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.

Acknowledgment.—The authors are grateful to Dr. G. Ungar for the pharmacological evaluation of the compounds, and to S. Herbstman and E. Chodos for their technical assistance.

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(14) A. E. Osterberg, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 185. For later runs, cyclohexene oxide was purchased from Arapahoe Chemicals, Inc., Boulder, Colo.

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

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

BY SEYMOUR L. SHAPIRO, VINCENT A. PARRINO AND LOUIS FREEDMAN

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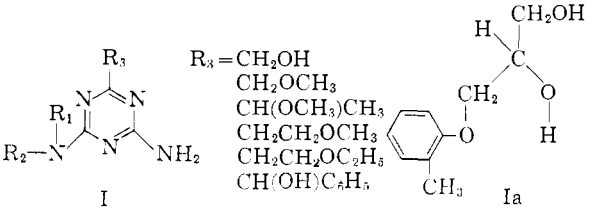
A series of oxyalkylguanamines of the type I have been synthesized and examined for anticonvulsant activity. Structure–activity relationships are discussed and peak anticonvulsant responses are noted with selected 2-amino-4-(substituted anilino)-6-oxyalkyltriazines. In the attempted synthesis of 2-amino-4-anilino-6-α-carboxy-α-chloromethyl-*s*-triazine,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

(1) Paper 1 of this series, S. L. Shapiro, V. A. Parrino, K. Geiger, S. Kobrin and L. Freedman, THIS JOURNAL, **79**, 5064 (1957).

(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).

(4) Analogs of the guanamine 1 previously prepared have been derivatives of biguanide and phenylbiguanide: (a) H. J. Sims, H. B. Parseghian and P. L. de Benneville, *J. Org. Chem.*, **23**, 724 (1958), for R_1, R_2 = hydrogen, R_3 = CH_2OH; (b) J. T. Thurston and M. H. Bradley, U. S. Patent 2,309,681, Feb. 2, 1943, for R_1, R_2 = H, R_3 = CH_2CH_2O alkyl; (c) F. C. Schaefer, U. S. Patent 2,777,848, Jan. 15, 1957, for R_1 = phenyl or hydrogen, R_2 = H, R_3 = CH_2O alkyl; (d) S. V. Sokolovskaya, V. N. Sokolova and O. Yu. Magidson, *Zhur. Obshcheĭ Khim.*, **27**, 765 (1957) [*C. A.*, **51**, 16493*d* (1957)] for R_1 = phenyl, R_2 = hydrogen, R_3 = CH_2OH; (e) C. G. Overberger and S. L. Shapiro, THIS JOURNAL, **76**, 1061 (1954), for R_1 = phenyl, R_2 = hydrogen, R_3 = CH_2CH_2O alkyl.

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(7) L. L. Smith, S. A. Muller, M. Marx, R. Winterbottom and A. P. Doerschuk, *J. Org. Chem.*, **23**, 721 (1958).

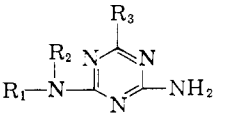
(8) H. Schroeder and C. Grundmann, Abstracts of Papers of American Chemical Society Meeting, Minneapolis, Minn., September, 1955, p. 14-O.

(9) A. C. Cuckler, C. M. Malanga, A. J. Basso and R. C. O'Neill, *Science*, **122**, 244 (1955).

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

TABLE I

OXYALKYLGUANAMINES

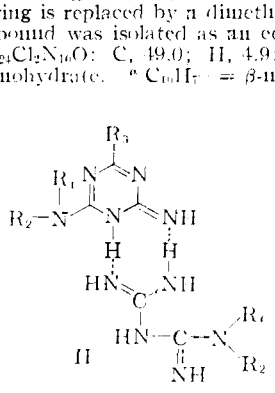


No.	R_1	R_2	M.p., °C.[a,b]	Yield, %	Formula	Analyses[c] Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
					R_3 = $HOCH_2$–						
1	$-(CH_2)_5-$		139–141	40	$C_9H_{15}N_5O$	51.7	51.7	7.2	6.9	33.5	33.3
2[d]	C_6H_5–	H	186–187	43	$C_{10}H_{11}N_5O$	55.3	55.1	5.1	5.0	32.2	32.0
3[e]	2-$C_2H_5C_6H_4$–	H									
4	2-$CH_3C_6H_4$–	C_2H_5–	116–118	35	$C_{13}H_{17}N_5O$	60.2	60.2	6.6	6.5	27.0	26.8
5	2-ClC_6H_4–	H	185–186	35	$C_{10}H_{10}ClN_5O$	47.9	47.9	4.0	4.0	27.8	28.2
6	3-ClC_6H_4–	H	161–163[b1]	42	$C_{10}H_{10}ClN_5O$	47.9	47.6	4.0	4.2	27.8	27.6
7	2-CH_3-4-ClC_6H_3–	H	221–223	42	$C_{11}H_{12}ClN_5O$	49.8	49.9	4.6	4.7	26.4	25.9
					R_3 = CH_3OCH_2–						
8	CH_3–	CH_3–	141–143	45	$C_7H_{13}N_5O$	45.9	46.0	7.2	7.9	38.2	38.0
9	C_3H_5–[f]	H	110–112	42	$C_6H_{13}N_5O$	49.2	49.3	6.7	6.8	35.9	36.2
10	n-C_5H_{11}–	H	95–99	61	$C_{10}H_{19}N_5O$	53.3	53.5	8.5	8.7	31.1	31.0
11	i-C_5H_{11}–	H	100–106	46	$C_{10}H_{19}N_5O$	53.3	53.3	8.5	8.7	31.1	31.0
12	$C_6H_5CH_2$–	CH_3–	125–127	48	$C_{13}H_{17}N_5O$	60.2	60.7	6.6	6.9	27.0	27.0
13	C_6H_5–	H	156–158	41	$C_{11}H_{13}N_5O$	57.1	57.1	5.7	5.7	30.3	30.3
14	3-$CH_3C_6H_4$–	H	91–94	46	$C_{12}H_{15}N_5O$	58.8	58.6	6.2	6.0	28.6	29.0
15	4-$CH_3C_6H_4$–	H	148–150	34	$C_{12}H_{15}N_5O$	58.8	58.8	6.2	6.5	28.6	29.2
16	2,3-di$CH_3C_6H_3$–	H	170–174	47	$C_{13}H_{17}N_5O$	60.2	60.0	6.6	6.3	27.0	26.8
17	2,4-di$CH_3C_6H_3$–	H	155–157	37	$C_{13}H_{17}N_5O$	60.2	60.3	6.6	6.4	27.0	27.0
18	2,5-di$CH_3C_6H_3$–	H	142–146[b3]	10	$C_{13}H_{17}N_5O$	60.2	60.0	6.6	6.4	27.0	27.4
19	2,6-di$CH_3C_6H_3$–	H	169–171	27	$C_{13}H_{17}N_5O$	60.2	59.9	6.6	6.7	27.0	26.8
20	2-$C_2H_5C_6H_4$–	H	189–192[b4]	44	$C_{13}H_{17}N_5O$	60.2	60.0	6.6	6.9	27.0	27.1
21	3-$CH_3CHOHC_6H_4$–	H	174–175[b2]	21	$C_{13}H_{17}N_5O_2$	57.1	56.7	5.5	6.1	25.6	25.4
22	$-C_6H_4CH_2CH_2-$[g]		198–199[b2]	30	$C_{13}H_{15}N_5O$	60.7	60.8	5.9	5.9	27.2	27.3
23[h]	2-$CH_3C_6H_4$–	C_2H_5–	145–147	31	$C_{14}H_{19}N_5O$					25.6	26.0
24	3-$CH_3C_6H_4$–	C_2H_5–	137–139	67	$C_{14}H_{19}N_5O$	61.5	61.4	7.0	6.9		
25	2,6-di$C_2H_5C_6H_3$–	H	203–205	46	$C_{15}H_{21}N_5O$	62.1	62.6	7.4	7.0	24.4	24.0
26	3-ClC_6H_4–	H	139–141	38	$C_{11}H_{12}ClN_5O$	49.8	50.1	4.6	4.6	26.4	26.0
27	3-BrC_6H_4–	H	160–162	34	$C_{11}H_{12}BrN_5O$	42.5	42.5	3.9	4.0	22.6	23.2
28	2-CH_3-3-ClC_6H_3–	H	191–193[b2]	21	$C_{12}H_{14}ClN_5O$	51.7	51.6	5.0	5.0	25.0	25.0
29	2-CH_3-5-ClC_6H_3–	H	160–162	31	$C_{12}H_{14}ClN_5O$	51.7	52.3	5.0	5.1	25.0	25.2
30	2-CH_3-4-BrC_6H_3–	H	163–164[b4]	28	$C_{12}H_{14}BrN_5O$	44.5	44.2	4.4	4.1		
31	3,4-diClC_6H_3–	H	195–197	30	$C_{11}H_{11}Cl_2N_5O$	44.0	44.6	3.7	4.0	23.3	23.3
32	2,5-di$CH_3OC_6H_3$–	H	131–132	12	$C_{13}H_{17}N_5O_3$	53.6	53.8	5.9	5.6	24.0	24.2
					R_3 = CH_3OCHCH_3–						
33	C_6H_5–	H	168–169	57	$C_{12}H_{15}N_5O$	58.8	58.1	6.2	5.9	28.6	28.5
34	2-$CH_3C_6H_4$–	H	198–199	29	$C_{13}H_{17}N_5O$	60.2	59.8	6.6	6.5	27.0	26.9
35	2,3-di$CH_3C_6H_3$–	H	168–181	20	$C_{14}H_{19}N_5O$	61.5	61.5	7.0	7.1	25.6	25.2
36	2,4-di$CH_3C_6H_3$–	H	165–167	40	$C_{14}H_{19}N_5O$	61.5	61.5	7.0	7.0	25.6	25.9
37	2-CH_3-5-ClC_6H_3–	H	173–174	33	$C_{13}H_{16}ClN_5O$	53.2	52.9	5.5	5.5	23.8	23.8
38	3-BrC_6H_4–	H	84–87	11	$C_{12}H_{14}BrN_5O$	44.4	44.1	4.4	4.6	21.6	21.8
39	3-IC_6H_4–	H	153–155	29	$C_{12}H_{14}IN_5O$	38.8	39.0	3.8	4.1	18.9	19.5
40	2,3-diClC_6H_3–	H	186–188	27	$C_{12}H_{13}Cl_2N_5O$	45.9	46.2	4.2	4.0	22.3	22.6
41	2,5-diClC_6H_3–	H	100–101	27	$C_{12}H_{13}Cl_2N_5O$	45.9	45.3	4.2	4.1	22.3	22.3
42	3,5-diClC_6H_3–	H	195–200	39	$C_{12}H_{13}Cl_2N_5O$	45.9	45.5	4.2	4.6		
43	3-$CH_3OC_6H_4$–	H	143–144	35	$C_{13}H_{17}N_5O_2$	56.7	56.8	6.2	6.3	25.4	25.2
44	2-$CH_3C_6H_4$–	C_2H_5–	230–232	32	$C_{15}H_{21}N_5O$	62.7	62.2	7.4	7.5	24.4	24.2
45[i]	2-CH_3-5-ClC_6H_3–	H	86–87	18	$C_{15}H_{20}ClN_5O$	56.0	56.0	6.3	6.0	21.8	22.2
					R_3 = $CH_3OCH_2CH_2$–						
46	C_6H_{11}–[j]	H	75–77[b5]	36	$C_{12}H_{21}N_5O$	57.3	56.7	8.4	8.4	27.9	27.9
47	$C_6H_5CH_2CH_2$–	H	140–142[b4]	40	$C_{14}H_{19}N_5O$	61.7	61.7	7.0	6.9	25.6	25.4
48[k]	C_6H_5–	H									
49	C_6H_5–	CH_3–	102–105	45	$C_{13}H_{17}N_5O$	60.2	60.1	6.6	6.8	27.0	27.2
50	C_6H_5–	C_2H_5–	109–111	50	$C_{14}H_{19}N_5O$	61.5	62.2	7.0	7.2	25.6	26.0

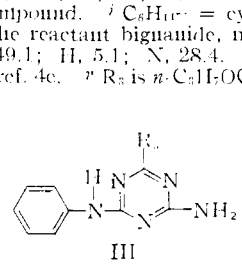
TABLE I (*continued*)

No.	R_1	R_2	M.p.,[a,b] °C.	Yield, %	Formula	Analyses[c] Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found	Nitrogen, % Calcd.	Found
51	C_6H_5-	*n*-C_4H_9-	67–69	53	$C_{16}H_{23}N_5O$	63.8	64.1	7.7	7.6		
52	C_6H_5-	*i*-C_5H_{11}-	86–89	41	$C_{17}H_{25}N_5O$	64.7	65.1	8.0	8.0	22.2	22.4
53	C_6H_5-	$C_6H_5CH_2$-	110–112[b2]	27	$C_{19}H_{21}N_5O$	68.0	67.8	6.3	6.2	20.9	20.6
54	2-$CH_3C_6H_4$-	H	121–124	35	$C_{18}H_{17}N_5O$	60.2	60.6	6.6	7.2		
55	2-$CH_3C_6H_4$-	C_2H_5-	105–106	50	$C_{15}H_{21}N_5O$	62.7	62.9	7.4	7.3	24.4	24.4
56	3-$CH_3C_6H_4$-	H	111–112	8	$C_{18}H_{17}N_5O$	60.2	60.3	6.6	6.6	27.0	27.2
57	4-$CH_3C_6H_4$-	H	119–121	23	$C_{18}H_{17}N_5O$	60.2	60.2	6.6	6.5	27.0	27.4
58	2-$C_2H_5C_6H_4$-	H	115–117	44	$C_{14}H_{19}N_5O$	61.5	62.0	7.0	7.1	25.6	25.6
59[d]	2-ClC_6H_4-	H									
60	3-ClC_6H_4-	H	162–163	32	$C_{12}H_{11}ClN_5O$	51.5	51.7	5.0	5.1	25.0	25.2
61	4-ClC_6H_4-	H	130–133	21	$C_{12}H_{14}ClN_5O$					25.0	25.4
62	4-ClC_6H_4-	C_2H_5-	107–112	29	$C_{14}H_{18}ClN_5O$	54.6	55.1	5.9	5.8	22.8	22.8
63	4-ClC_6H_4-	C_3H_5-[f]	111–112	43	$C_{15}H_{18}ClN_5O$	56.3	55.8	5.7	5.6	21.9	22.2
64	4-BrC_6H_4-	H	114–117	15	$C_{12}H_{14}BrN_5O$	44.5	44.2	4.4	4.5	21.6	21.6
65	4-IC_6H_4-	H	115 dec.[b5]	35	$C_{12}H_{16}IN_5O_2$[m]	37.0	36.8	4.1	4.1	18.0	17.8
66	4-FC_6H_4-	H	130–132[b3]	30	$C_{12}H_{14}FN_5O$	54.7	55.0	5.4	5.2	26.6	27.0
67	2-CH_3-4-ClC_6H_3-	H	128–129	4	$C_{13}H_{16}ClN_5O$					23.8	24.1
68	$C_{10}H_7$-[n]	H	149–170	31	$C_{16}H_{17}N_5O$	65.1	64.7	5.8	6.3	23.7	24.2
		R_3 = $C_2H_5OCH_2CH_2$-									
69[o]	C_6H_5-	H									
70[p]	C_6H_5-	H									
71	C_6H_5-	C_2H_5-	90–92	28	$C_{15}H_{21}N_5O$	62.7	62.4	7.4	7.0	24.4	24.0
72	C_6H_5-	*n*-C_4H_9-	63–64	30	$C_{17}H_{25}N_5O$	64.7	64.8	8.0	7.9	22.2	22.4
73	2-$CH_3C_6H_4$-	H	115–118	18	$C_{14}H_{19}N_5O$					25.6	25.7
74	3-$CH_3C_6H_4$-	H	149–151	36	$C_{14}H_{19}N_5O$	61.5	61.6	7.0	6.6		
75	4-$CH_3C_6H_4$-	H	112–114	16	$C_{14}H_{19}N_5O$	61.5	60.9	7.0	6.9		
76	2-$CH_3C_6H_4$-	C_2H_5-	79–81	51	$C_{16}H_{23}N_5O$	63.8	64.0	7.7	7.7	23.2	23.4
77	*p*-ClC_6H_4-	C_2H_5-	71–73	24	$C_{15}H_{20}ClN_5O$	56.0	55.6	6.3	6.2	21.8	22.0
78	*p*-ClC_6H_4-	C_3H_5-[f]	66–67	32	$C_{16}H_{20}ClN_5O$	57.6	58.3	6.0	5.8	21.0	21.0
		R_3 = $HOCH(C_6H_5)$-									
79	C_6H_5-	H	210–215[b2]	37	$C_{16}H_{15}N_5O$	65.5	65.7	5.2	4.8	23.9	23.6
80	2-$CH_3C_6H_4$-	C_2H_5-	115–120	11	$C_{19}H_{21}N_5O$	68.0	67.4	6.3	6.2	20.9	20.8
		R_3 = Pyrrolidinoethyl-									
81	C_6H_5-	*n*-C_4H_9-	102–103	65	$C_{19}H_{25}N_6$	67.0	67.0	8.3	8.5		
82	4-$CH_3C_6H_4$-	H	165–170	42	$C_{16}H_{22}N_6$	64.4	64.4	7.4	6.2		
83	4-ClC_6H_4-	C_3H_5-[f]	124–125	50	$C_{18}H_{23}ClN_6$	60.2	60.0	6.4	6.3	23.4	23.0

[a] Melting points are not corrected. [b] The recrystallizing solvent is acetonitrile unless otherwise shown; [b1] ethanol; [b2] 1-propanol; [b3] benzene; [b4] isopropyl alcohol; [b5] methanol. [c] Analyses by Weiler and Strauss, Oxford, England. [d] Reported in ref. 4d, m.p. 190–191°. [e] The compound was isolated as an equimolar complex with the reactant biguanide, m.p. 131–133° (65%). *Anal.* Calcd. for $C_{22}H_{30}N_{10}O$: C, 58.6; H, 6.7; N, 31.2. Found: C, 59.7; H, 6.6; N, 31.2. This complex was further characterized by the preparation of the constituent picrates following the procedure outlined in ref. 4e. The dipicrate of (*o*-ethylphenyl)-biguanide so formed melted at 175–176° (water) and did not depress the melting point of the authentic dipicrate, mixed m.p. 173–175°. *Anal.* Calcd. for $C_{22}H_{21}N_{10}O_{14}$: N, 23.2. Found: N, 23.0. The picrate of the desired product, 2-amino-4-(*o*-ethylanilino)-6-hydroxymethyl-*s*-triazine, melted at 185°. *Anal.* Calcd. for $C_{18}H_{18}N_8O_8$: C, 45.6; H, 3.8; N, 23.6. Found: C, 46.0; H, 4.0; N, 23.8. [f] C_3H_5- = allyl. [g] $-C_6H_4CH_2CH_2-$ with the attached nitrogen represents the indolino- group. [h] The compound was characterized as the picrate, m.p. 160–162° (water). *Anal.* Calcd. for $C_{20}H_{22}N_8O_8$: C, 47.9; H, 4.4; N, 22.3. Found: C, 47.3; H, 4.4; N, 22.4. [i] The amino group attached to the triazine ring is replaced by a dimethylamino group in this compound. [j] C_6H_{11}- = cyclohexyl. [k] Reported in ref. 4e. [l] The compound was isolated as an equimolar complex with the reactant biguanide, m.p. 135–137° (56%). *Anal.* Calcd. for $C_{20}H_{24}Cl_2N_{10}O$: C, 49.0; H, 4.9; N, 28.4. Found: C, 49.1; H, 5.1; N, 28.4. [m] Analyses have been calculated for the monohydrate. [n] $C_{10}H_7$- = β-naphthyl. [o] Reported in ref. 4c. [p] R_3 is *n*-$C_3H_7OCH_2CH_2$-; reported in ref. 4e.



The high melting point of III, R_3 = $-CH_2COOH$, and its poor solubility in organic solvents would indicate a betaine[12] as shown by IV, or an isomer of this structure. In the attempted synthesis of



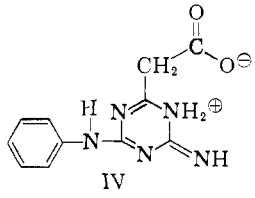
III

R_3 = $-CH(OH)CH_3$; $-\overset{O}{\overset{\|}{C}}-CH_2NHCNH_2$; $-CH_2CN$[11]; $-CH_2COOH$[11]; $-CHClCOOH$

(11) These compounds were reported in the Russian literature after our work had been completed; S. V. Sokolovskaya, V. N. Sokolova and O. Yu. Magidson, *Zhur. Obshchei Khim.*, **27**, 1021 (1957) [*C. A.*, **52**, 2870*e* (1958)].

(12) S. V. Sokolovskaya, V. N. Sokolova and O. Yu. Magidson, *ibid.*, **27**, 1968 (1957) [*C. A.*, **52**, 5425*i* (1958)].

IV, R_3 = –CHClCOOH, by the reaction of phenylbiguanide with diethyl chloromalonate, treatment of the presumably formed 2-amino-4-anilino-6-(α-carbethoxy-α-chloromethyl)-*s*-triazine with hydrochloric acid resulted in the formation of 2-amino-4-anilino-6-dichloromethyl-*s*-triazine. The mechanism of this halodecarboxylation requires further study, although it is interesting to note that whereas this reaction occurred with hydrochloric acid, other halodecarboxylations have employed either bromine[13] or N-halosuccinimide.[14]



IV

Pharmacology.—The anticonvulsant (antimetrazole) activity of the compounds that have been tested is reported in Table II and definite effects relating structure to activity are to be noted.

In terms of the R_3 variant, the groups wherein R_3 was retained as hydroxymethyl, methoxymethyl, β-methoxyethyl and β-ethoxyethyl yielded the most active structures, whereas R_3 as α-methoxyethyl (compounds 33–45), α-hydroxybenzyl (compounds 79, 80) and β-pyrrolidinoethyl (compounds 81–83) did not.

TABLE II

ANTICONVULSANT ACTIVITY[a]

4+	3+	2+	1+	0
4, 6, 7	17, 24	18, 26, 34	2, 14, 15	1, 3, 5, 8, 11
16, 23, 27	33, 51	36, 41, 57	20, 35, 38	13, 19, 25, 37, 40
28, 29, 50	63, 67	60, 64, 66	46, 48, 58	42, 43, 44, 45, 47
54, 55, 56	77, 78	75	65, 69, 70	49, 52, 59, 68, 72
61, 62, 74			71, 80	79, 81, 82, 83

[a] The method of testing has been described by S. L. Shapiro, I. M. Rose, E. Roskin and L. Freedman, THIS JOURNAL, **80**, 1648 (1958). The anticonvulsant response was established at one-half or one-fourth the $LD_{min.}$ and evaluated as protection afforded against metrazole seizures or death. The compound was administered (s.c.) to four mice at each dosage level and, 10 minutes later, metrazole was given 90 mg./kg. (i.p.) to each animal. Failure to protect against the administered metrazole is manifest by death or seizures. The seizures are graded as severe (maximal seizures with tonic extensor reflex); moderately severe (clonic seizures); mild; and very mild. A 4+ response indicates substantially complete protection (against seizures or death) when tested at one-fourth the $LD_{min.}$, and a 0 response indicates death or severe seizures at test doses of one-half the $LD_{min.}$

Within the active R_3 variants, substitution of R_1, R_2 as alkyl (compounds 1, 8, 11, 49, 47), or R_1 = phenyl, R_2 = hydrogen (compounds 2, 13, 48, 69, 70) yielded relatively ineffective compounds.

Best activities were obtained with R_1 = substituted phenyl and R_2 = hydrogen and ethyl. The effect of variation of R_2 is noted in relatively poor activity with hydrogen and methyl (compounds 48, 49), 4+ activity with ethyl (compound 50), diminishing with *n*-butyl (compound 51) and disappearing with *i*-amyl (compound 52); also see compounds 61, 62, 63.

The combination of R_1 = *o*-tolyl, R_2 = ethyl afforded high activities (compounds 4, 23, 55) and was the most uniformly effective structural combination. For active compounds wherein R_2 was hydrogen, R_1 was an *o*-tolyl or *m*-tolyl (compounds 56, 74) derivative with the exception of the active halophenyl structures (compounds 6, 27, 61). Compound 45 which was derived from a trisubstituted biguanide proved to be inactive.

Experimental[15]

Materials.—Most of the biguanides have been described elsewhere.[16–18] In a few instances the biguanides were isolated but not characterized (Table I, compounds 51, 52, 62–66). The acid chlorides have been described previously.[19] The preparation of β-methoxypropionyl chloride and β-ethoxypropionyl chloride followed the procedure of Jones and Powers.[20] The methyl β-pyrrolidinopropionate was prepared from pyrrolidine and methyl acrylate, b.p. 99° (22 mm.).[21]

N^1,N^1-Dimethyl-N^5-(2-methyl-5-chlorophenyl)-biguanide Nitrate.—A solution of 11.0 g. (0.062 mole) of 2-methyl-5-chloroaniline hydrochloride and 7.0 g. (0.062 mole) of dimethyldicyandiamide[22] in 35 ml. of water was heated under reflux for 6 hours. When cool, the formed precipitate of the biguanide hydrochloride (15.5 g.) was separated, dissolved in 250 ml. of water and filtered (carbon). The filtrate was treated with 200 ml. of saturated aqueous sodium nitrate and the product of 13.2 g. (67%) separated, m.p. 193–195°. Upon recrystallization (acetonitrile), it melted at 196–197°.

Anal. Calcd. for $C_{11}H_{17}ClN_6O_3$: C, 41.7; H, 5.4; N, 26.5. Found: C, 41.9; H, 5.5; N, 26.8.

Oxyalkylguanamines (from Esters).—The compounds of Table I were prepared by the same general procedure, and with the exception that those prepared from the acid chlorides (see below) were processed using the required methyl or ethyl ester.

A solution of 0.025 mole of the biguanide hydrochloride (or nitrate) in 25 ml. of methanol was treated with 24 ml. (0.05 mole) of 23% sodium methoxide in methanol followed by 0.025 mole of ester. The reaction mixture was maintained at 20° for 24–48 hours and then decanted into 60 ml. of water. After 72 hours, the formed precipitate of product was separated, dried and recrystallized.

Oxyalkylguanamines (from Acid Chlorides).—A suspension of 0.03 mole of the biguanide hydrochloride (or nitrate) in 25 ml. of acetonitrile was treated with a solution of 0.06 mole of sodium hydroxide in 16 ml. of water, stirred and maintained at 0° by external cooling during the addition of a solution of 0.045 mole of the acid chloride in 10 ml. of acetonitrile. The reaction mixture was stored at 20° for 4 hours and the solvents evaporated under vacuum. The residue was treated with 50 ml. of methanol and decanted into 125 ml. of water. After 72 hours, the precipitate of product was separated, dried and recrystallized.

These various compounds of Table I were prepared using this procedure: 33–45, 55, 58, 67, 71 and 76.

2-Amino-4-anilino-6-dichloromethyl-*s*-triazine (from Diethyl Chloromalonate).—Phenylbiguanide (17.7 g., 0.1 mole) was dissolved in a solution of 2.3 g. (0.1 mole) of sodium in 50 ml. of methanol. To this chilled solution (−40°) there was added 18.4 g. (0.1 mole) of diethyl chloromalonate over 15 minutes with continued stirring and cooling. The

(13) (a) E. V. Grovenstein, Jr., and U. V. Henderson, Jr., THIS JOURNAL, **78**, 569 (1956); (b) J. W. Wilt, *ibid.*, **77**, 6397 (1955).

(14) J. W. Wilt, *J. Org. Chem.*, **21**, 920 (1956).

(15) Descriptive data shown in the tables are not reproduced in the Experimental section.

(16) S. L. Shapiro, V. A. Parrino and L. Freedman, THIS JOURNAL, **81**, 2220 (1959).

(17) S. L. Shapiro, V. A. Parrino E. Rogow and L. Freedman, *ibid.*, **81**, 3725 (1959).

(18) S. L. Shapiro, V. A. Parrino and L. Freedman, *ibid.*, **81**, 3728 (1959).

(19) S. L. Shapiro, I. M. Rose and L. Freedman, *ibid.*, **80**, 6065 (1958).

(20) L. W. Jones and D. H. Powers, *ibid.*, **46**, 2518 (1924).

(21) W. Reppe, *Ann.*, **596**, 80 (1955), reports b.p. 66–68° (0.5 mm.).

(22) S. L. Shapiro, V. A. Parrino and L. Freedman, THIS JOURNAL, **81**, 3796 (1959).

reaction mixture was stored at 0° for 20 hours and then decanted onto 100 g. of cracked ice containing 35 cc. of 3 *N* hydrochloric acid. The formed precipitate was separated, heated with 150 ml. of water and filtered. The water-insoluble product, 5.2 g. (19%), m.p. 149–153°, was recrystallized (benzene) and melted at 149–151° not depressing the melting point of authentic 2-amino-4-anilino-6-dichloromethyl-*s*-triazine,[23] mixed m.p. 150–152°.

The picrate melted at 206° (ethanol). The mixed melting point with authentic picrate was not depressed, m.p. 205°.

Anal. Calcd. for $C_{16}H_{12}Cl_2N_8O_7$: C, 38.7; H, 2.4. Found: C, 38.7; H, 2.4.

2-Amino-4-anilino-6-(α-hydroxyethyl)-*s*-triazine.—A mixture of 8.9 g. (0.05 mole) of phenylbiguanide, 4.1 g. (0.025 mole) of lactide and 50 ml. of acetonitrile was heated under reflux for 16 hours. When cool, the reaction mixture was decanted into 100 ml. of water. The oil which formed was separated, dissolved in 30 ml. of methanol and added to the filtrate. After standing 24 hours, the formed crystals (6.0 g.) were separated and recrystallized (acetonitrile), yielding 4.5 g. (39%) of product which melted at 142–145°.

Anal. Calcd. for $C_{11}H_{12}N_5O$: C, 57.6; H, 4.8. Found: C, 57.0; H, 5.6.

The picrate melted at 199° (water).

Anal. Calcd. for $C_{17}H_{16}N_8O_8$: C, 44.4; H, 3.5; N, 24.4. Found: C, 44.5; H, 3.7; N, 24.0.

(23) S. L. Shapiro and C. G. Overberger, THIS JOURNAL, **76**, 97 (1954), report m.p. 154–155°.

2-Amino-4-anilino-6-(ureidomethyl)-*s*-triazine.—A solution of 7.3 g. (0.05 mole) of ethyl hydantoate in 50 ml. of methanol was treated with 8.9 g. (0.05 mole) of phenylbiguanide and the reaction stored at 20° for 4 days. The reaction mixture was added to 50 ml. of water and crystals (1.65 g.) were separated. Recrystallization (dimethylformamide–ether) yielded 1.44 g. (11%) of product which melted at 227° dec.

Anal. Calcd. for $C_{11}H_{13}N_7O$: C, 51.0; H, 5.1; N, 37.8. Found: C, 51.4; H, 5.0; N, 37.6.

2-Amino-4-anilino-1,3,5-triazin-6-ylacetic acid was obtained from phenylbiguanide and diethyl malonate in 20% yield and melted at 241° dec. (dimethylformamide–methanol).[24]

Anal. Calcd. for $C_{11}H_{11}N_5O_2$: C, 53.9; H, 4.5; N, 28.6. Found: C, 53.9; H, 4.6; N, 28.8.

2-Amino-4-anilino-1,3,5-triazin-6-ylacetonitrile was obtained from phenylbiguanide and ethyl cyanoacetate in 38% yield and melted at 149–152° (water).[25]

Anal. Calcd. for $C_{11}H_{10}N_6$: C, 58.4; H, 4.5; N, 37.1. Found: C, 58.5; H, 4.5; N, 37.2.

Acknowledgment.—The authors are indebted to Dr. G. Ungar and his staff for the pharmacological screening of the compounds.

(24) Reference 11 reported m.p. 239–240°.

(25) Reference 11 reported m.p. 152–153°.

YONKERS 1, N. Y.

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF IOWA STATE COLLEGE AND ST. LOUIS UNIVERSITY]

The Preparation and Rearrangement of 2-Allyl-1,2-dihydroquinoline

BY HENRY GILMAN, JOHN EISCH[1] AND THEODORE S. SODDY

RECEIVED JANUARY 15, 1959

The interaction of quinoline and allylmagnesium chloride in tetrahydrofuran with subsequent hydrolysis and isolation in a nitrogen atmosphere led to 2-allyl-1,2-dihydroquinoline (I). Compound I is thermally isomerized to 2-*n*-propylquinoline (II) and is transformed into 2-propenylquinoline (III) plus some II by hot nitrobenzene oxidation. The identities of II and III were demonstrated by independent syntheses. Attempts to prepare pure 2-allylquinoline (IV) from 2-bromoquinoline and allylmagnesium bromide led instead to a mixture of 2-allylquinoline (IV) and 2-propenylquinoline (III). The isomerization of IV into III was completed by heating this mixture with solid potassium hydroxide. Infrared data were used extensively in detecting the presence of allyl, propenyl and N–H groups in the products of the foregoing reactions. A reasonable course for the isomerization of I into II is proposed and evaluated in terms of the known properties of related systems.

The observation that allylmagnesium bromide in refluxing ether reacts rather readily with aza-aromatic heterocycles to form allylated products occasioned a study of the relative ease with which bases such as pyridine, quinoline and phenanthridine and others undergo this reaction.[2] Synthesis and structural determination showed the products to be α- or γ-allyl-dihydro derivatives of the respective bases. These partially reduced bases from pyridine and the benzopyridines were quite sensitive to oxidation as evidenced by their rapid discoloration in air. By way of illustration, the product from allylmagnesium bromide and quinoline was a pale yellow oil whose infrared spectrum was in accord with that expected of 2-allyl-1,2-dihydroquinoline. However, the broadening of certain spectral bands indicated partial oxidation of the dihydroquinoline presumably to 2-allylquinoline.

In evaluating the allylating ability of allylmagnesium chloride in tetrahydrofuran, it was therefore curious to note that quinoline gave in 80% yield a product whose infrared spectrum suggested the presence of a propenyl (—CH=CH—, bands at 6.0 and 10.3 μ), and not an allyl group.[3] As the spectrum contained only a weak N–H band, it seemed that extensive air oxidation had occurred during the isolation procedure. Consequently it was felt that the propenyl group was generated upon work-up, and not during the addition reaction or subsequent hydrolysis. In order to minimize the effects of atmospheric oxygen the reaction was repeated and the product isolated under a nitrogen atmosphere. The identity of the principal product as 2-allyl-1,2-dihydroquinoline (I) is strongly supported by its infrared spectrum; exceedingly sharp bands at 2.95 (NH), 6.1, 10.0 and 10.9 μ (C=CH_2) are in complete accord with this structure. Conversely, bands indicative of a propenyl group (—CH=CH—) are not present.

By comparison of the yields of 2-allyl-1,2-dihydroquinoline obtained by employing, in turn, (a) allylmagnesium chloride in tetrahydrofuran, (b) allylmagnesium chloride in ether and (c) allylmag-

(1) Department of Chemistry, St. Louis University, St. Louis, Mo.

(2) H. Gilman, J. Eisch and T. Soddy, THIS JOURNAL, **79**, 1245 (1957).

(3) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958, pp. 34–56.