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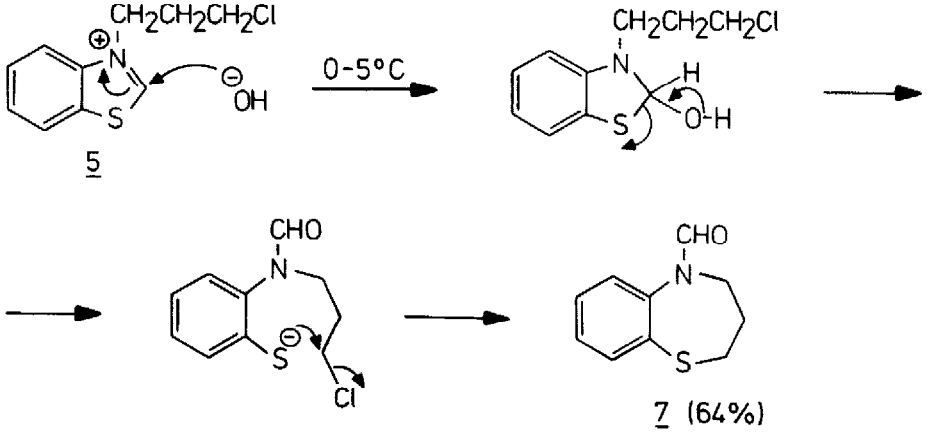
A NOVEL BASE-INDUCED RING EXPANSION OF QUATERNIZED HETEROCYCLES

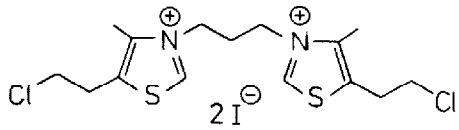
Hans-Jürgen Federsel* and Jan Bergman
Department of Organic Chemistry
Royal Institute of Technology
S-100 44 Stockholm, Sweden

Abstract: The synthesis of some 6-, 7- and 8-membered heterocycles through a base induced ring expansion of quaternized thiazolium, oxazolium and selenazolium salts is described.

During studies of base-induced rearrangements of quaternized 5-(ω-chloroalkyl)-thiazoles and oxazoles,[1] we have found a versatile ring expansion of benzothiazole, benzoxazole and benzoselenazole quaternized with various α,ω-dihalocompounds. Thus, an attempt to prepare the bis-quaternized compound 1,[2] resulted in a complex reaction mixture. However, dissolution of the crude product in water followed by treatment with sodium hydroxide to pH 10, afforded an oil, which on GC-MS analysis showed the presence of compounds 2 - 4.[3] The thietanylidene 2 is formed in complete accordance with our earlier findings,[1] *i.e.* ring closure has taken place in direction of the most reactive leaving group. On the other hand formation of the N-formyl-1,4-thiazepines 3 - 4 obviously must have taken place through the nucleophilic displacement of the ω-halogen of the quaternizing agent by the thiol anion. Quaternization followed by base treatment has thus led to incorporation of the carbon atoms originating from the quaternizing agent into the heterocyclic ring.

More detailed studies of this ring expansion were carried out on the quaternized benzothiazoles 5 - 6.[4] Dissolution of these salts in water, followed by NaOH-alkalization rapidly afforded compounds 7 - 8 in good yields.[5] A proposed reaction mechanism of the formation of 7 is shown in the scheme.





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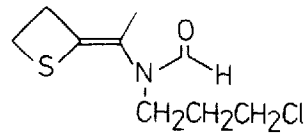

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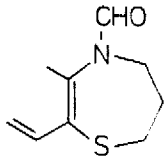

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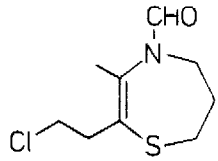

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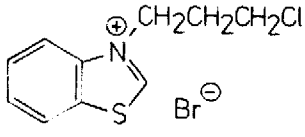

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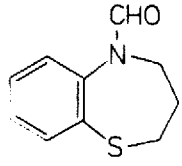

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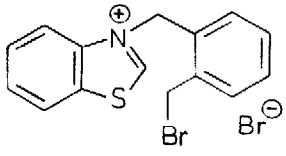

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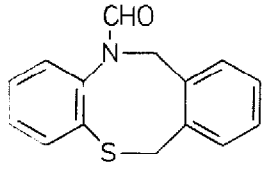

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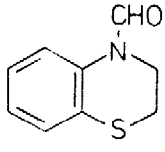

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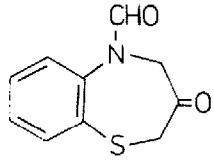

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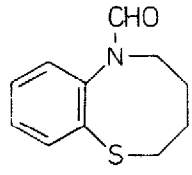

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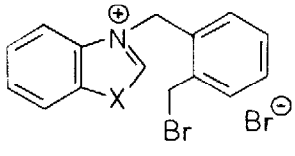
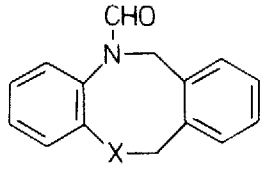


12(a-b)



13(a-b)

X
(12-13)a : O
b : Se

This ring expansion appears to be similar to the rearrangement described in our earlier work,[1] involving quaternized 5-(ω-chloroalkyl)thiazoles. In both cases the base-induced rearrangements are fast (completion within 1 - 5 min at 0-40°C) and variation of the reaction temperature only seems to affect the amount of by-products.

Our investigations were continued with the intention of synthesizing other ring expanded products. Thus, base treatment of the appropriate N-(ω-chloroalkyl)benzothiazolium compounds afforded 1,4-benzothiazine 9, 1,5-benzothiazepine-3-one 10 and 1,6-benzothiazocine 11. The synthesis of the compounds mentioned above, is related to a base-induced ring expansion of N-phenacylthiazolium compounds yielding 1,4-thiazines, briefly described by Adam and Wharmby in 1969.[6]

We have found that other quaternized heterocyclic systems also afford ring expanded products on base treatment, analogously to the thiazoles. Thus, compounds 12a-b,[7] *i.e.* the oxygen and selenium isologs of 6, smoothly gave the dibenzoxazocine 13a[8] and the previously unknown dibenzoselenazocine 13b,[9] respectively. Comparing the yields of compounds 8, 13a and 13b shows, that changing the heteroatom only has a minor influence upon the rearrangement. The potential of this reaction is easily envisaged by the very facile two-step synthesis of 13a (*i.e.* quaternization and base treatment), which gives a yield of 26%. In contrast, the multistep procedure of Yale and Spitzmiller[10] offers an overall yield of approx. 4%. On the other hand, the two-step synthesis of compound 8 through ring expansion gives a yield of 32%, which is comparable with the method of Yale[11] and co-workers.

This ring-expansion offers an alternative to the synthesis of a variety of heterocyclic systems, some of which have been extremely difficult to obtain by other routes. The possibilities of extending the scope of this reaction are presently under investigation.

REFERENCES AND NOTES

1. H-J. Federsel, J. Bergman, and U. Stenhede, Heterocycles, 1979, 12, 751.
H-J. Federsel and J. Bergman, Heterocycles, 1980, 14, 33.
2. The reaction of 2 equivalents of 5-(β-chloroethyl)-4-methylthiazole and 1 equivalent of 1,3-diiodopropane was performed in dry acetone and the reaction mixture was stored at room temperature for several weeks.
3. The GC-analysis (3% OV 17, 170°C) indicated the following relative amounts: 2 : 37%; 3 : 10%; 4 : 53%.
4. A general method for synthesizing the quaternized compounds was employed. Refluxing the heterocyclic base and the α,ω-dihalocompound in acetonitrile, usually afforded crystalline products, which were directly used in the subsequent rearrangement. Thus, N-(γ-chloropropyl)benzothiazolium bromide (5) was obtained as yellow-brown crystals (mp.: 150-153°C) in 35% yield, after reacting benzothiazole and 1-bromo-3-chloropropane for 27 h. Similarily, reacting benzothiazole and α,α'-dibromo-o-xylene for 4 h, afforded N-(2'-bromomethyl)-benzylbenzothiazolium bromide (6) as white-grey crystals (mp.: 199-201°C, dec.) in 78% yield.

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Institute of Nuclear Physics, Technische Hochschule Darmstadt, D-6100 Darmstadt, Germany, for the structure analyses of 6 and 12b, using fission fragment induced desorption mass spectrometry.

5. The rearrangements were generally carried out adding NaOH (s) to a water-trichloroethylene system at temperatures varying from 0-40°C. Evaporation of the organic phase gave the crude product. Thus, N-formyl-2,3,4,5-tetrahydro-1,5-benzothiazepine (7) was isolated as yellow crystals (mp.: 82.5-84.5°C) in 64% yield, after recrystallization from hexane-ethanol (1:1).
IR (KBr): 1660 cm^{-1} (amide C=O)
^{13}C-NMR ($CDCl_3$): δ (ppm) 29.7, 31.8, 44.5, 127.0, 127.8, 128.3, 132.7, 134.5, 143.6, 162.1
Mass spectrum (70 eV): m/e (rel. intensity) 194 (10), 193 (76, M^+), 160 (38), 137 (17), 136(100), 132 (20), 130 (14), 109 (24), 77 (11), 69 (13), 65 (20), 51 (10), 45 (14).
Recrystallization from hexane-ethanol (1:1) afforded N-formyl-6,11-dihydro-dibenzo[b,f]-[1,4]thiazocine (8) in 41% yield as white crystals with mp.: 142.5-144°C (lit.[10]: 143-145°C, dec).
IR (KBr): 1670 cm^{-1} (amide C=O)
^{13}C-NMR ($CDCl_3$): δ (ppm) 35.0, 48.9, 127.7, 127.8, 128.7, 129.3, 129.8, 130.4, 132.2, 134.3, 135.8, 162.6
Mass spectrum (70 eV): m/e (rel. intensity) 256 (16), 255 (87, M^+), 227 (12), 226 (39), 222 (18), 210 (40), 194 (22), 193 (13), 137 (14), 136 (100), 135 (95), 134 (18), 119 (14), 109 (22), 105 (16), 104 (29), 103 (31), 91 (31), 78 (30), 77 (26), 69 (12), 65 (26), 63 (12), 51 (19), 45 (12).
We are indebted to Dr. H.L. Yale, Squibb Institute for Medical Research, New Brunswick, New Jersey 08903, USA, for kindly providing reference samples of compounds 8 and 13a.

6. D.J. Adam and M. Wharmby, Tetrahedron Letters, 1969, 3063.

7. Compound 12a was obtained as pale yellow crystals (mp.: 167-172°C, dec) in 56% yield, after refluxing the starting materials for 6 h (see ref. 4).
Compound 12b was isolated as a grey powder (mp.: >200°C, dec) in 81% yield after refluxing for 3 h.

8. Recrystallization from di-isopropylether afforded N-formyl-6,11-dihydro-dibenzo[b,f][1,4]-oxazocine (13a) in 47% yield, as white crystals with mp.: 113-114°C (lit.[11]: 114-115°C).
IR (KBr): 1675 cm^{-1} (amide C=O)
^{13}C-NMR ($CDCl_3$): δ (ppm) 49.6, 75.3, 122.5, 124.1, 125.7, 128.1, 128.2, 128.7, 129.0, 130.5, 133.2, 134.6, 135.1, 153.5, 162.1

9. A flash-chromatographic separation on silica with hexane-ethanol (10:2) as eluent, afforded N-formyl-6,11-dihydro-dibenzo[b,f][1,4]selenazocine (13b) as yellow crystals (mp.: 162-165°C) in 20-25% yield.
Mass spectrum (70 eV): m/e (rel. intensity) 303 (100, M^+), 301 (48), 274 (35), 222 (48), 194 (74), 184 (77), 183 (77), 178 (45), 104 (74), 103 (82), 78 (71), 77 (87), 51 (42).

10. H.L. Yale, F. Sowinski, and E.R. Spitzmiller, J. Heterocyclic Chem., 1972, 9, 899.

11. H.L. Yale and E.R. Spitzmiller, J. Heterocyclic Chem., 1972, 9, 911.

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