speculate about the relative lack of significance for the partition factor, and the high dependence upon polar factors in our series.

Since our compounds have log P values higher than atropine by about 3.0 log units [$>CHCH_2OH$, log $P \cong -0.29$; $>C = C(C_6H_5)H$, log $P \cong 2.7$; for atropine, experimental value of log $P = 1.8$[8] so $1.8 + (2.7 + 0.29) = 4.8$], the range in log P caused by substitutions ranging from OH to CF_3 only alters the 4.3 value ± 1.2 log units, and all of these analogs therefore have log P values higher than atropine. The roughly equivalent antispasmodic activity for atropine and some of these compounds indicates that the partition factor plays only a small role in the antispasmodic activity of this series of compounds.

The significance of the electron density at the ortho position of this series (see formula, Table I, arrow) gives rise to several possibilities. First, models suggested the possibility of a slight spatial overlap between the π electron density at the ortho position and the carbonyl group π electrons. This could conceivably affect the rate of hydrolysis of these esters, and thus effect a stability change which might be important in the maintenance of a necessary drug concentration, or might be significant in some drug–receptor interaction involving the ester group. Second, the increased electron density at the ortho position of the α-phenyl ring may be involved in the actual binding at a receptor site (or enzyme surface) and may strengthen binding at a cationic (or partially electron deficient) site. Third, this effect may be reflected in an alteration of the rate of metabolic transformation in this series. The parabolic relationship found for σ (optimum value ≈ -0.346) is in line with the first and third of these possibilities, since kinetic processes are involved and easily lead to maximum effects. It is difficult to reconcile the second explanation with the parabolic relationship.

(8) Unpublished experimental value obtained by S. Anderson and C. Hansch.

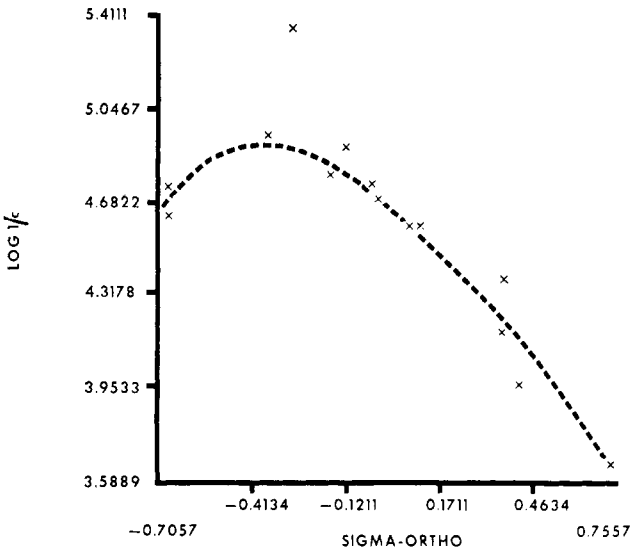

Figure 1.—Computer plot for eq 7, Table II.

Metabolic studies would be of value to help determine the reason for this relationship between biological activity and physical–chemical properties.

Acknowledgment.—The authors gratefully acknowledge the help given to this project by Professor Corwin H. Hansch.

New s-Triazine Derivatives as Depressants for Reticuloendothelial Hyperfunction Induced by Bacterial Endotoxin

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A series of 159 derivatives of s-triazine were synthesized and evaluated for their depressive effects on the reticuloendothelial hyperfunction induced by typhoid–paratyphoid vaccine. Among those, 20 derivatives were found to be as active as or superior to phenylbutazone. The most active depressants were 2-*n*-propyl-4,6-dicyclohexylamino-s-triazine (**9**), 2-amino-4-cyclohexylamino-6-(3-pyridyl)-s-triazine (**35**), and 2-ethyl-4,6-dipiperidino-s-triazine (**112**). These showed potent depressive effects on the reticuloendothelial hyperfunction as active as cortisone. Structure–activity relationships are discussed.

In recent years, reports have been published on the relationships between the phagocytic activity of the reticuloendothelial system (RES) and tumors,[1] inflammation,[2] or atherosclerosis.[3] The phagocytosis of the RES is enhanced systemically by means of bacterial polysaccharides, cholesterol, or inactive polymer colloids.[4] We found that some antiinflammatory drugs had an inhibitory effect on this hyperfunction of the RES. For the purpose of obtaining antiinflammatory or antiatherosclerotic drugs, many compounds were synthesized in our laboratory and screened with respect to the depressive effects on the hyperfunction of the RES. Recently, some s-triazine derivatives have been found to have reliable effects.

Some pharmacological activities of s-triazines have

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(1) "Reticuloendothelial Structure and Function," J. M. Heller, Ed., Ronald Press Co., 1960: K. Stern, p 233; B. N. Halpern, G. Biozzi, C. Stiffel, and D. Mouton, p 259.

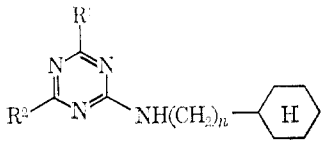
(2) M. Kozima, *Nippon Ketsueki Gakkai Zasshi*, **20**, 75 (1957); K. Akazaki and M. Kozima, *Saishin Igaku*, **13**, 986 (1958).

(3) P. R. Patek, S. Bernick, and V. A. de Mignard, *Advan. Exp. Med. Biol.* **1** 413 (1967).

(4) R. K. Fred and M. L. Shore, *ibid.*, **1**, 1 (1967); E. L. Dobson, L. S. Kelly, and C. R. Finney, *ibid.*, **1**, 63 (1967); S. Ota, *Nippon Byori Gakkai Kaishi*, **48**, 799 (1959).

TABLE I

2-CYCLOHEXYLAMINO- OR CYCLOHEXYLALKYLAMINO-4,6-DISUBSTITUTED-*S*-TRIAZINES



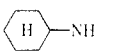
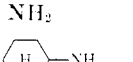
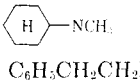
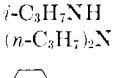
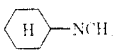
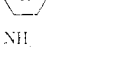
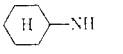
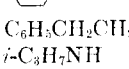
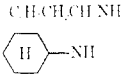
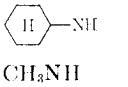
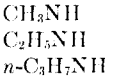
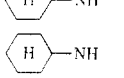
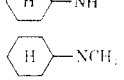
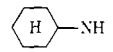
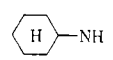
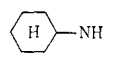
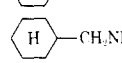
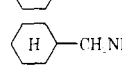
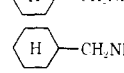
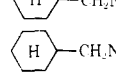
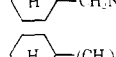
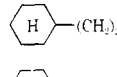
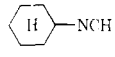
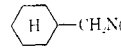
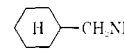
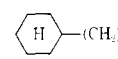
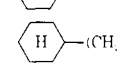
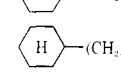
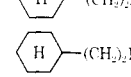
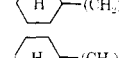
No.	*n*	R^1	R^2	Mp, °C	Recrystn solvent	Yield, %	Method	Formula[a]	LD_{50} (po), g/kg	Carbon in blood[b]	Efficacy[c]
1	0	CH_3		190–192	AcOEt	65	B	$C_{16}H_{27}N_5$	>4.0	214.0	+++
2	0	CH_3	$C_6H_5CH_2CH_2NH$	120–121	EtOH	97	A	$C_{18}H_{25}N_5$	*d*	146.0	+
3	0	C_2H_5	NH_2	149–151	MeCN	50	D	$C_{11}H_{19}N_5$		104.8	±
4	0	C_2H_5		179	MeCN	88	B	$C_{17}H_{29}N_5$	>4.0	168.8	++
5	0	C_2H_5		73–74	MeCN	63	A	$C_{18}H_{31}N_5$	>2.0	182.8	++
6	0	C_2H_5	$C_6H_5CH_2CH_2NH$	86–87	MeCN	79	A	$C_{19}H_{27}N_5$		109.5	±
7	0	*n*-C_3H_7	*i*-C_3H_7NH	81–83	MeCN	88	A	$C_{15}H_{27}N_5$		166.2	++
8	0	*n*-C_3H_7	$(n\text{-}C_3H_7)_2N$	138–139	MeCN	72	A	$C_{18}H_{34}ClN_5$[e]		106.1	±
9	0	*n*-C_3H_7		145–146	MeCN	68	B	$C_{18}H_{31}N_5$	>4.0	300.0	+++
10	0	*n*-C_3H_7		173–175	MeCN	43	A	$C_{19}H_{34}ClN_5$[e]		168.9	++
11	0	*n*-C_3H_7	$C_6H_5CH_2CH_2NH$	71–73	MeCN	87	A	$C_{20}H_{35}N_5$		116.2	±
12	0	*i*-C_3H_7	NH_2	129–130	MeCN	44	D	$C_{12}H_{21}N_5$	4.56	241.7	+++
13	0	*i*-C_3H_7	$(n\text{-}C_3H_7)_2N$	147–149	MeCN	32	A	$C_{18}H_{34}ClN_5$[e]		158.9	++
14	0	*i*-C_3H_7		149–150	MeCN	87	B	$C_{18}H_{31}N_5$		159.0	++
15	0	*n*-C_4H_9		96–98	MeCN	52	D	$C_{13}H_{23}N_5$	>4.0	234.0	+++
16	0	*n*-C_4H_9		136–137	*n*-C_6H_{14}	67	B	$C_{19}H_{33}N_5$	>2.0	152.3	++
17	0	*n*-C_4H_9	$C_6H_5CH_2CH_2NH$	187–189	MeCN	69	A	$C_{21}H_{31}N_5$		112.7	±
18	0	*n*-C_6H_{13}	*i*-C_3H_7NH	49–51	MeCN	41	A	$C_{18}H_{33}N_5$		135.1	+
19	0	*n*-C_6H_{13}	*n*-$C_6H_{13}NH$	38–40	MeCN	89	A	$C_{21}H_{39}N_5$		82.4	±
20	0	*n*-C_6H_{13}	$(n\text{-}C_3H_7)_2N$	42–42.5	MeCN	82	A	$C_{21}H_{39}N_5$		114.9	±
21	0	*n*-C_6H_{13}		114–115	MeCN	86	B	$C_{21}H_{37}N_5$		146.7	+
22	0	*n*-C_6H_{13}	$CH_3CH_2CH_2NH$	59–60	MeCN	92	A	$C_{23}H_{35}N_5$		124.3	±
23	0	$C_6H_5CH_2$		158–160	EtOH–H_2O	82	B	$C_{22}H_{31}N_5$		81.8	±
24	0	$C_6H_5(CH_2)_2$		131–133	MeCN	79	B	$C_{23}H_{33}N_5$		139.9	+
25	0	NH_2	CH_3NH	189–190	MeCN	93	A	$C_{10}H_{18}N_6$	>4.0	246.0	+++
26	0	NH_2	C_2H_5NH	160–161	EtOH	51	A	$C_{15}H_{24}N_6O_4$[f]	>4.0	226.4	+++
27	0	NH_2	*n*-C_3H_7NH	169–170	MeCN	62	A	$C_{16}H_{26}N_6O_4$[f]	>4.0	174.0	++
28	0	NH_2	*n*-C_4H_9NH	156–158	MeOH	49	A	$C_{17}H_{28}N_6O_4$[f]	>4.0	207.0	+++
29	0	NH_2	$(CH_3)_2N$	134–136	MeCN	74	A	$C_{11}H_{20}N_6$	4.56	189.0	++
30	0	NH_2	$(C_2H_5)_2N$	167–169	MeCN	86	A	$C_{17}H_{28}N_6O_4$[f]	>4.0	204.0	+++
31	0	NH_2	$(n\text{-}C_3H_7)_2N$	130–132	MeCN	61	A	$C_{19}H_{32}N_6O_4$[f]	>4.0	137.0	+
32	0	NH_2	$(n\text{-}C_4H_9)_2N$	121–122	MeCN	62	A	$C_{21}H_{36}N_6O_4$[f]		91.0	±
33	0	NH_2		123–127	EtOH–H_2O	73	A	$C_{14}H_{24}N_6$		130.2	+
34	0	NH_2		266–269	EtOH	78	A	$C_{13}H_{21}N_7O$		122.2	±
35	0	NH_2		163–165	MeCN	33	D	$C_{14}H_{18}N_6$	>4.0	305.4	+++
36	0	NH_2		169–170	MeCN	32	B	$C_{15}H_{26}N_6$	>4.0	239.9	+++
37	0	NH_2		186 dec	Me_2CO	49	B	$C_{19}H_{30}N_6O_4$[f]		181.1	++
38	0	NH_2		168–169	AcOEt	49	A	$C_{20}H_{32}N_6O_4$[f]		191.2	++
39	0	NH_2	$C_6H_5CH_2NH$	207–208	MeOH	73	A	$C_{20}H_{26}N_6O_4$[f]	>4.0	160.8	++

Table I (*Continued*)

No.	n	R_1	R_2	Mp, °C	Recrystn solvent	Yield, %	Method	Formula[a]	LD_{50} (po), g/kg	Carbon in blood[b]	Efficacy[c]
40	0	NH_2	$C_6H_5(CH_2)_2NH$	195–196	Me_2CO	24	A	$C_{21}H_{28}N_6O_4$[f]		178.9	++
41	0	n-$C_6H_{13}NH$		92–94	EtOH–H_2O	95	B	$C_{21}H_{38}N_6$[g]		100.0	±
42	0			229–230	EtOH	81	C	$C_{21}H_{36}N_6$		89.1	±
43	1	C_2H_5		107–108	MeOH	82	B	$C_{19}H_{33}N_5$		77.8	−
44	1	n-C_3H_7		81–82	MeCN	64	B	$C_{20}H_{35}N_5$	>2.0	67.7	−
45	1	i-C_3H_7		74–76	MeCN	38	B	$C_{20}H_{35}N_5$		132.1	+
46	1	n-C_4H_9		101–103	MeCN	53	B	$C_{21}H_{37}N_5$	>2.0	110.0	±
47	1	n-C_4H_9		79–80	MeCN	97	A	$C_{22}H_{39}N_5$		96.9	±
48	1	n-C_4H_9		67–69	MeCN	86	A	$C_{21}H_{37}N_5$		84.4	±
49	1	n-C_4H_9		55–57	-[h]	77	A	$C_{25}H_{45}N_5$		93.8	±
50	1	n-C_6H_{13}		81–82	MeCN	47	A	$C_{23}H_{41}N_5$		93.2	±
51	2	C_2H_5		145–146	MeOH	74	B	$C_{21}H_{37}N_5$	>4.0	108.2	±
52	2	n-C_3H_7		92–93.5	MeCN	59	B	$C_{22}H_{39}N_5$	>4.0	79.5	−
53	2	i-C_3H_7		104–105	MeOH	54	B	$C_{22}H_{39}N_5$		90.4	±
54	2	n-C_4H_9		78–79	MeOH	62	B	$C_{23}H_{41}N_5$		111.0	±
55	2	n-C_6H_{13}		73–74	MeCN	94	B	$C_{25}H_{45}N_5$		76.7	−
56	2	NH_2		151–153	EtOH–H_2O	65	B	$C_{19}H_{34}N_6$		141.4	+

[a] All compds were analyzed for C, H, N. [b] Remaining level of C in blood 5 min after injection of colloidal C, expressed as per cent ratio to the level in blood of the mouse treated with TAB vaccine alone. This value for normal mouse (before treatment with vaccine) was 910.6. [c] Judged from the remaining level of C in blood; −: <80, ±: 80–125, +: 126–150, ++: 151–200, +++: >200. [d] Not done. [e] Hydrochloride. [f] Maleate. [g] N: calcd, 22.44; found, 21.80. [h] Purified by column chromatography (Al_2O_3).

been reported, *e.g.*, CNS depressive,[5] hypotensive,[6] antiviral,[7] antitumor,[8] and nitrogen mustard-like,[9] or diuretic[10] activities. It was reported that 2,4-diamino-4-β-hydroxyphenethylamino-*s*-triazine had an anti-inflammatory activity as great as cortisone on the mustard-induced rat's paw edema,[11] but details were not divulged.

s-Triazine derivatives recorded in this paper are listed in Tables I–III. These derivatives and intermediates were prepared by the methods illustrated in Scheme I.

2-Alkyl or 2-aralkyl-4,6-dichloro-*s*-triazines (IIa) were synthesized by the reaction of 2,4,6-trichloro-*s*-triazine (I) with Grignard reagents according to Hirt, *et al.*[12] 2-Amino-4,6-dichloro-*s*-triazines (IIb) were prepared by replacing the Cl of I with an amino group according to the method of Diels, *et al.*[13] In method A, 2,4,6-trisubstituted-*s*-triazines (IV) were synthesized by the two-step reaction of 2-substituted-4,6-dichloro-*s*-triazines (IIa,IIb) with the corresponding amines *via* the intermediates III. In method B, compounds II were treated with twice the theoretical amount, or an equimolar amount, of amines in the presence of K_2CO_3 to give 2,4,6-trisubstituted-*s*-triazines (IV).

In method C, I was treated with a bimolar amount of the appropriate amine in the presence of Na_2CO_3 or $NaHCO_3$ to give 2-chloro-4,6-disubstituted-*s*-triazines (III) which were treated with another amine to obtain IV. In method D, 2-amino-4,6-disubstituted-*s*-triazines (VI) were easily prepared by the reaction of the corresponding biguanides (V) with the appropriate ester in MeOH. The oily trisubstituted-*s*-triazines were isolated as crystalline hydrochlorides or maleates.

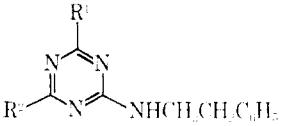
Pharmacology.—The effects of *s*-triazine derivatives on the hyperfunction of the RES induced by typhoid–paratyphoid vaccine (TAB vaccine) were tested with a simplified carbon clearance method. These results and the LD_{50} values are also listed in Tables I–III.

In Table I, compounds which have one or more

(5) Y. Takeo, S. Chiba, T. Mikoda, and T. Yui, *Takeda Kenkyusho Nempo*, **24**, 42 (1965).
(6) S. Chiba, Y. Takeo, T. Mikoda, and T. Yui, *ibid.*, **24**, 48 (1965).
(7) T. Ueda, S. Toyoshima, M. Furukawa, and Y. Seto, *Chemotherapy*, **12**, 148 (1964).
(8) M. R. Lewis and M. L. Crossley, *Arch. Biochem. Biophys.*, **26**, 319 (1950).
(9) F. S. Philips and J. B. Thiersch, *J. Pharmacol. Exp. Ther.*, **100**, 398 (1950).
(10) W. B. McKeon, Jr., *Arch. Int. Pharmacodyn.*, **151**, 225 (1964).
(11) D. E. Heitmeier and A. P. Gray, *J. Med. Chem.*, **7**, 288 (1964).
(12) R. Hirt, H. Nidecker, and R. Berchtold, *Helv. Chim. Acta*, **33**, 1365 (1950).
(13) O. Diels, *Ber.*, **32**, 691 (1899).

TABLE II

2-PHENETHYLAMINO-4,6-DISUBSTITUTED-*s*-TRIAZINES



No.	R_1	R_2	Mp, °C	Recrystn solvent	Yield, %	Method	Formula[a]	LD_{50} (po), g/kg	Carbon in blood[b]	Efficacy[c]
57	CH_3	NH_2	152–154	*i*-PrOH	60	D	$C_{12}H_{15}N_5$[d]	[e]	126.0	+
58	CH_3		135–136	$(i\text{-Pr})_2O$	86	A	$C_{16}H_{21}N_5$		135.8	+
59	CH_3		231–233	EtOH	74	A	$C_{16}H_{20}N_6O$		122.0	±
60	CH_3	$C_6H_5(CH_2)_2NH$	213–214	EtOH	75	B	$C_{20}H_{23}N_5$	>4.0	110.0	±
61	C_2H_5	NH_2	140.5–142	*i*-PrOH	55	D	$C_{13}H_{17}N_5$		115.8	±
62	C_2H_5	$C_6H_5(CH_2)_2NH$	147–148	MeCN	90	B	$C_{21}H_{25}N_5$		118.2	±
63	*n*-C_3H_7	NH_2	89–91	MeCN	61	D	$C_{14}H_{19}N_5$		126.2	+
64	*n*-C_3H_7	$C_6H_5(CH_2)_2NH$	96–97	MeCN	82	B	$C_{22}H_{27}N_5$		134.8	+
65	*i*-C_3H_7	NH_2	80–81	MeCN	43	D	$C_{14}H_{19}N_5$		135.0	+
66	*i*-C_3H_7	$C_6H_5(CH_2)_2NH$	90–91	MeCN	69	B	$C_{22}H_{27}N_5$	>2.0	152.0	++
67	*n*-C_4H_9	NH_2	93–95	*i*-PrOH	71	D	$C_{15}H_{21}N_5$	6.95	134.0	+
68	*n*-C_4H_9	$C_6H_5CH_2NH$	100–102	EtOH	60	A	$C_{22}H_{27}N_5$		92.1	±
69	*n*-C_4H_9	$C_6H_5(CH_2)_2NH$	66–67	MeCN	87	B	$C_{23}H_{29}N_5$		129.9	+
70	*n*-C_6H_{13}	$C_6H_5(CH_2)_2NH$	90–91	MeCN	97	B	$C_{25}H_{33}N_5$		127.0	+
71	*n*-$C_{11}H_{23}$	NH_2	75–75.5	EtOH	27	D	$C_{22}H_{35}N_5$		96.6	±
72	$C_6H_5CH_2$	$C_6H_5(CH_2)_2NH$	116–117	EtOH	68	B	$C_{29}H_{31}N_5$[f]		76.8	−
73	$C_6H_5CH{=}{=}CH$	NH_2	170–172	EtOH	28	D	$C_{19}H_{19}N_5$	>4.8	109.0	±
74	$C_6H_5CH_2CH_2$	$C_6H_5(CH_2)_2NH$	105–105.5	MeCN	95	B	$C_{27}H_{29}N_5$		98.2	±
75	NH_2	NH_2	171–173	*i*-PrOH	87	C	$C_{11}H_{14}N_6$		128.0	+
76	NH_2	CH_3NH	166–167	MeCN	48	A	$C_{12}H_{16}N_6$		123.5	±
77	NH_2	C_2H_5NH	161–162.5	MeOH	73	A	$C_{17}H_{22}N_6O_4$[g]	>7.55	219.5	+++
78	NH_2	*n*-$C_6H_{13}NH$	139–142	MeOH	65	A	$C_{21}H_{30}N_6O_4$[g]	>4.0	182.3	++
79	NH_2	$(n\text{-}C_3H_7)_2N$	118–120	C_6H_6	77	A	$C_{21}H_{30}N_6O_4$[g]	>6.0	107.4	±
80	NH_2	$(n\text{-}C_4H_9)_2N$	128–129	MeCN	61	A	$C_{23}H_{34}N_6O_4$[g]		110.3	±
81	NH_2		149–150	MeCN	31	A	$C_{19}H_{24}N_6O_4$[g]		142.4	+
82	NH_2		164–166	MeOH	48	A	$C_{20}H_{26}N_6O_4$[g]		101.5	±
83	NH_2		240–241	DMF–H_2O	49	A	$C_{15}H_{19}N_7O$	>20.0	205.0	+++
84	NH_2		151–152[h]	MeOH	50	A	$C_{19}H_{23}N_7O_5$[g,i]	>4.0	182.4	++
85	NH_2		142–145	EtOH	21	D	$C_{16}H_{16}N_6$	>4.0	205.0	+++
86	NH_2	$C_6H_5CH_2NH$	110–112	*i*-PrOH	67	A	$C_{18}H_{20}N_6$		115.9	±
87	NH_2	$C_6H_5(CH_2)_2NH$	140–142	*i*-PrOH	70	B	$C_{19}H_{22}N_6$	>20.0	154.0	++
88	$C_6H_5(CH_2)_2NH$	$C_6H_5(CH_2)_2NH$	140–141.5	MeOH	66	C	$C_{27}H_{30}N_6$	>4.0	197.7	++

[a,b,c] See corresponding footnotes in Table I. [d] C: calcd, 62.86; found 62.29. [e] See footnote *d*, Table I. [f] N: calcd, 17.10; found, 17.63. [g] Maleate. [h] Decomp. [i] C: calcd, 53.14; found, 52.59.

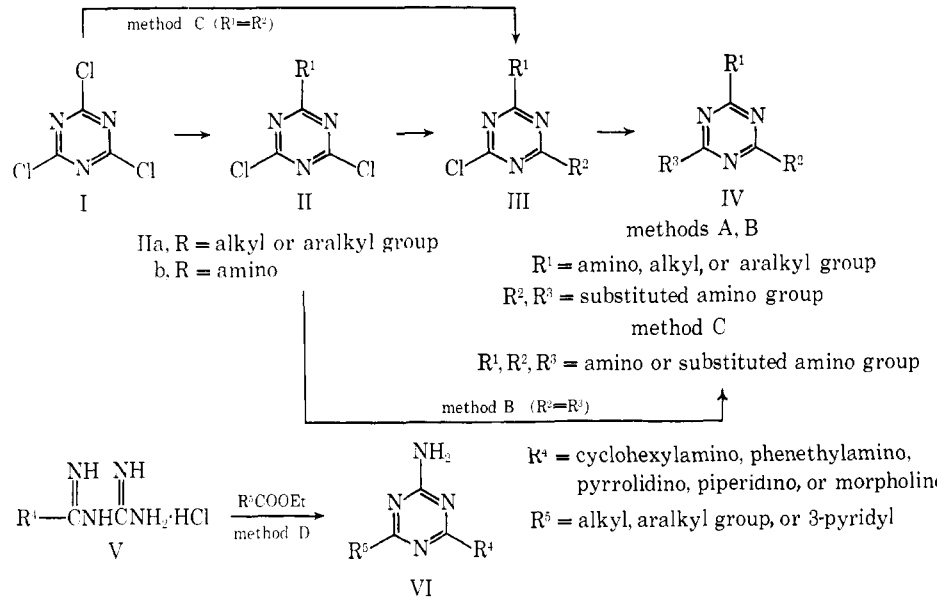
cyclohexylamino or cyclohexylalkylamino group as substituents are shown.

Among 2-alkyl-4-cyclohexylamino-6-substituted-*s*-triazines (**1**–**22**), 4,6-dicyclohexylamino derivatives (**1**, **4**, **9**, **14**, **16**, **21**) were active. 2-*n*-Propyl-4,6-dicyclohexylamino-*s*-triazine (**9**) was the most active of this series. The activity was slightly lowered when R_2 was *N*-methylcyclohexylamino (**5**, **10**). Potent activity was also observed when R_2 was amino and R_1 was *i*-Pr (**12**) or *n*-Bu (**15**). When R_2 was phenethylamino, the activity was reduced and also when R_2 was alkylamino or dialkylamino.

Among 2-amino-4-cyclohexylamino-6-substituted-*s*-triazines (**25**–**40**), potent activity was observed when R_2 was alkylamino (**25**–**28**). When R_2 was dialkylamino (**29**–**32**), the activity was reduced. Lengthening of the C chain of this alkylamino or dialkylamino group seems to result in reduced activity. When R_2 was an amino group such as cyclohexylamino (**36**), *N*-methylcyclohexylamino (**38**), benzylamino (**39**), and phenethylamino (**40**), some activity was observed. 2-Amino-4-cyclohexylamino-6-(3-pyridyl)-*s*-triazine (**35**), was the most active compound in this experiment.

In Table II, 2-phenethylamino-4,6-disubstituted-*s*-

Scheme I



triazines (**57–88**) are listed, except those having a cyclohexyl or cyclohexylalkylamino as the substituent (**2, 6, 11, 17, 22, 40, 47, 51–56**). When either of the substituents was an alkyl or aralkyl group (**57–74**), strong activity was not shown. Among 2-amino-4-phenethylamino-6-substituted-*s*-triazines (**75–87**), potent activity was observed when R_2 was ethylamino (**77**), *n*-hexylamino (**78**), oxopiperazino (**83**), 3-pyridyl (**85**), or phenethylamino (**87**). 2,4,6-Tris(phenethylamino)-*s*-triazine (**88**) was also active.

In Table III, some other *s*-triazine derivatives are listed. Among the alkyl-*s*-triazines, compounds with an amino group at R_2 and pyrrolidino at R_3 were very active (**94, 110**). Increasing the size of the alkyl resulted in loss of activity (**121, 126**). Good activity was also observed when both R_2 and R_3 were piperidino and the alkyl group was Me, Et, or *n*-Pr (**105, 112, 116**). 2-Ethyl-4,6-dipiperidino-*s*-triazine (**112**) showed the most potent activity. Activity was observed when both R_2 and R_3 were *N*-methylcyclohexylamino and the alkyl group was Me or Et (**108, 114**), but the activity was reduced when the number of C atoms of the alkyl group was increased to 3 (**117, 120**). When both the substituents were replaced with isopropylamino and the alkyl group was Et or *n*-Pr (**111, 115**), potent activity was observed, but replacing the alkyl group with *n*-hexyl (**125**) resulted in loss of activity. Aryl- or aralkyl-*s*-triazines (**128–138**) did not show interesting activity, except for **134** and **135**.

Among 2-amino-4,6-disubstituted-*s*-triazines (**139–154**), potent activity was observed when both R_2 and R_3 were pyrrolidino (**147**), 3-methylcyclohexylamino (**152**), or *N*-methylcyclohexylamino (**153**).

Cortisone and phenylbutazone showed high activity, as shown in Table III. 2-*n*-Propyl-4,6-dicyclohexylamino-*s*-triazine (**9**), 2-amino-4-cyclohexylamino-6-(3-pyridyl)-*s*-triazine (**35**), and 2-ethyl-4,6-dipiperidino-*s*-triazine (**112**) showed marked activity almost as high as cortisone. These compounds had low toxicity in spite of their effect on the hyperfunction of the RES. Antiinflammatory and antiatherosclerotic effects of these compounds will be reported in detail elsewhere.

Experimental Section[14]

Pharmacology.—Depressive activities of *s*-triazines, phenylbutazone, and cortisone on the induced hyperfunction of the RES were determined by the following procedure. Hyperfunction of the RES was induced by iv injection of 0.1 ml of typhoid-paratyphoid vaccine (TAB vaccine) to each mouse 3 times every other day. Tested compounds were administered orally 4 times to the mice, 1 hr before every administration and 24 hr after the last administration of vaccine. Dosage level of one administration was 300 mg/kg of body weight, except cortisone (50 mg/kg). One hour after the last administration of the test compounds, colloidal C was injected iv. This colloidal C was previously prepared by diluting Pelikan drawing ink with fourfold 0.8% gelatin soln and kept at 37°. Five minutes after the injection, the remaining level of colloidal C in the blood was determined. A higher level of colloidal C in the blood means greater depression of the hyperfunction of the RES. The oral LD_{50} values of *s*-triazines in mice were determined by the "up and down method" according to Brownlee, *et al.*[15]

Materials.—2,4,6-Trichloro-*s*-triazine (I) and most of the amines used in this work were obtained from commercial sources. Amines, not commercially available, were prepared as follows: cyclohexylmethylamine, β-cyclohexylethylamine, and *N*-*n*-butylcyclohexylmethylamine were prepared by LAH reduction of the corresponding amides in Et_2O. 3-Methylcyclohexylamine was obtained from 3-methylaniline by hydrogenation (PtO_2). The biguanides were prepared by the procedure of Shapiro, *et al.*[16] 2-Amino-4,6-dichloro-*s*-triazines (IIb) and 2-alkyl or 2-aralkyl-4,6-dichloro-*s*-triazines (IIa) were prepared as described before.[12,13] Preparations of **16, 60, 67, 81, 83, 93, 98,** and **156** depicted below are typical of each group.

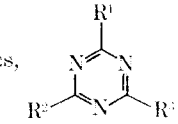
Method A. 2-Amino-4-phenethylamino-6-(3-oxopiperazin-1-yl)-*s*-triazine (83).—To a suspension of 2-amino-4,6-dichloro-*s*-triazine (IIb, 8.2 g, 0.05 mole) in H_2O (100 ml) was added dropwise with stirring phenethylamine (6.1 g, 0.05 mole) below 5°. The mixture was slowly heated to 70° and a soln of Na_2CO_3 (10.6 g, 0.1 mole) in H_2O (20 ml) was added. The resultant mixture was refluxed for 2 hr. After cooling, the precipitate was collected by filtration and recrystd from DMF to give 2-amino-4-phenethylamino-6-chloro-*s*-triazine (9.0 g, 72%) as

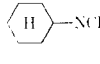
(14) The melting points were obtained on a micro hot stage and are uncorrected. Nmr spectral data were obtained using a Japan Electron Optics Lab Model 4H-100 (Me_4Si). All *s*-triazines were analyzed for C, H, N. Where analyses are indicated only by symbols of the elements (Tables I–III), analytical results obtained for those elements were within ±0.4% of the theoretical values.

(15) K. A. Brownlee, J. L. Hodges, and M. Rosenblatt, *J. Amer. Statist. Ass.*, **48**, 262 (1953).

(16) S. L. Shapiro, V. A. Parrino, and L. Freedman, *J. Amer. Chem. Soc.*, **81**, 2220 (1959); **81**, 3728 (1959).

TABLE III: 2,4,6-TRISUBSTITUTED-S-TRIAZINES,



No.	R¹	R²	R³	Mp, °C	Recrystn solvent	Yield, %	Method	Formula[a]	LD_{50} (po) g/kg	Carbon in blood[b]	Efficacy[c]
89	Cl	$HOOCCH_2NH$	$HOOCCH_2NH$	300	*d*	69	C	$C_7H_{10}ClN_5O_4$	7.65	93.4	±
90	Cl	$EtOOCCH_2NH$	$EtOOCCH_2NH$	180–182	EtOH	47	C	$C_{11}H_{16}ClN_5O_4$	>4.0	61.0	−
91	Cl	$EtOOCCH_2NH$		140–141	EtOH	52	A	$C_{12}H_{18}ClN_5O_2$		104.0	±
92	Cl	$HO(CH_2)_3NH$	$HO(CH_2)_3NH$	217–218	H_2O	59	C	$C_9H_{16}ClN_5O_2$		87.0	±
93	Cl			320	DMF	32	C	$C_{11}H_{14}ClN_7O_2$		122.0	±
94	CH_3	NH_2		195–196	EtOH	47	D	$C_8H_{13}N_5$	0.63	201.5	+++
95	CH_3	NH_2		193–195	MeOH	56	D	$C_9H_{15}N_5$	3.14	120.0	±
96	CH_3	NH_2		320–321[f]	EtOH	95	A	$C_8H_{12}N_6O$	>2.7	134.0	+
97	CH_3	*n*-C_4H_9NH	*n*-C_4H_9NH	167–168	AcOEt	83	B	$C_{12}H_{23}N_5$		107.7	±
98	CH_3	*n*-C_4H_9NH		91–92	*i*-PrOH	18	*g*	$C_{11}H_{21}N_5$		136.8	+
99	CH_3	*i*-C_4H_9NH	*i*-C_4H_9NH	184–185	AcOEt	32	B	$C_{12}H_{23}N_5$		89.4	±
100	CH_3	*n*-$C_6H_{13}NH$	*n*-$C_6H_{13}NH$	154–155	AcOEt	32	B	$C_{16}H_{31}N_5$		123.1	±
101	CH_3	$Et_2N(CH_2)_3NH$		62–63	PE[h]	53	A	$C_{14}H_{26}N_6$		120.9	±
102	CH_3	$EtOOCCH_2NH$	$EtOOCCH_2NH$	131–132	H_2O	66	B	$C_{12}H_{19}N_5O_4$		86.0	±
103	CH_3	$EtOOCCH_2NH$		127–128	PE[h]	46	A	$C_{12}H_{19}N_5O_2$	>3.0	143.0	+
104	CH_3			83–85	PE[h]	33	B	$C_{12}H_{19}N_5$	0.85	150.0	+
105	CH_3			81–83	PE[h]	87	B	$C_{14}H_{23}N_5$	1.4	163.5	++
106	CH_3			143–145	PE[h]	83	B	$C_{12}H_{19}N_5O_2$	1.0	122.0	+
107	CH_3			290–303	EtOH	69	B	$C_{12}H_{17}N_7O_2$[i]		94.0	±
108	CH_3			94.5–95.5	EtOH–H_2O	95	B	$C_{18}H_{31}N_5$	>4.0	222.7	+++
109	CH_3	$C_6H_5CH_2NH$	$C_6H_5CH_2NH$	211–213	EtOH	88	B	$C_{13}H_{19}N_5$[j]		133.3	+
110	C_2H_5	NH_2		152–153	*i*-PrOH	29	D	$C_9H_{15}N_5$		152.0	++
111	C_2H_5	*i*-C_3H_7NH	*i*-C_3H_7NH	97–98	MeCN	78	B	$C_{11}H_{21}N_5$	>3.0	221.7	+++

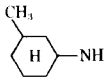
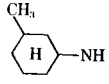
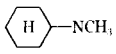
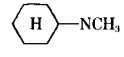
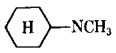
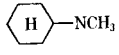
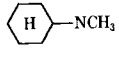
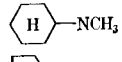
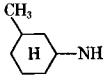
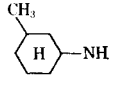
112	C_2H_5			64–65	MeCN	60	B	$C_{15}H_{25}N_5$	1.3	259.8	+++
113	C_2H_5			126–128	MeCN	57	B	$C_{19}H_{33}N_5$		111.0	±
114	C_2H_5			68–70	MeCN	63	B	$C_{19}H_{33}N_5$		164.2	++
115	n-C_3H_7			93–94	MeOH–H_2O	91	B	$C_{12}H_{23}N_5$	>4.0	202.2	+++
116	n-C_3H_7			91–92	MeCN	60	B	$C_{16}H_{21}N_5$	>4.0	223.9	+++
117	n-C_3H_7			75–77	EtOH–H_2O	64	B	$C_{20}H_{35}N_5$		90.4	±
118	i-C_3H_7	NH_2		196–198	MeOH	44	D	$C_{11}H_{17}N_5$	2.6	189.0	++
119	i-C_3H_7			81–82	MeCN	42	B	$C_{16}H_{27}N_5$		113.6	±
120	i-C_3H_7			52–53.5	EtOH–H_2O	61	B	$C_{20}H_{35}N_5$		97.0	±
121	n-C_4H_9	NH_2		154–156	EtOH	36	D	$C_{11}H_{19}N_5$	1.2	115.0	±
122	n-C_4H_9	n-$C_6H_{13}NH$	n-$C_6H_{13}NH$	97–98	AcOEt	60	B	$C_{19}H_{37}N_5$		107.9	±
123	n-C_4H_9			84–85	MeCN	64	B	$C_{21}H_{37}N_5$		123.2	±
124	n-C_4H_9	$C_6H_5CH_2NH$	$C_6H_5CH_2NH$	153–154	EtOH	83	B	$C_{21}H_{25}N_5$		107.7	±
125	n-C_6H_{13}	i-C_3H_7NH	i-C_3H_7NH	68–69	MeCN	52	B	$C_{15}H_{29}N_5$		95.7	±
126	n-$C_{11}H_{23}$	NH_2		98.5–99.5	EtOH	38	D	$C_{18}H_{33}N_5$	>4.8	126.0	+
127	n-$C_{11}H_{23}$	NH_2		91–92	EtOH	47	D	$C_{19}H_{35}N_5$	>4.0	111.0	±
128	C_6H_5			154–156	MeOH	28	D	$C_{14}H_{17}N_5$[k]	>2.0	78.6	−
129	$C_6H_5CH_2$	NH_2		187–189	EtOH	57	D	$C_{14}H_{17}N_5$		108.0	±
130	$C_6H_5CH_2$	CH_3NH	CH_3NH	229–232[f]	AcOEt	91	B	$C_{12}H_{15}N_5$		92.9	±
131	$C_6H_5CH_2$	n-C_4H_9NH	n-C_4H_9NH	107–108	EtOH–H_2O	65	B	$C_{18}H_{27}N_5$		71.7	−
132	$C_6H_5CH{=}CH$	NH_2		179–181	MeOH	31	D	$C_{16}H_{19}N_5$		78.6	−
133	$C_6H_5CH{=}CH$	NH_2		220–222	MeOH	22	D	$C_{15}H_{17}N_5O$		102.0	±
134	$C_6H_5CH_2CH_2$	CH_3NH	CH_3NH	200–201	MeOH	56	B	$C_{13}H_{17}N_5$		155.4	++
135	$C_6H_5(CH_2)_2$	n-C_4H_9NH	n-C_4H_9NH	113–114	MeCN	75	B	$C_{19}H_{29}N_5$		139.3	+
136	$C_6H_5(CH_2)_2$	n-$C_6H_{13}NH$	n-$C_6H_{13}NH$	116–117	MeCN	68	B	$C_{23}H_{37}N_5$		108.9	±
137	$C_6H_5(CH_2)_2$			85–86	MeOH	37	B	$C_{21}H_{29}N_5$		118.8	±
138	$C_6H_5(CH_2)_2$	$C_6H_5CH_2NH$	$C_6H_5CH_2NH$	121–122	MeCN	81	B	$C_{25}H_{25}N_5$		110.7	±
139	NH_2	NH_2		297–301	EtOH–H_2O	40	C	$C_7H_{12}N_6$	>2.0	134.0	+

TABLE III (*Continued*)

No.	R¹	R²	R³	Mp, °C	Recrystn solvent	Yield, %	Method	Formula[c]	LD_{50} (po) g/kg	Carbon in blood[b]	Efficacy[c]
140	NH_2	NH_2		221–223	EtOH–H_2O	96	C	$C_8H_{14}N_6$		120.0	±
141	NH_2	$EtOOCCH_2NH$		233–234	H_2O	59	A	$C_{11}H_{17}N_7O_3$		128.0	+
142	NH_2	*i*-C_3H_7NH	*i*-C_3H_7NH	125–126	(*i*-Pr)$_2O$	67	B	$C_9H_{18}N_6$		110.3	±
143	NH_2	*i*-C_4H_9NH	*i*-C_4H_9NH	131–132	EtOH–H_2O	80	B	$C_{11}H_{22}N_6$	>4.0	80.9	±
144	NH_2	*n*-$C_6H_{13}NH$	*n*-$C_6H_{13}NH$	61–63	EtOH–H_2O	35	B	$C_{15}H_{30}N_6$		147.6	+
145	NH_2	$(n\text{-}C_3H_7)_2N$	$(n\text{-}C_3H_7)_2N$	68–69	EtOH–H_2O	86	B	$C_{15}H_{30}N_6$		122.8	±
146	NH_2	$(n\text{-}C_4H_9)_2N$	$(n\text{-}C_4H_9)_2N$	69–70	EtOH–H_2O	67	B	$C_{19}H_{38}N_6$		95.6	±
147	NH_2			232–233	*i*-PrOH	83	B	$C_{11}H_{18}N_6$	0.6	184.0	++
148	NH_2			257–258	*i*-PrOH	62	A	$C_{11}H_{17}N_7O$	>5.8	138.0	+
149	NH_2			201–203	*i*-PrOH	90	B	$C_{13}H_{22}N_6$		123.9	±
150	NH_2			211–213	MeOH	41	D	$C_{12}H_{14}N_6$[l]	1.7	106.0	±
151	NH_2			173–174	MeOH	30	D	$C_{13}H_{16}N_6$	1.2	169.0	++
152	NH_2			112–113	MeCN	65	B	$C_{17}H_{30}N_6$	>4.0	189.0	++
153	NH_2			191–192	MeOH	85	B	$C_{17}H_{30}N_6$	>4.0	223.9	+++
154	NH_2	$C_6H_5CH_2NH$	$C_6H_5CH_2NH$	145–146	*i*-PrOH	86	B	$C_{17}H_{18}N_6$		106.5	±
155	$HOOCCH_2NH$	$HOOCCH_2NH$		288–289[f]	*d*	70	C	$C_{12}H_{20}N_6O_5$[m]		103.0	±
156	$EtOOCCH_2NH$	$EtOOCCH_2NH$		85–87	*i*-PrOH	57	C	$C_{16}H_{26}N_6O_4$		80.9	±
157	$EtOOCCH_2NH$	$EtOOCCH_2NH$		183–185	EtOH	66	C	$C_{15}H_{23}N_7O_5$		126.0	+
158	$EtOOCCH_2NH$			149–151	*i*-PrOH	63	B	$C_{15}H_{24}N_6O_2$	>3.0	128.0	+
159	$EtOOCCH_2NH$			132–133	(*i*-Pr)$_2O$	35	B	$C_{17}H_{28}N_6O_2$		102.0	+
	Cortisone	(50 mg/kg, po)								333.3	+++
	Phenylbutazone	(300 mg/kg, po)								222.9	+++

[a,b,c] See corresponding footnotes in Table I. [d] Product was dissolved in aq NaOH and then neutralized with HCl to give a white powder. [e] Not done. [f] Decomp. [g] See Experimental Section, other method. [h] Petroleum ether. [i] N: calcd, 33.66; found, 34.34. [j] C: calcd, 70.79; found, 70.25. [k] C: calcd, 65.86; found, 65.37. [l] C: calcd, 59.48; found, 58.99. [m] Monohydrate.

colorless crystals, mp 215–216°. *Anal.* ($C_{11}H_{12}ClN_5$) C, H, N. A mixture of the 2-amino-4-phenethylamino-6-chloro-*s*-triazine (3.7 g, 0.015 mole) and 2-piperazinone[17] (3.0 g, 0.03 mole) in H_2O (160 ml) was stirred under reflux for 2 hr. After cooling, the precipitate was collected by filtration, washed with H_2O, and recrystd from DMF–H_2O to give **83** as white crystals: nmr (in CF_3COOH) τ 1.39 (b s, 2 H, HNCO), 2.66 (b s, 7 H, C_6H_5, NH_2), 5.25 (s, 2 H, CH_2CO), 5.81–6.72 (m, 6 H), and 6.98 (t, 2 H, $C_6H_5CH_2$).

2-Amino-4-phenethylamino-6-pyrrolidino-*s*-triazine Maleate (81).—To a suspension of 2-amino-4-phenethylamino-6-chloro-*s*-triazine (6.2 g, 0.025 mole) in H_2O (120 ml) was added dropwise pyrrolidine (3.6 g, 0.05 mole) with stirring below 5°. The mixture was refluxed for 2 hr, cooled to room temperature, and extracted with $CHCl_3$. The extract was concentrated *in vacuo* leaving a syrup. The maleate was prepared by adding maleic acid (2.0 g, 0.017 mole) in MeOH (10 ml) to the syrup (7.0 g). A solid was obtained, which was recrystd from MeCN to give **81** as colorless needles.

Method B. 2-*n*-Butyl-4,6-bis(cyclohexylamino)-*s*-triazine (16).—Cyclohexylamine (8.0 g, 0.08 mole) was added to a soln of 2-*n*-butyl-4,6-dichloro-*s*-triazine (4.2 g, 0.02 mole) in H_2O (100 ml) under cooling with ice–water. The mixture was refluxed for 2 hr and then cooled to room temperature. The precipitate was collected and recrystd from hexane to give **16** as white crystals.

2-Methyl-4,6-bis(phenethylamino)-*s*-triazine (60).—A soln of phenethylamine (4.8 g, 0.04 mole) in $CHCl_3$ (20 ml) was added to a soln of 2-methyl-4,6-dichloro-*s*-triazine (3.2 g, 0.02 mole) in $CHCl_3$ (80 ml) and then a soln of K_2CO_3 (8.2 g, 0.06 mole) in H_2O (10 ml) was added. The soln was stirred at room temp for 2 hr. The reaction mixture was washed (H_2O), dried (Na_2SO_4), and concentrated *in vacuo* to give an oily residue which was recrystd from EtOH to give **60** as white crystals.

Method C. 2-Chloro-4,6-bis(3-oxopiperazin-1-yl)-*s*-triazine (93).—A soln of 2-piperazinone (4.0 g, 0.04 mole) in H_2O (40 ml) was added to a suspension of 2,4,6-trichloro-*s*-triazine (I, 3.7 g, 0.02 mole) and Na_2CO_3 (4.2 g, 0.04 mole) in $CHCl_3$ (50 ml) with stirring at 50° for 1 hr. After cooling, the precipitates were collected, washed with hot Me_2CO, and then recrystd from DMF with activated charcoal to give **93** as white granules.

2-Piperidino-4,6-bis(ethoxycarbonylmethylamino)-*s*-triazine (156).—To a soln of $NaHCO_3$ (8.4 g, 0.1 mole) in H_2O (240 ml) was added a soln of 2,4,6-trichloro-*s*-triazine (I, 18.4 g, 0.1 mole) in Me_2CO (160 ml) at 0° and then a soln of ethyl glycinate·HCl (13.9 g, 0.1 mole) and $NaHCO_3$ (8.4 g, 0.1 mole) in H_2O (100 ml). The mixture was stirred at 45° for 2 hr. The precipitate was collected and recrystd from EtOH to give **90**. To a soln of **90** (12.6 g, 0.04 mole) in $CHCl_3$ (350 ml) was added a soln of piperidine (3 4 g, 0.04 mole) in $CHCl_3$ (40 ml) and a soln of K_2CO_3 (5.6 g, 0.04 mole) in H_2O (40 ml). The mixture was stirred at room temp for 2 hr. The $CHCl_3$ layer was sepd, dried (Na_2SO_4), and concd *in vacuo*. The residue was recrystd from *i*-PrOH to give **156**.

Method D. 2-Amino-4-phenethylamino-6-*n*-butyl-*s*-triazine (67).—Phenethylbiguanide·HCl (24.2 g, 0.1 mole) was added to a NaOMe soln prepared from Na (2.3 g) and MeOH (80 ml) and the pptd NaCl was filtered off. Ethyl valerate (17.0 g, 0.1 mole) was added to the filtrate at −40°. The reaction mixture was diluted with H_2O (800 ml) and kept in an ice box overnight. The ppt was collected by filtration and recrystd from *i*-PrOH to give **67** as colorless crystals.

Other Method. 2-Methyl-4-pyrrolidino-6-*n*-butylamino-*s*-triazine (98).—A mixture of **94** (6.4 g, 0.036 mole) with *n*-BuBr (4.9 g, 0.036 mole) was heated in a sealed tube at 190–200° for 2 hr. After cooling, the reaction mixture was dissolved in H_2O (50 ml) and then filtered. The filtrate was treated with satd $NaHCO_3$ soln to yield a ppt. This was recrystd from *i*-PrOH–H_2O to give **98** as white needles.

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Synthesis and Pharmacological Evaluation of α,α-Disubstituted Naphthylacetaldehydes

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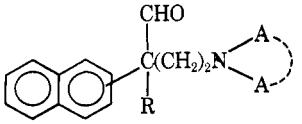
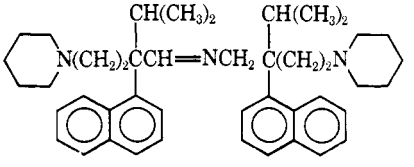
Thirty-eight α,α-disubstituted naphthylacetaldehydes were prepared for extensive pharmacological screening. Some of the compounds displayed marked antipyretic, analgetic, and antiinflammatory activity. None of the other actions investigated revealed anything of particular interest.

As part of our program in the field of naphthalene compounds, we have prepared for pharmacological screening 38 naphthylacetaldehydes of the general structures I and II, in which R was an alkyl or aminoalkyl group and NAA was a tertiary amino group.



I: substituted at position 1
II: substituted at position 2

Reduction of the appropriate nitriles with LAH or lithium mono- and diethoxyaluminohydrides afforded the desired naphthylacetaldehydes together with variable amounts of the related naphthylalkylamines,[1] which were removed from the reaction mixture by fractional precipitation before distilling. Reducing agent and reaction conditions were dependent on the steric hindrance of the nitriles. When the amines were not separated, subsequent distillation gave low yields of the aldehydes, due to formation of the related Schiff bases. In one case (**24**), the Schiff base (III) was isolated and



III

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