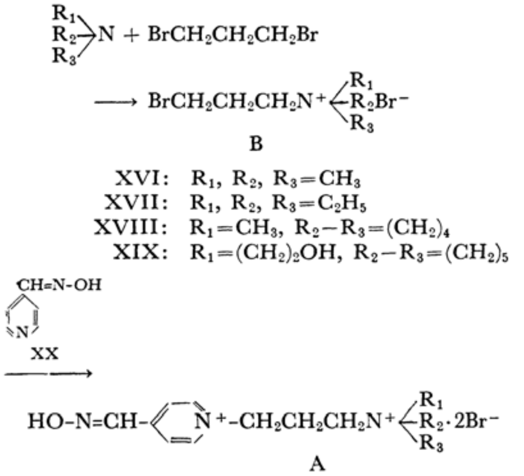
Antidotes for Organophosphate Poisoning. I. Synthesis of 1-(Quaternary ammonium)-3-(hydroxyiminomethylpyridinium)propane Dibromides

Tamio NISHIMURA, Chiji YAMAZAKI and Takako ISHIURA

Department of Chemistry, Kitasato University, Minato-ku, Tokyo

(Received January 16, 1967)

In connection with a study of antidotes in anticholinesterase poisoning,[1] fifteen compounds with the general formula A and four compounds with the general formula B were synthesized according to the following reaction scheme:



$R_1R_2R_3N + BrCH_2CH_2CH_2Br \longrightarrow BrCH_2CH_2CH_2N^+R_1R_2R_3\,Br^-$

B

XVI: $R_1, R_2, R_3=CH_3$

XVII: $R_1, R_2, R_3=C_2H_5$

XVIII: $R_1=CH_3$, $R_2-R_3=(CH_2)_4$

XIX: $R_1=(CH_2)_2OH$, $R_2-R_3=(CH_2)_5$

XX

$HO\text{-}N{=}CH\text{-}C_5H_4N^+\text{-}CH_2CH_2CH_2N^+R_1R_2R_3\cdot 2Br^-$

A

I—XV in Table 1

When *N*-methylmorpholine was allowed to react with 4-hydroxyiminomethyl-*N*-(3-bromopropyl)-pyridinium bromide,[2] the reaction mixture was intensely darked and the attempt to isolate the desired compound failed. Therefore, this alternative route to the A compounds was considered to be inadequate. The B compounds were, in general, difficult to crystallize, and the purification of crude B resulted in the loss of greater part of the material. Therefore, in most of the experiments to obtain A, crude B was prepared in the presence of a large excess of trimethylene bromide in order to prevent the formation of a bis-form compound, and it was used in the next step without further purification. A compounds, in some cases, crystallized out from the reaction mixture on cooling. However, the crystallization was usually very difficult; 1-(*N*-methylpyrrolidinium)-3-(4-hydroxyiminomethylpyridinium)propane dibromide, for instance, crystallized after 6 months. Furthermore, many of these compounds did not show a definite melting point.

The ultraviolet and infrared absorption spectra of the A compounds are shown in Table 1. Compounds I—XV showed an ultraviolet absorption maximum at 281 mμ (ε 16500—18000), different from that of pyridine-4-aldoxime (XX) (249 mμ, ε 14300). The presence of one pyridinium nucleus in the molecule was suggested by the fact that the intensity of the absorption band at 281 mμ was almost the same as that of XX-methiodide (281 mμ, ε 16940) and about half that of trimethylene bis(4-hydroxyiminomethylpyridinium) dibromide (281 mμ, ε 36270), which contains two chromophores in the molecule.

All the compounds, I—XV, exhibited infrared absorption bands at 1637—1647 cm^{-1} due to the C=N stretching vibration of the hydroxyiminomethyl group, at 740—758 cm^{-1} due to the rocking of the CH_2 of the trimethylene group, and at 1420—1441 cm^{-1} due to the deformation vibration of $-CH_2-N^+$. Furthermore, compounds XIII—XV, containing a morpholinium nucleus, showed a strong band at 1119—1129 cm^{-1} due to the antisymmetric stretching vibration of C–O–C.

Experimental[*1]

Materials. The following tertiary amines were prepared according to the methods described in the literature: *N*-Di(2-hydroxyethyl)ethylamine[3] (bp 133—135°C/18—20 mmHg; lit.[4] bp 113—118°C/ 7 mmHg; picrate, mp 98—100°C; lit.[4] mp 100—101°C). *N*-Ethylpiperidine[5] (bp 128—130°C; lit.[6] bp 126—128°C; picrate, mp 166—169°C; lit.[6] mp 168—169°C). *N*-Ethylmorpholine[7] (bp 135—139°C; lit.[7] bp 138—139°C; picrate, mp 186—187°C; lit.[8] mp 189—190°C). The following tertiary amines were prepared by methylating the corresponding secondary amines with formic acid and formaldehyde: Methyldiethylamine (yield, 58%; bp 65—66°C; lit. bp 66°C[9] or 65°C[10]); picrate,

---

[1] T. Nishimura, C. Tamura and Y. Uchida, *Nature*, **214**, 706 (1967).

[2] F. Hobbiger and P. W. Sadler, *Brit. J. Pharmacol.*, **14**, 192 (1959).

[*1] Melting points are uncorrected.

[3] Wm. F. Gresham, U. S. Pat. 2451942; *Chem. Abstr.*, **43**, 2633 (1949).

[4] C. C. Price, A. Pohland and B. H. Velzen, *J. Org. Chem.*, **12**, 315 (1947).

[5] A. Baeyer and V. Villiger, *Ber.*, **34**, 747 (1901).

[6] V. M. Micóvić and M. L. Mihailović, *J. Org. Chem.*, **18**, 1196 (1953).

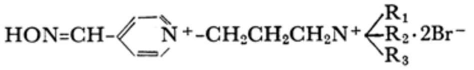
[7] S. Z. Kaplan, N. M. Grad and A. S. Zvontsova, *Zhur. Obshchei. Khim.*, **28**, 3285 (1958); *Chem. Abstr.*, **53**, 14106 (1959).

[8] L. Knorr, *Ann.*, **301**, 16 (1898).

[9] G. Robinson and R. Robinson, *J. Chem. Soc.*, **123**, 539 (1923).

[10] J. v. Braun and E. Anton, *Ber.*, **64**, 2867 (1931).

Table 1.* Ultraviolet and infrared absorption spectra of 1-(quaternary ammonium)-3-(4-hydroxyiminomethylpyridinium)propane dibromides



$HON{=}CH{-}C_5H_4N^+{-}CH_2CH_2CH_2N^+R_1R_2R_3 \cdot 2Br^-$

Compd. No.	R_1	R_2	R_3	UV		IR, cm^{-1}			
				λ_{max} mμ	ε, ×10^4	$\nu_{C=N}$	trimethylene δ CH_2	CH_2N^+ δ CH	ν anti-*O*-
I	CH_3	CH_3	CH_3	281	1.69	1640 (s)	750 (w)	1437 (s)	
II	CH_3	C_2H_5	C_2H_5	281	1.71	1642 (s)	750 (m)	1429 (s)	
III	CH_3	C_2H_4OH	C_2H_4OH	281	1.80	1639 (s)	748 (w)	1430 (w)	
IV	C_2H_5	C_2H_5	C_2H_5	281	1.70	1643 (s)	756 (w)	1432 (s)	
V	C_2H_5	C_2H_5	C_2H_4OH	281	1.70	1643 (s)	753 (w)	1435 (s)	
VI	C_2H_5	C_2H_4OH	C_2H_4OH	281	1.70	1640 (s)	746 (w)	1440 (s)	
VII	CH_3	$(CH_2)_4$		281	1.76	1640 (s)	748 (w)	1431 (s)	
VIII	C_2H_5	$(CH_2)_4$		281	1.78	1641 (s)	753 (w)	1421 (s)	
IX	C_2H_4OH	$(CH_2)_4$		281	1.72	1643 (s)	756 (m)	1431 (s)	
X	CH_3	$(CH_2)_5$		281	1.75	1643 (s)	758 (w)	1435 (s)	
XI	C_2H_5	$(CH_2)_5$		281	1.65	1637 (s)	757 (m)	1420 (s)	
XII	C_2H_4OH	$(CH_2)_5$		281	1.70	1640 (s)	756 (m)	1430 (s)	
XIII	CH_3	$(CH_2)_2O(CH_2)_2$		281	1.79	1647 (s)	740 (w)	1441 (s)	1129 (s)
XIV	C_2H_5	$(CH_2)_2O(CH_2)_2$		281	1.74	1641 (s)	740 (w)	1430 (s)	1130 (s)
XV	C_2H_4OH	$(CH_2)_2O(CH_2)_2$		281	1.79	1639 (s)	742 (w)	1441 (s)	1119 (s)

* The infrared spectra were measured in KBr with a Hitachi recording spectrophotometer, Model EPI-S_2. The ultraviolet spectra were measured in ethanol with a Hitachi recording spectrophotometer, Model EPS-3.

Table 2. 1-Quaternary ammonium-3-bromopropane bromide

Compound No.	Reaction condition		Mp °C	Solvent for recrystallization	Appearance	Yield %
	°C	hr				
XVII	65	3.5	129—132	Acetone/methanol (2 : 1)	Colorless prisms	68
XVIII*	70	2.5	176—178	Acetone/methanol (2 : 1), then abs. ethanol	Colorless prisms	8.2
XIX	Reflux	5	165	Acetone/methanol (2 : 1)	Colorless prisms	15

* Dry benzene was used instead of absolute ethanol.

mp 183—184°C; lit.[11] mp 185°C). *N, N*-Di(2-hydroxyethyl)methylamine (yield, 57%; bp 134—135°C/14 mmHg; lit.[12] bp 141—142°C/18 mmHg; picrate, mp 94—95°C; lit.[13] mp 94—95°C). *N*-Methylpyrrolidine (yield, 60%; bp 78—80°C; lit.[14] bp 78.5—79°C; picrate, mp 218°C (decomp.); lit.[15] mp 218°C). *N*-Methylpiperidine (yield, 63%; bp 106—106.5°C; lit.[16] bp 107°C; picrate, mp 220°C (decomp.); lit.[16] mp 223—224°C). *N*-Methylmorpholine (yield, 63%; bp 115—116°C; lit.[17] bp 115—116°C; picrate, mp 222°C (decomp.); lit.[17] mp 225—226°C). The following tertiary amines were obtained by reacting the corresponding secondary amines with ethylene chlorohydrin in the presence of sodium hydroxide: *N*-(2-Hydroxyethyl)pyrrolidine (yield, 63%; bp 85—86°C/20 mmHg; lit.[18] bp 86—88°C/23 mmHg; picrate, mp 85—87°C (Found: C, 41.91; H, 4.99; N, 16.27%. Calcd for $C_{12}H_{16}O_8N_4$: C, 41.86; H, 4.68; N, 16.28%); lit.[19a] mp 96°C). *N*-(2-Hydroxyethyl)piperidine (yield, 69%; bp 92°C/20 mmHg; lit.[20] bp 89—91°C/20 mmHg; picrate, mp 97—100°C; lit.[19b] mp 100°C). *N*-(2-Hydroxyethyl)morpholine (yield, 69%; bp 120°C/25 mmHg; lit.[21] bp 118—120°C/24 mmHg). *N*-Ethylpyrrolidine was prepared from ethyl bromide and

---

11) C. K. Ingold and E. Rothstein, *J. Chem. Soc.*, **1931**, 1680.

12) F. F. Blicke and F. B. Zienty, *J. Am. Chem. Soc.*, **61**, 772 (1939).

13) L. Knorr and W. Schmidt, *Ber.*, **31**, 1077 (1898).

14) K. Löffler and C. Freytag, *ibid.*, **42**, 3429 (1909).

15) G. Ciamician and A. Piccinini, *ibid.*, **30**, 1791 (1897).

16) Heilbron *et al.*, "Dictionary of Organic Compounds," Vol. 3, Oxford University Press, New York (1953), p. 490.

17) L. Knorr, *Ann.*, **301**, 11 (1898).

18) A. Weickmann, Ger. Pat. 803903; *Chem. Abstr.*, **45**, 8047 (1951).

19) a) J. v. Braun, O. Braunsdorf and K. Räth, *Ber.*, **55**, 1673 (1922); b) *ibid.*, **55**, 1674 (1922).

20) O. A. Barnes and R. Adams, *J. Am. Chem. Soc.*, **49**, 1312 (1927).

21) J. H. Gardner and E. O. Haenni, *ibid.*, **53**, 2765 (1931).

Table 3. 1-(Quaternary ammonium)-3-(4-hydroxyiminomethylpyridinium)propane dibromide

Compound No.	Reaction condition Step 1		Step 2		Mp °C	Solvent for recrystallization	Yield %
	°C	hr	°C	hr			
I	70	4.5	Reflux	3	159—160	Abs. EtOH	33
II	65	6.5	Reflux	4	180—192	Abs. EtOH, then abs. EtOH+MeCO**	15
III	90—97*	6	95	9	141—143	94%EtOH+MeOH**	20
IV***	65	6.5	Reflux	3	223 (decomp.)	Abs. EtOH	22
V	70	7	Reflux	2	215.5 (decomp.)	96%EtOH	28
VI	Reflux	5	Reflux	5	173—174 (decomp.)	95%EtOH	18
VII	70	12	Reflux	4	212 (decomp.)	Abs. EtOH	19
VIII	Reflux	5	Reflux	4	215—216 (decomp.)	Abs. EtOH	14
IX	Reflux	5.5	Reflux	2.5	183—184	99%EtOH	28
X	Reflux	8	Reflux	5	217 (decomp.)	Abs. EtOH	55
XI	Reflux	5	Reflux	4	225 (decomp.)	Abs. EtOH, then MeOH+MeCO**	7.3
XIII	68—71	10	Reflux	8	213 (decomp.)	MeOH	34
XIV	70—75	11	Reflux	4	226—227 (decomp.)	95%EtOH	11
XV	98*	15	94—98	9.5	210—211 (decomp.)	95%EtOH	9.6

* In a sealed glass tube.

** Dissolved in the formed solvent and then the latter solvent added.

*** Berry *et al.*[26] described this substance as a deliquescent gum or solid. Their product was presumably impure.

pyrrolidine (yield, 47%; bp 105—106°C; lit.[22] bp 106°C; picrate, mp 183—183.5°C; lit.[22] mp 185°C). Pyridine-4-aldoxime,[23] its methiodide,[23] and trimethylene bis(4-hydroxyiminomethylpyridinium) dibromide[2,24] were synthesized according to the methods described in the literature.

1-Trimethylammonium-3-bromopropane Bromide[*2] **(XVI).** *(A Typical Example of the General Procedure)*. In a sealed tube were placed 7.8 g of a 23% trimethylamine solution in absolute ethanol (trimethylamine 1.8 g, 30 mmol) and trimethylene bromide (30.3 g, 150 mmol). The mixture was heated at 70°C for 4.5 hr and then evaporated to dryness under reduced pressure to give an almost colorless powder (7.3 g), mp 184°C. Repeated recrystallizations from acetone-methanol (1 : 1) gave 2.6 g (32.6%) of large plates melting at 88—150°C. This material changed to a white powder with a melting point of 205°C (decomp.) when dried at 70°C under reduced pressure. An additional recrystallization from the same solvent and drying raised the melting point to 207°C (decomp.); lit.[25] mp 208°C.

XVII, XVIII and XIX were similarly synthesized (Table 2.)

1-*N*-(2-Hydroxyethyl)piperidinium-3-(4-hydroxyiminomethylpyridinium)propane Dibromide (XII) *(A Typical Example of the General Procedure)*. Crude XIX (6.6 g), obtained as in the preparation of XVI (refluxed for 5 hr) from *N*-(2-hydroxyethyl)piperidine (2.6 g) was dissolved with XX (2.4 g, 20 mmol) in absolute ethanol (10 m*l*). The solution was refluxed for 2 hr, and then evaporated nearly to dryness under reduced pressure to yield a viscous, reddish brown oil, which gradually crystallized on the addition of a small amount of absolute ethanol and acetone. To this acetone (10 m*l*) was added, and the mixture was allowed to stand in a refrigerator for 2 days, giving a hygroscopic, slightly brown, crystalline powder (3.9 g), mp 209°C (decomp.). This was dissolved in boiling ethanol (11 m*l*) and absolute ethanol (8 m*l*), the solution was concentrated to 1/2 volume and then allowed to cool, giving 2.2 g (24%) of pale yellow prisms, mp 208.5—209°C (decomp.).

By a procedure similar to that described above, compounds I—XI and XIII—XV were all obtained as pale yellow prisms, except for VI, XIII, and XIV, which were pale yellow powder (Table 3).

All the new compounds gave satisfactory elemental analyses.

[*2] Lucius[25] obtained this substance as a by-product of preparation of 1, 3-bis(trimethylammonium)propane dibromide.

22) J. v. Braun, *Ber.*, **44**, 1256 (1911).

23) S. Ginsburg and I. B. Wilson, *J. Am. Chem. Soc.*, **79**, 481 (1957).

24) E. J. Poziomek, B. E. Hackley, Jr. and G. M. Steinberg, *J. Org. Chem.*, **23**, 714 (1958).

25) R. Lucius, *Archiv. der Pharmazie*, **245**, 249 (1907).

26) W. K. Berry, D. R. Davis and A. L. Green, *Brit. J. Pharmacol.*, **14**, 186 (1959).