(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 $175-178^{\circ}$ and weighed 100 mg. (95%).

Anal. Caled. for C12H16ClN4S: 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. Caled. for C₁₂H₁₅ClN₄S·C₆H₃N₈O₇: C, 42.22; H, 3.55. Found: C, 42.77; H, 3.54.

S-Methyl-N-p-chlorophenyl-N'-amidinoisothiourea (VI). -N-p-chlorophenyl-N'-aminothiourea (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. Caled. 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. 180°, were prepared in the golden yel-low picrate, m.p. 181°, were prepared in the usual manner. Anal. Calcd. for $C_9H_{11}ClN_4S$: C, 44.52; H, 4.57; N, 23.08. Found: C, 45.00; H, 4.34; N, 22.47. Calcd. for $C_9H_{11}ClN_4S$: $C_6H_8N_3O_7$: C, 38.17; H, 2.99. Found: C, 38.44; H, 3.15. The Actions of Hardreeblack Acid on S. Mathel N & Allow

The Action of Hydrochloric Acid on S-Methyl-N-p-chlorophenyl-N'-amidinoisothiourea in Acetone .--- The hydriodide of the above described S-methylisothiourea compound (VI) (0.53 g.) was heated with acetone (25 ml.) and concentrated hydrochloric acid (0.5 ml.) under reflux for five hours. The acctone 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 acctone (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 C₃H₇N₃OS·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'-amidinoisothiourea (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 $m\mu$ (log ϵ 4.41).

Anal. Calcd. for C₁₂H₁₅ClN₄S·C₆H₄N₃O₇: 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-A tempted Animolysis of 1-p-control phenomenon (a) The methylthic 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 pre-pared 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 C₇H₈ClN₈·C₆H₃N₈O₇: C, 39.15; H, 2.78. Found: C, 38.76; H, 2.71.

(b) A solution of the methylthic 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 pictic 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}

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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 9membered 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.

$$(CH_2)_x > \overset{-}{N} < (CH_2)_y A^{-I},$$

$$x = 4, 5, \text{ or } 6$$

$$y = 4, 5, 6, 7 \text{ or } 8$$

$$-CH_2 + \overset{+}{N} < (CH_2)_x A^{-I}, x = 6, 7, \text{ or } 8$$

(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,



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

Braun, et al.,^{3,4} namely, the condensation of a polymethylenimine or morpholine with a polymethylene halide.

For the preparation of the second type of quaternary salt II, we used a method which was employed first by Scholtz,⁵ that is the interaction of *o*-xylylene bromide with a polymethylenimine.

The initial material required for the synthesis of compounds of types III and IV was 4,4'-bipyridyl. The dimethobromide of this base was reduced catalytically to N,N'-dimethyl-4,4'-bipiperidine dihydrobromide. The corresponding base was treated with methyl or allyl bromide to form products of type III.

The dihydrochloride of 4,4'-bipyridyl was reduced catalytically to 4,4'-bipiperidine dihydrochloride. The base of this substance was condensed with a polymethylene bromide to yield compounds of type IV.

The general method of von Braun was used also to prepare N,N',N,N'-diethylenedipyrrolidinium dibromide from piperazine and tetramethylene bromide; this compound has been obtained also by two different methods.6

The products were evaluated in anesthetized dogs for depressor activity in The Wm. S. Merrell Co. laboratories. The material to be tested was administered intravenously and blood pressure changes were recorded from the femoral artery. Compounds of type I were depressors. In general, the maximal response was a 10-15% decrease in blood pressure lasting from 1 to 3 minutes using doses in the 1 to 4 mg./kg. range. In spite of their structural analogy to hexamethonium (V) the compounds of types III and IV were essentially devoid of activity. We were greatly surprised to find that the compounds of type II were potent pressor agents; doses in the 0.1 to 0.5 mg./kg. range were capable of producing an 80 to 115% increase in blood pressure.

Experimental

Each compound found in Table I was prepared by the

(A) N.N-Hexamethylenepyrrolidinium Bromide (Table I, 17).—A mixture of 43.2 g. (0.2 mole) of tetramethylene bromide, 8.0 g. (0.2 mole) of sodium hydroxide and 200 cc. bromide, 8.0 g. (0.2 mole) of sodium hydroxide and 200 cc. of water was stirred and refluxed while 19.8 g. (0.2 mole) of hexamethylenimine⁷ was added, dropwise, during the course of one-half hour. After the mixture had been stirred for an additional one-half hour, a clear yellow solution was obtained. The mixture was cooled in an ice-salt-bath, stirred and 100 cc. of ice-cold 40% aqueous sodium hydroxide solution was added. The precipitated oil was extracted with chloroform. Upon the addition of ether to the extract, the product precipitated in crystalline form; yield 43.8 g. (93%). The material, dissolved in methanol, was treated with charcoal, the solution was filtered and the product was precipitated from the filtrate with ether; m.p. 259-260° dec.

(B) N,N-Heptamethylenepiperidinium Bromide (Table 1, 47).—A mixture of 11.3 g. (0.1 mole) of heptamethylenim-ine,⁷ 23.0 g. (0.1 mole) of pentamethylene bromide, 4.0 g. (0.1 mole) of sodium hydroxide and 100 cc. of water was treated in the manner described above. The oil, which precipitated after the addition of 50 cc. of 40% aqueous

(1954).

sodium hydroxide solution, did not dissolve in the chloroform layer but soon became semi-solid. After filtration through a sintered glass filter, the product was washed with acetone; yield 18.8 g. (72%), m.p. 266–268° dec. after recrystallization from isopropyl alcohol.

(C) N,N-Hexamethylenepyrrolidinium Bromide (Table I, 17).—This method was used in those instances in which a polymethylenimine was condensed with hexamethylene bromide with subsequent cyclization to form a spiro compound which contained a seven-membered ring.

To a stirred mixture of 24.4 g. (0.1 mole) of hexamethylene bromide, 5.0 g. (0.125 mole) of sodium hydroxide and 1 liter of isopropyl alcohol, heated to 60°, there was added during a 2-hour period 7.1 g. (0.1 mole) of pyrrolidine dis-solved in 100 cc. of isopropyl alcohol. The mixture was solved in 100 cc. of isopropyl alcohol. The mixture was maintained at 60° and stirred for 15 hours. The cooled solution was filtered and the filtrate was concentrated to a volume of about 50 cc. The hot solution was filtered and the filtrate was cooled in an ice-bath, whereupon the product precipitated; yield 9.6 g. (41%). After recrystallization from isopropyl alcohol, the product melted at $261-263^{\circ}$ dec., mixed m.p. with a sample prepared by method A, 260-262° dec.

Conversion of Quaternary Bromides into Other Salts.-The quaternary bromides decomposed when treated with aqueous suspensions of silver oxide or silver carbonate. The following successful procedure, illustrated in the case of N,N-hexamethylenepyrrolidinium chloride, was suggested by Dr. M. G. Van Campen, Jr

Alcoholic potassium hydroxide (43.0 cc., 0.995 N) was added to 10.0 g. (0.0429 mole) of N,N-hexamethylenepyrrolidinium bromide dissolved in 50 cc. of absolute The precipitated potassium bromide was removed ethanol. by filtration through a sintered glass filter and the filtrate was concentrated in vacuo to a volume of about 20 cc. After the addition of 50 cc. of dry ether and filtration, the filtrate which contained the quaternary hydroxide was neutralized with ethereal hydrogen chloride. T cipitated chloride weighed 3.0 g., m.p. 266–267° dec. The pre-

From an aqueous solution of the chloride, the chloro-platinate and the chloraurate were prepared in the usual manner. Picrates were obtained by the addition of picric acid to an aqueous solution of the bromides.

 $N-(\gamma-Chloropropyl)$ -pyrrolidine.—This compound was prepared in the hope that it might be cyclized to N,N-trimethylenepyrrolidinium chloride; however, only intractable ma-terial was obtained on attempted cyclization.

A mixture of 119 g. of thionyl chloride and 200 cc. of benzene was refluxed and 129 g. of N- $(\gamma$ -hydroxypropyl)benzene was refluxed and 129 g. of N- $(\gamma$ -nydroxypropu)-pyrrolidine⁸ was added, dropwise. After the mixture had been refluxed for 1 hour, it was cooled, the precipitated hydrochloride was filtered, dissolved in water and the base was precipitated by the addition of sodium hydroxide; b.p. 88–89° (22 mm.). Hydrogen chloride was passed into an ethereal solution of the base; the very hygroscopic hydrochloride, which precipitated, melted at 139–141°.

Anal. Caled. for C7H14NCl·HCl: N, 7.60; Cl⁻, 19.26. Found: N, 7.49; Cl-, 19.26.

The bromides listed in Table II were prepared by procedure C except that only 300 cc. of isopropyl alcohol was used and o-xylvlene bromide was substituted for the polymethylene bromide.

N N', N, N'-Diethylenedipyrrolidinium Dibromide. -- This substance was prepared by procedure B except that piperazine was substituted for the polymethylenimine; yield 24%, m.p. 344-345° dec., mixed m.p. (ref. 6), 342-344° dec.

Anal. Caled. for C12H24N2Br2: Br, 44.88. Found: Br, 44.83.

N,N'-Dimethyl-4,4'-bipiperidine.---4,4'-Bipyridyl dihvdrochloride⁹ was converted into the corresponding dimetho-bromide.¹⁰ The latter substance (15.3 g.), suspended in 75 cc. of acetic acid, was hydrogenated in the presence of 0.7 g. of platinum oxide catalyst under an initial pressure of 45 pounds at 65°. After completed hydrogenation (3

(8) H. G. Kolloff, J. H. Hunter, E. H. Woodruff and R. B. Moffett, ibid., 70, 3862 (1948).

(9) Purchased from Light and Co., Ltd., Bucks, England

(10) B. Emmert and J. Stawitz, Ber., 56, 83 (1923). These investigators did not report a melting point. We found that the product darkened gradually above 340° and did not melt below 360°. A nal. Caled. for C12H14N2Br2: 46.19. Found: Br, 46.29.

⁽³⁾ J. von Braun, C. Müller and E. Beschke, Ber., 39, 4347 (1906).

⁽⁴⁾ J. von Braun, ibid., 49, 966 (1916).

⁽⁵⁾ M. Scholtz, ibid., 24, 2402 (1891); 31, 414 (1898).

⁽⁶⁾ F. F. Blicke and Eric B. Hotelling, THIS JOURNAL, 76, 2422

⁽⁷⁾ F. F. Blicke and N. J. Doorenbos, *ibid.*, 76, 2317 (1954).

TABLE I

BICYCLIC SPIROQUATERNARY SALTS

Analyses, % Found Yield, % x y A⁻ M.p., °C. ^{Vield,} % Formula Calcd. Found Compound 1 was recrystallized from chloroform-ether; 2, 5, 6, 7, 8, 17 and 18 from methanol-ether; 29, 30, 39 and 40 from absolute ethanol; 11, 13, 15, 21, 23, 25, 27, 33, 35, 37, 43, 45, 47, 49, 51, 53, 55, 59 and 61 from isopropyl alcohol; 4, 10, 20, 32, 42 and 57 from water. The chloraurates were triturated with hot water and dried at 25°. The picrates were dissolved in acetone and precipitated with water; when necessary, the mixture was concentrated. + +

| | | | | (a) | N,N-Polymethylene | polymethylenin | ninium S | Salts, $(CH_2)_x > N <$ | $(CH_2)_y A^-$ | |
|----------------|------------------|-------------|----------------|----------------------|------------------------------|-------------------------|----------|---|------------------|---------------|
| 1 | \mathbf{A}^{a} | 4 | 4 | | $\operatorname{Bromide}^{b}$ | $250 - 252^{c,d}$ | 55 | $C_8H_{16}NBr$ | N, 6.80 | N, 6.64 |
| | | | | | , | | | | Br, 38.78 | Br, 38-69 |
| 2 | | 4 | 4 | | Chloride [°] | $277-279^{c,a}$ | | $C_8H_{16}NC1$ | N. 8.65 | N, 8.58 |
| | | | | | | | | | Cl, 21.94 | Cl, 21.94 |
| 3 | | 4 | 4 | | Chloraurate | $254-256^{\circ}$ | | C ₈ H ₁₆ NAuCl ₄ | Au, 42.4 | Au, 42.5 |
| 4 | | 4 | 4 | | Chloroplatinate" | $236-238^{\circ}$ | | $C_{16}H_{32}N_2PtCl_6$ | Pt, 29.5 | Pt, 29.3 |
| $\overline{5}$ | Α | 4 | 5 | | Bromide ^e | $248 - 250^{c,a}$ | 98 | $C_9H_{18}NBr$ | N, 6.36 | N, 6.23 |
| | | | | | | | | | Br, 36.30 | Br, 36.17 |
| 6 | | 4 | 5 | | Chloride | $279-280^{c,d}$ | | C ₉ H ₁₈ NCl | N, 7.97 | N, 7.79 |
| | | | | | | , | | | Cl, 20.18 | C1, 20.06 |
| 7 | | 4 | 5 | | Iodide ^e | $188 - 189^{c,a}$ | | $C_{9}H_{18}NI$ | I, 47.50 | I, 47.31 |
| 8 | | 4 | $\overline{5}$ | | Nitrate | 131–132 ^{e, a} | | $\mathrm{C}_{9}\mathrm{H}_{18}\mathrm{O}_{3}\mathrm{N}_{2}$ | Quat. N 6.93 | Quat. N, 6.83 |
| 9 | | 4 | $\tilde{2}$ | | Chloraurate ^e | $234-235^{\circ}$ | | $C_{9}H_{18}NAuCl_{4}$ | Au, 41.1 | Au, 41.0 |
| 10 | | 4 | 5 | | Chloroplatinate ^e | 221-222° | | $C_{18}H_{36}N_2PtCl_6$ | Pt, 28.3 | Pt, 28.5 |
| 11 | Α | 4 | $\overline{5}$ | (2-CH ₃) | Bromide | $294-295^{c,a}$ | 91 | $C_{10}H_{20}NBr$ | N, 5.98 | N, 5.96 |
| | | | | | | | | | Br, 34.12 | Br, 34.30 |
| 12 | | 4 | 5 | $(2-CH_3)$ | Picrate | 274 - 277 | | $C_{16}H_{22}O_7N_4$ | N, 14 65 | N, 14.58 |
| 13 | В | 4 | 5 | (3-CH ₃) | Bromide | 276 - 277 | 61 | $C_{10}H_{20}NBr$ | N, 5.98 | N, 5.88 |
| | | | | | | | | | Br, 34.12 | Br, 34.27 |
| 14 | | 4 | 5 | (3-CH ₃) | Pierate | 166 - 168 | | $C_{16}H_{22}O_7N_4$ | N, 14.65 | N, 14.67 |
| 15 | А | 4 | 5 | $(4-CH_3)$ | Bromide | 211 - 213 | 50 | $C_{10}H_{20}NBr$ | N, 5.98 | N, 5.85 |
| | | | | | | | | | Br, 34.12 | Br, 34.26 |
| 16 | | 4 | 5 | $(4-CH_3)$ | Picrate | 140 - 142 | | $C_{16}H_{22}O_7N_4$ | N, 14.65 | N, 14.72 |
| 17 | Α | 4 | 6 | | Bromide | $259-260^{\circ}$ | 93 | $C_{10}H_{20}NBr$ | N, 5.98 | N, 5.95 |
| | | | | | | | | | Br, 34.12 | Br, 34.11 |
| 18 | | 4 | 6 | | Chloride | $266-267^{\circ}$ | | $C_{10}H_{20}NCl$ | N, 7.38 | N, 7.30 |
| | | | | | | | | | Cl, 18.69 | Cl, 18.88 |
| 19 | | 4 | 6 | | Chloraurate | Indefin. | | $C_{10}H_{20}NAuCl_4$ | Au, 40.0 | Au, 39.8 |
| 20 | | 4 | 6 | | Chloroplatinate | $245 - 246^{\circ}$ | | $C_{20}H_{40}N_2PtCl_6$ | Pt, 27.2 | Pt, 27.0 |
| 21 | Α | 4 | 6 | $(2-CH_3)$ | Bromide | 209-211 | 93 | $C_{11}H_{22}NBr$ | N, 5.64 | N, 5.59 |
| | | | | | | | | | Br, 32.20 | Br, 32.32 |
| 22 | | 4 | 6 | $(2-CH_3)$ | Picrate | 191 - 194 | | $C_{17}H_{24}O_7N_4$ | N, 14.14 | N, 14.00 |
| 23 | В | 4 | 6 | $(4-CH_3)$ | Bromide | $263-264^{\circ}$ | 42 | $C_{11}H_{22}NBr$ | N, 5.64 | N, 5.54 |
| | | | | | | | | | Br, 32.20 | Br, 32.10 |
| 24 | | 4 | 6 | $(4-CH_3)$ | Picrate | 104-106 | | $\mathrm{C_{17}H_{24}O_7N_4}$ | N, 14.14 | N, 14.26 |
| 25 | в | 4 | 7 | | Bromide | $253-255^{\circ}$ | 62 | $C_{11}H_{22}NBr$ | N, 5.64 | N, 5.64 |
| | | | | | | | | | Br, 32.20 | Br, 32.26 |
| 26 | | 4 | 7 | | Pierate | 154 - 156 | | $C_{17}H_{24}O_7N_4$ | C, 51.51 | C, 51.60 |
| | | | | | | | | | Н, 6.10 | Н, 6.18 |
| | | | | | | | | | N, 14.14 | N, 13.93 |
| 27 | Α | 4 | 8 | | Bromide | 236-238 | 74 | $C_{12}H_{24}NBr$ | N, 5.34 | N, 5.31 |
| | | | | | | | | | Br, 30.48 | Br, 30.58 |
| 28 | | 4 | 8 | | Picrate | 124-126 | | $\mathrm{C_{18}H_{26}O_7N_4}$ | N, 13.65 | N, 13.57 |
| 29 | В | 5 | 5 | | Bromide | $311 - 312^{c,f}$ | 93 | $C_{10}H_{20}MBr$ | N, 5.98 | N, 5.86 |
| | | | | | | | | | Br, 34.12 | Br, 33.92 |
| 30 | | $\tilde{5}$ | 5 | | Chloride | 310 - 311° | | $C_{10}H_{20}NC1$ | N, 7.38 | N, 7.23 |
| | | | | | | | | | Cl, 18.69 | Cl, 18.59 |
| 31 | | 5 | 5 | | Chloraurate | Indefin. | | $C_{10}H_{20}NAuCl_4$ | Au, 40 .0 | Au, 39.7 |
| 32 | | 5 | 5 | | Chloroplatinate | $249-250^{c,j}$ | | $C_{20}H_{40}PtCl_6$ | Pt, 27.2 | Pt, 27.3 |
| 33 | Α | 5 | 5 | $(2-CH_3)$ | Bromide | $248 - 250^{g}$ | 80 | $C_{11}H_{22}NBr$ | N, 5.64 | N, 5.59 |
| | | _ | _ | | | | | | Br, 32.20 | Br, 32-33 |
| 34 | | ā | 5 | $(2-CH_3)$ | Picrate | 227 - 229 | | $C_{17}H_{24}O_7N_4$ | N, 14.14 | N, 13.99 |
| 35 | В | 5 | 5 | (3-CH ₃) | Bromide | $321 - 322^{e}$ | 31 | $C_{11}H_{22}NBr$ | N, 5.64 | N, 5.66 |
| | | _ | - | (0.077.) | T | | | a | Br, 32.20 | Br, 32.22 |
| 36 | T | ð - | 5 | (3-CH₃) | Picrate | 140-141 | ~~~ | $C_{17}H_{24}O_7N_4$ | N, 14.14 | N, 14.03 |
| 37 | в | ð | ð | (4-CH ₃) | Bromide | 313–314° | 83 | $C_{11}H_{22}NBr$ | N, 5.64 | N, 5.56 |
| 0.2 | | _ | - | (1.0**) | T . | 100 100 | | a | Br, 32.20 | Br, 32.39 |
| 38 | | õ | 5 | (4-CH₃) | Picrate | 130 - 132 | | $C_{17}H_{24}O_7N_4$ | N, 14.14 | N, 14.11 |

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| | | | | | | I ABLE I | Continuea | | | |
|----|---|----------------|----------|----------------------|-------------------|-------------------------------|-------------|---|--------------------------------------|-------------------|
| | | x | ν | | A - | М.р., °С. | Yield | Formula | Analyses, Caled. | . % Found |
| 39 | в | 5 | 6 | | Bromide | 277-278° | 81 | C ₁₁ H ₂₂ NBr | N. 5.64 | N. 5.60 |
| | | | | | | | - | - 11 22 | Br. 32,20 | Br, 32.34 |
| 40 | | 5 | 6 | | Chloride | 270-272° | | $C_{11}H_{22}NC1$ | N, 6.87 | N, 6.89 |
| | | | | | | | | | Cl, 17.40 | Cl, 17.48 |
| 41 | | 5 | 6 | | Chloraurate | Indefin. | | $C_{11}H_{22}NAuCl_4$ | Au, 39.9 | Au, 38.8 |
| 42 | | 5 | 6 | | Chloroplatinate | 246–247 ^{c,h} | | $C_{22}H_{44}N_2PtCl_6$ | Pt, 26.2 | Pt, 26.2 |
| 43 | в | $\overline{5}$ | 6 | (2-CH ₃) | Bromide | 215 - 217 | 50 | $C_{12}H_{24}NBr$ | N, 5.34 | N, 5.23 |
| | | _ | | / · | | | | | Br, 30.48 | Br, 30.42 |
| 44 | | 5 | 6 | $(2-CH_3)$ | Picrate | 141-144 | | $C_{18}H_{26}O_7N_4$ | N, 13.65 | N, 13.49 |
| 45 | A | ō | 6 | $(4-CH_3)$ | Bromide | $281 - 282^{\circ}$ | 82 | $C_{12}H_{24}NBr$ | N, 5.34 | N, 5.33 |
| | | ~ | 0 | (1.011) | | 00.00 | | 0.11.0.11 | Br, 30.48 | Br, 30.51 |
| 40 | n | 0 | 6 | $(4-CH_3)$ | Picrate | 88-90 | 50 | $C_{18}H_{26}O_7N_4$ | N, 13.65 | N, 13.46 |
| 47 | в | б | 1 | | Bromide | 266-268° | 72 | $C_{12}H_{24}NBr$ | $N_{1} = \frac{5}{20} \frac{49}{49}$ | N, 5.23 |
| 40 | | | | | T) | 196 190 | | CHON | Br, 30.48 | Br, 30.52 |
| 48 | ٨ | 0 5 | 1 | | Picrate | 130-138 | 05 | $C_{18}H_{26}O_7N_4$ | N, 13.00 | 10, 10.40 |
| 49 | A | 9 | ð | | Bromide | 247-248 | 85 | C13H26NDF | N, 0.07 D= 09.04 | $R_{\pi} = 20.15$ |
| 50 | | 5 | Q | | Diarata | 04-05 | | C.H. O.N. | N = 12, 20.94 | N 13 03 |
| 51 | C | 6 | 0 6 | | Bromide | 9 1 -90 981-989 | 18 | C.H. NB+ | N, 15.20 | N 5 24 |
| 01 | C | U | 0 | | DIOMIGE | 201-202 | 40 | C12112410D1 | $B_r = 30.48$ | Br 30 64 |
| 52 | | 6 | 6 | | Picrate | 147-149 | | CuHa:O-N | N 13 65 | N. 13.62 |
| 53 | С | 6 | 6 | $(4-CH_{2})$ | Bromide | 280-282 | 42 | CuHaeNBr | N. 5.07 | N. 4.9. |
| 00 | ÷ | ~ | 0 | (1 0113) | Diomitae | 100 102 | 1.4 | 013112011201 | Br. 28.94 | Br. 28.80 |
| 54 | | 6 | 6 | (4-CH ₃) | Picrate | 91-93 | | C10H98O7N4 | N. 13.20 | N. 13.21 |
| 55 | С | 6 | 7 | (| Bromide | 276-277° | 24 | C ₁₈ H ₂₆ NBr | N. 5.07 | N. 4.99 |
| | | | | | | | | | Br, 28.94 | Br, 28-88 |
| 56 | | 6 | 7 | | Picrate | 125 - 127 | | C ₁₉ H ₂₈ O ₇ N ₆ | N, 13.20 | N, 13.12 |
| 57 | С | 6 | 8 | | Bromide | $263 - 264^{\circ}$ | 11 | $C_{14}H_{28}NBr$ | C, 57.91 | C, 57.44 |
| | | | | | | | | | н, 9.72 | н, 9.57 |
| | | | | | | | | | Br, 27.54 | N, 4.75 |
| | | | | | | | | | N, 4.83 | Br, 27.48 |
| 58 | | 6 | 8 | | Picrate | 134–135 | | $C_{20}H_{30}O_7N_4$ | N, 12.78 | N, 12.78 |
| | | | | | | | | + CH2- | -CH2 | |
| | | | | (b) N, | N-Polymethylenemo | orpholinium S | Salts, (CH2 | $_{\rm ch_2}$ > N $<$ CH ₂ - | -CH ₂ O A ⁻ | |
| 59 | В | 4 | | | Bromide | 199-201 | 20 | C ₈ H ₁₆ ONBr | N, 6.31 | N, 6.33 |
| | | | | | | | | | Br, 35.98 | Br, 35.87 |
| 60 | | 4 | | | Picrate | 241 - 242 | | $\mathrm{C}_{14}\mathrm{H}_{18}\mathrm{O}_8\mathrm{N}_4$ | N, 15.13 | N, 15.05 |
| 61 | В | 5 | | | Bromide | 235 - 238 | 20 | C ₉ H ₁₈ ONBr | N, 5.93 | N, 5.90 |
| | | | | | | | | | Br, 33.86 | Br, 33.82 |
| 62 | | 5 | | | Pierate | 221 - 223 | | $C_{15}H_{20}O_8N_4$ | N, 14.58 | N, 14.37 |

⁶² ⁵ Picrate ^{221–223} ^C(¹₁⁴)₂₀⁶₈, ^A ^N, ^{14,38} ^N, ^{14,37} ^a Method employed. ^b It was stated (ref. 4) that the chloride, bromide and iodide were very hygroscopic, and they were not analyzed; the chloroplatinate melted at 230°. ^a Melts with decomposition. ^d Hygroscopic. ^e A. Albert [*Ber.*, **42**, 545 (1909)] found the chloride to be very hygroscopic, and it was not analyzed; the chloroplatinate, m.p. 237° dec., was not analyzed; the chloraurate melted at 246° dec. von Braun (ref. 4) stated that the bromide, m.p. 230°, was very hygroscopic and it was not analyzed; the iodide, m.p. 178–180°, was found to be very hygroscopic and it was not analyzed; the chloroplatinate was obtained as a hygroscopic mass; the chloraurate, m.p. 255°, was not analyzed; the chloroplatinate melted at 228°. ^J It was reported (ref. 3) that the bromide did not melt below 250°; the chloroplatinate melted at 245° dec. ^e The corresponding iodide, m.p. 268°, was prepared by A. Müller and E. Rölz, *Ber.*, **61**, 570 (1928). The corresponding iodide was obtained by J. von Braun [*Ber.*, **43**, 2853 (1910)], but the melting point was not mentioned; the chloroplatinate melted at 231° dec. J. von Braun and F. Zobel [*Ber.*, **59**, 1786 (1926)], stated that the hygroscopic bromide melted at 257°. P. van Romburgh and J. H. N. van der Burg [*Proc. Acad. Sci. Amsterdam*, **25**, 335 (1922); *C.A.*, **17**, 1214 (1923)] found that the bromide melted at 290°. ^h The corresponding iodide, according to A. Müller and E. Rölz [*Ber.*, **61**, 570 (1928)] melted at 273°; the chloroplatinate melted at 240–241° dec.

hours) and filtration, the acetic acid was removed by distillation, the residue was dissolved in water and the solution was made strongly alkaline. The solid precipitate was extracted with chloroform, the solvent was removed from the extract and the residue was distilled; b.p. 137-138° (14 mm.),¹¹ m.p. 54-55°, yield 7.3 g. (84%).

The dihydrochloride precipitated when a few drops of concentrated hydrochloric acid was added to an alcoholic solution of the base; m.p. 312-314° dec.

Anal. Calcd. for $C_{12}H_{26}N_2Cl_2$: N, 10.41; Cl, 26.34. Found: N, 10.40; Cl, 26.17.

N,N' - Dimethyl - N,N' - diallyl - 4,4' - bipiperidinium Dibromide (III, R = CH₃, R' = CH₂=:CHCH₂).--Allyl bromide (3.7 g.) was added to 3.0 g. of N,N'-dimethyl-4,4'-bipiperidine dissolved in 20 cc. of methanol. After 24 hours, dry ether was added to the solution, the precipitate (5.1 g., 76%) was dissolved in the minimum amount of water, the solution was treated with charcoal, filtered and the product was precipitated by the addition of isopropyl alcohol and then acetone; yield 3.0 g., m.p. 246-248° dec.

Anal. Calcd. for $C_{18}H_{34}N_2Br_2$: N, 6.39; Br, 36.46. Found: N, 6.36; Br, 36.34.

The dipicrate melted at 253–255° dec.

Anal. Calcd. for C30H38O14N8: N, 15.26. Found: N, 15.18.

⁽¹¹⁾ E. Ochiai and H. Kataoka (J. Pharm. Soc. Japan, **62**, 241 (1942); C.A. **45**, 5150 (1951)), b.p. 105-108° (4 mm.).

Oct. 20, 1954

Tricyclic Spiroquaternary Salts H_2 + H_2 + H_2 + H_2 + H_2 + H_2 + H_2 + H_2 + H_2 + H_2 + H_2 + H_2 + H_2 + H_2 + H_2 + H_2 + H_2 + H_2 + H_2 + H_2 + H_2 + H_2 + H_2 + H_2 + H_2 + H_2 + H_2 + H_2 + H_2 + H_2 + H_2 + H_2 + H_2

TABLE II

Compounds 1, 3 and 5 were precipitated from a concentrated aqueous solution by the addition of isopropyl alcohol and ether. Compounds 2, 4 and 6 were dissolved in acetone and precipitated by the addition of water; when necessary, the solution was concentrated.

| | | | | | | Analyses, % | | |
|----------|---|---------|---------------|----------|----------------------|--------------------|--------------------|--|
| | x | A - | M.p., °C. | Vield, % | Formula | Calcd. | Found | |
| 1 | 6 | Bromide | $240-242^{a}$ | 44 | $C_{14}H_{20}NBr$ | C, 59.57; H, 7.15 | C, 59.33; H, 7.04 | |
| | | | | | | N, 4.96; Br, 28.32 | N, 4.88; Br, 28.56 | |
| 2 | 6 | Picrate | 135 - 137 | | $C_{20}H_{22}O_7N_4$ | N, 13.02 | N, 12.85 | |
| 3 | 7 | Bromide | 208 - 210 | 63 | $C_{15}H_{22}NBr$ | C, 60.80; H, 7.49 | C, 60.55; H, 7.70 | |
| | | | | | | N, 4.73; Br, 26.98 | N, 4.71; Br, 27.18 | |
| 4 | 7 | Picrate | 135 - 137 | | $C_{21}H_{24}O_7N_4$ | N, 12.61 | N, 12.51 | |
| 5 | 8 | Bromide | 204 - 206 | 60 | $C_{16}H_{24}NBr$ | C, 61.93; H, 7.80 | C, 62.20; H, 7.84 | |
| | | | | | | N, 4.51; Br, 25.76 | N, 4.49; Br, 25.82 | |
| 6 | 8 | Picrate | 140 - 142 | | $C_{22}H_{26}O_7N_4$ | N, 12.22 | N, 12.18 | |
| | | | | | | | | |

^a Melts with decomposition.

N,N,N',N'-Tetramethyl-4,4'-bipiperidinium Dibromide (III, R and R' = CH₃).—A solution of 4.0 g. of N,N'dimethyl-4,4'-bipiperidine in 25 cc. of absolute ethanol in a pressure bottle was cooled and 9.5 g. of methyl bromide was added. After 24 hours at room temperature, the precipitate, 7.9 g. (100%) was filtered, dissolved in 25 cc. of water, the solution was treated with charcoal, filtered and the product precipitated with isopropyl alcohol; m.p. above 360°.

Anal. Calcd. for $C_{14}H_{30}N_2Br_2$: N, 7.26; Br, 41.39. Found: N, 7.21; Br, 41.58.

The dipicrate melted at 266–267° dec.

Anal. Caled. for $C_{25}H_{34}O_{14}N_8$: N, 16.42. Found: N, 16.33.

4,4'-Bipiperidine.—This compound was obtained in 78% by hydrogenation of 4,4'-bipyridyl in the presence of platinum oxide.¹²

The dihydrochloride was obtained by the addition of ethereal hydrogen chloride to the base dissolved in methanol; m.p. above 360° .

(12) C. R. Smith, THIS JOURNAL, 50, 1936 (1928).

Anal. Calcd. for $C_{10}H_{22}N_2Cl_2$: N, 11.62; Cl, 29.40. Found: N, 11.58; Cl, 29.26.

N,N - Tetramethylene - N',N' - tetramethylene - 4,4'bipiperidinium Dibromide (IV, x = 4).—This hygroscopic compound was obtained in 48% yield by method B; m.p. 328-329° dec.

Anal. Calcd. for $C_{18}H_{34}N_2Br_2$: N, 6.39; Br, 36.46. Found: N, 6.40; Br, 36.44.

The dipicrate melted at $226-228^{\circ}$.

Anal. Calcd. for $C_{30}H_{38}O_{14}N_8$: N, 15.26. Found: N, 15.09. N,N - Pentamethylene - N',N' - pentamethylene - 4,4'bipiperidinium Dibromide (IV, x = 5).—By the use of method B, the yield of this compound was 40%; m.p. 356-357° dec.

Anal. Calcd. for $C_{20}H_{38}N_2Br_2$: N, 6.01; Br, 34.27. Found: N, 5.88; Br, 34.47.

The dipicrate melted at 264-266°.

Anal. Caled. for $C_{22}H_{42}O_{14}N_8$: N, 14.70. Found: N, 14.65. ANN Arbor, Michigan

[Contribution from the Department of Entomology of the University of California, Citrus Experiment Station, Riverside]

Isomerization of β -Ethylmercaptoethyl Diethyl Thionophosphate (Systox)¹⁻³

BY T. R. FUKUTO AND R. L. METCALF

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The rearrangement of β -ethylmercaptoethyl diethyl thionophosphate to its isomer β -ethylmercaptoethyl diethyl thiophosphate has been investigated using P³²-labeled phosphate and paper chromatography and found to show first-order kinetics. The effect of solvents also has been investigated. Ethyl alcohol markedly increases the isomerization rate, chloroform to a lesser degree, while ethyl acetate, dioxane, methyl ethyl ketone, benzene and 2,2,4-trimethylpentane have little or no effect.

Recent reports^{4,5} show that β -ethylmercaptoethyl diethyl thionophosphate (I, thiono isomer) isomerizes rapidly and cleanly to β -ethylmercaptoethyl di-

(1) Paper No. 811, University of California Citrus Experiment Station, Riverside, Calif.

(2) Supported in part by generous grants from the U. S. Atomic Energy Commission, Contract AT (11-1) 34, Project 6, Dr. F. M. Turrell, Director; and from the Chemagro Corporation, New York, N. Y.

(3) Systox is the trade-name given by the Chemagro Corporation, New York, N. Y., for technical β -ethylmercaptoethyl diethyl thionophosphate.

(4) G. Schrader, "Die Entwicklung neur Insektizide auf Grundlage organischer Fluor und Phosphor-Verbindungen," Monograph No. 62, Angewandte Chemie, 1952.

(5) D. F. Heath, Paper presented to Third International Congress of Crop Protection, Paris, France, Sept., 1952.

ethyl thiophosphate (II, thiol isomer) at elevated temperatures.

$$C_{2}H_{3}O \xrightarrow{P} OCH_{2}CH_{2}SCH_{2}CH_{3} \xrightarrow{130^{\circ}} I$$

$$C_{2}H_{3}O \xrightarrow{P} OCH_{2}CH_{2}SCH_{2}CH_{3} \xrightarrow{130^{\circ}} I$$

$$C_{2}H_{3}O \xrightarrow{P} OCH_{2}CH_{2}SCH_{2}CH_{3$$

Commercial Systox, a powerful systemic insecticide is a mixture of the two isomers. The physical and chemical properties of these isomers differ somewhat, and there are indications that the systemic activity and toxicity depend to a considerable ex-