in moderate to good yield.

Pharmacology.—In view of the initial stimulus of this work as an investigation of simple congeners of reserpine, it was of interest to evaluate the compounds as hypotensive agents,[8a] inhibitors of central nervous system response[8b] and potentiators of Evipal sleeping time.[8b] In addition, the majority of compounds were screened for local anesthetic[8c] and anti-Parkinson effects.[8c] The data have been compiled in Table II.

Many of the compounds evaluated show local anesthetic activity of a far greater intensity than procaine. In the assessment of the structural effects two particular group variations showed the best activity. The use of $-NR_1R_2$ = N-methyldiethylaminoethylamino is associated generally with the highest absolute activities as well as over-all effectiveness (compounds 27, 23, 25), while the use of the pyrrolidino group is the next most effective (compounds 8, 5, 7, 6).

The hypotensive effect was confined largely to the N-methylpiperazine derivatives. Significant depression in central nervous system activity was noted with relatively few compounds and, interestingly, while the only structure which afforded this effect coupled with hypotension was a 3,4,5-trimethoxybenzoate (compound 36), this compound failed to prolong Evipal sleeping time.[9] The fail-

(1) (a) C. F. Huebner, H. B. MacPhillamy, E. Schlittler and A. F. St. Andre, *Experientia*, **11**, 303 (1955); (b) C. F. Huebner and E. Wenkert, THIS JOURNAL, **77**, 4180 (1955); (c) P. A. Diassi, F. L. Weisenborn, C. M. Dylion and O. Wintersteiner, *ibid.*, **77**, 4687 (1955).

(2) R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey and R. W. Kierstead, *Tetrahedron*, **2**, 1 (1958).

(3) (a) B. V. Rama Sastry and A. Lasslo, *J. Org. Chem.*, **23**, 1577 (1958); (b) G. Di Paco and C. S. Tauro, *Farmaco (Pavia), Ed. sci.*, **64**, 429 (1958); (c) R. A. Lucas, M. E. Kuehne, M. J. Ceglowski, R. L. Dziemian and H. B. MacPhillamy, American Chemical Society Meeting, Chicago, Ill., September, 1958, p. 6-O; (d) F. A. Turner and J. E. Gearien, *ibid.*, p. 6-O; (e) F. M. Miller and M. S. Weinberg, American Chemical Society Meeting, Atlantic City, N. J., September, 1956, p. 11-N.

(4) Important pharmacological activity has been noted by Friess and co-workers with *cis*-2-dimethylaminocyclohexanol and related structures; (a) P. A. French, W. C. Alford and S. L. Friess, *J. Org. Chem.*, **23**, 24 (1958); (b) S. L. Friess, THIS JOURNAL, **79**, 3269 (1957).

(5) T. S. Kusner, *Ukrain. Khem. Zhur.*, **7**, Wiss. Abt., 179 (1932) [*C. A.*, **27**, 3476 (1933)]; (b) H. Heckel and R. Adams, THIS JOURNAL, **49**, 1303 (1927); (c) F. E. King and D. Holmes, *J. Chem. Soc.*, 164 (1947); (d) R. Granger and J. Fraux, *Trav. soc. pharm. Montpellier*, **7**, 22 (1947–1948) [*C. A.*, **48**, 10804*h* (1954)].

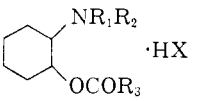
(6) More recent work has been reported during the course of our investigations; (a) L. Dúbravková, I. Ježo, P. Šefčovič and Z. Votický, *Chem. Zvesti*, **11**, 150 (1957) [*C. A.*, **51**, 15455*d* (1957)]; (b) J. Kovář and K. Bláha, *Chem. Listy*, **52**, 283 (1958) [*C. A.*, **52**, 11005f (1958)].

(7) An extensive literature indicates that the reaction of amines with cyclohexene oxide yields the *trans*-2-substituted aminocyclohexanol; (a) F. N. Hayes, L. C. King and D. E. Peterson, THIS JOURNAL, **78**, 2527 (1956); (b) T. Taguchi and M. Nakayama, *ibid.*, **73**, 5679 (1951); (c) K. Bláha and J. Kovář, *Chem. Listy*, **52**, 77 (1958) [*C. A.*, **52**, 12864*f* (1958)]; (d) L. R. Hawkins and R. A. B. Bannard, *Can. J. Chem.*, **36**, 220 (1958); (e) F. G. Bordwell and R. J. Kern, THIS JOURNAL, **77**, 1141 (1955).

(8) The methods used for evaluation of the noted pharmacological responses have been detailed previously; (a) S. L. Shapiro, H. Soloway and L. Freedman, *ibid.*, **80**, 2743 (1958); (b) S. L. Shapiro, I. M. Rose, E. Roskin and L. Freedman, *ibid.*, **80**, 1648 (1958); (c) S. L. Shapiro, H. Soloway, E. Chodos and L. Freedman, *ibid.*, **81**, 203 (1959).

(9) For the mechanism of the sedative action of reserpine, see S. Garattini and L. Valzelli, *Science*, **128**, 1278 (1958).

TABLE I

trans-2-SUBSTITUTED AMINOCYCLOHEXYL ESTERS 

No.	R_3	HX	M.p.,[a] (RS)[b] or b.p., °C.(mm.)	Yield,[c] %	Formula	Analyses[d] Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
			$-NR_1R_2$ = dimethylamino								
1	TMP[e]		170–178 (0.05)	46							
2	TMP[e]	HCl	195–197 (A)		$C_{18}H_{28}ClNO_5$	57.8	58.3	7.6	7.6	3.8	3.8
			$-NR_1R_2$ = diethylamino								
3	2-$CH_3OC_6H_4$–		148–150 (0.2)	23	$C_{18}H_{27}NO_3$	70.8	70.5	8.9	8.9		
4	TMP[e]		172–176 (0.1)	37	$C_{20}H_{31}NO_5$					3.8	3.9
4a	TMP[e]	HPic.	155–157 (B)		$C_{26}H_{34}N_4O_{12}$					9.4	9.3
			$-NR_1R_2$ = pyrrolidino								
5	C_6H_5–		132–140 (0.07)	86	$C_{17}H_{23}NO_2$	74.7	74.9	8.5	8.3		
6	2-$CH_3OC_6H_4$–		180 (0.1)	66	$C_{18}H_{25}NO_3$	71.3	71.3	8.3	8.5	4.6	4.7
7	TMP[e]		198–200 (0.3)	28	$C_{20}H_{29}NO_5$	66.1	66.1	8.0	8.1	3.9	3.8
8	4-$NO_2C_6H_4$–	HCl	173–176 (C)	50	$C_{17}H_{23}ClN_2O_4$					7.9	8.0
9	4-$NH_2C_6H_4$–	2 HCl	186–189 (D)	19	$C_{17}H_{26}Cl_2N_2O_2$	56.5	56.6	7.3	7.4	7.8	7.6
			$-NR_1R_2$ = 4-morpholino								
10	2-$CH_3OC_6H_4$–		170–172 (0.05)	31	$C_{18}H_{25}NO_4$	67.7	68.4	7.9	7.9	4.4	4.0
11	TMP[e]		101–103 (E)	23	$C_{20}H_{29}NO_5$	63.3	63.3	7.7	7.3	3.7	3.5
			$-NR_1R_2$ = N-methylanilino								
12	2-$CH_3OC_6H_4$–		105–107 (F)	35	$C_{21}H_{25}NO_3$	74.3	74.6	7.4	7.6	4.1	4.2
13	TMP[e]		139–141 (B)	14	$C_{23}H_{29}NO_5$	69.2	69.3	7.3	7.0	3.5	3.7
			$-NR_1R_2$ = N-methyl-2,6-dimethylanilino								
14	C_6H_5–		170–174 (0.05)	14	$C_{22}H_{27}NO_2$	78.3	78.2	8.1	7.7	4.2	3.8
			$-NR_1R_2$ = N-methylbenzyl								
15	2-$CH_3OC_6H_4$–		186–190 (0.28)	11	$C_{22}H_{27}NO_3$	74.8	75.0	7.7	7.8	4.0	3.9
16	TMP[e]		194–204 (0.04)	16	$C_{24}H_{31}NO_5$	69.7	69.8	7.6	7.9		
			$-NR_1R_2$ = N-methyldimethylaminoethylamino								
17	C_6H_5–	HCl	129–130 (G)	72	$C_{18}H_{29}ClN_2O_2$	63.4	63.1	8.6	8.8		
18	2-$CH_3OC_6H_4$–		158–160 (0.07)	37	$C_{19}H_{30}N_2O_3$	68.2	68.6	9.0	9.3	8.4	8.0
19	4-$CH_3OC_6H_4$–		160–162 (0.08)	58							
20	4-$CH_3OC_6H_4$–	2 HCl	206–207 (B)		$C_{19}H_{32}Cl_2N_2O_3$	56.0	56.4	7.9	8.0	6.9	7.0
21	$C_6H_5OCH_2$–	HCl	160 (C)	45	$C_{19}H_{31}ClN_2O_3$	61.5	61.4	8.4	7.9	7.6	7.6
22	C_6H_5CH=CH—		156 (0.04)	67	$C_{20}H_{30}N_2O_2$	72.7	72.3	9.2	9.0	8.5	8.9
			$-NR_1R_2$ = N-methyldiethylaminoethylamino								
23	C_6H_5–		142–144 (0.07)	70	$C_{20}H_{32}N_2O_2$	72.3	72.2	9.7	9.7	8.4	8.2
24	2-$CH_3OC_6H_4$–		164–168 (0.05)	52	$C_{21}H_{34}N_2O_3$	69.6	69.7	9.5	9.5		
25	4-$CH_3OC_6H_4$–	HCl	137–139 (H)	77	$C_{21}H_{35}ClN_2O_3$	63.2	63.3	8.8	8.8	7.0	6.9
26	$C_6H_5OCH_2$–	HCl	110–111 (H)	59	$C_{21}H_{35}ClN_2O_3$	63.2	63.3	8.8	8.9	7.0	7.0
27	C_6H_5CH=CH—	HCl	143–144 (H)	58	$C_{22}H_{33}ClN_2O_2$	66.9	66.9	8.9	8.8	7.1	7.2
			$-NR_1R_2$ = N-methyldimethylaminopropylamino								
28	C_6H_5–		130 (0.02)	63	$C_{19}H_{30}N_2O_2$	71.7	71.8	9.3	9.6	8.8	8.7
29	2-$CH_3OC_6H_4$–		156–158 (0.05)	62	$C_{20}H_{32}N_2O_3$	68.9	69.0	9.3	9.2	8.0	7.6
30	4-$CH_3OC_6H_4$–		158–160 (0.04)	24	$C_{20}H_{32}N_2O_3$					8.0	8.3
31	$C_6H_5OCH_2$–	HCl	119–120 (I)	26	$C_{20}H_{33}ClN_2O_3$	62.4	61.9	8.6	8.4	7.3	7.3
32	C_6H_5CH=CH—		176 (0.01)	7	$C_{21}H_{32}N_2O_2$	73.2	72.8	9.4	9.7	8.1	7.9
			$-NR_1R_2$ = N-methylpiperazino								
33	CH_3–	HCl	205–206 (B)	40	$C_{13}H_{25}ClN_2O_2$	56.4	56.0	9.1	9.0	10.1	10.4
34	C_6H_5–		168–172 (0.1)	75	$C_{18}H_{26}N_2O_2$	71.5	71.7	8.7	8.8		
35	2-$CH_3OC_6H_5$–		190–192 (0.1)	70	$C_{19}H_{28}N_2O_3$	68.6	68.9	8.5	8.0	8.4	8.1
36	TMP[e]		198–200 (0.03)	59	$C_{21}H_{32}N_2O_5$					7.1	6.9
36a	TMP[e]	2 HCl	220–223 (J)	10	$C_{21}H_{34}Cl_2N_2O_5$					6.0	5.5
37	4-$NO_2C_6H_4$–	HCl	222–224 (C)	3	$C_{18}H_{26}ClN_3O_4$[f]	55.0	55.1	6.9	7.0	10.7	10.8
38	4-$NH_2C_6H_4$	HCl	164 dec. (D)	32	$C_{18}H_{28}ClN_3O_2$[g]	56.8	57.2	8.2	8.7	11.0	11.0
39	4-$NH_2C_6H_4$–	2 HPic.	239–241 (K)		$C_{30}H_{33}N_9O_{16}$	46.5	46.4	4.3	4.4	16.3	16.0

TABLE I (*continued*)

$-NR_1R_2$ = N-phenylpiperazino

40	CH_3-		68–69 (E)	10	$C_{18}H_{26}N_2O_2$	71.5	71.2	8.7	8.8	9.3	9.5
41	C_6H_5-		98–99 (C)	12							
42	C_6H_5-	2 HPic.	192–196 (C)		$C_{35}H_{34}N_8O_{16}$	51.1	51.1	4.2	4.2	13.6	13.9
43	$2\text{-}CH_3OC_6H_4-$	HCl	178–179 (H)	11	$C_{24}H_{31}ClN_2O_3$	66.9	66.8	7.3	7.1	6.5	6.6
44	$4\text{-}C_2H_5OC_6H_4-$	HCl	193–196 (B)	37	$C_{25}H_{33}ClN_2O_3$	67.5	67.5	7.5	7.6	6.3	6.4
45	C_4H_3O-[h]	HCl	195–198 (H)	8	$C_{21}H_{27}ClN_2O_3$	64.5	64.2	7.0	7.0	7.2	7.4
46	$C_6H_5CH{=}CH-$		159 (H)	20	$C_{25}H_{30}N_2O_3$	76.9	76.8	7.7	7.6	7.2	7.0

[a] Melting points are not corrected. [b] RS = recrystallizing solvent as shown; A = ethanol-ethyl acetate; B = isopropyl alcohol; C = ethanol; D = ethanol-isopropyl ether; E = hexane; F = pentane; G = methyl ethyl ketone-isopropyl ether; H = methyl ethyl ketone; I = isopropyl alcohol-isopropyl ether; J = methyl ethyl ketone-ethanol; K = methanol-water. [c] Yields where shown are based on recrystallized or distilled product. [d] Analysis are by Weiler and Strauss, Oxford, England. [e] TMP = 3,4,5-trimethoxyphenyl. [f] Analysis indicates compound is hemihydrate, not shown in empirical formula. [g] Analysis indicates compound to have 1.5 moles of water, not shown in empirical formula. [h] C_4H_3O = 2-furyl.

TABLE II

PHARMACOLOGICAL SCREENING OF COMPOUNDS OF TABLE I[a,b]

No.	$LD_{min.}$	$ANED_{50}$, mg./ml.	No.	$LD_{min.}$	$ANED_{50}$, mg./ml.
27	200	0.11	25	100	0.72
23	750	0.88	10	1000	8.0
17	150	0.29	3	300	3.5
8	1000	2.0	22	200	3.1
28	500	1.1	4	200	4.7
29	750	2.3	19	150	3.7
5	750	2.4	18	250	6.5
35	200	1.1	24	150	4.4
7	150	0.8	2	100	3.3
6	500	3.5			

[a] The data for the anesthetic testing have been detailed in the table for those compounds having activity greater than procaine, in order of decreasing effectiveness. Numbers correspond to compound numbers in Table I, and details for determining the $LD_{min.}$ (lethal dose minimum) and $ANED_{50}$ (concentration of anesthetic agent causing a 50% reduction in the number of blinks) have been described in ref. 8c. [b] Other pharmacological effects of interest which have been observed and the reference to method used to evaluate the test are: hypotension, ref. 8a: 3+ response with compounds 16, 28, 34, 35, 36; 2+ response with compound 25. Hypertension noted with compound 41. Depression of central nervous system, ref. 8b (compound number/per cent. reduction in activity/test dose in mg./kg.): 8/29/20; 24/40/50; 36/38/20; 37/35/20. Potentiation of Evipal sleeping time, ref. 8b: compound 2, 109%; other compounds showing less pronounced potentiation were 4, 10, 32, 35, 41, 45. Tremorine ED_{50}, ref. 8c (compound number/ED_{50}): 7/50; 10/220; 11/150; 17/27; 35/70.

ure to obtain prolongation of the Evipal sleeping time would reflect that the activity of the compounds herein described is not truly reserpine-like. A more extensive description of the activity of 3,4,5-trimethoxybenzoates in this series, as well as *cis* analogs[4] of the active structures, will form the subject of later reports.

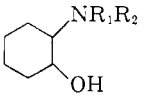
Compound 17 was the only structure which yielded a reasonable order of anti-tremorine activity, although its order of effectiveness was considerably less than that of some recently described compounds.[8c,10]

In terms of a definition of the structural parameters which afford activities in this series, it is of interest to point out that using compound 35 as a guide, replacement of R_3 as CH_3 (compound 33) or replacement of the N-methylpiperazino group by N-phenylpiperazino (compounds 40–46) is associated with diminution or loss of biological activity in the categories examined.

(10) H. E. Zaugg and R. J. Michaels, THIS JOURNAL, **80**, 2770 (1958).

TABLE III

SUBSTITUTED AMINOCYCLOHEXANOLS[i]



No.	R_1	R_2	M.p.,[a] (RS)[b] or b.p., °C. (mm.)	Yield,[c] %	Analyses,[d] Nitrogen, % Calcd.	Found
1[j]	CH_3-	CH_3-	94–96 (25)	66		
2[k]	C_2H_5-	C_2H_5-	105–110 (15)	50	8.2	7.9
3	$-(CH_2)_4-$		88–90 (5)	62	8.3	8.0
4[l]	$-(CH_2)_2-O-(CH_2)_2-$		104–106 (4)	41	7.6	7.6
5	C_6H_5-	CH_3-	128–130 (1)	32	6.8	6.9
6	C_8H_9-[m]	CH_3-	118–120 (0.3)	17	6.0	5.6
7	$C_6H_5CH_2-$	CH_3-	142 (1)	74	6.4	6.2
8	DME[n]	CH_3-	103–104 (3)	61	14.0	13.5
9	DEE[o]	CH_3-	112 (2)	66	12.3	12.4
10	DMP[p]	CH_3-	116–119 (2)	60	13.1	12.8
11[q]	NMP[r]		129–131 (4)	73	14.1	14.0
12[s]	NPP[t]		127–128	75	10.8	10.3

[i] Footnotes *a–h* have the same significance as in Table I. [j] The compound was characterized as the monohydrochloride, m.p. 184–187° (ethanol–ether); ref. 7c reports 183–184° for the hydrochloride of *trans*-(2-dimethylamino)-cyclohexanol; the hydrobromide of the compound melted at 169–171° (ethanol–ether); ref. 7c reports m.p. 169°. [k] Reported by M. Mousseron, R. Grange, G. Combes and V. A. Pertzoff, *Bull. soc. chim. France*, 850 (1947). [l] Reported by M. Mousseron, J. Julien and Y. Jolchine, *ibid.*, 757 (1952). [m] C_8H_9 = 2,6-dimethylphenyl. [n] DME = dimethylaminoethyl. [o] DEE = diethylaminoethyl. [p] DMP = dimethylaminopropyl. [q] The compound also was characterized as the dipicrate, m.p. 226–228° (methyl ethyl ketone). *Anal.* Calcd. for $C_{23}H_{28}N_8O_{15}$: C, 42.1; H, 4.3; N, 17.1. Found: C, 42.1; H, 4.2; N, 17.2. On standing, the free base of the product crystallized and melted at 46–47° (pentane). [r] NMP = N-methylpiperazine. [s] The compound also was characterized as its dihydrochloride, m.p. 253–257° (ethanol). *Anal.* Calcd. for $C_{16}H_{26}Cl_2N_2O$: C, 57.7; H, 7.9; N, 8.4. Found: C, 57.9; H, 8.0; N, 8.4. [t] NPP = N-phenylpiperazine.

Experimental[11]

Cyclohexene Oxide.—The method of Coleman and Johnstone[12] was used for preparation of 2-chlorocyclohexanol employing a commercial laundry bleach[13] as a source of hypochlorous acid. The chlorohydrin was obtained in 71%

(11) Data shown in the tables are not repeated in the Experimental section.

(12) G. H. Coleman and H. F. Johnstone, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 158.

(13) Bright Sail Bleach (assaying 3.3% sodium hypochlorite). Similarly used is Clorox; see H. Bauer and H. Tabor, "Biochemical Preparations," Vol. V, John Wiley and Sons, Inc., New York, N. Y., 1957, p. 97.

yield, b.p. 95–103° (39 mm.), and converted to cyclohexene oxide in 75% yield, b.p. 129°.[14]

trans-2-**Pyrrolidinocyclohexanol** (Compound 3, Table III).—Pyrrolidine (20.7 g., 0.29 mole) was heated to reflux with stirring, and 18.6 g. (0.19 mole) of cyclohexene oxide was added dropwise over 30 minutes. After continued heating for 2 hours the excess pyrrolidine was removed and upon distillation the residue gave 19.9 g. of product, b.p. 88–90° (5 mm.).

In a similar manner other disubstituted aminocyclohexanols were prepared and have been collected in Table III.

trans-2-(**4-Methylpiperazino**)-**cyclohexyl Benzoate** (Compound 34, Table I).—A solution of 8.0 g. (0.04 mole) of 2-(4-methylpiperazino)-cyclohexanol (compound 11, Table III) in 40 ml. of acetonitrile was added over 30 minutes to 5.6 g. (0.04 mole) of benzoyl chloride in 35 ml. of acetonitrile. A vigorous exothermic reaction ensued with precipitation of a white solid. After storage for 20 hours at 20°, the solvent was removed and the residual solid washed with ether and separated. The 12.0 g. so obtained was dissolved in water and made basic with continued cooling with 40% aqueous sodium hydroxide. The liberated free base was extracted with five 100-ml. portions of ether. The extracts were combined, dried (anhydrous magnesium sulfate), then filtered and distilled. After removal of the solvent and a small forerun, 9.0 g. of product distilled at 168–172° (0.1 mm.).

The other cyclohexyl esters described in Table I were prepared essentially by the same procedure.

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[CONTRIBUTION FROM THE ORGANIC RESEARCH LABORATORIES OF THE U. S. VITAMIN AND PHARMACEUTICAL CORP.]

Guanamines.[1] II. Oxyalkylguanamine Anticonvulsants[2]

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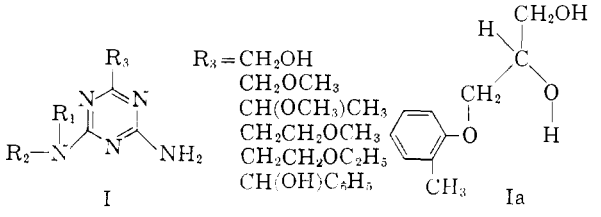
A series of oxyalkylguanamines of the type I have been synthesized and examined for anticonvulsant activity. Structure–activity relationships are discussed and peak anticonvulsant responses are noted with selected 2-amino-4-(substituted anilino)-6-oxyalkyltriazines. In the attempted synthesis of 2-amino-4-anilino-6-α-carboxy-α-chloromethyl-*s*-triazine, halodecarboxylation by hydrochloric acid was observed to yield 2-amino-4-anilino-6-dichloromethyl-*s*-triazine.

This paper extends our exploration[1] of triazine derivatives to oxyalkylguanamines of the type I which have been envisioned as Mephanesin[3] analogs (Ia) and examined for anticonvulsant activity. The groups R_1 and R_2 were varied extensively,



particularly with structures wherein R_1 was substituted phenyl and R_2 was hydrogen and alkyl (Table I).[4]

The synthesis of the guanamines (I) was effected in moderate yield by familiar procedures[4e] through reaction of the biguanide with the appropriate acylating agent $R_3COOC_2H_5$ or R_3COCl. Of particular interest was the isolation of an equimolar complex[4e] of the reactant biguanide and product in the synthesis of compounds 3 and 59 of Table I. Similar complexes in polynitrogen systems have been widely described.[5–9]

An examination of the yields of the guanamines (I), which in the instances of those structures prepared from arylbiguanides and esters are all less than 50%, suggests that in the course of the reaction, one equivalent of biguanide is bound to the formed guanamine and is thus rendered invulnerable to further acylation and cyclization to the desired product. In turn, the stability and ease of isolation of the molecular complex appears to be influenced by steric factors in the reactant biguanide and in the R_3 group.[4e,10] Hydrogen-bonded forms, similar to those proposed by Birtwell[6] between isomers of I[1] and the biguanide to yield II, would account for the molecular complex and the relatively poor yields.

As the work progressed, noted activity with selected structures of the type I indicated extension of the structural scope of R_3 which was further varied as β-pyrrolidinoethyl (compounds 81–83) and as shown for III.

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(2) Presented in part at the Meeting-in-Miniature, New York Section, American Chemical Society, Brooklyn, N. Y., March 20, 1959.

(3) (a) J. P. Lambooy, THIS JOURNAL, **73**, 349 (1951); (b) Y. M. Beasley, V. Petrow, O. Stephenson and A. M. Wild, *J. Pharm. Pharmacol.*, **11**, 36 (1958).

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(10) S. L. Shapiro, V. A. Parrino and L. Freedman, further papers in this series in preparation.