nitroacetophenone (55%), m.p. 79–80° (ethanol), confirmed by its 2,4-dinitrophenylhydrazone, m.p. 218–221° (ethanol).

Anal. Calcd. for $C_{14}H_{11}N_5O_6$: C, 48.7; H, 3.2; N, 20.3. Found: C, 48.4; H, 3.1; N, 20.5.

Ultraviolet absorption data. Selected spectra were established in methanol and are reported in Table III.

YONKERS 1, N. Y.

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

Guanamines. VI. Aminomethylguanamines

SEYMOUR L. SHAPIRO, ELAINE S. ISAACS, AND LOUIS FREEDMAN

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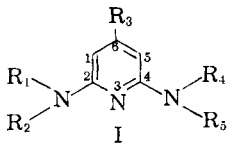
A series of guanamines of the class I, R_3 = $-CH_2NR_6R_7$ has been synthesized and examined for antiinflammatory, analgesic, and tranquilizing activity.

In continuation of our explorations of guanamines with pharmacological activity,[1] compounds of type I, R_3 = $-CH_2NR_6R_7$ have been examined for pharmacological activity. These compounds have



I

R_1R_2N- = substituted amino and anilino
R_4R_5N- = $-NH_2$ and $-N(CH_3)_2$

been envisioned as chlorpromazine analogs wherein the R_1R_2N-, as indolino, tetrahydroquinolino, and tetrahydroisoquinolino, replaces the phenothiazine ring and the trimethylene chain of chlorpromazine has been substituted by a four atom unit extending from the 2-position of the triazine ring to the amino methyl nitrogen.[2] Treatment of the halomethylguanamine[3] with an excess of the required amines under mild heat gave the aminomethylguanamine (see Table I) in good yield.

There was no evidence of *trans*-amination of the 2- and 4-amino substituents of I.[4] Further, when the reactant was a primary amine, there were no indications of formation of the tertiary amines involving reaction of two equivalents of I, R_3 = $-CH_2Cl$.[5] Monoethanolamine reacted readily[6] to give I, R_3 = $-CH_2NHCH_2CH_2OH$.

Although I, R_3 = $-CHCH_3Cl$ was not as active in other systems,[8] it reacted readily with *N*-methylpiperazine to give the required aminomethylguanamine.

The compounds were inspected, in particular, for tranquilizing,[7] antiinflammatory,[8] and analgesic[9] properties with effective compounds being found in each category. Other interesting effects were the antihistamine activity of compound 2 and the marked potentiation of adrenalin by compound 25.

EXPERIMENTAL[10]

The biguanides[1b,4,11] and halomethylguanamines[3] required as intermediates have been described.

2-Amino-4-indolino-6-[(N-ethyl)ethanolaminomethyl]-s-triazine (Compound 7). A mixture of 2.6 g. of 2-amino-4-indolino-6-chloromethyl-*s*-triazine and 6 ml. of *N*-ethylethanolamine was warmed to effect complete solution and then heated in an oil bath maintained at 100° for 5 min. When cool, the reaction mixture was decanted into 100 ml. of water, and 3.4 g. of the product separated.

Unless otherwise stated the compounds were prepared by this general procedure.

2-Dimethylamino-4-indolino-6-dimethylaminomethyl-s-triazine (Compound 16). A mixture of 2.9 g. of 2-dimethylamino-4-indolino-6-chloromethyl-*s*-triazine and 10 g. of dimethylamine in a pressure bomb was heated at 100° for 30

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(2) S. L. Shapiro, H. Soloway, and L. Freedman, *J. Am. Pharm. Assoc. (Sci. Ed.)*, **46**, 333 (1957).

(3) S. L. Shapiro, E. Isaacs, V. A. Parrino, and L. Freedman, *Guanamines V. Chloromethylguanamines*, *J. Org. Chem.*, **26**, 68 (1961).

(4) J. T. Thurston, F. C. Schaefer, J. R. Dudley, and D. Holm-Hansen, *J. Am. Chem. Soc.*, **73**, 2992 (1951).

(5) S. L. Shapiro, V. A. Parrino, and L. Freedman, *J. Am. Chem. Soc.*, **81**, 3728 (1959).

(6) C. B. Kremer, M. Meltsner, and H. Hindin, *J. Am. Chem. Soc.*, **64**, 1010 (1942).

(7) The procedure in S. L. Shapiro, I. M. Rose, E. Roskin, and L. Freedman, *J. Am. Chem. Soc.*, **80**, 1648 (1958) gave the following: compound no./LD_{min} mg./kg. s.c. (mice)/% reduction in motor activity at a test dose of 100 mg./kg. s.c.: 4/450/53; 16/300/48; 17/400/31; 19/150/31; 20/400/52; and at 50 mg./kg. s.c.: 5/200/47; 11/200/31; 13/300/39; 24/350/47.

(8) The procedure of E. Siegmund, R. Cadmus, and G. Lu, *Proc. Soc. Exp. Biol. Med.*, **95**, 729 (1957) gave the following: compound no./LD_{min}/% protection at 50 mg./kg. s.c.: 2/400/75; 4/450/75; 5/200/69; 6/200/82; 7/300/88; 9/500/63; 11/20/94; 14/20/69; 16/300/100; 17/400/56; 19/150/90; 21/350/50; 24/350/63.

(9) The procedure of C. Bianchi and J. Franceschini, *Brit. J. Pharmacol.*, **9**, 280 (1954) gave the following: compound no./LD_{min}/analgesic ED_{50} mg./kg. s.c.: 4/450/147; 10/1000/225; 19/150/31; 20/400/96.

(10) Descriptive data shown in Table I are not reproduced in the Experimental.

(11) S. L. Shapiro, V. A. Parrino, E. Rogow, and L. Freedman, *J. Am. Chem. Soc.*, **81**, 3725 (1959).

TABLE I

AMINOMETHYLGUANAMINES[a] (FORMULA I)

No.	R_6	R_7	M.P.[b]	S[c]	Yield,[d] %	Formula	Analyses[e] Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
	R_1R_2N = *m*-chloroaniline											
1	CH_3—	CH_3—	73–75	A		$C_{12}H_{15}ClN_6O$					30.2	30.0
2	$HOCH_2CH_2$—	H	146–148	A	59	$C_{12}H_{15}ClN_6O$	48.9	48.9	5.1	5.5	28.5	28.6
3	$HOCH_2CH_2$—	$HOCH_2CH_2$—	114–115	A	80	$C_{14}H_{19}ClN_6O_2$	49.6	49.6	5.7	5.8	24.8	24.7
4	—$(CH_2)_4$—		185–188	B	60	$C_{14}H_{23}Cl_3N_6O_2$[f]	40.6	41.4	5.6	5.8	20.3	19.9
5	—$(CH_2)_2NCH_3(CH_2)_2$—		211–212	C	43	$C_{15}H_{20}ClN_7$	54.0	54.1	6.0	6.2	29.4	29.3
	R_1R_2N = indolino											
6	CH_3—	CH_3—	169–170	C	24	$C_{14}H_{18}N_6$	62.2	61.8	6.7	6.8	31.1	30.8
7	$HOCH_2CH_2$—	H	165–168	D	43	$C_{14}H_{18}N_6O$	58.7	58.2	6.3	6.3	29.4	29.6
8	*n*-C_5H_{11}—	H	131–134	D	52	$C_{17}H_{24}N_6$	65.4	65.1	7.7	8.0	26.9	27.1
9	—$(CH_2)_5$—		189–191	B	64	$C_{16}H_{20}N_6$	64.8	64.8	6.8	6.6	28.4	28.2
10	—$(CH_2)_2O(CH_2)_2$—		178–180	D	47	$C_{16}H_{20}N_6O$	61.5	61.2	6.5	6.5		
11	—$(CH_2)_2NCH_3(CH_2)_2$—		216–220	C	58	$C_{17}H_{23}N_7$	62.7	62.2	7.1	7.3	30.1	27.8
12	HEP[g]		158–160	D	50	$C_{18}H_{26}N_7O$	59.6	59.8	7.4	7.2	28.6	28.8
13	$C_6H_5CH_2CH_2$—	H	145–147	D	46	$C_{20}H_{22}N_6$					24.3	24.4
14	$HOCH_2CH_2$—	C_2H_5—	125–126	D	76	$C_{16}H_{22}N_6O$	61.1	61.2	7.1	7.2	26.7	26.7
15	$(CH_3)_2N(CH_2)_3$—	H	106–119	E	22	$C_{17}H_{25}N_7$	62.4	62.1	7.7	7.6	30.0	30.3
16[a1]	CH_3—	CH_3—	119–120	A	87	$C_{16}H_{22}N_6$	64.4	63.9	7.4	7.7	28.2	27.9
17[a1]	$HOCH_2CH_2$—	H	156–157	A	61	$C_{16}H_{22}N_6O$	61.1	61.1	7.1	7.0	26.7	26.9
18[a1]	$HOCH_2CH_2$—	$HOCH_2CH_2$—	93–94	A	63	$C_{18}H_{26}N_6O_2$	60.3	60.2	7.3	7.2	23.5	23.7
19[a1]	—$(CH_2)_4$—		229–234	A	21	$C_{18}H_{24}N_6$					25.9	25.9
20[a1]	—$(CH_2)_2NCH_3(CH_2)_2$—		105–107	A	62	$C_{19}H_{27}N_7$					27.8	28.1
	R_1R_2N— = tetrahydroquinolino											
21	$HOCH_2CH_2$—	H	138–139	A	45	$C_{15}H_{26}N_6O$	60.0	60.3	6.7	6.1		
22	$HOCH_2CH_2$—	$HOCH_2CH_2$—	103–105	A	58	$C_{17}H_{24}N_6O_2$	59.3	59.7	7.0	7.3	24.4	24.2
23	—$(CH_2)_2N(CH_2)_2$—		149–151	A	47	$C_{18}H_{25}N_7$	63.7	63.6	7.4	7.3	29.0	29.1
24	$(CH_3)_2N(CH_2)_3$—	H	126–128	A	14	$C_{18}H_{27}N_7$	63.3	63.4	7.8	8.1	28.7	28.8
25[h]	—$(CH_2)_2NCH_3(CH_2)_2$—		148–150	A	16	$C_{18}H_{25}N_7$	63.7	63.9	7.4	7.4		

[a] R_4, R_5 = hydrogen unless otherwise specified; [a1] R_4, R_5 = methyl. [b] Melting points are uncorrected. [c] S = recrystallizing solvent; A = ethyl acetate; B = isopropyl alcohol; C = ethanol; D = acetonitrile; E = methanol. [d] Yields are reported as recrystallized product. [e] Analyses by Weiler and Strauss, Oxford, England. [f] Isolated as dihydrochloride dihydrate: chlorine, Calcd./Found: 25.6/25.3. The dipicrate melted 188–189°d. (water). *Anal.* Calcd. for $C_{26}H_{23}ClN_{12}O_{14}$: C, 40.9; H, 3.0; N, 22.1. Found: C, 40.7; H, 3.3; N, 21.9. [g] R_6R_7N— = *N*-hydroxyethylpiperazino. [h] R_1R_2N— = tetrahydroisoquinolino.

min. When cool, the reaction mixture was decanted into 100 ml. of water, and 3.4 g. of product separated.

Compounds 1 and 6 were processed in this manner.

2-Amino-4-(β-phenethyl)amino-6-α-(4-methylpiperazino)-ethyl-s-triazine. A mixture of 2.8 g. (0.01 mole) of 2-amino-6-chloromethyl-4-β-phenethylamino-s-triazine and 6 ml. of *N*-methylpiperazine were maintained in an oil bath at 100° for 30 min. On standing 5 days the reaction mixture solidified, and after washing with water, gave 3.02 g. (89%), m.p. 140–152°; recrystallized (acetonitrile), m.p. 162–163° yielded 70% of product.

Anal. Calcd. for $C_{18}H_{27}N_7$: C, 63.3; H, 8.0; N, 28.7. Found: C, 63.2; H, 8.0; N, 28.5.

Ethyl α-pyrrolidino acetate was prepared in 63% yield from pyrrolidine and ethyl bromoacetate,[12] b.p. 58–60° (3 mm.).[13]

(12) W. V. Drake and S. M. McElvain, *J. Am. Chem. Soc.*, 56, 697 (1934).

(13) G. R. Clemo and T. A. Melrose, *J. Chem. Soc.*, 424 (1942) report b.p. 110° (27 mm.).

2-Amino-4-m-chloroanilino-6-pyrrolidinomethyl-s-triazine (Compound 4, free base, from ester and the biguanide) was prepared from the ester above, and *m*-chlorophenylbiguanide following the general procedure previously described,[1b] in 34% yield (ethyl acetate), m.p. 166–167°.

Anal. Calcd. for $C_{14}H_{17}ClN_6$: N, 27.6. Found: N, 27.3.

Its identity was confirmed by its dipicrate, m.p. 188–189° (water) which did not depress the melting point of the picrate prepared from compound 4, processed from pyrrolidine and 2-amino-4-*m*-chloroanilino-6-chloromethyl-*s*-triazine, mixed m.p. 187–188°.

Acknowledgment. The authors are indebted to Dr. G. Ungar and his staff for the pharmacological screening of the compounds and to V. Parrino for the synthesis of several compounds.

YONKERS 1, N. Y.

[CONTRIBUTION NO. 29 FROM THE L. G. RYAN RESEARCH LABORATORIES OF MONSANTO CANADA LIMITED]

Novel Condensation of Cyclohexanone with Urea

A. F. McKAY, E. J. TARLTON, AND C. PODESVA

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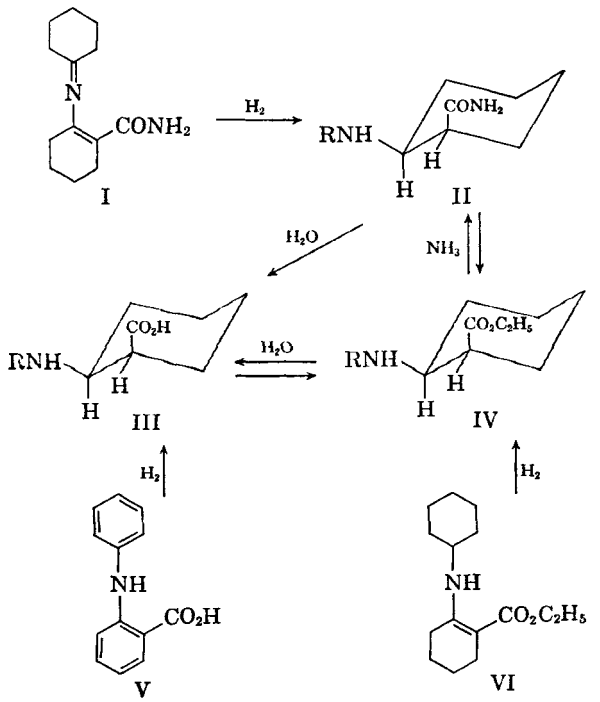
Cyclohexanone condenses with urea in an alkaline medium to give cyclohexylidene 2-carbamylcyclohex-1-enylamine. This compound on hydrogenation and acid hydrolysis gave an amino acid hydrochloride which was identical with cyclohexyl 2-carboxycyclohexylamine hydrochloride prepared from the product of the catalytic hydrogenation of *N*-phenylanthranilic acid.

Cyclohexanone condenses with urea in an alkaline medium to give an unsaturated amino acid amide which has been identified as cyclohexylidene 2-carbamylcyclohex-1-enylamine (I). The structure of this compound was verified by conversion to the saturated amino acid, cyclohexyl 2-carboxycyclohexylamine (III). The hydrochloride salt of this amino acid did not depress the melting point of a sample of cyclohexyl 2-carboxycyclohexylamine hydrochloride prepared by treating the product from the catalytic hydrogenation of *N*-phenylanthranilic acid (V) with hydrochloric acid. Since hydrogenation of *N*-phenylanthranilic acid gave a low yield (11%) of cyclohexyl 2-carboxycyclohexylamine hydrochloride, the latter acid also was prepared in 55% overall yield by the hydrogenation and hydrolysis of cyclohexyl 2-carbethoxycyclohex-1-enylamine (VI).

Preparations of cyclohexyl 2-carbethoxycyclohexylamine (IV) from the catalytic hydrogenation of cyclohexyl 2-carbethoxycyclohex-1-enylamine (VI) and the esterification of cyclohexyl 2-carboxycyclohexylamine (III) were found to be identical by a comparison of their physical constants and infrared spectra.

Hünig and Kahanek[1] have shown that catalytic hydrogenation of 3,4,5,6-tetrahydroanthranilic acid yields the *cis* isomer of 2-aminocyclohexanecarboxylic acid. Since the cyclohexane compounds, II, III, and IV described in this study have been prepared by the catalytic hydrogenation of unsaturated intermediates, they have been assigned the *cis*



R = cyclohexyl

(1) S. Hünig and H. Kahanek, *Ber.*, 86, 518 (1953).