removed by filtration, and the filtrate was dried over potassium carbonate. Dry hydrogen chloride was bubbled through the dry solution, and the oil which separated was dissolved in 3*N* sodium hydroxide. The basic solution was extracted with ether-pentane. After drying over sodium sulfate, hydrogen bromide was passed into the solution, and the precipitated camphidine hydrobromide weighed 2.231 g. (28%). Crystallization from ethanol-ether gave granules, m.p. 304–307°, $[\alpha]_D^{29}$ +11.1° (50% ethanol, *c*, 3.2). No efforts were made to study the reduction with a view to determining optimal conditions.

Cyclocamphidine hydrobromide. Camphidine hydrobromide (968.3 mg., 4.14 mmol.) was chlorinated in pentane solution by the procedure of Coleman.[7] Removal of the solvent left an oil to which was added 30 ml. of 90% sulfuric acid cooled to 0°. The solution was placed in a quartz flask and irradiated with a mercury arc lamp at 0°. After 16 hr. the solution was poured onto ice and made alkaline with sodium hydroxide. The resulting suspension was heated to boiling, allowed to cool, and extracted twice with ether. Dry hydrogen bromide was passed into the ether solution, and the oily precipitate was stirred with 3*N* sodium hydroxide solution and 3 ml. of benzenesulfonyl chloride overnight. The solution was acidified with hydrochloric acid, and the benzenesulfonamide of secondary amine was removed by washing with ether. The aqueous solution was made alkaline with sodium hydroxide and extracted with ether. The ether was dried over magnesium sulfate, and dry hydrogen bromide was passed in. The amine hydrobromide was filtered and dried over phosphorus pentoxide at 0.1 mm. The product weighed 0.6444 g. (67%) and crystallized from ethanol-ether as microcrystals, m.p. 353–357° (dec.), $[\alpha]_D^{29}$ +2.4° (50% ethanol, *c*, 2.5).

Anal. Calcd. for $C_{10}H_{18}NBr$: C, 51.73; H, 7.81; N, 6.03. Found: C, 52.02; H, 7.78; N, 6.00.

Picrate, crystals from ethanol, m.p. 259.5–262° (dec.).

Anal. Calcd. for $C_{16}H_{20}N_4O_7$: C, 50.52; H, 5.30; N, 14.73. Found: C, 50.80; H, 5.34; N, 14.63.

The nuclear magnetic resonance spectrum of cyclocamphidine hydrobromide (in D_2O solution with methylene chloride as the external standard) had a split band at 62 cps. (at 40 megacycles), (+N—CH_2—), a split band at 116 cps. (CH_2), and a sharp doublet at 172 cps. (CH_3). The nuclear magnetic resonance spectrum of camphidine hydrobromide had split bands at 55–71 cps. (+N—CH_2—), a band at 111 cps. (CH_2) and a sharp triplet at 143, 149, and 151 cps. (CH_3). The ratio of the area under the peaks corresponding to +N—CH_2— to the area under the peaks corresponding to CH_3 in the product divided by the same ratio found in the starting material is equal to 2.66. The theoretical value based on the change camphidine → cyclocamphidine II is 2.25.

NOYES CHEMICAL LABORATORY
UNIVERSITY OF ILLINOIS
URBANA, ILL.

(7) G. H. Coleman, G. Nichols, and F. F. Martens, *Org. Syntheses*, Coll. Vol. III, 159 (1955).

New Dihydrotriazines of Chemotherapeutic Interest

SAMUEL SCHALIT AND ROYAL A. CUTLER

Received November 27, 1957

From the urine of animals and human volunteers who had received chlorguanide, [1-(*p*-chlorophenyl) - 5 - isopropylbiguanide], Rose[1] and coworkers isolated a metabolite which they characterized as 4,6-diamino-1-(*p*-chlorophenyl)-1,2-dihydro-2,2-dimethyl-*s*-triazine (I, free base, R_1 = Cl, R_2, R_3 = CH_3). In addition their studies indicated that this metabolite was ten times as active as the parent drug against infections of *P. gallinaceum* in chicks. Subsequent work by Carrington,[2] Loo,[3] Basu,[4] Modest,[5] and Lux[6] elaborated on the structure, synthesis, and chemotherapeutic activity of the above compound and of a number of its analogs.

Since work done in our laboratories had demonstrated the superior antibacterial properties of racemic *threo*-2-dichloroacetamido-1-(*p*-methylthiophenyl)-1,3-propanediols[7] as compared to the corresponding *p*-chloro analog,[8] it was considered of interest to examine the effect on chemotherapeutic activity of replacing the *p*-chloro atom in the chlorguanide metabolite by groups such as alkylthio as well as other suitable substituents. Accordingly we synthesized a number of compounds which may be represented by the general formula I and which are listed in Table I.

Preliminary testing[9] of the dihydrotriazine hydrochlorides against *P. lophurae* infections in ducks indicated a similar level of activity for the *p*-methylthio-2,2-dimethyl (Ia) and the *p*-chloro analogs.[1] However the latter proved to be considerably more toxic with evidence of toxicity even at the lower effective dose levels. The *p*-sulfamyl analog (Ie) showed slight[10] and the *p*-acetyl analog (Id) moderate antimalarial activity.[11]

It was also found that the *p*-methylthio-2,2-dimethyl compound (Ia) when combined with bithionol [2,2′-thiobis(2,4-dichlorophenol)] gave a synergistic or potentiated mixture having a greater anticoccidial effect in fowl than the sum of the anticoccidial effects of the individual ingredients.

Two of the hydrochlorides, the *p*-methylthio-2,2-dimethyl compound (Ia) and the *p*-methylthio-2-(*n*-propyl) compound (Ic), showed moderate anthelmintic activity against the oxyurid worms

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

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

(3) T. L. Loo, *J. Am. Chem. Soc.*, **76**, 5096 (1954).

(4) U. P. Basu, A. K. Sen, and A. K. Ganguly, *Sci. and Culture (Calcutta)*, **18**, 45 (1952).

(5) E. J. Modest, *J. Org. Chem.*, **21**, 1 (1956); E. J. Modest and P. Levine, *J. Org. Chem.*, **21**, 14 (1956).

(6) R. E. Lux, *Antibiotics & Chemotherapy*, **4**, 971 (1954).

(7) R. A. Cutler, R. J. Stenger, and C. M. Suter, *J. Am. Chem. Soc.*, **74**, 5475 (1952).

(8) Ng. Ph. Buu-Hoï, Ng. Hoan, P. Jacquignon, and Ng. H. Khoï, *J. Chem. Soc.*, 2766 (1950).

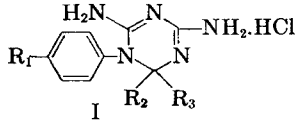
(9) Preliminary testing of these compounds was done by the biology division of these laboratories.

(10) No report of antimalarial activity was given by Basu, *et al.* (ref. 4).

(11) This compound was found by Lux (ref. 6) to be inactive against *E. tenella* infections in chicks, but no report was made of its antimalarial activity.

TABLE I

SUBSTITUTED PHENYLDIHYDROTRIAZINE MONOHYDROCHLORIDES



I

	R_1	R_2	R_3	Time of Reflux, Hr.	Yield, %	Solvent[a]	Cryst. Form	M.P., °C.	Formula	Analyses: Chlorine Calcd.	Chlorine Found	Nitrogen[i] Calcd.	Nitrogen[i] Found
Ia	CH_3S	CH_3	CH_3	4	65.6	H_2O[b]	White needles	204.4–207.8	$C_{12}H_{17}N_5S.HCl$	11.83	11.69	23.36	23.44
Ib	C_2H_5S	CH_3	CH_3	5	56.5	H_2O[b]	White prisms	214.2–220.8	$C_{13}H_{19}N_5S.HCl$	11.30	11.10	22.33	22.20
Ic	CH_3S	H	$CH_2CH_2CH_3$	4 (at 50°)	67.3	abs. EtOH	White powder	230.2–231.1	$C_{13}H_{19}N_5S.HCl$	11.30	11.23	22.33	22.51
Id	CH_3CO[c]	CH_3	CH_3	6	81.3	H_2O[b]	White needles	210.0–211.6[d]	$C_{13}H_{17}N_5O.HCl$	11.99	11.70	23.68	23.90
Ie	H_2NSO_2[c]	CH_3	CH_3	6	90.6	H_2O[b] then EtOH-H_2O 5:1	White powder	207.4–214.8[e]	$C_{11}H_{16}N_6O_2S.HCl$	10.65	10.66	[f]	[f]
	Free Bases of Above Substituted Phenyldihydrotriazine Monohydrochlorides												
	CH_3S	CH_3	CH_3		54		White prisms	149.2–152.2	$C_{12}H_{17}N_5S$	[g]	[g]		
	C_2H_5S	CH_3	CH_3		59		Pale yellow powder	132.0–138.7	$C_{13}H_{19}N_5S$	[h]	[h]	25.25	25.15
	CH_3S	H	$CH_2CH_2CH_3$		65.3		White	143.0–144.6	$C_{13}H_{19}N_5S$			25.25	24.92

[a] Charcoal was added in most of the recrystallizations. [b] Where water alone was used as the solvent, a few drops of conc. hydrochloric acid were added. [c] Subsequent to the preparation of Id and Ie, these compounds were disclosed in the literature. See refs. 6 and 4, respectively. [d] No melting point was reported by Lux (ref. 6) for this compound. [e] Basu, *et al.* (ref. 4) reported a m.p. of 206–208° with resolidification and decomposition for the hydrate. No m.p. of the anhydrous triazine was given. [f] Sulfur: calcd., 9.64; found, 9.52 [g] Sulfur: calcd., 12.17; found, 12.35. [h] Sulfur: calcd., 11.56; found, 11.23. [i] Compounds Ia, b, d were Dumas determinations. Compound Ic and the two bases were Kjeldahl determinations.

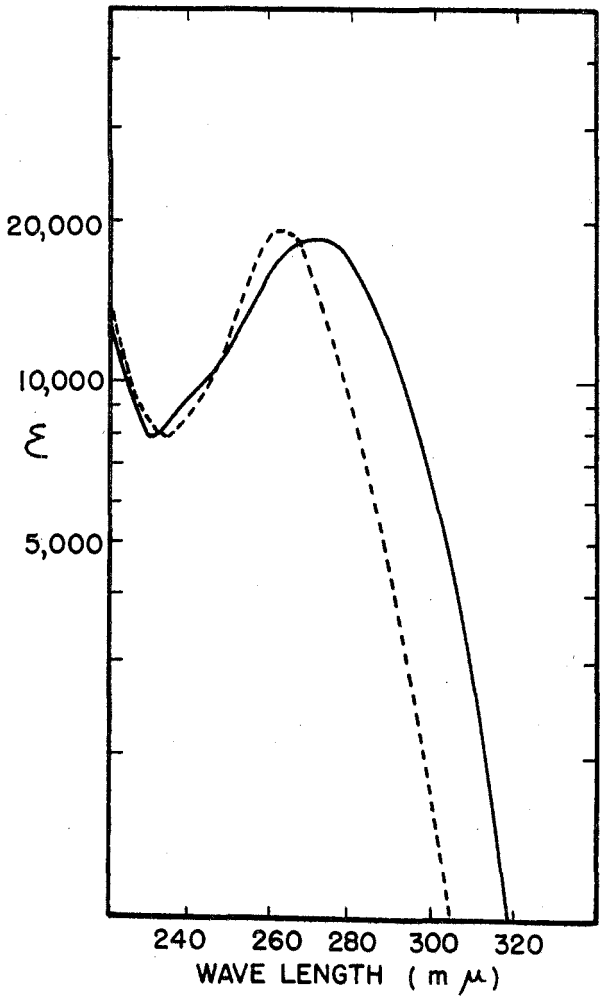
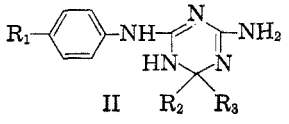


Fig. 1. Ultraviolet absorption spectra in water. ------, 4,6-diamino-1,2-dihydro-1-(*p*-methylthiophenyl)-2-(*n*-propyl)-*s*-triazine hydrochloride (Ic), [$\lambda_{max.}^{H_2O}$ 262 mμ, ε19,200; $\lambda_{min.}^{H_2O}$ 235 mμ, ε8200]; ————, 4-amino-1,2-dihydro-1-(*p*-methylthioanilino)-2-(*n*-propyl)-*s*-triazine hydrochloride (IIc), [$\lambda_{max.}^{H_2O}$ 269 mμ, ε18,600; $\lambda_{min.}^{H_2O}$ 232 mμ, ε8,000].

Syphacea obvelata and *Aspicularis tetraptera* in mice. Further details of the biological activity of the newly prepared dihydrotriazines will appear in subsequent papers.

In the preparation of the *p*-methylthio-2-(*n*-propyl) compound (Ic), the triazine was first isolated as the free base after treatment of the reaction liquid at 5° with excess strong alkali. Since triazines of this type have been shown to isomerize when heated with excess alkali to the corresponding anilino compound II[5] (for IIc, R_1 = CH_3S, R_2 = H, R_3 = n-C_3H_7), it was thought of interest to prepare the isomerized anilino base and hydrochloride for comparison of the properties of Ic and IIc. The isomerization of Ic was done by



II

heating the hydrochloride with a large excess of alkali in water. Ultraviolet absorption data for the hydrochlorides Ic and IIc (Fig. I) show the same type of shift that has been shown in the literature[2,5] for similar compounds. Also, in line with previous work,[5] the pK_a[1] of the anilino dihydrotriazine base is 10.6 while that of the aryl dihydrotriazine base (Ic) is 11.0.

EXPERIMENTAL[12]

4,6-Diamino-1,2-dihydro-2,2-dimethyl-1-(p-methylthiophenyl)-s-triazine hydrochloride (Ia). The preparation of Ia illustrates the general method used for the synthesis of Ia, b, d, and e (hydrochlorides). The method of preparation of the free base was the same for all compounds.

To a warm solution of 29.4 g. (0.211 mole) *p*-methylthioaniline in 300 ml. acetone was added first 17.4 g. (0.207 mole) dicyandiamide, then 18 ml. (0.216 mole) conc. hydrochloric acid. All of the solid dissolved on addition of the acid but 5–10 min. after the beginning of reflux solid began to separate. After about 1 hr. of reflux all solid had again dissolved and after 1.5 hr. of reflux solid began to separate. The reaction mixture was refluxed for a total of 4 hr. after which it was chilled and the product collected. Further details on the yield, purification, and properties of the solid are found in Table I.

To prepare the free base, 1 g. (0.00334 mole) of the pure triazine hydrochloride was dissolved in 10 ml. boiling water. To this solution was added 0.27 ml. (0.00336 mole) of 35% aqueous sodium hydroxide solution and the resulting reaction mixture was immediately chilled. The white solid which separated was collected. None of the free bases required further purification. In each case, reconversion of the base to the hydrochloride with one equivalent of hydrochloric acid gave a solid which, by mixed melting point determination, appeared to be identical with the original hydrochloride. Ultraviolet spectral data (Table II) on the hydrochlorides obtained from the reaction and after reconversion from the base also show the compounds to be the same, thus indicating that rearrangement to the corresponding anilino compound (II) had not occurred.

TABLE II

ULTRAVIOLET SPECTRAL DATA ON ORIGINAL AND RECONVERTED HYDROCHLORIDES

	Original Hydrochloride		Reconverted Hydrochloride	
	$\lambda_{max(m\mu)}^{H_2O}$	ε	$\lambda_{max(m\mu)}^{H_2O}$	ε
Ia	260	20,000	260	19,300
Ib	260	18,500	261	17,833
Ic	260	19,200	261	18,900

4,6-Diamino-1,2-dihydro-1-(p-methylthiophenyl)-2-(n-propyl)-s-triazine hydrochloride (Ic). A mixture of 55 g. (0.212 mole) 1-(*p*-methylthiophenyl)biguanide hydrochloride, 300 g. (4.15 moles) *n*-butyraldehyde, 17.9 ml. (0.215 mole) conc. hydrochloric acid, and 595 ml. water was heated at 50 ± 2° for 4 hr. The two-phase reaction liquid was treated with charcoal and filtered through Filter Cel. After evaporation *in vacuo* to about one half the original volume the residual liquid was treated with charcoal and filtered

(12) The analyses and melting point determinations were performed by the staffs of M. E. Auerbach and K. D. Fleischer of these laboratories. All melting points, unless otherwise specified, are corrected. The ultraviolet absorption spectra were obtained by the staff of F. C. Nachod of these laboratories.

through Filter Cel. To the yellow filtrate was added 550 ml. ether and the mixture was cooled to 5°. On addition of 49.5 ml. (0.62 mole) of 35% aqueous sodium hydroxide solution, yellow solid separated. This was collected, washed with ether, and dried; yield, 41 g. (69.6%), m.p. 136–140° (uncorr.). Thirty-four g. of the crude base was taken up in 170 ml. dilute hydrochloric acid and the resulting liquid was treated with charcoal and filtered through Filter Cel. After cooling the filtrate to 0–5°, conc. ammonium hydroxide was added until the mixture was neutral. The yellow solid was collected and dried. Details on yield, purification, and properties of the solid are found in Table I.

4-Amino-1,2-dihydro-6-(p-methylthioanilino)-2-(n-propyl)-s-triazine. To a warm solution of 8.6 g. (0.0274 mole) 4,6-diamino-1,2-dihydro-1-(*p*-methylthiophenyl)-2-(*n*-propyl)-s-triazine hydrochloride in 86 ml. water was added 11.2 ml. (0.14 mole) 35% aqueous sodium hydroxide. White solid separated immediately which then changed to an oil on further heating. After 1.5 hr. of heating on a steam bath the mixture was cooled to room temperature, whereupon the oil changed to a gum. The supernatant liquid was decanted and the gum was washed once with water. After decantation, as much water as possible was removed *in vacuo*. Absolute ether was added and the mixture was allowed to stand. The powdery white solid which separated was collected and washed with absolute ether; yield 3 g. (39.4%), m.p. 125.8–129.2°.

Anal. Calcd. for $C_{13}H_{19}N_5S$: N, 25.25; S, 11.56. Found: N, 24.93; S, 11.50.

The hydrochloride was formed from the above base by warming 3 g. (0.0108 mole) of the base with 6 ml. (0.121 mole) of 2.02*N* hydrochloric acid in 15 ml. water. After chilling, the hydrochloride separated as a white powder; yield 2.3 g. (67.9%), m.p. 137–141° (uncorr.). Recrystallization from ethanol gave a white powder, m.p. 158.8–161.4°.

Anal. Calcd. for $C_{13}H_{19}N_5S.HCl$: Cl, 11.30; S, 10.22. Found: Cl, 11.50; S, 10.40.

p-Alkylthioanilines. These compounds, used in the preparation of Ia, b, and c, were prepared through a known method[13] using an iron–acetic acid reduction of the appropriate alkyl *p*-nitrophenylsulfide.[14]

1-(p-Methylthiophenyl) biguanide. The biguanide hydrochloride was obtained in 73% yield by the method of Curd[15] who made 1-(*p*-chlorophenyl) biguanide. The crude hydrochloride, a pink solid with m.p. 215–217° (uncorr.), was used to prepare Ic. Treating a hot aqueous solution of the biguanide hydrochloride with an excess of 35% aqueous sodium hydroxide gave crude pink base; yield, 84%, m.p. 147–150° (uncorr.). After two recrystallizations with water-ethanol (20:1) mixtures, the free base was obtained as yellow platelets, m.p. 152.9–154°.

Anal. Calcd. for $C_9H_{13}N_5S$: N, 31.37. Found: N, 31.36.

STERLING-WINTHROP RESEARCH INSTITUTE
RENSSELAER, N. Y.

(13) W. R. Waldron and E. E. Reid, *J. Am. Chem. Soc.*, 45, 2399 (1923).

(14) P. Oxley, M. W. Partridge, T. D. Robson, and W. F. Short, *J. Chem. Soc.*, 763 (1946).

(15) F. H. S. Curd and F. L. Rose, *J. Chem. Soc.*, 362 (1946).

Decyanoethylation of *N,N*-Bis(2-cyanoethyl)amides

L. A. PURSGLOVE*

Received August 25, 1958

The preparation of 3,3′-iminodipropionitrile from ammonia and acrylonitrile,[1–3] and its reaction with acyl halides to form *N,N*-bis(2-cyanoethyl)-amides[4–7] are well known. Some work has been reported on the pyrolytic decyanoethylation of these amides to form β-alanine derivatives, and this route has even been suggested as a possible practical preparative method for β-alanine itself.[8,9] This note deals with a more satisfactory method of decyanoethylation.

Treatment of *N,N*-bis(2-cyanoethyl)amides with bases such as sodium ethoxide and KOH in alcoholic solution leads smoothly to the formation of the corresponding *N*-(2-cyanoethyl)amides at temperatures below 100°, considerably below those necessary for pyrolytic decyanoethylation. A similar reaction was noted in passing by Petersen and Müller with substituted ureas, but the product was not isolated and the yield is unknown.[10]

Both infrared analysis and vapor phase chromatography indicated that 3-ethoxypropionitrile was produced in the decyanoethylation of *N,N*-bis (2-cyanoethyl)benzamide in NaOEt-EtOH, indicating that the alcohol used as solvent forces the reaction to completion by combining with the acrylonitrile formed. The reaction apparently does not proceed in pure benzene.

Further decyanoethylation would lead to a primary amide, which might compete with the ethanol for acrylonitrile, thus explaining why only one mole of acrylonitrile is removed.

Under anhydrous conditions, the reaction proceeds smoothly with *N,N*-bis(2-cyanoethyl)benzamides, acetamides, and benzenesulfonamides. If the reaction is carried out in the presence of water, it leads to an *N*-acyl-β-alanine or to an *N*-(2-carbamoylethyl)amide.

For example, it has recently been shown by Misra and Asthana[11] that alkaline hydrolysis of *p*-chloro-*N,N*-bis(2-cyanoethyl)benzenesulfonamide leads to decyanoethylation and formation of *N*-(*p*-chlorobenzenesulfonyl)-β-alanine. We have found that use of smaller amounts of water leads to formation of *N*-(2-carbamoylethyl)benzamide

(*) Bay City Junior College, Bay City, Mich.

(1) F. C. Whitmore, H. S. Mosher, R. R. Adams, R. B. Taylor, E. C. Chapin, C. Weisel and W. Yanko, *J. Am. Chem. Soc.*, 66, 725 (1944).

(2) O. F. Wiedeman and W. H. Montgomery, *J. Am. Chem. Soc.*, 67, 1994 (1945).

(3) S. R. Buc, *Org. Syntheses*, 27, 3 (1947).

(4) A. N. Kost, *Vestnik Moskov. Univ.*, No. 2, 141 (1947); *Chem. Abstr.*, 42, 3722i.

(5) A. P. Terent'ev, K. I. Chursina, and A. N. Kost, *Zhur. Obshchei Khim.*, 20, 1073 (1950).

(6) H. Feuer and S. M. Pier, *J. Am. Chem. Soc.*, 74, 4706 (1952); 76, 105 (1954).

(7) A. A. Goldberg and W. Kelly, *J. Chem. Soc.*, 1369 (1947).

(8) F. E. Kung, U. S. Patent 2,401,429 (1946).

(9) Saul Chodroff, Roland Kapp, and Charles O. Beckmann, U. S. Patent 2,492,554 (1949); *J. Am. Chem. Soc.*, 69, 256 (1947).

(10) S. Petersen and E. Müller, *Chem. Ber.*, 81, 31 (1948).

(11) G. S. Misra and R. S. Asthana, *J. prakt. Chem.*, [4], 4, 270 (1957).