(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 $C_{12}H_{15}ClN_4S$: 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 $C_{12}H_{15}ClN_4S \cdot C_6H_3N_3O_7$: 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. Calcd. for $C_9H_{11}ClN_4S \cdot HI$: 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 $C_9H_{11}ClN_4S$: C, 44.52; H, 4.57; N, 23.08. Found: C, 45.00; H, 4.34; N, 22.47.

Calcd. for $C_9H_{11}ClN_4S \cdot C_6H_3N_3O_7$: 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′-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 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 $C_3H_7N_3OS \cdot HCl$: 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, $\lambda_{max.}$ 245 mμ (log ε 4.41).

Anal. Calcd. for $C_{12}H_{15}ClN_4S \cdot C_6H_3N_3O_7$: 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 $C_7H_8ClN_3 \cdot C_6H_3N_3O_7$: 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]

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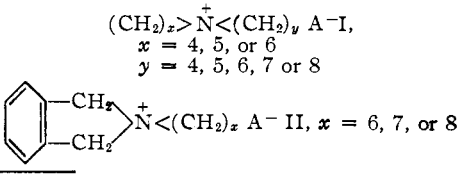
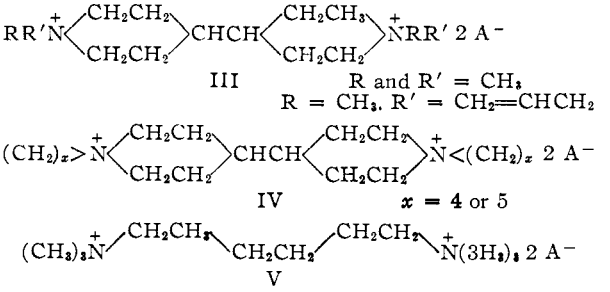
Polymethylenimines or morpholine were condensed with tetra-, penta- or hexamethylene bromide or *o*-xylylene bromide to obtain bicyclic spiroquaternary and tricyclic spiroquaternary salts. Many of these compounds contain 7-, 8- and 9-membered heterocyclic rings. In addition, quaternary salts of 4,4′-bipiperidine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

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 use of the general method A, B or C illustrated below.

(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. of water was stirred and refluxed while 19.8 g. (0.2 mole) of hexamethylenimine[7] 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 I, 47).—A mixture of 11.3 g. (0.1 mole) of heptamethylenimine,[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 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 dissolved 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° 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 ethanol. The precipitated potassium bromide was removed 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. The precipitated chloride weighed 3.0 g., m.p. 266–267° dec.

From an aqueous solution of the chloride, the chloroplatinate 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-(γ-Chloropropyl)-pyrrolidine.—This compound was prepared in the hope that it might be cyclized to N,N-trimethylenepyrrolidinium chloride; however, only intractable material 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-(γ-hydroxypropyl)-pyrrolidine[8] 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. Calcd. for $C_7H_{14}NCl\cdot HCl$: 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*-xylylene 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. Calcd. for $C_{12}H_{24}N_2Br_2$: Br, 44.88. Found: Br, 44.83.

N,N′-Dimethyl-4,4′-bipiperidine.—4,4′-Bipyridyl dihydrochloride[9] was converted into the corresponding dimethobromide.[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

(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 (1954).

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

(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°. *Anal.* Calcd. for $C_{12}H_{14}N_2Br_2$: 46.19. Found: Br, 46.29.

TABLE I

BICYCLIC SPIROQUATERNARY SALTS

		x	y		A^-	M.p., °C.	Yield, %	Formula	Analyses, % 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-Polymethylenepolymethyleniminium Salts, $(CH_2)_x{>}\overset{+}{N}{<}(CH_2)_y\ A^-$										
1	A[a]	4	4		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[b]	277–279[c,d]		$C_8H_{16}NCl$	N, 8.65	N, 8.58
									Cl, 21.94	Cl, 21.94
3		4	4		Chloraurate	254–256[c]		$C_8H_{16}NAuCl_4$	Au, 42.4	Au, 42.5
4		4	4		Chloroplatinate[b]	236–238[c]		$C_{16}H_{32}N_2PtCl_6$	Pt, 29.5	Pt, 29.3
5	A	4	5		Bromide[e]	248–250[c,d]	98	$C_9H_{18}NBr$	N, 6.36	N, 6.23
									Br, 36.30	Br, 36.17
6		4	5		Chloride[e]	279–280[c,d]		$C_9H_{18}NCl$	N, 7.97	N, 7.79
									Cl, 20.18	Cl, 20.06
7		4	5		Iodide[e]	188–189[c,d]		$C_9H_{18}NI$	I, 47.50	I, 47.31
8		4	5		Nitrate	131–132[c,d]		$C_9H_{18}O_3N_2$	Quat. N 6.93	Quat. N, 6.83
9		4	5		Chloraurate[e]	234–235[c]		$C_9H_{18}NAuCl_4$	Au, 41.1	Au, 41.0
10		4	5		Chloroplatinate[e]	221–222[c]		$C_{18}H_{36}N_2PtCl_6$	Pt, 28.3	Pt, 28.5
11	A	4	5	(2-CH_3)	Bromide	294–295[c,d]	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	B	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)	Picrate	166–168		$C_{16}H_{22}O_7N_4$	N, 14.65	N, 14.67
15	A	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	A	4	6		Bromide	259–260[c]	93	$C_{10}H_{20}NBr$	N, 5.98	N, 5.95
									Br, 34.12	Br, 34.11
18		4	6		Chloride	266–267[c]		$C_{10}H_{20}NCl$	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[c]		$C_{20}H_{40}N_2PtCl_6$	Pt, 27.2	Pt, 27.0
21	A	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	B	4	6	(4-CH_3)	Bromide	263–264[c]	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		$C_{17}H_{24}O_7N_4$	N, 14.14	N, 14.26
25	B	4	7		Bromide	253–255[c]	62	$C_{11}H_{22}NBr$	N, 5.64	N, 5.64
									Br, 32.20	Br, 32.26
26		4	7		Picrate	154–156		$C_{17}H_{24}O_7N_4$	C, 51.51	C, 51.60
									H, 6.10	H, 6.18
									N, 14.14	N, 13.93
27	A	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		$C_{18}H_{26}O_7N_4$	N, 13.65	N, 13.57
29	B	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		5	5		Chloride	310–311[c]		$C_{10}H_{20}NCl$	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,f]		$C_{20}H_{40}PtCl_6$	Pt, 27.2	Pt, 27.3
33	A	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		5	5	(2-CH_3)	Picrate	227–229		$C_{17}H_{24}O_7N_4$	N, 14.14	N, 13.99
35	B	5	5	(3-CH_3)	Bromide	321–322[c]	31	$C_{11}H_{22}NBr$	N, 5.64	N, 5.66
									Br, 32.20	Br, 32.22
36		5	5	(3-CH_3)	Picrate	140–141		$C_{17}H_{24}O_7N_4$	N, 14.14	N, 14.03
37	B	5	5	(4-CH_3)	Bromide	313–314[c]	83	$C_{11}H_{22}NBr$	N, 5.64	N, 5.56
									Br, 32.20	Br, 32.39
38		5	5	(4-CH_3)	Picrate	130–132		$C_{17}H_{24}O_7N_4$	N, 14.14	N, 14.11

TABLE I *Continued*

		x	y		A⁻	M.p., °C.	Yield %	Formula	Analyses, % Calcd.	Found
39	B	5	6		Bromide	277–278[c]	81	$C_{11}H_{22}NBr$	N, 5.64	N, 5.60
									Br, 32.20	Br, 32.34
40		5	6		Chloride	270–272[c]		$C_{11}H_{22}NCl$	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	B	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	5	6	(4-CH_3)	Bromide	281–282[c]	82	$C_{12}H_{24}NBr$	N, 5.34	N, 5.33
									Br, 30.48	Br, 30.51
46		5	6	(4-CH_3)	Picrate	88–90		$C_{18}H_{26}O_7N_4$	N, 13.65	N, 13.46
47	B	5	7		Bromide	266–268[c]	72	$C_{12}H_{24}NBr$	N, 5.34	N, 5.23
									Br, 30.48	Br, 30.52
48		5	7		Picrate	136–138		$C_{18}H_{26}O_7N_4$	N, 13.65	N, 13.43
49	A	5	8		Bromide	247–248	85	$C_{13}H_{26}NBr$	N, 5.07	N, 5.08
									Br, 28.94	Br, 29.15
50		5	8		Picrate	94–95		$C_{19}H_{28}O_7N_4$	N, 13.20	N, 13.03
51	C	6	6		Bromide	281–282[c]	48	$C_{12}H_{24}NBr$	N, 5.34	N, 5.24
									Br, 30.48	Br, 30.64
52		6	6		Picrate	147–149		$C_{18}H_{26}O_7N_4$	N, 13.65	N, 13.62
53	C	6	6	(4-CH_3)	Bromide	280–282[c]	42	$C_{13}H_{26}NBr$	N, 5.07	N, 4.99
									Br, 28.94	Br, 28.80
54		6	6	(4-CH_3)	Picrate	91–93		$C_{19}H_{28}O_7N_4$	N, 13.20	N, 13.21
55	C	6	7		Bromide	276–277[c]	24	$C_{13}H_{26}NBr$	N, 5.07	N, 4.99
									Br, 28.94	Br, 28.88
56		6	7		Picrate	125–127		$C_{19}H_{28}O_7N_4$	N, 13.20	N, 13.12
57	C	6	8		Bromide	263–264[c]	11	$C_{14}H_{28}NBr$	C, 57.91	C, 57.44
									H, 9.72	H, 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

(b) N,N-Polymethylenemorpholinium Salts, $(CH_2)_x > \overset{+}{N}\langle CH_2—CH_2 \rangle O \quad A^-$ ($CH_2—CH_2$)

59	B	4			Bromide	199–201	20	$C_8H_{16}ONBr$	N, 6.31	N, 6.33
									Br, 35.98	Br, 35.87
60		4			Picrate	241–242		$C_{14}H_{18}O_8N_4$	N, 15.13	N, 15.05
61	B	5			Bromide	235–238	20	$C_9H_{18}ONBr$	N, 5.93	N, 5.90
									Br, 33.86	Br, 33.82
62		5			Picrate	221–223		$C_{15}H_{20}O_8N_4$	N, 14.58	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°. [c] 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 chloride was obtained as a hygroscopic mass; the chloraurate, m.p. 255°, was not analyzed; the chloroplatinate melted at 228°. [f] It was reported (ref. 3) that the bromide did not melt below 250°; the chloroplatinate melted at 245° dec. [g] 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.

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

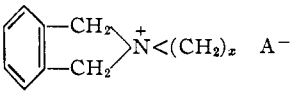
N,N′ - Dimethyl - N,N′ - diallyl - 4,4′ - bipiperidinium Dibromide (III, R = CH_3, R′ = CH_2=$CHCH_2$).—Allyl bromide (3.7 g.) was added to 3.0 g. of N,N′-dimethyl-4,4′-bipiperidine dissolved in 20 cc. of methanol. After 24 hours, dry ether was added to the solution, the precipitate (5.1 g., 76%) was 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 $C_{30}H_{38}O_{14}N_8$: N, 15.26. Found: N, 15.18.

TABLE II

TRICYCLIC SPIROQUATERNARY SALTS 

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.

	x	A⁻	M.p., °C.	Yield, %	Formula	Analyses, % Calcd.	Found
1	6	Bromide	240–242[a]	44	$C_{14}H_{20}NBr$	C, 59.57; H, 7.15 N, 4.96; Br, 28.32	C, 59.33; H, 7.04 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 N, 4.73; Br, 26.98	C, 60.55; H, 7.70 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 N, 4.51; Br, 25.76	C, 62.20; H, 7.84 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' = CH_3).—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. Calcd. for $C_{26}H_{34}O_{14}N_8$: 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°.

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°.

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. Calcd. for $C_{32}H_{42}O_{14}N_8$: N, 14.70. Found: N, 14.65.

ANN ARBOR, MICHIGAN

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

[CONTRIBUTION FROM THE DEPARTMENT OF ENTOMOLOGY OF THE UNIVERSITY OF CALIFORNIA, CITRUS EXPERIMENT STATION, RIVERSIDE]

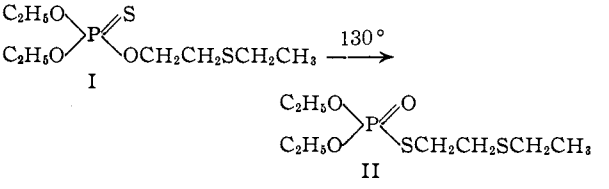
Isomerization of β-Ethylmercaptoethyl Diethyl Thionophosphate (Systox)[1-3]

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

RECEIVED MARCH 20, 1954

The rearrangement of β-ethylmercaptoethyl diethyl thionophosphate to its isomer β-ethylmercaptoethyl diethyl thiophosphate has been investigated using P^{32}-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 diethyl thiophosphate (II, thiol isomer) at elevated temperatures.



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-

(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.