ACTA CHEMICA SCANDINAVICA 11 (1957) 1698—1705

# Bifunctional Amines and Ammonium Compounds

## VI.* Further Homologs and Analogs of bis-Choline Ether Salts

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As an extension of earlier work twelve aliphatic bis-alkylammonium alkyl ethers, representing different chain-lengths, distribution and size of N-substituents, and chain branching, are reported together with twenty-four quaternary salts. Six aromatic ethers are reported along with eight bis-quaternary and three mono-quaternary salts derived therefrom. Transformation to non-halide salts is discussed. Alkylation of bis-(2-dimethyl-2'-diethyl)-aminoethyl ether with various alkyl halides gave ten different quaternary salts, which are reported.

In the current investigations on the relation of structure to pharmacological activity in an extended series of bis-ammonium salts, the need arose for salts representing further extensions on the structural theme exemplified by bis-choline ether. A number of such variations have been reported earlier from this laboratory [1-4].

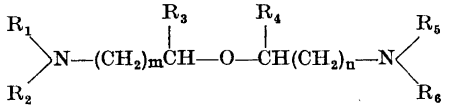
The present paper reports twelve additional bis-tertiary aliphatic ethers, representing variations in chain-length, degree of asymmetry, size of N-substituents and chain-branching (Table 1). These ethers were obtained essentially as described earlier [1]. They were prepared, in most cases, from known aminoalcohols or aminoalkylhalides, respectively.

This paper further presents six bis-tertiary ethers having an aromatic ring system in the chain (Table 2). The bis-tertiary ethers have been transferred to their corresponding methiodides and ethobromides or ethiodides, respectively. The twenty-four salts corresponding to the aromatic ethers are shown in Table 4. The quaternary salts were obtained by conventional procedures.

The substituted choline phenyl ethers are formed with considerable difficulty, and in several cases only the mono-quaternary salt (retaining the tertiary amino group on the aromatic ring) was obtained. Three such mono-quaternary salts are shown in Table 5.

* Part V. *Acta Chem. Scand.* 10 (1956) 15.

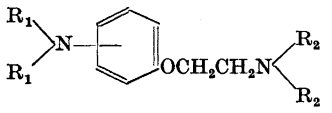
*Table 1.*



| Code No. | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | $R_6$ | m | n | B.p. °C | Press. mm Hg | Yield % | Emp. formula | M | Analysis, % Calc. C | Calc. H | Calc. others | Found C | Found H | Found others |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Asa- 85 | $CH_3$ | $CH_3$ | $CH_3$ | $CH_3$ | $CH_3$ | $CH_3$ | 1 | 1 | 82—85 | 12 | 37 | $C_{10}H_{24}N_2O$ | 188.31 | 63.78 | 12.85 | N 14.88 | 63.04 | 12.21 | N 14.13 |
| Asa-120 | $CH_3$ | $C_2H_5$ | H | H | $CH_3$ | $CH_3$ | 1 | 1 | 81—82 | 8 | 64 | $C_9H_{22}N_2O$ | 174.28 | 62.02 | 12.72 | N 16.08 | 60.55 | 12.64 | N 14.87 |
| | | | | | | | | | | | | | | | | | | | E 99.8 a) |
| Asa-121 | $CH_3$ | $C_2H_5$ | H | H | $C_2H_5$ | $C_2H_5$ | 1 | 1 | 103 | 8 | 12 | $C_{11}H_{26}N_2O$ | 202.33 | 65.29 | 12.95 | N 13.85 | 64.35 | 12.45 | N 12.29 |
| | | | | | | | | | | | | | | | | | | | E 100.3 |
| Asa-122 | $C_4H_8$ b) | | H | H | $CH_3$ | $CH_3$ | 1 | 1 | 121—124 | 25 | 40 | $C_{10}H_{22}N_2O$ | 186.29 | 64.47 | 11.90 | N 15.04 | 64.33 | 11.97 | N 14.68 |
| Asa-123 | $C_4H_8$ | | H | H | $C_2H_5$ | $C_2H_5$ | 1 | 1 | 140—144 | 25 | 30 | $C_{12}H_{26}N_2O$ | 214.34 | 67.24 | 12.23 | N 13.07 | 67.01 | 12.22 | N 12.70 |
| Asa-124 | $C_4H_8$ | | H | H | $C_4H_8$ | | 1 | 1 | 150—151 | 15 | 22 | $C_{12}H_{24}N_2O$ | 212.33 | 67.88 | 11.39 | N 13.19 | 67.90 | 11.32 | E 100.6 |
| Asa-135 | $C_2H_5$ | $n$-$C_3H_7$ | H | H | $CH_3$ | $HC_3$ | 1 | 1 | 106—110 | 12 | 12.3 | $C_{11}H_{26}N_2O$ | 202.33 | 65.29 | 12.95 | N 13.85 | — | — | E 97.3 |
| Asa-136 | $C_2H_5$ | $n$-$C_4H_9$ | H | H | $CH_3$ | $CH_3$ | 1 | 1 | 115—118 | 13 | 11.5 | $C_{12}H_{28}N_2O$ | 216.36 | 66.61 | 13.04 | N 12.95 | — | — | E 98.6 |
| Asa-165 | $CH_3$ | $CH_3$ | H | H | $CH_3$ | $CH_3$ | 1 | 2 | 89 | 18 | 55 | $C_9H_{22}N_2O$ | 174.28 | 62.02 | 12.72 | N 16.08 | 61.70 | 12.82 | E 98.2 |
| Asa-166 | $C_2H_5$ | $C_2H_5$ | H | H | $CH_3$ | $CH_3$ | 1 | 2 | 110—111 | 17 | 59 | $C_{11}H_{26}N_2O$ | 202.33 | 65.29 | 12.95 | N 13.85 | 64.70 | 12.54 | E 99.4 |
| Asa-167 | $CH_3$ | $CH_3$ | H | H | $CH_3$ | $CH_3$ | 2 | 2 | 115—120 | 25—30 | 42.1 | $C_{10}H_{24}N_2O$ | 188.31 | 63.78 | 12.85 | N 14.89 | 63.79 | 12.91 | N 14.49 |
| Asa-178 | $CH_3$ | $CH_3$ | H | H | $C_2H_5$ | $C_2H_5$ | 2 | 2 | 95 | 2 | 37.9 | $C_{12}H_{28}N_2O$ | 216.36 | 66.61 | 13.04 | N 12.95 | 66.40 | 12.83 | N 12.95 |

a) E: Percent base by perchloric acid titration.
b) pyrrolidino.

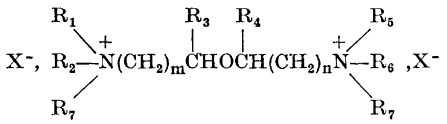
*Table 2.*



| Code No. | $R_1$ | $R_2$ | Position | B.p. °C | Press. mm Hg | Yield % | Emp. formula | M | Analysis, % Calc. C | Calc. H | Calc. others | Found C | Found H | Found others |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Asa-129 | $C_2H_5$ | $CH_3$ a) | *m* | 155 | 2 | 69.9 | $C_{14}H_{24}N_2O$ | 236.35 | 71.14 | 10.24 | N 11.85 | 71.14 | 10.13 | N 11.26 |
| Asa-130 | $C_2H_5$ | $C_2H_5$ b) | *m* | 158 | 2.5 | 62.1 | $C_{16}H_{28}N_2O$ | 264.40 | 72.68 | 10.66 | N 10.60 | 72.21 | 10.27 | N 10.61 |
| Asa-133 | $CH_3$ | $C_2H_5$ | *p* | 140 | 2 | 42.1 | $C_{14}H_{24}N_2O$ | 236.35 | 71.14 | 10.24 | N 11.85 | — | — | N 11.89 |
| Asa-134 | $CH_3$ | $CH_3$ | *p* | 169—73 | 18 | 48.9 | $C_{12}H_{20}N_2O$ | 208.30 | 69.19 | 9.68 | N 13.45 | — | — | N 12.35 |
| Asa-142 | $CH_3$ | $CH_3$ | *m* | 178—80 | 20 | 70 | $C_{12}H_{20}N_2O$ | 208.30 | 69.19 | 9.68 | N 13.45 | 69.35 | 9.63 | N 11.35 |
| | | | | | | | | | | | | | | E 96.7 |
| Asa-143 | $CH_3$ | $C_2H_5$ | *m* | 185—86 | 18 | 32 | $C_{14}H_{24}N_2O$ | 236.35 | 71.14 | 10.24 | N 11.85 | 70.90 | 10.22 | N 9.93 |
| | | | | | | | | | | | | | | E 99.65 |

a) bis-HCl(As-12935), m.p. 184°C. Found Cl 23.01; calc. for $C_{14}H_{26}N_2OCl_2$ (309.28) Cl 22.93
b) bis-HCl(As-13036), m.p. 187°C. Found Cl 21.32; calc. for $C_{16}H_{30}N_2OCl_2$ (337.33) Cl 21.02.

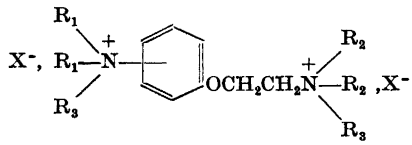
*Table 3*



| Code No. | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | $R_6$ | $R_7$ | $X^-$ | m | n | M.p. °C | Crystall. from [a] | Yield % | Emp. formula | M | Analysis, % Calc. | | Found | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| As-8558 | $CH_3$ | $CH_3$ | $CH_3$ | $CH_3$ | $CH_3$ | $CH_3$ | $CH_3$ | I | 1 | 1 | 128—130 | dil. A | 84 | $C_{12}H_{30}N_2OI_2$ | 472.21 | I | 53.76 | I | 52.10 |
| As-8559 | $CH_3$ | $CH_3$ | $CH_3$ | $CH_3$ | $CH_3$ | $CH_3$ | $C_2H_5$ | Br | 1 | 1 | 98—100 | E-A | 61 | $C_{14}H_{34}N_2OBr_2$ | 406.27 | Br | 39.34 | Br | 38.06 |
| As-12045 | $CH_3$ | $C_2H_5$ | H | H | $CH_3$ | $CH_3$ | $CH_3$ | I | 1 | 1 | 290 | E-W | 66 | $C_{11}H_{28}N_2OI_2$ | 458.18 | I | 55.40 | I | 55.09 |
| As-12046 | $CH_3$ | $C_2H_5$ | H | H | $CH_3$ | $CH_3$ | $C_2H_5$ | Br | 1 | 1 | 270—272 | E-W | 51 | $C_{13}H_{32}N_2OBr_2$ | 392.24 | Br | 40.75 | Br | 40.87 |
| As-12117 | $CH_3$ | $C_2H_5$ | H | H | $C_2H_5$ | $C_2H_5$ | $CH_3$ | I | 1 | 1 | 268 | A | 48 | $C_{13}H_{32}N_2OI_2$ | 486.24 | I | 52.20 | I | 52.91 |
| As-12118 | $CH_3$ | $C_2H_5$ | H | H | $C_2H_5$ | $C_2H_5$ | $C_2H_5$ | Br | 1 | 1 | 245 | A | 48 | $C_{15}H_{36}N_2OBr_2$ | 420.29 | Br | 38.03 | Br | 37.15 |
| As-12203 | $C_4H_8$ | | H | H | $CH_3$ | $CH_3$ | $CH_3$ | I | 1 | 1 | 260—262 | dil. A | 98 | $C_{12}H_{28}N_2OI_2$ | 470.19 | I | 53.99 | I | 53.55 |
| As-12204 | $C_4H_8$ | | H | H | $CH_3$ | $CH_3$ | $C_2H_5$ | Br | 1 | 1 | 255—256 | — | 87 | $C_{14}H_{32}N_2OBr_2$ | 404.25 | Br | 39.56 | Br | 39.45 |
| As-12305 | $C_4H_8$ | | H | H | $C_2H_5$ | $C_2H_5$ | $CH_3$ | I | 1 | 1 | 263—266 | dil. A | 98 | $C_{14}H_{32}N_2OI_2$ | 498.25 | I | 50.95 | I | 50.58 |
| As-12306 | $C_4H_8$ | | H | H | $C_2H_5$ | $C_2H_5$ | $CH_3$ | Br | 1 | 1 | 233 | — | 46 | $C_{16}H_{36}N_2OBr_2$ | 432.30 | Br | 36.97 | Br | 36.90 |
| As-12487 | $C_4H_8$ | | H | H | $C_4H_8$ | | $CH_3$ | I | 1 | 1 | 244—246 | — | 100 | $C_{14}H_{30}N_2OI_2$ | 496.20 | I | 51.16 | I | 50.33 |
| As-12488 | $C_4H_8$ | | H | H | $C_4H_8$ | | $C_2H_5$ | Br | 1 | 1 | 223—225 | A-E | 69 | $C_{16}H_{34}N_2OBr_2$ | 430.29 | Br | 37.15 | Br | 36.91 |
| As-13569 | $C_2H_5$ | $n$-$C_3H_7$ | H | H | $CH_3$ | $CH_3$ | $CH_3$ | I | 1 | 1 | 196 | E | 65 | $C_{13}H_{32}N_2OI_2$ | 486.24 | I | 52.20 | I | 52.40 |
| As-13570 | $C_2H_5$ | $n$-$C_3H_7$ | H | H | $CH_3$ | $CH_3$ | $C_2H_5$ | Br | 1 | 1 | 172—180 | E-A-EE | 47 | $C_{15}H_{36}N_2OBr_2$ | 420.29 | Br | 38.03 | Br | 36.54 |
| As-13671 | $C_2H_5$ | $n$-$C_4H_9$ | H | H | $CH_3$ | $CH_3$ | $CH_3$ | I | 1 | 1 | 205 | E | 52 | $C_{14}H_{34}N_2OI_2$ | 500.26 | I | 50.74 | I | 50.67 |
| As-13672 | $C_2H_5$ | $n$-$C_4H_9$ | H | H | $CH_3$ | $CH_3$ | $C_2H_5$ | Br | 1 | 1 | 163—166 | E-A-EE | 37 | $C_{16}H_{38}N_2OBr_2$ | 434.32 | Br | 36.80 | Br | 34.88 |
| As-16575 | $CH_3$ | $CH_3$ | H | H | $CH_3$ | $CH_3$ | $CH_3$ | I | 1 | 2 | 204—206 | — | 82 | $C_{11}H_{28}N_2OI_2$ | 458.18 | I | 55.40 | I | 54.76 |
| As-16576 | $CH_3$ | $CH_3$ | H | H | $CH_3$ | $CH_3$ | $C_2H_5$ | Br | 1 | 2 | 217—219 | — | 87 | $C_{13}H_{32}N_2OBr_2$ | 392.24 | Br | 40.75 | Br | 40.12 |
| As-16677 | $C_2H_5$ | $C_2H_5$ | H | H | $CH_3$ | $CH_3$ | $CH_3$ | I | 1 | 2 | 244—246 | — | 91 | $C_{13}H_{32}N_2OI_2$ | 486.23 | I | 52.21 | I | 51.40 |
| As-16678 | $C_2H_5$ | $C_2H_5$ | H | H | $CH_3$ | $CH_3$ | $C_2H_5$ | Br | 1 | 2 | 195—196 | — | 72 | $C_{15}H_{36}N_2OBr_2$ | 420.29 | Br | 38.03 | Br | 37.88 |
| As-16701 | $CH_3$ | $CH_3$ | H | H | $CH_3$ | $CH_3$ | $CH_3$ | I | 2 | 2 | 233 | E-W | 62 | $C_{12}H_{30}N_2OI_2$ | 472.21 | I | 53.76 | I | 53.50 |
| As-16702 | $CH_3$ | $CH_3$ | H | H | $CH_3$ | $CH_3$ | $C_2H_5$ | Br | 2 | 2 | 254—256 | E-A | 30 | $C_{14}H_{34}N_2OBr_2$ | 406.27 | Br | 39.34 | Br | 38.67 |
| As-17842 | $CH_3$ | $CH_3$ | H | H | $C_2H_5$ | $C_2H_5$ | $CH_3$ | I | 2 | 2 | 144—145 | E | 70 | $C_{17}H_{34}N_2OI_2$ | 500.26 | I | 50.74 | I | 50.31 |
| As-17843 | $CH_3$ | $CH_3$ | H | H | $C_2H_5$ | $C_2H_5$ | $C_2H_5$ | I | 2 | 2 | 201—202 | E | 66 | $C_{16}H_{38}N_2OI_2$ | 528.31 | I | 48.05 | I | 46.11 |

[a] A: acetone; E: ethanol; W: water; dil. A. 70 % acetone dil.w.water; EE: ethyl ether; M: methanol; iso-Pr: *iso*propyl alcohol.

*Table 4.*



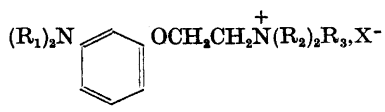
| Code No. | $R_1$ | $R_2$ | $R_3$ | X | Position | M.p. °C | Yield % | Emp. formula | M | Analysis, % Calc. | Found |
|---|---|---|---|---|---|---|---|---|---|---|---|
| As-12982 | $C_2H_5$ | $CH_3$ | $CH_3$ | I | *m* | 186 | 80 | $C_{16}H_{30}N_2OI_2$ | 520.26 | I 48.79 | I 48.31 |
| As-13030 | $C_2H_5$ | $C_2H_5$ | $CH_3$ | I | *m* | 158 | 40 | $C_{18}H_{34}N_2OI_2$ | 548.31 | I 46.29 | I 45.28 |
| As-13345 | $CH_3$ | $C_2H_5$ | $CH_3$ | I | *p* | 200 | 83 | $C_{16}H_{30}N_2OI_2$ | 520.26 | I 48.79 | I 48.03 |
| As-13346 | $CH_3$ | $C_2H_5$ | $C_2H_5$ | I | *p* | 188—90 | 77 | $C_{18}H_{34}N_2OI_2$ | 548.31 | I 46.29 | I 45.75 |
| As-14235 | $CH_3$ | $CH_3$ | $CH_3$ | I | *m* | 188—94 | 67 | $C_{14}H_{26}N_2OI_2$ | 492.20 | I 51.57 | I 50.25 |
| As-14213 | $CH_3$ | $CH_3$ | $C_2H_5$ | I | *m* | 115 | 48 | $C_{16}H_{30}N_2OI_2$ | 520.26 | I 48.79 | I 48.75 |
| As-14340 | $CH_3$ | $C_2H_5$ | $CH_3$ | I | *m* | 175—76 | 74 | $C_{16}H_{30}N_2OI_2$ | 520.26 | I 48.79 | I 48.23 |
| As-14310 | $CH_3$ | $C_2H_5$ | $C_2H_5$ | I | *m* | 153—56 | — | $C_{18}H_{34}N_2OI_2$ | 548.31 | I 46.29 | I 46.17 |

Among the bis-quaternary salts described in the second paper of the series [1], high ganglion blocking activity was found in the asymmetric compound N,N,N,N'-tetraethyl-N',N'-dimethyl-3-oxa-pentane-1,5-diammonium di-bromide (As-4179) [5]. Because of the toxic nature of the bromide anion, it was of importance to study other salts of the biologically active ion. A number of such salts have been prepared or their preparation attempted. Most of them were not useful in that they were either deliquescent, or contained toxic anions (Table 6). One of the few salts which seemed to be of interest, was the acid tartrate (As-4137) *. This salts has been the basis of further pharmacological and clinical work [6,7].

The tartrate and the other salts were available by addition of the appropriate acid to a solution of the free alkyl ammonium hydroxide. A number of methods for the transformation of the direct products of quaternization, bromide, iodide or alkyl sulfate, into salts of any given anion have been in-

* 'Oxaditon' (Regd. Trade Mark).

*Table 5.*



| Code No. | $R_1$ | $R_2$ | $R_3$ | X | M.p. °C | Emp. formula | M | Analysis % Calc. | Found |
|---|---|---|---|---|---|---|---|---|---|
| As — 12932 | $C_2H_5$ | $CH_3$ | $CH_3$ | I | 190 | $C_{15}H_{27}N_2OI$ | 378.3 | I 33.55 | I 33.36 |
| As — 12933 | $C_2H_5$ | $CH_3$ | $C_2H_5$ | Br | 98 | $C_{16}H_{29}N_2OBr$ | 345.3 | Br 23.14 | Br 23.05 |
| As — 13031 | $C_2H_5$ | $C_2H_5$ | $C_2H_5$ | Br | 135 | $C_{18}H_{33}N_2OBr$ | 373.4 | Br 21.35 | Br 21.37 |

*Table 6.*

| Code No. | Anion | M.p. °C | Crystall. from a) | Emp. formula | M | Analysis | Remarks |
|---|---|---|---|---|---|---|---|
| As-4194 | maleate | 164 | M-A | $C_{22}H_{40}O_9N_2$ | 476.3 | Ep: 94.24 b) | deliquescent |
| As-4193 | carboxymethyl-theophyllin | 210 | not | $C_{32}H_{52}O_9N_{10}$ | 720.5 | N calc. 19.52<br>found 19.41 | decomposes when recryst. |
| As-4120 | cinnamate | 110—114 | M-A | $C_{32}H_{48}O_5N_2$ | 540.7 | — | oil after recryst. |
| As-4127 | retene-3-sulfonate | 115 | E-A | $C_{50}H_{74}O_7N_4$ | 871.2 | N calc. 3.2<br>found 3.05 | |
| As-4182 | bis-OH-naphthoate | 272 d | not | $C_{38}H_{60}O_{13}N_2$ | 618.4 | Ep: 100.6 | |
| As-4176 | perchlorate | 220 d | EW | $C_{14}H_{34}O_9N_2Cl_2$ | 445.1 | N calc. 6.30<br>found 6.19 | |
| As-4101 | D-camphorate | 200 | — | $C_{34}H_{64}O_5N_2$ | 588.6 | Ep: 94.45 | deliquescent |
| As-4122 | fumarate | 230 | — | $C_{22}H_{40}O_9N_2$ | 476.3 | Ep: 93.80 | oil after recryst. |
| As-4178 | monohydrogen tartrate | 184 | E-W | $C_{22}H_{44}O_{13}N_2,2H_2O$ | 580.2 | C calc. 45.51<br>found 45.66<br>H calc. 7.63<br>found 8.18<br>N calc. 4.83<br>found 5.07 | |

a) *cf.* footnote to Table 3.
b) Purity % by perchloric acid titration.

vestigated. This examination shows the need for still better methods, when commercial production is contemplated and yield and other operational factors become critical. The hydroxide solution can be had by ion exchange, using a strongly basic resin (*e.g.* "Amberlite IRA-400") *, by hydrolysis of etho-

* Regd. Trade Mark of Rohm & Haas Co., Philadelphia, Penn. U.S.A.

*Table 7.*

$X^-,R(CH_3)_2\overset{+}{N}CH_2CH_2OCH_2CH_2\overset{+}{N}(C_2H_5)_2R,X^-$

| Code No. | R | X | M.p. °C | Recryst. from a) | Yield % | Emp. formula | M | Analysis, Found | Analysis, Calc. |
|---|---|---|---|---|---|---|---|---|---|
| As-4144 | $CH_3$ | $CH_3SO_4$ | 143 | E-EE | 70 | $C_{14}H_{36}N_2O_9S_2$ | 40.56 | N 6.15 | N 6.36 |
| As-4124 | $C_2H_5$ | $C_2H_5SO_4$ | 88—90 | *iso*-Pr-EE | 75 | $C_{18}H_{44}N_2O_9S_2$ | 496.67 | N 5.63 | N 5.64 |
| As-4107 | *n*-$C_3H_7$ | Br | 164—66 | E-A(1:1) | 26 | $C_{16}H_{38}N_2OBr_2$ | 434.28 | Br 36.36 | Br 36.80 |
| As-4101 | *n*-$C_4H_9$ | Br | 138—40 | E-A(1:1) | 13 | $C_{18}H_{42}N_2OBr_2$ | 462.37 | Br 34.82 | Br 34.57 |
| As-4147 | *n*-$C_5H_{11}$ | Br | 110 | E-EE | 20 | $C_{20}H_{46}N_2OBr_2$ | 490.23 | Br 32.21 | Br 32.60 |
| As-4148 | *n*-$C_6H_{13}$ | Br | 158—60 | A-E(5:1) | 10 | $C_{22}H_{50}N_2OBr_2$ | 518.47 | Br 30.20 | Br 30.83 |
| As-4149 | *n*-$C_7H_{15}$ | Br | 120 | E-EE | 14 | $C_{24}H_{54}N_2OBr_2$ | 546.52 | Br 28.90 | Br 29.25 |
| As-4159 | $C_2H_4OH$ | Br | 194 | E | 50 | $C_{14}H_{34}N_2O_3Br_2$ | 438.26 | Br 36.18 | Br 36.47 |
| As-4182 II | $C_3H_5$ | Br | 118—24 | E-A(2:1) | 56 | $C_{16}H_{34}N_2OBr_2$ | 430.27 | Br 36.67 | Br 37.15 |
| As-4182 IV | $CH_2C_6H_5$ | Cl | 185—86 | — | 21 | $C_{24}H_{38}N_2OCl_2$ | 441.47 | Cl 15.98 | Cl 16.06 |

a) *cf.* footnote to Table 3.

sulfate according to Barber and Gaimster [8], by addition of propylene oxide to an aqueous solution of the quaternary bromide and the desired acid (*cf.* Sackur [9]). A special method for transformation into chloride is that of Phillips and Baltzley [10]. The use of double decomposition with salts of aromatic acids was also explored. Since the sodium salt of retene-3-sulfonic acid is soluble, while the potassium salt is not, it was hoped that an insoluble salt of the bis-quaternary ion would form with this acid. This was, however, not the case. Similarly no sparingly soluble salt is formed with 2,2'-dihydroxy-1,1-dinaphthylmethane-3,3'-dicarboxylic acid (Barner and Gaimster's [11] "embonic acid"). Sparingly soluble salts were obtained, however, with 2,2'-dihydroxy-1,1'-dinaphthyl-3,3'-dicarboxylic acid ("bis-hydroxy-naphtoic acid" [11]) and with 4,4'-diamino-stilbene-2,2'-disulfonic acid as disclosed by Slack [12]. Tartaric acid expels these weak acids from their salts in the form of the insoluble free acid.

In view of the interesting pharmacological results obtained with the simple quaternary salts of the asymmetric base, bis-(2-diethylamino-2'-dimethylamino)-ethyl ether (Asa 41), it appeared of interest to prepare some salts containing higher alkyls as N-substituents. These salts were obtained in conventional fashion and are shown in Table 7.

Attempts to prepare the "totally asymmetric" 2-trimethylammonium-ethyl-2'-triethylammoniumethyl ether by various routes were unsuccessful. In several cases N-dialkyl morpholinium ions, however, were obtained from the reaction mixtures.

## EXPERIMENTAL *

Bis-tertiary *amino ethers.* With the exceptions mentioned below these substances were obtained simply by Williamson ether condensation of the appropriate tertiary amino alcohols resp. amino halides as described earlier [1].

### Bis-(2-ethylmethyl-2'-dimethyl)-aminoethyl ether

*a) Bis-(2-ethyl-2'-dimethyl)-aminoethyl ether.* Twenty-three grams of sodium (1 mole) was dissolved by heating in a solution of 90 g of N-ethylethanolamine in 800 ml dry toluene. Condensation with N-dimethyl-aminoethyl chloride prepared *in situ* from 144 g (1 mole) of the corresponding hydrochloride. After removal of sodium chloride and toluene the residue is distilled in vacuum to give 10 g of oil, b.p. 87—95°C/20 mm Hg. (Found: N 16.41. Calc. for $C_8H_{20}N_2O$ (160.6): N 17.48). Purity (by perchloric acid titration) 98.0 %.

*b) Methylation of (a) (Eschweiler-Hess procedure) (Asa 120).* To 49 g (0.3 mole) of the amine in a flask is added 45 g of 85 % formic acid (0.6 mole) at such a rate that the temperature never exceeds 60°C. After cooling to room temperature 11 g of 37 % formalin is added at once. The mixture is heated to approximately 60° at which temperature an exothermic evolution of $CO_2$ begins. After this has subsided the mixture is refluxed for 3 h. The mixture is made just acid with 4 N HCl and air blown through for 1 h for removal of volatile products. More HCl is added and the mixture is evaporated in vacuum till the residue is semisolid. After addition of a large excess of NaOH extraction with ether, 200 ml, three times. The residue from the dried ether is distilled. Yield: 34 g (64 %). See Table 1 for analytical data.

*Bis-(2-ethylmethyl-2'-diethyl)-aminoethyl ether* is obtained in essentially similar fashion from the intermediate bis(2-ethyl-2'-diethyl)-amino ethyl ether (b.p. 120°C at 20 mm Hg).

* All melting and boiling points are uncorrected. The nitrogen and halogen values are semi-micro determinations by Mrs. G. Speggers and her staff. Carbon and hydrogen values are micro determinations by Messrs. W. Egger and P. Hansen, University of Copenhagen.

### Bis-(2-ethyl-*n*-propyl-2'-dimethyl)-aminoethyl ether (Asa-135)

From 32 g (0.2 mole) of bis-(2'-ethyl-2'-dimethyl)-aminoethyl ether and 25 g of *n*-propylbromide in *iso*propanol. Yield 5 g (12 %). See Table 1 for analytical data.

By substituting 27.4 g of *n*-butylbromide for the propyl bromide in the procedure given immediately above one obtains the corresponding *bis-(2-ethyl-n-butyl-2'-dimethyl)-aminoethyl ether (Asa-136)*. Yield 6 g (11 %). See Table 1 for analytical data.

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