Acknowledgment. The authors are indebted to Mr. W. Fulmor and staff for spectral data; to Mr. L. Brancone and staff for microanalyses; to Dr. J. L. Fedrick, Mr. E. K. Norton, and Mr. R. Zambrano for large-scale preparation of certain intermediates; to Drs. A. C. Osterberg and J. R. Cummings and associates and Mrs. E. Markley for evaluation of the biological activity of compounds described herein; and to Drs. E. Cohen and S. M. Gadekar for helpful discussions.

Isomeric Benzyldiaminodihydrotriazines

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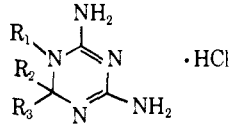
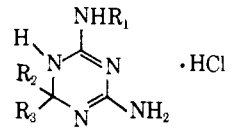
Interest in dihydrodiaminotriazines of type I[2] developed over a decade ago when the antimalarial



I

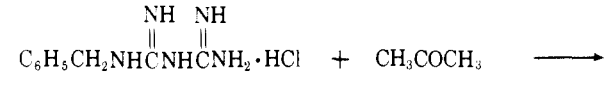


II

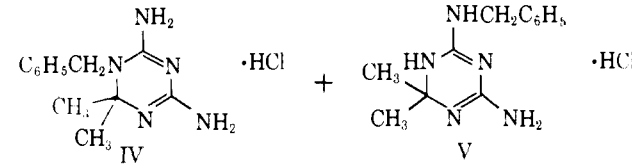
metabolite, 4,6-diamino-1-*p*-chlorophenyl-1,2-dihydro-2,2-dimethyl-*s*-triazine (I, R_1 = *p*-chlorophenyl; R_2 = R_3 = CH_3) was isolated from the urine of rabbits and humans receiving doses of the antimalarial chlorguanide.[3] Besides antimalarial activity, antitumor,[4] anticoccidial,[5,6] antibacterial,[7,8] and anthelmintic[9] activity have been reported for a number of different 4,6-diamino-1-aryl-dihydro-*s*-triazines, as well as synergistic action with sulfonamide drugs.[5,8,10]

Synthetic routes to compounds of type I in which R_1 = aryl and R_2 and R_3 are either both alkyl, or aryl and hydrogen were developed independently by workers at ICI in England[3,11] and by Modest, *et al.*, in the United States.[12–14] These involved the reaction of either an arylbiguanide hydrochloride and a ketone or aromatic aldehyde (method A), or the reaction of an arylamine hydrochloride, dicyandiamide, and the carbonyl component (method B). In both of these methods an excess of mineral acid was used. These two methods were used to prepare a large number of analogs of the antimalarial metabolite I (R_1 = *p*-chlorophenyl; R_2 = R_3 = CH_3). The exclusive product from either of the two methods were compounds of type I; compounds of type II, which *a priori* might have been expected, were not observed. This is a particularly interesting result in view of the ease with which compounds of type I are isomerized to those of type II,[13] indicating the latter to be thermodynamically more stable.

With regard to the preparation of *alkyl* diaminodihydrotriazines, Furukawa[15a] reported the failure of alkylbiguanides to react according to method A. More recently, 1-alkyl-2,2-dimethyldiaminodihydrotriazines (I, R_1 = alkyl; R_2 = R_3 = CH_3) were reportedly isolated from the reaction of alkylbiguanide hydrochlorides and acetone[15b] essentially according to this method. No mention was made of the formation of the isomeric compounds of type II. In contrast, we have found (before the appearance of the work cited in ref. 15b) that under the conditions of method A, benzylbiguanide hydrochloride (III) reacts with acetone to give IV and V in roughly equal amounts. That V was formed directly rather than by rearrange-



III

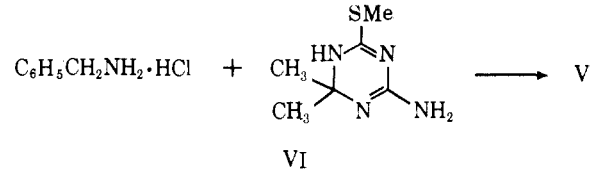


IV V

ment of the initially formed IV was demonstrated by the recovery of I unchanged after exposure to the reaction conditions of method A.

Increasing the temperature of the reaction to 110° (sealed tube) resulted in exclusive formation of V after 20 hr., while after 5 hr. the ratio of IV to V was roughly 1:2. It appeared probable that at this elevated temperature IV does rearrange to V, and this was, indeed, found to be the case. Thus, exposure of IV to these reaction conditions for 17.5 hr. resulted in its complete transformation to V. This isomerization was also effected in base.[13]

The structure of V was unequivocally established by independent synthesis from 2,2-dimethyl-4-amino-1,2-dihydro-6-methylthio-*s*-triazine (VI) and benzylamine hydrochloride according to the procedure of Birtwell,



VI

(1) Lederle Laboratories Division, American Cyanamid Co., Pearl River, N. Y.

(2) The tautomeric form indicated is done so arbitrarily. There is no evidence to date which favors this one over the other alternatives.

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

(4) For leading reference see A. F. Crowther, British Patent 709,906 (1954); U. S. Patent 2,803,628 (1957).

(5) R. E. Lux, *Antibiot. Chemotherapy*, **4**, 971 (1954).

(6) R. E. Lux, U. S. Patent 2,823,161 (1958).

(7) G. E. Foley, E. J. Modest, J. R. Cataldo, and H. D. Riley, *Biochem. Pharmacol.*, **3**, 18, 31 (1959).

(8) M. W. Fisher and L. Doub, *ibid.*, **3**, 10 (1959).

(9) (a) Burroughs-Wellcome Co., Inc., U. S. Patent 2,977,361 (1961); British Patent 899,404 (1962); (b) B. Roth, R. B. Burrows, and G. H. Hitchings, *J. Med. Chem.*, **6**, 370 (1963).

(10) S. B. Kendall and L. P. Joyner, *Vet. Record*, **70**, 632 (1958).

(11) H. C. Carrington, A. F. Crowther, and G. J. Stacey, *J. Chem. Soc.*, 1017 (1954).

(12) E. J. Modest, G. E. Foley, M. M. Pechet, and S. Farber, *J. Am. Chem. Soc.*, **74**, 855 (1952).

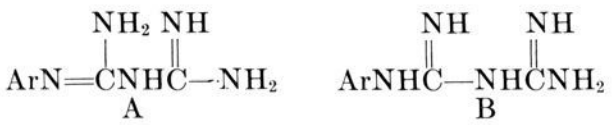
(13) E. J. Modest, *J. Org. Chem.*, **21**, 1 (1956).

(14) E. J. Modest and P. Levine, *ibid.*, **21**, 14 (1956).

(15) (a) M. Furukawa, Y. Seto, and S. Toyoshima, *Chem. Pharm. Bull.* (Tokyo), **9**, 911 (1961); (b) J. Lombardino, *J. Med. Chem.*, **6**, 213 (1963).

et al.[16] The infrared spectra of isomers IV and V were clearly different and served as a basis for differentiating between the two (see Experimental). The ultraviolet spectra of the two isomers were, on the other hand, quite similar [λ_{max}^{MeOH} 245 mμ (ϵ 10,300) and 241 mμ (ϵ 14,150), respectively, for IV and V].[17]

That extensive work by various groups[3,11,13–15b] on the dihydro-*s*-triazine-forming reactions of arylbiguanides has failed to disclose the formation of type II compounds (in the presence of excess mineral acid) may be related to a preference of the arylbiguanides for the tautomeric form A over B owing to conjugation with the aromatic ring. Reaction at the doubly bonded nitrogen would seem reasonable by analogy with the established fact[18] that protonation of an amidine takes place on the imino nitrogen.



Biological Data.—Compounds IV and V exhibited no interesting biological activity. In coccidiosis in the chick, they were inactive at 0.5% in the diet against a severe challenge of *Eimeria tenella*.[19] They were inactive at 0.1% by drug diet against *Salmonella choleraesuis* in the mouse. In the anthelmintic screening program they were inactive in mice when fed at 0.1% in the diet for 7 days.

Experimental[20]

Reaction of Benzylbiguanide Hydrochloride with Acetone. Formation of 4,6-Diamino-1-benzyl-1,2-dihydro-2,2-dimethyl-*s*-triazine Hydrochloride (IV) and 4-Amino-6-benzylamino-1,2-dihydro-2,2-dimethyl-*s*-triazine Hydrochloride (V).—A suspension of 2 g. (0.009 mole) of benzylbiguanide hydrochloride in a mixture of 25 ml. of commercial absolute ethanol and 10 ml. of reagent grade acetone containing 1 ml. (0.01 mole) of concentrated HCl was heated under reflux for 24 hr. The reaction mixture became homogeneous after 4 hr. of heating. After the solvents were removed under reduced pressure, the yellow syrupy residue was taken up in 10 ml. of water, and the pH of the solution was adjusted to 6–7 (alkacid test paper) with 2 *N* NaOH; 4,6-diamino-1-benzyl-1,2-dihydro-2,2-dimethyl-*s*-triazine hydrochloride separated as a colorless solid. After refrigerating the suspension for 1 hr., the compound was collected by filtration, washed with a small amount of cold water, and air dried; yield 0.7 g. (29%), m.p. 191–194°, λ_{max}^{MeOH} 245 mμ (ϵ 10,300). The analytical sample was obtained by recrystallization from water; m.p. 194–197°.

Anal. Calcd. for $C_{12}H_{18}ClN_5 \cdot H_2O$: C, 50.43; H, 7.05; Cl, 12.41; N, 24.50; H_2O, 6.30. Found: C, 50.39; H, 7.15; Cl, 12.33; N, 24.58; H_2O, 5.21.

Treatment of the aqueous filtrate (~10 ml.) with 3–4 ml. of 10% aqueous Na_2CO_3 resulted in the separation of 0.9 g. (35%) of the bicarbonate of 4-amino-6-benzylamino-1,2-dihydro-2,2-dimethyl-*s*-triazine, m.p. 180–184° eff., which was in turn converted to the hydrochloride salt, m.p. 190–194°, as described under the following section. Its infrared spectrum was identical with that of authentic V prepared according to the method of Birtwell[16] (see below).

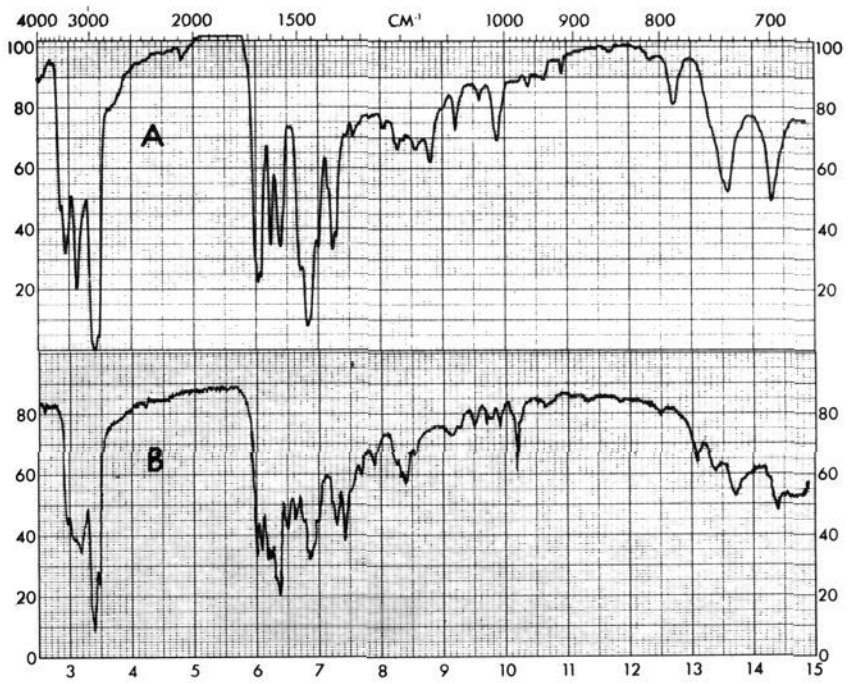


Figure 1.—Infrared spectra in Nujol of (A) 4,6-diamino-1-benzyl-1,2-dihydro-2,2-dimethyl-*s*-triazine hydrochloride (IV), and (B) 4-amino-6-benzylamino-1,2-dihydro-2,2-dimethyl-*s*-triazine hydrochloride (V).

The remaining aqueous filtrate was evaporated to dryness, the colorless solid residue was acidified with saturated ethanolic HCl, and the mixture was again evaporated to dryness, the last traces of solvent being removed by pumping (vacuum pump) for 2 hr. The solid residue was extracted with hot ethanol. Evaporation of the ethanol extract left a gummy residue which was heated in boiling acetone and kept at room temperature overnight. Removal of the acetone left a pasty solid (0.6 g., 26%) which gave a positive biguanide test (formation of a lavender solid) with ammoniacal $CuSO_4$. Its infrared spectrum was essentially identical with that of an authentic sample of benzylbiguanide dihydrochloride, m.p. 231–232°, prepared from the monohydrochloride by recrystallization from saturated ethanolic HCl.

Anal. Calcd. for $C_9H_{15}Cl_2N_5$: C, 40.91; H, 5.72; Cl, 26.84; N, 26.51. Found: C, 41.15; H, 5.81; Cl, 26.74; N, 26.46.

With 2 molar equiv. of concentrated HCl only a 10% yield of IV was obtained.

Reaction of Benzylbiguanide Hydrochloride with Acetone at 110°. 4-Amino-6-benzylamino-1,2-dihydro-2,2-dimethyl-*s*-triazine Hydrochloride (V).—A mixture of 2.27 g. (0.01 mole) of benzylbiguanide hydrochloride, 25 ml. of commercial absolute ethanol, 10 ml. of reagent grade acetone, and 1 ml. (0.01 mole) of concentrated HCl were placed in a Fisher–Porter glass pipe sealed at one end and closed at the open end by means of a Teflon gasket and aluminum fittings. The reaction mixture was heated in an oil bath at 110° for 20 hr. (reaction mixture became homogeneous within 15 min.), cooled, transferred to a round-bottom flask, and evaporated under reduced pressure. The syrupy residue was taken up in 10 ml. of water, the pH of the solution was adjusted to 6–7 (alkacid test paper) with 2 *N* NaOH, and the solution was refrigerated. No solid separated even after 2.5 hr. (compare with the preparation of IV above). After 18 hr. 0.41 g. (15%) of crystalline V separated, m.p. 192–194°, m.m.p. 174–185° with unrearranged IV. Its infrared spectrum was identical with that of authentic V prepared as described below. The aqueous mother liquor was treated with 10% Na_2CO_3 solution. The cream-colored bicarbonate which separated (1.6 g., 55%), m.p. 178–182° eff., was converted to the hydrochloride salt in 70% yield by treatment with a minimal amount of 10% HCl. Partial solution accompanied by effervescence took place with concurrent formation of a new solid. A small amount of water was added to the resulting pasty solid, the suspension was refrigerated for 30 min., and the solid was collected by direct transfer onto a filter pad without the use of any additional water; m.p. 190–194°. Recrystallization from acetonitrile gave V melting at 196–197°, λ_{max}^{MeOH} 241 mμ (ϵ 14,150). Its infrared spectrum was identical with that of authentic V prepared as described below.

Anal. Calcd. for $C_{12}H_{18}ClN_5$: C, 53.82; H, 6.77; Cl, 13.24; N, 26.16. Found: C, 53.40; H, 7.02; Cl, 13.22; N, 26.09.

(16) S. Birtwell, F. Curd, J. Hendry, and F. Rose, *J. Chem. Soc.*, 1645 (1948).

(17) Had we only one of the two isomers in hand,[15b] it would have proved quite impossible to assign a structure to it on the basis of spectral data alone.[15b]

(18) R. C. Neuman, Jr., G. S. Hammond, and T. J. Dougherty, *J. Am. Chem. Soc.*, **84**, 1506 (1962).

(19) E. Waletsky and C. O. Hughes, *Am. J. Vet. Res.*, **7**, 365 (1946).

(20) Melting points are corrected. Microanalyses are by Galbraith Laboratories, Inc., Knoxville, Tenn. Infrared spectra were taken as Nujol mulls with a Perkin-Elmer Infracord spectrophotometer. Ultraviolet spectra were measured with a Cary recording spectrophotometer.

When the reaction time was decreased to 5 hr., IV was also obtained. The ratio of IV to V was roughly 1:2 in contrast to the 1:1 ratio of the two obtained in refluxing acetone-ethanol (see above).

The infrared spectra of IV and V were distinctly different throughout the entire spectral range (Figure 1). That IV was obtained pure, uncontaminated with its rearranged isomer V, is indicated by the sharp medium-intensity band at 10.2 μ present in the mull spectrum of V and completely absent from that of IV.

Treatment of 4,6-Diamino-1-benzyl-1,2-dihydro-2,2-dimethyl-*s*-triazine with HCl. A. In Refluxing Acetone–Ethanol.—A solution of 100 mg. (0.37 mmole) of IV in a mixture of 1.3 ml. of commercial absolute ethanol and 0.5 ml. of reagent grade acetone containing 0.05 ml. (0.5 mmole) of concentrated HCl was heated under gentle reflux for 27 hr. The residue obtained after evaporating the solvents was dissolved in 1 ml. of water and the solution was neutralized with 2 *N* NaOH. IV (50 mg.) was recovered (the compound began separating as the pH of the solution approached neutrality), m.p. 197–198.5°. Its infrared spectrum was identical with that of authentic IV. Evaporation of the aqueous filtrate left a 19-mg. residue. Its very simple infrared spectrum was considerably different from either IV or V. Thus 72.5% of the material isolated was unrearranged IV.

B. In Acetone–Ethanol at 110°.—The reaction mixture described in A was heated at 110° (sealed tube) for 17.5 hr. The resulting yellow solution was evaporated, the residual oil was taken up in 0.7 ml. of water, and the pH of the solution was adjusted to 6–7 (alkacid test paper) with 2 *N* NaOH. The solution remained homogeneous (compare with A). After 15 min. at room temperature, the solution was refrigerated (0 to −10°) for 2 days. The highly crystalline solid which separated melted 190–193°, yield 47 mg. (47%). Its infrared spectrum was identical with that of authentic V.

Base-Catalyzed Rearrangement of IV to V.—A suspension of 155 mg. of IV in 1 ml. of 2 *N* NaOH was heated on a steam bath for 15 min. An additional 1 ml. of water was added, and heating continued for 1 hr. The reaction mixture was cooled and the pH of the solution was adjusted to 6–7 (alkacid test paper) with dilute HCl. Crystalline material began separating from the resulting turbid solution within 1 hr. After refrigerating at 0 to −10° overnight, 115 mg. (74%) of V was collected, m.p. 194–196°, m.m.p. 181–193° with IV. Its infrared spectrum was identical with that of an authentic sample of V prepared from VI and benzylamine hydrochloride.

When IV was treated with 2 *N* NaOH at room temperature (aqueous phase strongly alkaline), it dissolved, and almost immediately thereafter a new solid separated which was collected after 10 min. Acidification of this material with a small amount of concentrated HCl caused it to dissolve. Dilution with a small amount of water resulted in the separation of a crystalline solid which was collected after adjusting the pH of the aqueous phase to 3–4 with 2 *N* NaOH. This compound was identified as unchanged IV by its melting point (198–201°), mixture melting point (197–200°), and infrared spectrum (identical with that of an authentic sample).

4-Amino-6-benzylamino-1,2-dihydro-2,2-dimethyl-*s*-triazine Hydrochloride V from Benzylamine Hydrochloride and 4-Amino-1,2-dihydro-2,2-dimethyl-6-methylthio-*s*-triazine (VI).—The procedure described by Birtwell, *et al.*,[16] for the preparation of the 6-anilinodihydrotriazine from aniline hydrochloride and VI was extended to the preparation of the 6-benzylamino analog. Thus, a solution of 2 g. (0.012 mole) of VI and 1.6 g. (0.011 mole) of benzylamine hydrochloride in 5 ml. of water was heated under reflux for 26 hr., and the gummy residue obtained by evaporating the aqueous solution to dryness *in vacuo* was treated with dilute Na_2CO_3 solution. After rubbing with a metal spatula, the reaction mixture solidified on standing for a short while. The solid was collected and heated in boiling acetone; 18 g. of the bicarbonate was thus obtained, which was converted to the hydrochloride salt V as described above; m.p. 194–195.5°, m.m.p. 194–195.5° with V prepared *via* the sealed tube reaction. The infrared spectra of the compounds prepared by the two routes were identical.

Acknowledgment.—We thank Dr. G. Berkelhammer for his continued interest and active participation in the preparation of this manuscript.

Spiranes. IX. Amides of 3,9-Dicarboxy-2,4,8,10-tetraoxaspiro[5.5]undecane[1]

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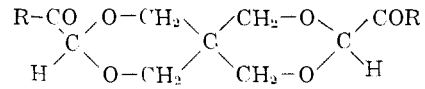
The bisalkyl- and bisdialkylaminoalkylamides of 3,9-dicarboxy-2,4,8,10-tetraoxaspiro[5.5]undecane have been prepared, and the latter possess interesting pharmacological activity. We have previously reported improved methods for the synthesis of 3,9-dicarbomethoxy-2,4,8,10-tetraoxaspiro[5.5]undecane (Ib) and several of its homologs.[2] The present report deals with the preparation of some derivatives of the parent acid Ia and their pharmacological properties.



Ia, R = OH
b, R = OCH_3
c, R = alkyl
d, R = dialkylaminoalkyl or heterocyclicalkyl

The ester Ib is saponified with remarkable ease. Indeed, simply dissolving the ester in water effects saponification. Series of bisalkyl and bisdialkylaminoalkylamides (Ic and Id), were prepared from the ester Ib by reaction with the appropriate primary amines in methanol. The reaction proceeded readily in all cases and gave high yields of pure product.

The bisalkylamides are listed in Table I and the bisdialkylaminoalkyl- and heterocyclicalkylamides in Table II. Of the bisalkylamides the lower members were soluble in water as well as common organic solvents. All of the bisdialkylaminoalkyl- and heterocyclicalkylamides prepared in this study were quite soluble in water.

Gross pharmacological screening of these amides, according to previously described techniques,[1,3] showed that the bisalkylamides possessed no remarkable pharmacological activity. However, the bisdialkylaminoalkylamides produced sedation, muscle relaxation and tranquilization in varying degree in the rat and the rabbit.

When compared with meprobamate, the bisdialkylaminoalkylamides possessed from 0.6 to 1.0 times the activity of meprobamate. Maximum activity of the compounds studied resided in the bisdimethylaminoethyl- and dimethylaminopropylamides.

Experimental

All melting points were obtained with a Thomas-Hoover capillary type apparatus and are corrected.

(1) C. H. Grogan, C. F. Geschickter, M. E. Freed, and L. M. Rice, *J. Med. Chem.*, **8**, 62 (1965).

(2) J. B. Clements and L. M. Rice, *J. Org. Chem.*, **24**, 1958 (1959).

(3) C. H. Grogan, C. F. Geschickter, and L. M. Rice, *J. Med. Chem.*, **7**, 78 (1964).