TABLE II
BACTERIOSTATIC ACTIVITY OF 1,3-BENZOXAZINE-2,4-DIONES

Number[a]	Substituents	Concentration for inhibition of *S.a.*[b]
1	3-Phenyl	T
3	3-(4-Bromophenyl)	T
6	3-(2,4-Dichlorophenyl)	M
7	3-(2,5-Dichlorophenyl)	+
8	3-(3,4-Dichlorophenyl)	M
9	3-(3,5-Dichlorophenyl)	M
10	6,8-Dichloro-3-phenyl	M
12	6-Bromo-3-(4-chlorophenyl)	M
13	3-(2,4,5-Trichlorophenyl)	+
14	6-Chloro-3-(3,4-dichlorophenyl)	M
16	6,8-Dichloro-3-(3,4-dichlorophenyl)	M
17	3-(3,4-Dichlorophenyl)-6-nitro	M
18	3-(3,4-Dichlorophenyl)-8-nitro	M

[a] These numbers correspond to those in Table I. [b] *S.a.* = *Staphylococcus aureus;* + represents growth at a concentration of 1×10^3. T and M represent no growth at a concentration of 1×10^3 and 1×10^6, respectively.

Anal. Calcd. for $C_{13}H_9Cl_2NO_2$: Cl, 25.1; N, 4.95. Found: Cl, 25.2; N, 4.80.

2',4',5'-Trichlorosalicylanilide.—This anilide was prepared in essentially the same manner as the preceding compound; m.p. 280–281° (from dimethylformamide–ethanol); yield, 63%.

Anal. Calcd. for $C_{13}H_8Cl_3NO_2$: N, 4.43. Found: N, 4.60.

3-Phenyl-1,3-benzoxazine-2,4-diones (Table I).—A solution or a suspension of 0.02–0.1 mole of the salicylanilide in 50 ml. of pyridine and 30 ml. of acetonitrile was stirred at 2–5° during the dropwise addition of 1.1 times the equimolar quantity of ethyl chloroformate. Stirring was continued while the temperature was gradually increased to 120–125° over a period of 1–2 hr. and 60 ml. of distillate was collected in a Barrett trap. The residue was cooled, and before it solidified 150 ml. of water and 5 ml. of concd. hydrochloric acid were added slowly with stirring and further cooling. After thoroughly stirring the mixture, the crude product was collected, washed with water, dried and recrystallized after decolorization with activated carbon, if required.

The infrared spectra (Nujol mull) of compounds 1, 3, 15 and 16 were obtained using a Beckman IR-5 spectrophotometer. Examination of the spectra revealed the presence of two carbonyl absorptions at 1690 and 1760 $cm.^{-1}$ and the absence of the characteristic NH and OH bands of the salicylanilides.

Acknowledgment.—We wish to thank Mr. P. D. McDonald for the microbiological evaluations and Messrs. John L. O'Sullivan and Ottmar Kring for part of the analytical data.

(6) S. L. Shapiro, I. M. Rose, and L. Freedman, *J. Am. Chem. Soc.*, **79**, 2811 (1957).

(7) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958, pp. 176, 205, 221.

(8) For the test procedure, see D. J. Beaver, D. P. Roman, and P. J. Stoffel, *J. Am. Chem. Soc.*, **79**, 1236 (1957).

(9) All melting points, taken on a Fisher–Johns Melting Point Apparatus, are corrected.

(10) (a) R. Anschütz and H. Mehring, *Ann.*, **346**, 300 (1906); (b) C. F. H. Allen and J. Van Allan, *Org. Syntheses*, Coll. Vol. III, 765 (1955); (c) V. E. Schraufstätter, W. Meiser, and R. Gönnert, *Z. Naturforsch.*, **16b** (2), 95 (1961).

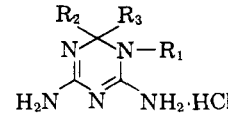
4,6-Diamino-1-alkyl-1,2-dihydro-*s*-triazines

JOSEPH G. LOMBARDINO

Medicinal Chemical Research Department, Chas. Pfizer and Co., Inc., Groton, Conn.

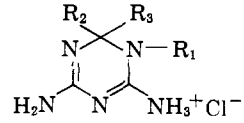
Received September 27, 1962

Preparative methods for 4,6-diamino-1-aryl-1,2-dihydro-2,2-disubstituted-*s*-triazines (Ia) are well documented in the literature.

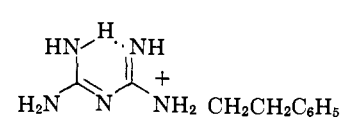


Ia, R_1 = aryl
Ib, R_1 = alkyl

These 1-aryl derivatives of I have been prepared from N^1-aryl-substituted biguanides and aldehydes or ketones under a variety of conditions.[1,2,3] Products from these reactions are reported to have antimalarial,[1,4] antimicrobial,[5] antiparasitic,[6] antitumor[7] activity and to be plant growth inhibitors.[8] This interesting spectrum of activity, together with their possible steric relationship to biguanides with antidiabetic activity (*vide infra*), prompted an investigation of the preparation of the previously unknown[9,10] 4,6-diamino-1-alkyl-1,2-dihydro-2,2-disubstituted-*s*-triazines (Ib). These compounds were then tested for hypoglycemic activity since they were thought to resemble sterically the hydrogen bonded, cyclic structure proposed[11] for a known antidiabetic drug, phenethylbiguanide hydrochloride (II).



Ib



II

Modest[3] has reported a convenient synthetic technique for the 1-aryl-1,2-dihydro-*s*-triazines Ia but was unsuccessful[3a] in an attempt to prepare the 1-alkyl compounds Ib.

$$ArNH_2 + NH_2C(=NH)NHCN + R_2COR_3 \xrightarrow{HCl} Ia$$

Since attempts to apply the conditions of Modest[3d] to the cyclization of alkylbiguanides were similarly unsuccessful, a variety of other conditions were studied. This has resulted in the successful synthesis of Ib from N^1-alkylbiguanides and aldehydes or ketones.

$$R_1NHC(=NH)NHC(=NH)NH_2 + R_2COR_3 \xrightarrow{H^+} Ib$$

The technique is essentially the "two component" method of Modest[3d]; however, continuous removal of water from the reaction system and careful control of acid concentration (15–20% excess over 1 *M* equivalent was optimal) were found to be critical factors in this reaction. All compounds of type Ib were prepared by a similar technique as illustrated in the experimental

(1) H. C. Carrington, A. F. Crowther, D. G. Davey, A. A. Levi, and F. L. Rose, *Nature*, **168**, 1080 (1951).

(2) S. Birtwell, F. H. S.Curd, J. A. Hendry, and F L. Rose, *J. Chem. Soc.*, 1645 (1948).

(3) (a) E. J. Modest, *J. Org. Chem.*, **21**, 1 (1956); (b) E. J. Modest, G. E. Foley, M. M. Pechet, and S. Farber, *J. Am. Chem. Soc.*, **74**, 855 (1952); (c) E. J. Modest, U. S. Patent 2,900,385 (1959); (d) E. J. Modest and P. Levine, *J. Org. Chem.*, **21**, 14 (1956).

(4) (a) A. F. Crowther and A. A. Levi, *Brit. J. Pharmacol.*, **8**, 93 (1953); (b) H. C. Carrington, A. F. Crowther, and G. J. Stacey, *J. Chem. Soc.*, 1017 (1954).

(5) G. E. Foley, *Proc. Soc. Exp. Biol. Med.*, **83**, 733, 740, 742 (1953).

(6) G. H. Hitchings and B. Roth, U. S. Patent 2,977,361 (1961).

(7) S. Farber, G. E. Foley, V. Downing, R. Appleton, and J. King, *Proc. Am. Assoc., Cancer Research*, **1**, 15 (1953).

(8) L. Rudenberg, G. E. Foley, and W. D. Winter, Jr., *Science*, **121**, 899 (1955).

(9) E. M. Smolin and L. Rapoport, "*s*-Triazines and Derivatives," Interscience Publishers, Inc., New York, N. Y., 1959, pp. 258 ff.

(10) E. J. Modest, "Heterocyclic Compounds," Vol. 7, R. C. Elderfield, ed., John Wiley and Sons, Inc., New York, N. Y., 1961, pp. 697 ff.

(11) S. L. Shapiro, V. A. Parrino, and L. Freedman, *J. Am. Chem. Soc.*, **81**, 2220 (1959).

TABLE I

4,6-DIAMINO-1-ALKYL-1,2-DIHYDRO-2,2-DISUBSTITUTED-*s*-TRIAZINE HYDROCHLORIDES (Ib)

	R_1	R_2	R_3	M.p., °C.[a]	Yield, %	Carbon, %		Hydrogen, %		Nitrogen, %	
						Calcd.	Found	Calcd.	Found	Calcd.	Found
Ib-1	$C_6H_5CH_2CH_2$	CH_3	CH_3	195–198	20	55.11	55.34	7.15	7.01	24.86	24.83
Ib-2	$C_6H_5CH_2CH_2$	$CH_3(CH_2)_2$	H	240–241	7	56.95	56.89	7.51	7.62	23.72	23.16
Ib-3	$C_6H_5CH_2CH_2$	3,4-$(CH_2O_2)C_6H_3$	H	208–212	21	57.82	57.97	5.39	5.62	18.71	18.97
Ib-4	$C_6H_5CH_2CH_2$	C_6H_{11}	H	249–250	13	60.78	60.66	7.50	7.67	20.85	20.55
Ib-5	$C_6H_5CH_2CH_2$	$-(CH_2)_2-CH(CH_3)-(CH_2)_2-$	---	223–224	19	60.79	61.02	7.80	7.76	20.85	21.25
Ib-6	$CH_3(CH_2)_4$	*p*-FC_6H_4	H	201–203	20	53.26	53.18	6.75	6.69	22.32	22.10
Ib-7	$(CH_3)_2-CH-(CH_2)_2$	*p*-FC_6H_4	H	199–200[b]	51	17.41	17.47	6.22	5.97	21.69	25.01
Ib-8	$CH_3-(CH_2)_7$	*p*-ClC_6H_4	H	195 dec.[b]	20	51.21	51.11	6.84	6.72	21.07	21.12
Ib-9	$C_6H_5CH_2CH_2$	*p*-FC_6H_4	H	214–216	33	58.77	59.09	5.22	5.60	20.23	19.82
Ib-10	$C_6H_5CH_2CH_2$	*p*-$CH_3SC_6H_4$	H	229–230	29	57.51	57.61	5.90	5.92	18.63	18.61

[a] All compounds were recrystallized from ethanol–ether. [b] Nitrate salts. Prepared by substituting nitric acid for hydrochloric acid as catalyst (see Experimental section).

section for 4,6-diamino-1-amyl-1,2-dihydro-2-(*p*-fluorophenyl)-*s*-triazine hydrochloride. Table I summarizes some representative compounds while Table II lists infrared and ultraviolet data.

Yields in reactions with aliphatic aldehydes were very low (*e.g.*, Ib-2) while certain other carbonyl compounds (*i.e.*, pyridine-4-carboxaldehyde, *p*-dimethylaminobenzaldehyde and cycloheptanone) gave unpurifiable mixtures. An examination of Table II reveals that all infrared spectra of Ib exhibit strong peaks near 6.4 and 6.6 μ, supporting the assignment of Degraw[12] of absorptions due to the triazine ring near 6.40 and 6.60 μ.

TABLE II

SPECTRAL DATA OF Ib

Compound	Ultraviolet (Ethanol) λ_{max}	ϵ	Infrared (KBr)[a] μ			
Ib-1	246	10650	5.95	6.15	6.35	6.70
Ib-2	245	7290	5.95	6.10	6.35	6.68
Ib-3	248	12200	5.96	6.10	6.40	6.70
Ib-4	246	7200	5.96	6.01	6.35	6.71
Ib-5	247	8460	5.96	6.10	6.50	6.75
Ib-6	250	6780	5.96	6.10	6.40	6.70
Ib-7	251	6340	5.96	6.09	6.35	6.62
Ib-8	251	7070	5.95	6.05	6.30	6.66
Ib-9	249	8680	5.97	6.10	6.40	6.71
Ib-10	264	20590	5.95	6.10	6.40	6.72

[a] Strong intensity bands in all cases.

Compounds of type Ib were administered subcutaneously to guinea pigs at 20, 40, or 50 mg./kg. and blood glucose levels measured. Blood glucose was determined on diluted whole blood samples using a micro-adaptation of the method of Hoffman[13] on an Auto-Analyzer. Most derivatives of Ib had little effect on blood glucose levels, however, Table III summarizes those compounds having a mild effect. Increasing doses did not increase this effect. For comparison, data on phenethylbiguanide hydrochloride are included in Table III. They show that compounds of type Ib do not approach the potency of phenethylbiguanide as hypoglycemic agents. Apparently, any similarities in structure to the cyclic form of II are either too subtle or are offset by the possible change in pharmacodynamic properties due to the difference in basic strength of diamino dihydrotriazines[3a] as compared to biguanides (*e.g.*, pK_a of 9–10 *vs.* pK_a *ca.* 12 for the latter).

Possible antitumor activity is presently under study while no antiviral activity could be detected in representative structures Ib.

(12) J. J. Degraw, L. O. Ross, L. Goodman, and B. R. Baker, *J. Org. Chem.*, **26**, 1933 (1961).

(13) W. S. Hoffman, *J. Biol. Chem.*, **120**, 51 (1937).

TABLE III

ADMINISTRATION OF Ib TO GUINEA PIGS[a]

Compound	R_1	R_2	R_3	Dose, mg./kg.	% Fall in blood glucose[b]
Ib-1	$C_6H_5CH_2CH_2$	CH_3	CH_3	20	25
				50	20
Ib-2	$C_6H_5CH_2CH_2$	n-C_3H_7	H	20	25
Ib-9	$C_6H_5CH_2CH_2$	*p*-FC_6H_4	H	20	22
Ib-10	$C_6H_5CH_2CH_2$	*p*-$CH_3SC_6H_4$	H	40	18
PhenethylbiguanideHCl				15	40[c]

[a] Subcutaneous administration. [b] Pooled values for 6 animals at 3 hr. post-administration. Percentage fall from normal blood glucose level. [c] Value for 6 animals at 4 hr. post-administration.

Experimental[1]

4,6-Diamino-1-amyl-1,2-dihydro-2-(*p*-fluorophenyl)-*s*-triazine Hydrochloride (Ib-6).—In a 250 ml., 3-necked flask under a Soxhlet extractor containing calcium sulfate was placed 2.08 g. (0.010 mole) of N^1-(*n*-amyl)-biguanide hydrochloride, 1.36 g. (0.011 mole) of *p*-fluorobenzaldehyde, 0.10 ml. (0.0012 mole) 12 *N* hydrochloric acid and 75 ml. of ethanol. The solution was placed under a nitrogen atmosphere and refluxed for 24 hr. Tests on reaction samples with copper ammonium sulfate[14] solution showed all biguanide to be gone after approximately 20 hr. of reflux. Concentration to 25 ml. under vacuum and cooling yielded 0.620 g. (20%) of white solid in two crops, m.p. 201–203°. Certain derivatives of Ib required the addition of ether and cooling in order to induce crystallization. An analytical sample was prepared by recrystallizing from ethanol–ether. Table I summarizes physical properties of Ib.

Acknowledgment.—The author is indebted to Mr. C. F. Gerber for the blood glucose determinations and to Mr. Nelson Treadway, Jr., for his technical assistance.

(14) Ref. 3a, footnote 35.

Synthesis of Substituted 2-Phenyl-1,4-benzothiazin-3(4H)-ones and their Activity as Inhibitors of 1,4-Dipyrrolidino-2-butyne

JOHN KRAPCHO, ATTILA SZABO, AND JUNE WILLIAMS

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

Received August 15, 1962

During the course of pharmacological evaluation of a variety of compounds, 4-(2-diethylaminoethyl)-2-