[Contribution from the Venable Chemical Laboratory of the University of North Carolina and from the Venereal Disease Experimental Laboratory, U. S. Public Health Service]

2-(1-ETHYL-3-GUANIDINO)-4-*p*-CHLOROPHENYLTHIAZOLE

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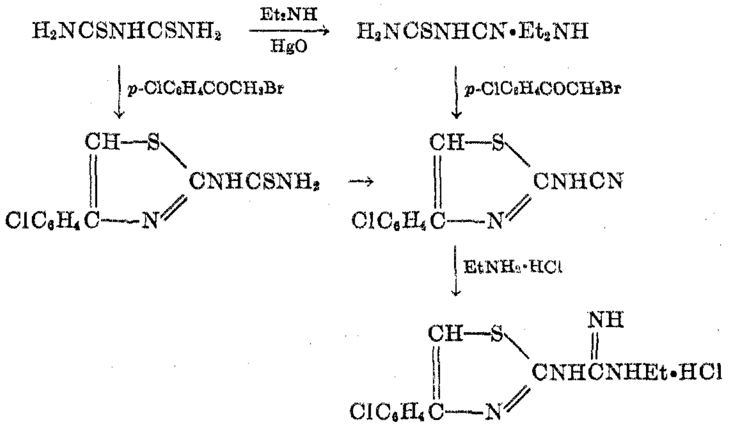
Preliminary encouraging antibacterial properties of certain guanidinoquinazolines (1) have lead to the present investigation of a method for the synthesis of 2-guanidinothiazoles.

It was initially hoped that dithiobiuret might be caused to react with a series of amines to form a series of guanylthioureas which could be readily converted into the desired thiazoles. However, interaction of diethylamine with dithiobiuret in the presence of mercuric oxide formed a compound believed to be the diethylammonium salt of cyanothiourea. This substance reacted smoothly with *p*-chlorophenacyl bromide to form 2-cyanamido-4-*p*-chlorophenylthiazole. The latter was also prepared by the action of lead acetate upon 2-thioureido-4-*p*-chlorophenylthiazole, which was obtained by interaction of *p*-chlorophenacyl bromide and dithiobiuret, according to the procedure of Sperry (2). Upon fusion with ethylammonium chloride, 2-cyanamido-4-*p*-chlorophenylthiazole was converted into *2-(1-ethyl-3-guanidino)-4-p-chlorophenylthiazole* which was isolated as its hydrochloride, a fine white powder, soluble in warm water but quite sparingly soluble in very dilute hydrochloric acid.



A representative portion of the bacterial spectrum of 2-(1-ethyl-3-guanidino)-4-*p*-chlorophenylthiazole is shown below, the figures being the concentrations (micrograms per ml.) required for complete inhibition of growth: *C. diphtheriae-mitis*, 5; *B. subtilis*, *Staph. aureus*, *K. pneumoniae*, and *Myco. ranae*, 19; *P. vulgaris*, *Strep. hemolyticus*, C 203, and *V. comma*, 37; *Myco. tuberculosis*, $H_{37}Rv$, 50; *E. coli*, *S. dysenteriae*, *S. typhosa*, *Ps. fluorescens*, *D. pneumoniae* I and III, and *H. pertussis*, 150.

The *per os* toxicity for mice shows an LD_{50} of about 100 mg./kg.

Plasmodium berghei infection in mice was treated with oral doses of 1.0 mg.

daily for three days and twice on the fourth day. Peripheral blood smears examined on the fifth and seventh days failed to show reduction of malaria parasites when compared with untreated infected mice.

EXPERIMENTAL

2-Amino-4-p-chlorophenylthiazole was prepared from equimolar amounts of *p*-chlorophenacyl bromide and thiourea in methanol. After crystallization from alcohol-water, it appeared as white needles melting at 172–174°. It is sparingly soluble in hot water and in dilute hydrochloric acid.

Anal. Calc'd for $C_9H_7ClN_2S$: C, 51.30; H, 3.35; Cl, 16.83; N, 13.30; S, 15.22.
Found: C, 51.37; H, 3.50; Cl, 16.85; N, 13.11; S, 15.28.

Diethylamine salt of N-cyanothiourea. Dithiobiuret (13.5 g., 0.1 mole) and mercuric oxide (21.6 g., 0.1 mole) were mixed with 300 cc. of methanol. Upon addition of 14.6 g. (0.2 mole) of diethylamine, the mixture immediately darkened and became warm. The mixture was stoppered and shaken for four hours, filtered from mercuric sulfide, and the filtrate was evaporated to dryness *in vacuo*. The residue consisted of 14.5 g. of slightly orange crystalline material melting from 110° to 128°. This was dissolved in 100 cc. of methanol, treated with Norit, and precipitated with 200 cc. of ether to give 12 g. of white crystals melting at 133–138°. Repetition of this process produced 10 g. of white needles whose melting point (137–139°) was not further raised by crystallization. The compound is practically insoluble in ether and acetone and is very soluble in water; the resulting solution is slightly acidic, and on treatment with sodium hydroxide, an immediate ammoniacal odor is produced.

Anal. Calc'd for $C_6H_{14}N_4S$: C, 41.34; H, 8.10; N, 32.15; S, 18.39.
Found: C, 41.42; H, 8.26; N, 31.83; S, 18.55.

2-Thioureido-4-p-chlorophenylthiazole. Dithiobiuret (13.5 g.) in 300 cc. of hot acetone was treated with 21.8 g. of *p*-chlorophenacyl bromide. Although crystallization began almost immediately, the mixture was refluxed for one hour, chilled, filtered, and the crystals thoroughly washed with cold acetone and with ether. The material so obtained weighed 22.5 g.; on heating, it darkened appreciably at about 170° and appeared to melt from about 216° to 231°. A small portion was repeatedly recrystallized from acetone until its melting point behavior was constant. With rather rapid heating, this material darkened at about 215° and melted from 236–243° with gas evolution; upon further heating, it solidified and remelted at 251°.

Anal. Calc'd for $C_{10}H_8ClN_3S_2$: C, 44.51; H, 2.99; Cl, 13.14; N, 15.58; S, 23.77.
Found: C, 44.60; H, 3.12; Cl, 13.16; N, 15.35; S, 23.71.

2-Cyanamido-4-p-chlorophenylthiazole. A. *p*-Chlorophenacyl bromide (2.3 g.) was dissolved in about 5 cc. of methanol and added to 1.7 g. of the diethylamine salt of N-cyanothiourea in 5 cc. of methanol. After warming for ten minutes, 25 cc. of water containing 1 cc. of conc'd hydrochloric acid was added and the mixture was chilled and filtered. The product so obtained was dissolved in hot dilute sodium hydroxide, treated with Norit, and reprecipitated with acid to give 2.5 g. of a white powder melting at 176–178°. A single recrystallization from a mixture of alcohol and acetone afforded 2.3 g. of white needles, melting at 179–181° to a remarkably clear, emerald-green liquid.

Anal. Calc'd for $C_{10}H_6ClN_3S$: C, 50.95; H, 2.57; Cl, 15.04; N, 17.83; S, 13.60.
Found: C, 51.04; H, 2.70; Cl, 14.86; N, 17.75; S, 13.59.

This substance was quite stable to boiling alkali, but on heating 500 mg. in 2 cc. of 50% phosphoric acid for one hour, it was decomposed to give 300 mg. of a substance identical with the above *2-amino-3-p-chlorophenylthiazole*.

B. 2-Thioureido-4-*p*-chlorophenylthiazole (1 g.) was dissolved in a hot solution of 5 g. of sodium hydroxide in 50 cc. of water. To this was added dropwise a solution of 1.5 g. of lead acetate in 50 cc. of water. After boiling the mixture for 30 minutes, it was filtered, acidified, chilled, and filtered and the product washed thoroughly with water. The material so obtained melted at 179–181°, alone and when mixed with the compound prepared by procedure *A*, to the characteristic green liquid.

2-(1-Ethyl-3-guanidino)-4-p-chlorophenylthiazole hydrochloride. 2-Cyanamido-4-*p*-chlorophenylthiazole (4 g.) and 2 g. of ethylammonium chloride were mixed, dried at 100° *in vacuo*, and fused at 150° for 2 hours. At the end of this time, the mass had re-solidified. The melt was leached with 10 cc. of hot alcohol and the resulting solution was made basic (sodium hydroxide), diluted with 100 cc. of hot water, and filtered (from the filtrate, about 500 mg. of the impure cyanamide was obtained). The residue was taken up in boiling, very dilute hydrochloric acid, filtered from a small amount of insoluble material, and precipitated by addition of excess hydrochloric acid. The hydrochloride was dissolved in water, filtered from additional insoluble material, and again precipitated with hydrochloric acid to give 2.4 g. of a white powder, m.p. 249–254°. Recrystallization once from dilute hydrochloric acid and twice from alcohol afforded 1.9 g. of a fine white powder of constant melting point, 254–256°.

Anal. Calc'd for $C_{12}H_{13}ClN_4S \cdot HCl$: C, 45.43; H, 4.45; Cl, 22.35; N, 17.66; S, 10.11.
Found: C, 45.31; H, 4.57; Cl, 22.16; N, 17.36; S, 10.32.

SUMMARY

1. Dithiobiuret reacts with diethylamine in the presence of mercuric oxide to form a compound believed to be the diethylammonium salt of cyanothiourea. This salt reacted with *p*-chlorophenacyl bromide to give 2-cyanamido-4-*p*-chlorophenylthiazole.

2. With ethylammonium chloride, 2-cyanamido-4-*p*-chlorophenylthiazole gave 2-(1-ethyl-3-guanidino)-4-*p*-chlorophenylthiazole.

3. Data on a portion of the bacterial spectrum of the latter compound have been determined.

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REFERENCES

(1) THEILING AND McKEE, *J. Am. Chem. Soc.*, 74, 1834 (1952).
(2) SPERRY, U. S. Patent 2,470,585 (May 17, 1949).