

of 5% acetic acid to yield 2.31 g. of orange micro crystals. This material was recrystallized again from 700 ml. of 5% acetic acid, producing 2.03 g. (64%) of micro needles, m.p. 261–262° dec.

Anal. Calcd. for $C_{15}H_{17}O_2N_4Cl$: C, 48.4; H, 4.3; N, 14.1. Found: C, 48.4; H, 4.5; N, 14.0.

Biological Data.—The microbiological assays were carried out in the usual manner.²² The 6-chloro-7-methyl analog did not support the growth of *L. casei* at levels up to 75 $\mu\text{g.}/10$ ml., nor the 6-methyl-7-chloro analog at levels up to 100 $\mu\text{g.}/10$ ml. To study the inhibition of riboflavin by the analogs culture tubes containing 0.3 $\mu\text{g.}/10$ ml. of riboflavin plus graded amounts of the analogs from 0 to 100 $\mu\text{g.}/10$ ml. were prepared. Acid production was measured

(22) Association of Vitamin Chemists, "Methods of Vitamin Assay," Interscience Publishers, Inc., New York, N. Y., 1951.

by the glass electrode in the 6-chloro-7-methyl analog study and by both glass electrode and titration in the 6-methyl-7-chloro analog study. The inhibition index²³ for 6-chloro-7-methyl-9-(1'-D-ribityl)-isoalloxazine was found to be 85, while the values for 6-methyl-7-chloro-9-(1'-D-ribityl)-isoalloxazine were 22 and 28, respectively, by the two methods of acid measurement.

In studies with the 6-methyl-7-chloro analog the basal medium and flavin solutions were autoclaved separately, then mixed and inoculated, since it was found that the analog undergoes a reversible reduction when autoclaved in the presence of the medium.

(23) Inhibition indices were calculated in both cases from the pH represented by the hydrogen ion concentration at half maximal growth, and in the latter case also from titration values.

ROCHESTER, NEW YORK

[CONTRIBUTION FROM THE CHRIST HOSPITAL INSTITUTE OF MEDICAL RESEARCH]

1-*p*-Chlorophenyl-2,4-diamino-6,6-dimethyl-1,6-dihydro-1,3,5-triazine

BY TI LI LOO¹

RECEIVED FEBRUARY 25, 1954

1-*p*-Chlorophenyl-2,4-diamino-6,6-dimethyl-1,6-dihydro-1,3,5-triazine (I) was prepared by condensation of *p*-chlorophenylbiguanide with acetone in the presence of concentrated hydrochloric acid. In an effort to obtain unequivocal proof of structure, an attempt was made to synthesize the above compound *via* 1-*p*-chlorophenyl-2-methylthio-4-amino-6,6-dimethyl-1,6-dihydro-1,3,5-triazine (V); this failed at the final stage because of unsuccessful aminolysis.

In the course of studies on the metabolic fate of the antimalarial drug chlorguanide (N^1 -*p*-chlorophenyl- N^6 -isopropylbiguanide), Crouse² isolated a crystalline material from the urine of rhesus monkeys receiving this drug. He identified the substance as 2-*p*-chloroanilino-4-amino-6,6-dimethyl-1,6-dihydro-1,3,5-triazine (II) by comparison with the product resulting from condensation of *p*-chlorophenylbiguanide with acetone in glacial acetic acid. The same triazine had been prepared independently by Birtwell, *et al.*,³ using essentially the above procedure.

Subsequently, Carrington and co-workers⁴ isolated from the urine of men and the feces of rabbits given chlorguanide a base which, largely on the basis of X-ray crystallographic studies, was assigned the structure 1-*p*-chlorophenyl-2,4-diamino-6,6-dimethyl-1,6-dihydro-1,3,5-triazine (I). This base was believed to be isomeric with II and was shown to be converted to II during exposure to alkali. Later, work by the present author,^{5,6} and

independent studies of Modest,⁷ showed that replacement of glacial acetic acid by concentrated hydrochloric acid in the Crouse condensation formed a product which appeared on chemical grounds to be identical with I and isomeric with II and which could be converted to II by heating in dilute alkali.^{7c} Studies of antimalarial properties⁸ also indicated that the synthetic product was identical with the "active metabolite" of chlorguanide isolated by Carrington.

With a view to proving unequivocally the structure of the new isomeric compound, designated I, an alternate scheme of synthesis was devised, which, together with the molecular rearrangement of this compound to II, is illustrated in the following diagram. The present investigation, conceived in its entirety independently of Birtwell⁸ whose paper on essentially the same subject appeared at the last stage of this work, is reported hereby as a confirmation of some of his results.

The starting material, *N*-*p*-chlorophenyl- N' -amidinothiourea (III), was prepared by a modified Slotta procedure.^{9,10} This product was caused to active metabolite of chlorguanide reported later by Carrington and co-workers.⁴

(6) L. H. Schmidt, T. L. Loo, R. Fradkin and H. B. Hughes, *Proc. Soc. Exptl. Biol. Med.*, **80**, 367 (1952).

(7) (a) E. J. Modest, G. E. Foley, M. M. Pechet and S. Farber, *THIS JOURNAL*, **74**, 855 (1952); (b) E. J. Modest, Abstract of Papers, Am. Chem. Soc., 122, 9-L (1952); (c) E. J. Modest and H. Kangur, *ibid.*, **124**, 26 (1953).

(8) S. Birtwell, *J. Chem. Soc.*, 1279 (1952).

(9) K. H. Slotta, R. Tschesche and H. Dressler, *Ber.*, **63**, 208 (1930).

(1) Research Division, National Distillers Chemical Co., 1275 Section Rd., Cincinnati 37, Ohio.

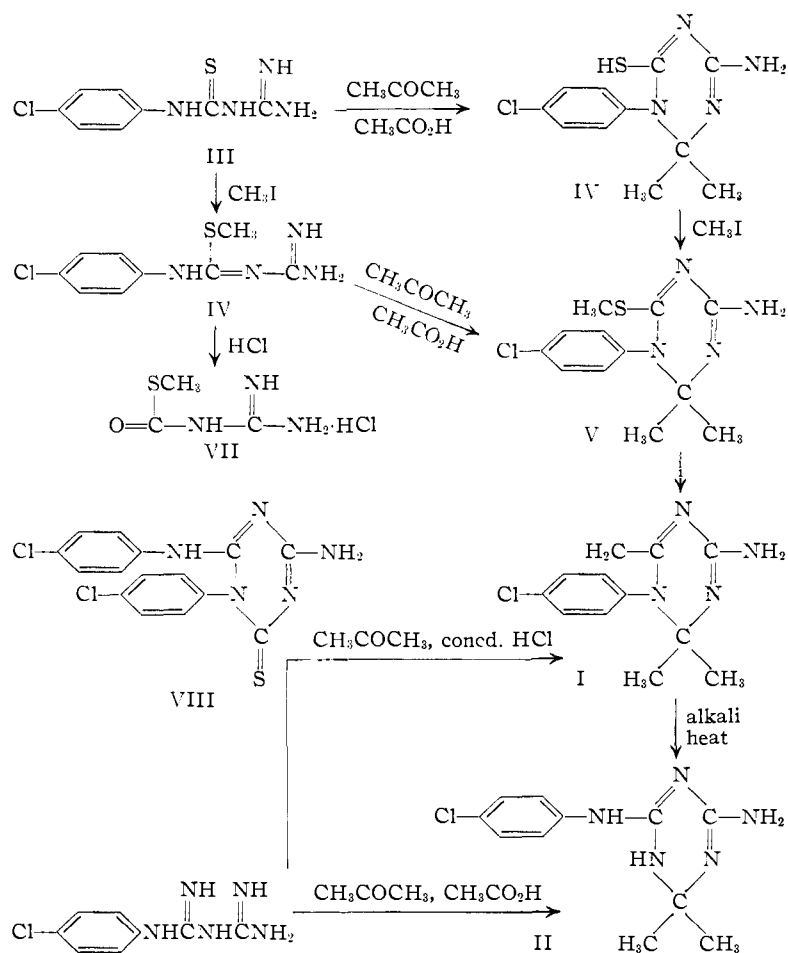
(2) N. N. Crouse, *J. Org. Chem.*, **16**, 492 (1951).

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

(4) (a) H. C. Carrington, A. F. Crowther, D. G. Davey, A. A. Levi and F. L. Rose, *Nature*, **168**, 1080 (1951); the synthesis of I was also reported in very general terms in this communication; (b) A. F. Crowther and A. A. Levi, *Brit. J. Pharmacol.*, **8**, 93 (1953); (c) since the submission of this paper for publication, the excellent and thorough work of the British workers has appeared: H. C. Carrington, A. F. Crowther and G. J. Stacey, *J. Chem. Soc.*, 1017 (1954).

(5) This work grew out of attempts to improve the synthesis of II according to the Crouse method.² During recrystallization of *p*-chlorophenylbiguanide hydrochloride from acetone, a crystalline product altogether different from the starting material was obtained. Its elementary analysis corresponded very well with the monohydrochloride of II, yet it had an utterly different ultraviolet absorption spectrum. However, on warming with dilute alkali, the spectrum changed to that of II. This sequence of reactions, similar to those made available to us in a private communication from Dr. H. C. Carrington, suggested that this new compound might be identical with the

(10) This method also yielded a small quantity of a higher m.p. crystalline material which had the composition $C_{15}H_{13}Cl_2N_4S$. Although its structure has not been established conclusively, the expression 1-*p*-chlorophenyl-2-*p*-chloroanilino-4-amino-6-thio-1,6-dihydro-1,3,5-triazine (VIII) appears to be a reasonable assumption. Its existence may be due to the equimolecular condensation of *N*-*p*-chlorophenyl- N' -amidinothiourea with *p*-chlorophenylisothiocyanate and the elimination of a molecule of hydrogen sulfide. A similar conclusion had been reached earlier by A. F. Crowther, *et al.*, *J. Chem. Soc.*, 1638 (1948), and Birtwell (reference 8).



react with acetone in glacial acetic acid under conditions employed by Crouse.² The resulting 1-*p*-chlorophenyl-2-mercapto-4-amino-6,6-dimethyl-1,6-dihydro-1,3,5-triazine (IV) was converted to the methylthio compound (V) by means of methyl iodide under such mild conditions as to preclude possible N-methylation.

That the methylthio compound was correctly designated by the expression (V)¹¹ received confirmation from the demonstration that the identical compound (isolated as the picrate) resulted from condensation of S-methyl-N-*p*-chlorophenyl-N'-amidinoisothiourea (VI) with acetone in glacial acetic acid. Since in compound VI the sulfur atom was effectively blocked by the methyl group, subsequent ring closure with acetone would most likely involve only N¹ and N⁴, although other possibilities are not absolutely excluded. It was interesting to note that the S-methylisothiourea compound (VI) failed to condense with acetone in the presence of concentrated hydrochloric acid. Instead, cleavage of the molecule took place, and the hydrochloride of a base, $\text{C}_9\text{H}_7\text{N}_3\text{OS}\cdot\text{HCl}$, was obtained. Elementary analysis gave indications that it might possibly be methyl-N-amidinothiocarbamate (hydrochloride) (VII).

Unfortunately, the attempted alternate synthesis

(11) Birtwell (reference 8) assigned the same structure on the basis of more tenuous arguments. He also reported compounds III, IV and VIII with analyses.

leading to I broke down at the final step, namely, the aminolysis of 1-*p*-chlorophenyl-2-methylthio-4-amino-6,6-dimethyl-1,6-dihydro-1,3,5-triazine (V). Because of the hazards of molecular rearrangement of I to II, use of aqueous ammonia had to be avoided. Various conditions were tried, including the use of ammonium chloride and also liquid ammonia, with or without mercuric oxide; in no case was the ultimate goal achieved. Two typical examples are described briefly in the Experimental part.

In distinguishing between structures I and II, infrared absorption spectroscopy proved to be ineffective.¹² However, X-ray crystallographic analysis was reported to have established beyond reasonable doubt that the compound formed by condensation of *p*-chlorophenylbiguanide with acetone in the presence of hydrochloric acid possessed the structure I.⁴ It should be observed upon examination of models that, in structure I, the steric interaction of the two methyl groups would force the *p*-chlorophenyl ring to assume a non-coplanar configuration with respect to the dihydrotriazine ring. As a result, compounds conforming to structure I with the chlorine atom (or any other atom or radical) in positions other than *para*, might theoretically be

asymmetric and therefore resolvable. However, in the case of the *para* compounds, a plane of symmetry clearly exists. Possible resolution of compounds related to I would thus provide additional means of differentiating them from analogs of II. Support for this argument no doubt rests on further work.

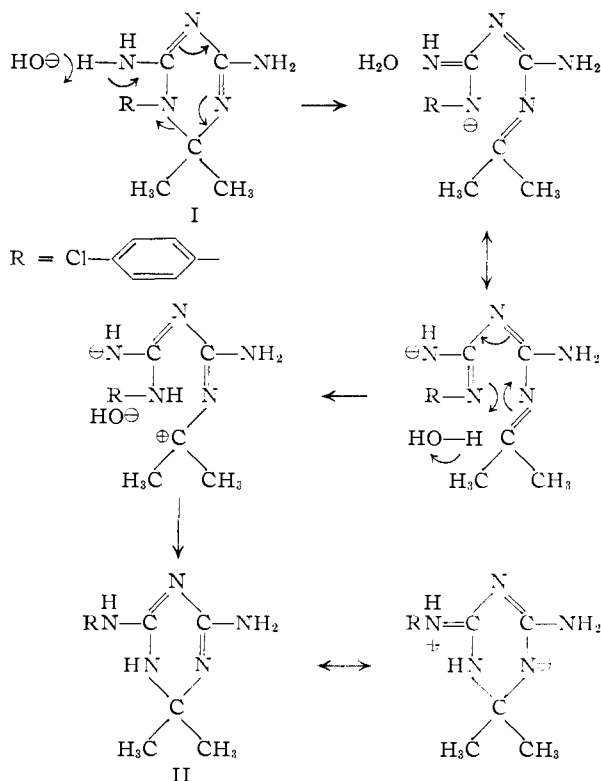
The molecular rearrangement reported first by Carrington, *et al.*,⁴ and confirmed by Dr. Hughes of this Institute, the author and Modest⁷ finds a number of analogies in the literature. For example, Dimroth¹³ described the rearrangement of numerous 1-phenyl-5-amino- and 1-phenyl-5-methylamino-1,2,3-triazoles. Quite recently, Henry and co-workers,^{14a} and Herbst and colleagues^{14b} reported similar rearrangements in the tetrazole series. While the mechanism of the rearrangement of compound I to II has not been studied, it may be speculated that the rearrangement proceeds through the following steps, the hydroxyl ion being the catalyst¹⁵

(12) Personal communication from Dr. R. O. Roblin, Jr., of American Cyanamid Co. to Dr. L. H. Schmidt of this Institute.

(13) O. Dimroth, *Ann.*, **364**, 183 (1909). The author is indebted to Dr. H. C. Carrington for drawing his attention to this paper.

(14) (a) W. G. Finnegan, R. A. Henry and E. Lieber, *J. Org. Chem.*, **18**, 779 (1953); (b) W. L. Garbrecht and R. M. Herbst, *ibid.*, **18**, 1269 (1953), and also later papers.

(15) The author acknowledges the suggestion of this point by one of the referees.



The driving force of such a rearrangement would be the achievement of the coplanarity of the benzene ring with the dihydrotriazine ring, as in structure II in which the conjugation in the former ring could now be extended to part of the latter as shown by one of the mesomeric forms of II. This scheme probably cannot be extended to the rearrangements cited above in other heterocyclic systems¹³⁻¹⁵ in which thermal rearrangement was observed. Future work planned by the author on the kinetics of these rearrangements would be expected to throw more light on the mechanism.

Experimental^{16,17}

1-*p*-Chlorophenyl-2,4-diamino-6,6-dimethyl-1,6-dihydro-1,3,5-triazine (I).—*p*-Chlorophenylbiguanide¹⁸ (anhydrous) (4.3 g.) was dissolved in acetone (10 ml.) to which solution concd. hydrochloric acid (3.7 ml.) was added. The solution was heated under reflux for four hours. On cooling, the colorless crystals which separated were filtered off, washed with acetone, and dried; m.p. 204–208°, yield 4.1 g. or 65%.

Anal. Calcd. for C₁₁H₁₄ClN₅·HCl¹⁹: C, 45.85; H, 5.25; N, 24.32. Found: C, 45.82; H, 5.13; N, 24.12.

Careful neutralization of the hydrochloride with sodium carbonate in the cold, followed by extraction and recrystallization from a copious amount of ether, afforded the free base as colorless crystals, m.p. 145°.

Anal. Calcd. for C₁₁H₁₄ClN₅: C, 52.47; H, 5.61. Found: C, 52.58; H, 5.69.

The picrate was prepared as golden crystals, m.p. 215–

218°,²⁰ and differed entirely from the picrate of the isomer II.²

Anal. Calcd. for C₁₁H₁₄ClN₅·C₆H₃N₃O₇: C, 42.46; H, 3.56; N, 23.30. Found: C, 42.72; H, 3.13; N, 22.68.

The Rearrangement of 1-*p*-Chlorophenyl-2,4-diamino-6,6-dimethyl-1,6-dihydro-1,3,5-triazine (I) into 2-*p*-Chlorophenyl-4-amino-6,6-dimethyl-1,6-dihydro-1,3,5-triazine (II).²¹—The free base (I) described above was heated in sodium hydroxide (2 *N*) at 100° for 20 minutes. The isomeric base was isolated in the usual way as colorless crystalline material, m.p. 132°, differing distinctly from the starting base I in ultraviolet absorption spectrum (see below). In addition, it depressed the m.p. of I very noticeably. On the other hand, it was identical with the Crouse compound II with regard to ultraviolet absorption spectrum and m.p.

Anal. Calcd. for C₁₁H₁₄ClN₅·H₂O: C, 48.98; H, 5.97. Found: C, 48.80; H, 5.59.

The picrate, yellow needles, m.p. 244–245°, was likewise shown to be different from the picrate of compound I, but identical with that of the Crouse compound.²

Anal. Calcd. for C₁₁H₁₄ClN₅·C₆H₃N₃O₇: C, 42.46; H, 3.56; N, 23.30. Found: C, 42.80; H, 3.40; N, 23.11.

The course of the rearrangement could be followed spectroscopically⁶ in the ultraviolet region, for the hydrochloride of compound I showed λ_{max}, 240 mμ (log ε 4.17), as against compound (II), λ_{max}, 255 mμ (log ε 4.23).^{6,7}

Boiling of the Crouse compound (methanolate) in methanol for about one hour yielded its polymorphic form, m.p. 188–190°, identical with the low m.p. form in elementary composition, ultraviolet absorption spectrum, and also in the picrate formed.

***N-p*-Chlorophenyl-*N'*-amidinothiourea (III).**—The procedure of Slotta, *et al.*,⁹ was adopted with modifications. Sodium (0.37 g.) was dissolved in dry acetone²² (20 ml.) with external cooling, followed by the addition of guanidine hydrochloride (1.53 g.) and *p*-chlorophenyl isothiocyanate (2.54 g.). The mixture was stirred²³ vigorously for 15 minutes while cooled by an ice-bath, then for a half-hour at room temperature. The reaction mixture, reddish-brown in color, was immediately poured into ice (about 100 g.). The product, which separated out as colorless crystals, was filtered off, washed with water and recrystallized from methanol; m.p. 192°; yield 2.6 g. or 76%.

On standing, the aqueous alkaline filtrate from which the above was removed gave a small amount of colorless crystalline material which melted at 293° after recrystallization from a large volume of ethanol. The analytical data corresponded very well with formula VIII.

Anal. Calcd. for C₁₃H₁₁Cl₂N₄S: N, 19.03; Cl, 19.55; S, 8.38. Found: N, 19.23; Cl, 19.46; S, 8.80.

1-*p*-Chlorophenyl-2-mercapto-4-amino-6,6-dimethyl-1,6-dihydro-1,3,5-triazine (IV).—*N-p*-chlorophenyl-*N'*-amidinothiourea (2.29 g.) was refluxed with acetone (20 ml.) and glacial acetic acid (30 ml.) in an oil-bath for 24 hours. The solution was poured into ice (100 g.) and made strongly alkaline with concentrated sodium hydroxide (80 ml. of 12.5 *N*). After standing in the ice-bath for 5.5 hours, the solution was filtered. The colorless crystalline product was washed with water and recrystallized from acetone; m.p. 230–231°, yield 0.6 g. The alkaline mother liquor was saturated with sodium chloride and chilled. On standing overnight in the cold, 0.7 g. more of the crystalline product was collected, m.p. 228–230°, making a total yield of 1.3 g., or 49%.

Anal. Calcd. for C₁₁H₁₃ClN₄S: C, 49.14; H, 4.87; N, 20.84. Found: C, 49.53; H, 4.74; N, 20.57.

1-*p*-Chlorophenyl-2-methylthio-4-amino-6,6-dimethyl-1,6-dihydro-1,3,5-triazine (V).—The mercapto compound IV (100 mg.) was refluxed with methyl iodide (3 ml.) for eight hours. The solution was poured into water (about 2 ml.) and the residue washed by a stream of ethanol. The unreacted methyl iodide was removed by evaporation. Ice

(16) All m.p.'s not corrected.

(17) Microanalyses chiefly by the Clark Microanalytical Laboratory, Urbana, Ill.; a few by Dr. Carl Tiedcke of Teaneck, N. J.

(18) The author wishes to thank the American Cyanamid Co. for generous supplies of dicyandiamide used in these experiments.

(19) The hydrated dihydrochloride reported earlier⁶ was prepared in the presence of a large excess of concd. hydrochloric acid. Later, it was found the present procedure yielded the monohydrochloride. Several analogs of I were similarly prepared, and will be reported in another paper.

(20) Carrington, *et al.*,⁴ reported m.p. 206°.

(21) Ultraviolet absorption spectra were determined by Dr. Hettie B. Hughes of this Institute.

(22) Acetone of high grade purity was critical in this preparation. As a rule, Mallinckrodt reagent grade acetone proved to be most satisfactory.

(23) Inefficient stirring tended to give more of the high m.p. (293°) compound.

(about 5 g.) and concentrated sodium hydroxide solution (1 ml. of 12.5 *N*) were added to the aqueous solution. After chilling in the ice-bath, the suspension was filtered, and the colorless crystals collected, washed with water and dried. These melted at 175–178° and weighed 100 mg. (95%).

Anal. Calcd. for C₁₂H₁₅ClN₄S: C, 50.97; H, 5.35. Found: C, 51.16; H, 5.11.

The picrate, yellow shining scales, m.p. 208–210°, was also prepared.

Anal. Calcd. for C₁₂H₁₅ClN₄S·C₆H₃N₃O₇: C, 42.22; H, 3.55. Found: C, 42.77; H, 3.54.

S-Methyl-N-*p*-chlorophenyl-N'-amidinoisothiurea (VI).—*N-p*-chlorophenyl-N'-aminothiurea (1.25 g.) and methyl iodide (2 ml.) were refluxed for eight hours. The product was filtered off and recrystallized twice from an equi-volume solution of benzene in acetone: colorless crystals, m.p. 184°, yield 1.9 g. or 94%.

Anal. Calcd. for C₉H₁₁ClN₄S·HI: C, 29.16; H, 3.26; N, 15.11. Found: C, 29.48; H, 3.41; N, 14.85.

The colorless free base, m.p. 150–152° and the golden yellow picrate, m.p. 181°, were prepared in the usual manner.

Anal. Calcd. for C₉H₁₁ClN₄S: C, 44.52; H, 4.57; N, 23.08. Found: C, 45.00; H, 4.34; N, 22.47.

Calcd. for C₉H₁₁ClN₄S·C₆H₃N₃O₇: C, 38.17; H, 2.99. Found: C, 38.44; H, 3.15.

The Action of Hydrochloric Acid on S-Methyl-N-*p*-chlorophenyl-N'-amidinoisothiurea in Acetone.—The hydriodide of the above described S-methylisothiurea compound (VI) (0.53 g.) was heated with acetone (25 ml.) and concentrated hydrochloric acid (0.5 ml.) under reflux for five hours. The acetone was distilled off and methanol (25 ml.) was added to the red oily residue. The long, colorless needles, that formed on standing, were washed thoroughly with ethereal acetone (10:1) and melted above 300° (ebullience at 210°). The product gave satisfactory analysis for the hydrochloride of the methyl ester of N-amidinothiocarbamate (VII).

Anal. Calcd. for C₈H₇N₃OS·HCl: C, 21.23; H, 4.76; Cl, 20.90; N, 24.77; S, 18.89. Found: C, 21.12; H, 5.31; Cl, 20.93; N, 25.19; S, 18.74.

Condensation of S-Methyl-N-*p*-chlorophenyl-N'-amidinoisothiurea (VI) with Acetone in Glacial Acetic Acid.—The free base VI (0.24 g.) was dissolved in acetone (10 ml.) to

which was added a little glacial acetic acid (1 ml.). After refluxing in the oil-bath for 24 hours, the solution was poured into ice (25 g.) and made strongly alkaline with sodium hydroxide (3 ml. of 12.5 *N*). The oil which separated failed to crystallize despite repeated attempts. The picrate was therefore prepared in the usual way: yellow shining scales, m.p. 208–210°, not depressed by the previously prepared picrate of compound V. Furthermore, both picrates exhibited the same ultraviolet absorption spectra, λ_{max}. 245 mμ (log ε 4.41).

Anal. Calcd. for C₁₂H₁₅ClN₄S·C₆H₃N₃O₇: C, 42.22; H, 3.55; N, 19.17. Found: C, 41.95; H, 3.61; N, 18.88.

Attempted Aminolysis of 1-*p*-Chlorophenyl-2-methylthio-4-amino-6,6-dimethyl-1,6-dihydro-1,3,5-triazine.—(a) The methylthio compound V (100 mg.), ammonium chloride (500 mg.) and yellow mercuric oxide (1 g.) were mixed well with hydrochloric acid (1 ml. of 6 *N*) and ethanol (3 ml.). The paste was stirred at room temperature for 29 hours, then extracted with methanol (15 ml.) and the methanolic extract saturated with hydrogen sulfide. A small amount of mercuric sulfide was filtered off and the filtrate concentrated. The colorless residue, mostly ammonium chloride, was triturated with acetone. A yellow picrate was prepared from the acetone solution, m.p. 255–256°, which, although it had the same elementary composition as the picrate of *p*-chlorophenylguanide (m.p. 235°), depressed the m.p. of an authentic sample of the latter.

Anal. Calcd. for C₇H₉ClN₃·C₆H₃N₃O₇: C, 39.15; H, 2.78. Found: C, 38.76; H, 2.71.

(b) A solution of the methylthio compound V (60 mg.) in methanol (1.5 ml.) was placed in a thick-walled Pyrex glass tube, cooled to –80°, after which liquid ammonia (2 ml.) was introduced. The tube was sealed and held at room temperature for one week, then cooled and opened. The content was washed out with methanol. After the excess ammonia was expelled, a saturated alcoholic solution of picric acid was added to the residual oil. The yellow precipitate was inhomogenous and failed to yield a pure compound.

Acknowledgment.—The author wishes to express his appreciation to Dr. L. H. Schmidt for his interest and encouragement.

CINCINNATI, OHIO

[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

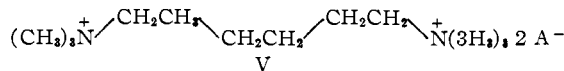
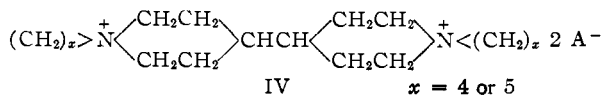
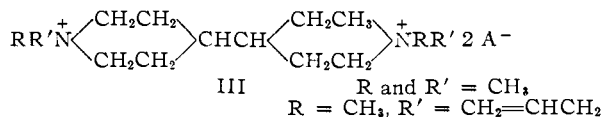
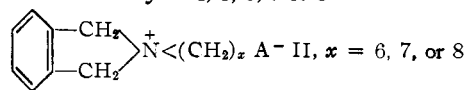
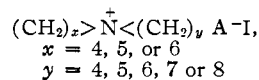
Polycyclic Quaternary Ammonium Salts. III

By F. F. BLICKE AND ERIC B. HOTELLING^{1,2}

RECEIVED APRIL 30, 1954

Polymethylenimines or morpholine were condensed with tetra-, penta- or hexamethylene bromide or *o*-xylylene bromide to obtain bicyclic spiroquaternary and tricyclic spiroquaternary salts. Many of these compounds contain 7-, 8- and 9-membered heterocyclic rings. In addition, quaternary salts of 4,4'-bipiperidine were synthesized. The products were tested for depressor activity.

This paper describes the preparation of bicyclic I and tricyclic II spiroquaternary salts and of some related 4,4'-bipiperidinium salts III, IV. In some instances one of the polymethylenimino groups in compounds of type I was replaced by a methyl-substituted polymethylenimino or a morpholino radical.



Compounds of types III and IV are of special interest because of their analogy with hexamethonium (V).

Salts of type I were obtained by three modifications (A, B and C) of a method described by von

(1) This paper represents part of a dissertation submitted by Eric B. Hotelling in partial fulfillment of the requirements for the Ph.D. degree in the University of Michigan, 1953.

(2) The Wm. S. Merrell Co. Fellow.