RAPID REARRANGEMENT OF QUATERNIZED OXAZOLES AND THIAZOLES THROUGH BASE TREATMENT

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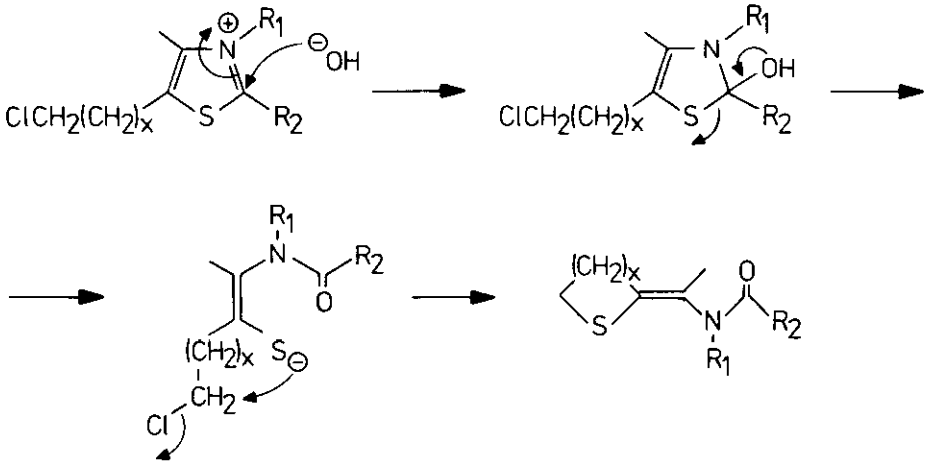
Abstract - Isolation and structure elucidation of some new compounds obtained through the base-induced rearrangement of oxazolium and thiazolium compounds.

In a previous communication,[1] the facile base-induced rearrangement of some 5-(β-chloroethyl)-4-methylthiazolium compounds (1a-f) to the corresponding 2-thietanylidenes (2a-f) was described and discussed. Our investigations have now been extended to some analogous oxazolium- and thiazolium compounds.[2]

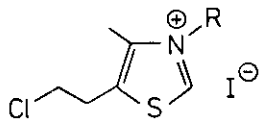
Base treatment of the quaternized compounds of 5-(γ-chloropropyl)-4-methylthiazole (3)[3] and 5-(δ-chlorobutyl)-4-methylthiazole (4)[4] gave the expected rearrangement products, i.e. the 2-thiolanylidene 5 and the 2-thianylidene 6 respectively, in good yields.[5]

The steric requirements for the OH^--addition were studied with the 2-substituted thiazolium compounds 7a,b.[6] No changes in the reaction rates, as compared to the unsubstituted thiazolium analogues, were observed and the 2-thietanylidenes 8a,b[7] were formed.

Thus, the proposed reaction mechanism[1] can be generalized as shown in the scheme.



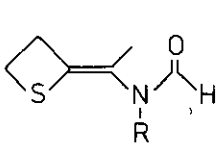
R_1 = Me, Ar; R_2 = Me, Ph; x = 1,2,3



1(a-f)

R

(1-2) a : Me



2(a-f)

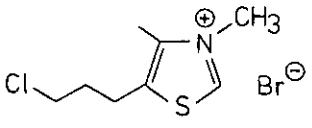
b : CH_2CH_2 

c CH_2Ph

d : $CH_2C_6H_4Br$-4

e : $CH_2C_6H_4NO_2$-4

f . $CH_2C_6H_2(OMe)_3$-3,4,5



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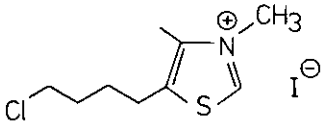

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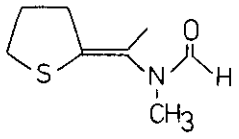

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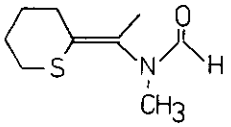

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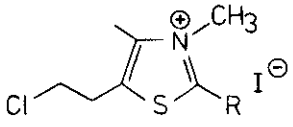
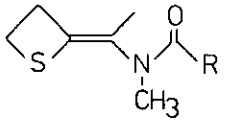


7(a-b)

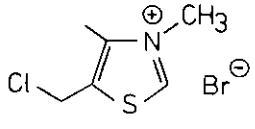


8(a-b)

R

(7-8) a . Me

b . Ph



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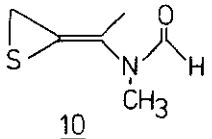

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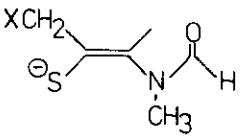
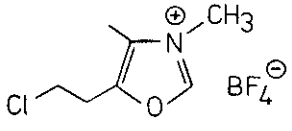


11a X=OH

b X=Cl



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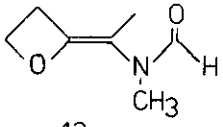

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Our investigations concerning the base treatment of the quaternized 5-chloromethyl-4-methylthiazole 9[8] have indicated a possible existence of the highly strained thiiranylidene compound 10.[9] However, the yield of the crude product is rather low. This may imply, that the thiiranylidene initially formed is unstable and undergoes further reactions, such as a base-induced ring-opening leading to the mercaptide 11a or to the corresponding disulfide. The main reaction pathway may, however, well be the direct transformation of 9 to 11a,b, without the intermediate formation of 10.

Upon base treatment, the oxazolium compound 12[10] rearranges to the 2-oxetanylidene 13,[11] analogous to the corresponding thiazolium compound. In contrast to the thietanylidenes, however, the yield of 13 is very low. This apparently is due to the much poorer nucleophilicity of oxygen as compared with sulfur.

Further studies of the rearrangement are in progress.

REFERENCES AND NOTES

1. H-J. Federsel, J. Bergman, and U. Stenhede, Heterocycles, 1979, 12, 751.

2. The base treatment was performed in a water-trichloroethylene system at room temperature. Addition of NaOH (s) was continued until pH >10 and was generally completed within 5 min. The crude reaction product was separated on a silica gel column (Kieselgel 60 reinst, 0.063-0.200 mm, Merck) with n-hexane-ethanol (10:2) as eluent.
   Analyses performed: ^{13}C-NMR (Bruker WP 200), GC (Hewlett-Packard 5830A and Varian Aerograph 204-1B), IR (Perkin-Elmer 257), MS (Finnigan 4000 and LKB 9000) and TLC (precoated silica plates, Merck; n-hexane-ethanol (10:2)).

3. The ethanedisulphonate of the thiazole was obtained from de Laire Chimie SA, F-62104 Calais, France.
   Liberation of the base (Na_2CO_3), followed by quaternization with MeBr (acetone, room temperature) afforded 3 as an almost colourless oil in nearly quantitative yield.

4. We gratefully acknowledge a sample of the ethanedisulphonate of the thiazole provided by Professor P. Lechat, Institut de Pharmacologie, Université Pierre et Marie Curie - Paris VI, F-75270 Paris Cedex 06, France.
   After liberation of the base (Na_2CO_3) and treatment with MeI at room temperature, 4 was isolated as yellow crystals (m.p. 95-96°C) in 96% yield.

5. Compound 5 was obtained as white crystals (m.p. 49-51°C) in 92% yield.
   IR ($CHCl_3$): 1665 cm^{-1} (amide C=O)

^{13}C-NMR ($CDCl_3$): δ (ppm) 18.7, 28.3, 30.6, 33.4, 33.7, 122.5, 141.3, 163.1.

Mass spectrum (70 eV): m/e (rel. intensity) 171(78, M^+), 143(10), 142(16), 130(45), 124(65), 115(10), 114(16), 112(26), 111(18), 110(10), 109(10), 87(10), 82(19), 71(10), 59(10), 58(12), 56(100).

Compound 6 was obtained as a colourless oil in 60% yield.

IR (neat): 1675 cm^{-1} (amide C=O)

^{13}C-NMR ($CDCl_3$): δ (ppm) 17.2, 25.7, 26.0, 29.3, 29.8, 30.0, 130.7, 131.7, 163.0.

Mass spectrum (70 eV): m/e (rel. intensity) 186(11), 185(100, M^+), 156(12), 152(29), 144(18), 138(25), 128(16), 126(24), 124(88), 111(22), 95(20), 82(17), 56(77).

6. The thiazoles were obtained through a modification of the method of U.H. Lindberg, G. Bexell, and B. Ulff, Acta Pharm. Suecica, 1971, 8, 49.

Reacting γ-aceto-γ-chloropropylacetate (Roche) with thioacetamide (Fluka) and thiobenzamide (Fluka) respectively, in boiling ethyl acetate, followed by hydrolysis (NaOH) and chlorination ($SOCl_2$) afforded the bases in overall yields of 26% and 48%. Quaternizations were performed with MeI at room temperature. Compound 7a was obtained as white crystals (m.p. 124-125°C) in 72% yield. Compound 7b was isolated as yellow crystals (m.p. 156-158°C). The yield of 7b was poor (5-10%), indicating the necessity of more vigorous conditions.

7. Compound 8a was obtained as a colourless oil in 68% yield.

IR (neat): 1655 cm^{-1} (amide C=O)

^{13}C-NMR ($CDCl_3$): δ (ppm) 14.6, 20.3, 20.8, 31.5, 34.0, 126.6, 132.4, 170.4.

Mass spectrum (70 eV): m/e (rel. intensity) 171(23, M^+), 138(54), 125(78), 124(14), 110(12), 100(22), 95(24), 94(11), 82(28), 56(100).

Compound 8b was obtained as an orange coloured oil with GC-purity (3% OV17, 200°C) of 95.8%.

IR (neat): 1640 cm^{-1} (amide C=O)

Mass spectrum (70 eV): m/e (rel. intensity) 233(23, M^+), 201(11), 200(69), 187(69), 186(20), 158(20), 118(33), 105(98), 95(40), 94(11), 77(100), 56(62).

8. The starting material ethyl 4-methylthiazole-5-carboxylate was synthesized by an improvement of the method of H.T. Clark and S. Gurin, J. Am. Chem. Soc., 1935, 57, 1876. Reacting ethyl 2-chloroacetoacetate (Fluka) and thioformamide in ethyl acetate for 3 h at 50°C, afforded the thiazole in a yield of 86%, (lit.: 0-5°C, 96 h, 35% yield). Reduction (LAH), chlorination ($SOCl_2$) and quaternization (MeBr, acetone) yielded 9 as white crystals (m.p. 155-157°C).

9. The crude reaction mixture was analysed with TLC and showed spots at R_f = 0.30, 0.23, 0.19, 0.14, 0.10, and 0.06. The reference compound 2a has an R_f = 0.22.
A GC-study (3% OV17, 140°C) shows peaks at longer ret. times than for the starting materials.

10. The oxazole was synthesized according to the method of U.H. Lindberg, Acta Pharm. Suecica, 1966, 3, 161.
Quaternization of the base was extremely difficult and several methods were tried, i.e. varying the quaternizing agent, solvent and temperature. The best results were obtained with trimethyloxonium tetrafluoroborate (Fluka) in nitromethane at room temperature. Compound 12 was isolated as a yellow oil.

11. Compound 13 was isolated as slightly yellow coloured crystals (m.p. 93-95°C).
IR ($CHCl_3$): 1660 cm^{-1} (amide C=O)
Mass spectrum (70 eV): m/e (rel. intensity) 141(2, M^+), 113(6), 86(100), 58(83), 56(13), 55(11), 42(14).
TLC: R_f = 0.18 (ref. compound 2a, R_f = 0.22).

Received, 15th October, 1979