

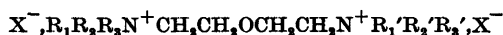
Bifunctional Amines and Ammonium Compounds

IV.* Higher Bis-dialkylamino Ethers and Their Quaternary Ammonium Salts

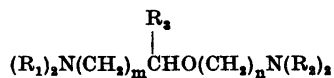
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A previous paper of this series reported the preparation of bis- β -trialkylammoniummethyl ether salts (I), by a Williamson condensation and quaternization, of the bis-*tert.*-amino ether formed, with alkyl halide to give the desired salts.



This paper describes some further quaternary ammoniumalkyl ether salts, which are either homologs of I with respect to length of chain between the two charged N-atoms (II to IV), or analogs in which one or both quaternary nitrogen atoms are part of a heterocyclic nucleus (VII to XII).



II, $R_1 = CH_3,$	$R_2 = C_2H_5,$	$R_3 = H,$	$m = 1,$	$n = 3$
III, $R_1 = C_2H_5,$	$R_2 = C_2H_5,$	$R_3 = H,$	$m = 1,$	$n = 3$
IV, $R_1 = C_2H_5,$	$R_2 = C_2H_5,$	$R_3 = H,$	$m = 2,$	$n = 3$
V, $R_1 = CH_3,$	$R_2 = C_2H_5,$	$R_3 = CH_3,$	$m = 1,$	$n = 2$
VI, $R_1 = CH_3,$	$R_2 = C_2H_5,$	$R_3 = CH_3,$	$m = 1,$	$n = 2$



VII, $A = C_5H_{10}N^{**},$	$B = (CH_2)_2N$
VIII, $A = C_5H_{10}N,$	$B = (C_2H_5)_2N$
IX, $A = C_5H_{10}N,$	$B = C_4H_9N$
X, $A = C_4H_8ON^{***},$	$B = (CH_2)_2N$
XI, $A = C_4H_8ON,$	$B = (C_2H_5)_2N$
XII, $A = C_4H_8ON,$	$B = C_4H_8ON$

* Part III. Acta Chem. Scand. 8 (1954) 346.

** piperidino-, *** morpholino

Twenty-two quaternary salts were obtained from these eleven amino ethers by reaction with methyl iodide and ethyl bromide in conventional fashion.

A report on the pharmacological properties of the salts will appear elsewhere.

EXPERIMENTAL *

The procedure followed for the preparation of ethers was identical to that set forth in the second paper of the series¹. The quaternary compounds were obtained by mixing the appropriate amine with an excess of either methyl iodide or ethyl bromide, dissolved in acetone-ethanol (4 : 1). Generally the ethers with the not too bulky N-substituents reacted readily, while heating in sealed tubes was necessary to ensure complete reaction with the piperidine and morpholine substituted ethers. All yields given are after purification.

2-Dimethylaminoethyl-3-diethylaminopropyl ether (II)

From 32.8 g of 3-diethylaminopropanol (0.25 mole), 5.75 g of sodium, and 36 g of dimethylaminoethyl chloride, HCl (0.25 mole). Solvent toluene, heating period 8 hours. Yield 18 g (36 %), b. p. 104–108° C at 10–12 mm Hg. n_D^{25} 1.4373. $C_{11}H_{21}N_2O$ (202.3): Calc. C 65.33, H 12.96, N 13.85; found C 64.91, H 13.10, N 13.81.

Bis-methiodide (As-8428). Yield 72 %, m. p. 210–212° C (from anhydrous ethanol). $C_{13}H_{23}N_2OI_2$ (486.2): Calc. I 52.21; found 51.74.

Bis-ethobromide (As-8429). Yield 48 %, m. p. 225–228° C (diss. ethanol, reprecip. ether). $C_{15}H_{26}N_2OBr_2$ (420.3): Calc. Br 38.02; found Br 37.63.

2-Diethylaminoethyl-3-diethylaminopropyl ether (III)

From 65.6 g of 3-diethylaminopropanol (0.5 mole), 11.5 g of sodium, and 86.1 g of diethylaminoethyl chloride, HCl (0.5 mole). Solvent toluene, heating period 8 hours. Yield 54 g (47 %), b. p. 124–129° C at 15–16 mm Hg. n_D^{25} 1.4406. $C_{15}H_{26}N_2O$ (230.4): Calc. C 67.78, H 13.12, N 12.16; found C 67.47, H 13.18, N 11.92.

Bis-methiodide (As-8302). Yield 86 %, m. p. 223° C (ethanol-water (80 : 1)). $C_{17}H_{28}N_2OI_2$ (514.3): Calc. I 48.41; found I 49.35.

Bis-ethobromide (As-8303). Yield 90 %, m. p. 225–226° C (diss. ethanol, reprecip. ether). $C_{17}H_{28}N_2OBr_2$ (448.4): Calc. Br 35.64; found Br 35.19.

Bis-3-diethylaminopropyl ether (IV)

From 39.4 g of 3-diethylaminopropanol (0.3 mole), 6.9 g of sodium, and 55.8 g of 3-diethylaminopropyl chloride, HCl (0.3 mole). Solvent benzene, heating period 6 hours. Yield 29 g (40 %), b. p. 144–149° C at 12–14 mm Hg. n_D^{25} 1.4421. $C_{14}H_{28}N_2O$ (244.4): Calc. C 68.82, H 13.20, N 11.47; found C 68.73, H 13.11, N 11.28.

Bis-methiodide (As-8211). Yield 57 %, m. p. 215–216° C (from anhydrous ethanol). $C_{16}H_{28}N_2OI_2$ (528.3): Calc. I 48.05; found I 47.86.

Bis-ethobromide (As-8212). Yield 43 %, m. p. 258–260° C (from anhydrous ethanol). $C_{18}H_{32}N_2OBr_2$ (462.4): Calc. Br 34.56; found Br 34.22.

2-Dimethylaminoethyl-2'-dimethylamino-*iso*-propyl ether (V)

From 44.5 g of 2-dimethylaminoethanol (0.5 mole), 12.5 g of sodium, and 93 g of 2-dimethylamino-*iso*-propyl chloride, HCl (0.5 mole). Solvent toluene, heating period 10

* All melting and boiling points are uncorrected. The nitrogen and halogen values are macro determinations by Mrs. G. Spæggers of this laboratory. Carbon and hydrogen values are micro determinations by Messrs. A. Grossmann and W. Egger, University of Copenhagen.

hours. Yield 40 g (46 %), b. p. 85–88° C at 12–14 mm Hg. n_D^{25} 1.4320. $C_9H_{11}N_2O$ (174.3): Calc. C 62.03, H 12.72, N 16.08; found C 62.65, H 11.95, N 15.54.

Bis-methiodide (As-8670). Yield 72 %, m. p. 280–282° C (from 80 % ethanol). $C_{11}H_{19}N_2OI_2$ (458.2): Calc. I 55.40; found I 55.09.

Bis-ethobromide (As-8671). Yield 92 %, m. p. 248–250° C (washed with acetone). $C_{11}H_{19}N_2OBr_2$ (392.3): Calc. Br 40.74; found Br 40.63.

2-Diethylaminoethyl-2'-dimethylamino-*iso*-propyl ether (VI)

From 58.5 g of diethylaminoethanol (0.5 mole), 12.5 g of sodium, and 93 g of 2-dimethylamino-*iso*-propyl chloride, HCl (0.5 mole + 20 % excess). Solvent toluene, heating time 8 hours. Yield 41 g (41 %), b. p. 103–106° C at 10–12 mm Hg. n_D^{25} 1.4370. $C_{11}H_{21}N_2O$ (202.3): Calc. C 65.33, H 12.96, N 13.85; found C 65.15, H 12.43, N 13.36.

Bis-methiodide (As-8772). Yield 97 %, m. p. 244–246° C (from 80 % ethanol). $C_{13}H_{23}N_2OI_2$ (486.2): Calc. I 52.21; found I 52.15.

Bis-ethobromide (As-8773). Yield 83 %, m. p. 240–242° C (from 90 % ethanol). $C_{13}H_{23}N_2OBr_2$ (420.3): Calc. Br 38.02; found Br 38.12.

Bis-(2-dimethylamino-2'-piperidino)-ethyl ether (VII)

From 12.9 g of 2-piperidinoethanol (0.1 mole), 2.3 g of sodium, and 14.4 g of 2-dimethylaminoethyl chloride, HCl (0.1 mole). Solvent toluene, heating period 8 hours. Yield 7 g (35 %), b. p. 125–128° C at 12 mm Hg. n_D^{25} 1.4599. $C_{11}H_{24}N_2O$ (200.3): Calc. C 65.98, H 12.08, N 13.99; found C 65.67, H 11.77, N 13.63.

Bis-methiodide (As-10793). Yield 87 %, m. p. 268–270° C (washed with acetone). $C_{13}H_{26}N_2OI_2$ (484.2): Calc. I 52.42; found I 52.59.

Bis-ethobromide (As-10794). Yield 72 %, m. p. 255–258° C (diss. ethanol, reprecip. ether). $C_{13}H_{26}N_2OBr_2$ (418.3): Calc. Br 38.21; found Br 38.88.

Bis-(2-diethylamino-2'-piperidino)-ethyl ether (VIII)

From 27 g of 2-piperidinoethanol (0.21 mole), 4.8 g of sodium, and 35.9 g of 2-diethylaminoethyl chloride, HCl (0.21 mole). Solvent toluene, heating period 20 hours. Yield 24 g (50 %), b. p. 145–148° C at 12–14 mm Hg. n_D^{25} 1.4608. $C_{13}H_{28}N_2O$ (228.4): Calc. C 68.38, H 12.36, N 12.27; found C 68.44, H 12.50, N 11.94.

Bis-methiodide (As-8986). Yield 92 %, m. p. 260–262° C (from 80 % ethanol). $C_{15}H_{34}N_2OI_2$ (512.3): Calc. I 49.55; found I 48.76.

Bis-ethobromide (As-8987). Yield 95 %, m. p. 226–227° C (from 96 % ethanol). $C_{17}H_{38}N_2OBr_2$ (446.4): Calc. Br 35.80; found Br 35.20.

Bis-2-piperidinoethyl ether (IX)

From 14.75 g of piperidinoethanol (0.114 mole), 2.62 g of sodium, and 21.0 g of piperidinoethyl chloride, HCl (0.114 mole). Solvent toluene, heating period 16 hours. Yield 9 g (33 %), b. p. 168–170° C at 12–14 mm Hg. n_D^{25} 1.4801. $C_{14}H_{28}N_2O$ (240.4): Calc. C 69.97, H 11.74, N 11.65; found C 69.12, H 11.92, N 11.31.

Bis-methiodide (As-10800). Yield 86 %, m. p. 248–251° C (from 80 % ethanol). $C_{16}H_{34}N_2OI_2$ (524.3): Calc. I 48.40; found I 48.59.

Bis-ethobromide (As-10801). Yield 55 %, m. p. 205–207° C (from 95 % ethanol). $C_{18}H_{40}N_2OBr_2$ (458.4): Calc. Br 34.87; found Br 34.21.

Bis-(2-dimethylamino-2'-morpholino)-ethyl ether (X)

From 32.8 g of hydroxyethyl morpholine (0.25 mole), 5.75 g of sodium, and 36 g of dimethylaminoethyl chloride, HCl (0.25 mole). Solvent toluene, heating period 8 hours. Yield 23 g (46 %), b. p. 125–130° C at 10–12 mm Hg. n_D^{25} 1.4596. $C_{10}H_{22}N_2O_2$ (202.3): Calc. C 59.37, H 10.96, N 13.85; found C 59.46, H 10.67, N 13.47.

Bis-methiodide (As-8026). Yield 56 %, m. p. 275–276° C (from 75 % ethanol). $C_{13}H_{22}N_2O_2I_2$ (486.2): Calc. I 52.21; found I 52.10.

Bis-ethobromide (As-8027). Yield 95 %, m. p. 256° C (from anhydrous ethanol). $C_{14}H_{22}N_2O_2Br_2$ (420.3): Calc. Br 38.02; found Br 38.30.

Bis-(2-diethylamino-2'-morpholino)-ethyl ether (XI)

From 65.6 g of hydroxyethyl morpholine (0.5 mole), 11.5 g of sodium, and 86.1 g of diethylaminoethyl chloride, HCl (0.5 mole). Solvent toluene, heating period 10 hours. Yield 72.5 g (63 %), b. p. 146–148° C at 12 mm Hg. n_D^{25} 1.4600. $C_{13}H_{24}N_2O_2$ (230.3): Calc. C 62.59, H 11.38, N 12.16; found C 62.52, H 11.14, N 11.78.

Bis-methiodide (As-8101). Yield 96 %, m. p. 260–262° C (from 80 % ethanol). $C_{14}H_{22}N_2O_2I_2$ (514.1): Calc. I 49.36; found I 48.70.

Bis-ethobromide (As-8102). Yield 45 %, m. p. 216° C (from anhydrous ethanol). $C_{15}H_{26}N_2O_2Br_2$ (448.3): Calc. Br 35.64; found Br 34.98.

Bis-2-morpholinoethyl ether (XII)

From 19.3 g of hydroxyethyl morpholine (0.15 mole), 3.4 g of sodium, and 27.5 g of morpholinoethyl chloride, HCl (0.15 mole). Solvent toluene, heating period 8 hours. Yield 13 g (36 %), b. p. 188–192° C at 15 mm Hg. (Ref.² 178.0–180.5° at 7 mm), n_D^{25} 1.4772. $C_{12}H_{24}O_2N_2$ (244.3): Calc. C 59.00, H 9.90, N 11.47; found C 59.02, H 9.91, N 10.99.

Bis-methiodide (As-7909). Yield 61 %, m. p. 252–253° C (from 75 % ethanol). $C_{14}H_{20}N_2I_2$ (528.2): Calc. I 48.05; found I 47.70.

Bis-ethobromide (As-7910). Yield 37 %, m. p. 223–225° C (diss. ethanol, reprecip. ether). $C_{15}H_{24}O_2N_2Br_2$ (462.3): Calc. Br 34.57; found 34.33.

SUMMARY

Eleven bis-alkylaminoalkyl ethers, having ethyl-, methyl-, morpholino-, and piperidino-groups as N-substituents, and containing ethyl, *n*-propyl, and *iso*-propyl in the alkylene chain, together with the twenty-two corresponding methiodides and ethobromides are described.

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