RAPID BASE INDUCED REARRANGEMENT OF SOME QUATERNIZED THIAZOLES TO THIETANES

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Abstract - The synthesis of various thietanylidene compounds through sodium hydroxide treatment of some quaternized 5-(β-chloroethyl)-4-methylthiazoles is described and discussed.

During evaluation of GC-analytical procedures for the drug Heminevrin® (1),[1] a minor extra peak was found,[2] which did not correspond to any of the previously known impurities that might be formed during preparation of the drug. Examination of the analytical methods revealed that the new compound was formed when treating the drug with aqueous sodium hydroxide.

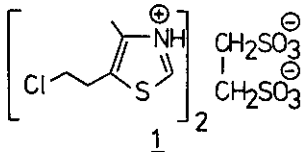
A GC-MS analysis[3] of the unknown compound showed a molecular ion at m/e 268. The spectrum also revealed the presence of two sulfur atoms, as well as the absence of chlorine. These facts indicated a possible relation to the known ionic dimer 2 (mol wt 323), the formation of which could easily be anticipated from the drug base 5-(β-chloroethyl)-4-methylthiazole (3a), by a simple nucleophilic substitution.[4]

In a paper of Yonemoto[5] from 1957 it was shown, that by treating the chloro analogue of thiamine (4a) with base, the corresponding rearranged thietane 5 (thiamine anhydride) was formed.

In order to gain insight into the mechanism of formation, the model compound 6 was synthesized[6] and treated with base in a two-phase system.[7] Chromatographic separation of the reaction mixture yielded a slightly yellow coloured oil,[8] which on the basis of MS, IR, and ^{13}C-NMR analysis[9] could be assigned structure 7 (N-[1-(2-thietanylidene)ethyl]-N-methylformamide).[10]

Using similar experimental methods, the rearrangement of the dimeric salt 2[11] yielded compound 8.[12]

In continuation, some N-benzyl derivatives of 3a were synthesized, which after base treatment and work-up gave compounds 9 - 12.[13]



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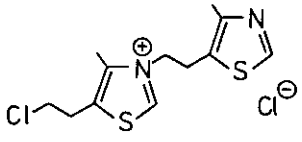

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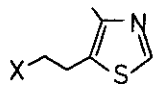
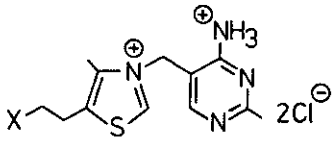
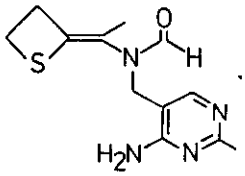


3

a X=Cl
b X=OH
c X=OCOCH$_3$



4 a X=Cl
b X=OH



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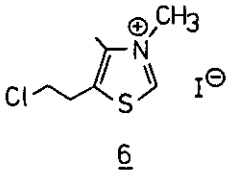

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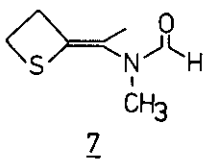

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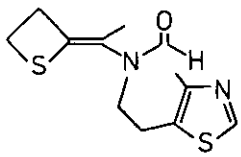

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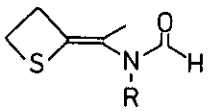
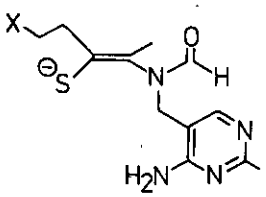


9-12

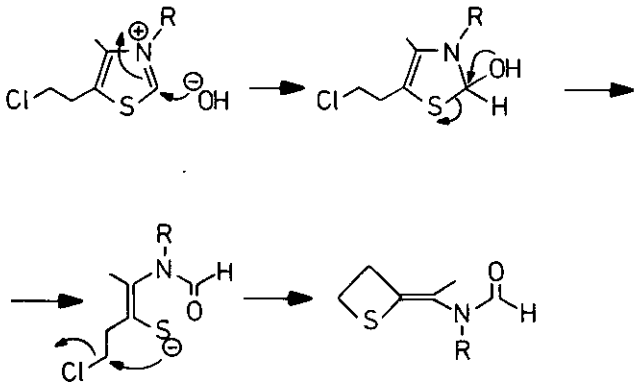
9 R=benzyl
10 R=4-bromobenzyl
11 R=4-nitrobenzyl
12 R=3,4,5-trimethoxybenzyl



13

a X=OH
b X=OSO$_2$C$_6$H$_5$
c X=OSO$_2$C$_6$H$_4$CH$_3$

The rearrangement of the quaternized thiazoles to the thietanes is obviously initiated by the OH^--attack on the ring-position 2. Apparently the high nucleophilicity of the generated S^--function, coupled with the good leaving-group properties of the chloro atom, then leads to the observed rapid rearrangement, whose mechanism is outlined below.



During further studies we have found that the character of the leaving-group in the thiazole system is essential for a successful rearrangement. This is clearly seen by the impossibility to rearrange the benzyl quaternized hydroxy- and acetoxy compounds 3b and 3c under the conditions given. Furthermore, there are several examples in the literature[14] of base-induced ring opening of thiamine (Vitamine B_1), 4b, leading only to the mercaptide anion 13a. The cyclization of 13a to the thietane 5 can, however, easily be performed after its transformation to 13b or 13c, i.e. after changing the hydroxyl group into a more appropriate leaving-group.[15]
There have also been some investigations concerning the further reactivity of 5.[16]
The generality of the rearrangement is now under investigation and will also include oxazole systems.

REFERENCES AND NOTES

1. Heminevrin® (clomethiazole ethanedisulphonate) is the registered trade name by the manufacturer Astra Läkemedel AB, S-151 85 SÖDERTÄLJE, Sweden.
2. The GC was recorded on a Perkin-Elmer F 11 instrument with a 8% BDS column (1,8m) at 170°C. The retention time for the unknown was approx. 32 min.
3. The GC-MS was recorded on a LKB 9000 instrument; using a 3% OV-17 column at 220°C gave a retention time for the unknown of approx. 13 min.
4. HPLC-studies have shown the occurence of the dimer 2 in samples of the drug base 3a.
5. H. Yonemoto, Yakugaku Zasshi, 1957, 77, 1128.
6. The quaternary salts were obtained by refluxing the thiazole base with the corresponding halide in dry acetone or acetonitrile.

   Literature describing the quaternization of thiazoles:

   a) N.I. Fisher and F.M. Hamer, J. Chem. Soc., 1930, 2502.

   b) E.R. Buchman, R.R. Williams, and J.C. Keresztesy, J. Am. Chem. Soc., 1935, 57, 1849.

   c) H.T. Clarke and S. Gurin, J. Am. Chem. Soc., 1935, 57, 1876.

   d) H. Stetter, Angew. Chem. Int. Ed. Engl., 1976, 15, 639.
7. The quaternized thiazole was dissolved in water (approx 0.5M-solution). An equal volume of dichloromethane or trichloroethylene was added. While stirring at room temperature, the stepwise addition of an aqueous NaOH-solution (1M) or NaOH(s) was continued until the waterphase became alkaline (pH=10-12). Completion of the reaction was estimated to occur within 5 min. Two extractions, drying (Na_2SO_4), and evaporation of the organic phase yielded 76% of a yellow coloured oil, with a GC-purity of approx. 80%. A TLC-test of the crude product (precoated silica gel plate, Merck) using n-heptane-ethanol (10:1) as eluent gave a main spot at R_f = 0,11 and traces of 3a at R_f = 0,18.
8. The crude product was purified by running HPLC on a 250 × 10 mm SiO_2 (10µ) column (Waters Associates) with n-hexane-ethanol (10:1) as eluent. The product was obtained in a total yield of 40%, showing a GC-purity of ≥ 99.9%.

9. The MS was recorded on a LKB 9000, the IR on a Perkin-Elmer 257, and the ^{13}C-NMR on a JEOL FX-60.

Mass spectrum (70eV): m/e (rel. intensity) 157 (42,M^+), 124 (66), 116 (43), 111 (84), 68 (37), 56 (100). Only relevant peaks are listed.

IR (neat): 1670 cm^{-1} (amide C = O)

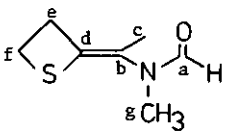
^{13}C-NMR ($CDCl_3$): δ-assignments (ppm)

a = 162,4 e = 20,6

b = 129,3 f = 34,2

c = 15,0 g = 28,7

d = 124,3



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10. All available analytical results coupled with the proposed reaction mechanism strongly indicate product 7 to be the pure Z-isomer.

At present we are still investigating methods that could give an unambiguous proof of the proposed geometrical configuration.

11. The crude compound was isolated by filtration from samples of 3a, stored for long time (months) at approx. 5°C. Washing with toluene and ether followed by drying, gave a crystalline product with mp: 90-91°C.

12. Liquid chromatography on 0.063 - 0.200 mm silica gel (Merck) with toluene-ethanol (9:1) gave a yellow coloured oil.

MS and ^{13}C-NMR spectra were in agreement with the proposed structure.

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13. Purification of the crude products by HPLC or liquid chromatography. Compounds 9 and 10 were isolated as slightly yellow coloured solids (mp: 62 - 63°C respectively 59 - 61°C) whereas 11 and 12 were obtained as coloured oils. MS and ^{13}C-NMR spectra were in agreement with the proposed structures.

14. a) O. Zima and R.R. Williams, Chem. Ber., 1940, 73, 941.

b) A. Watanabe and Y. Asahi, J. Pharm. Soc. Japan, 1955, 75, 1046.

c) G.D. Maier and D.E. Metzler, J. Am. Chem. Soc., 1957, 79, 4386.

d) H. Hirano, Yakugaku Zasshi, 1957, 77, 1004, 1007

e) J.M. Sprague and A.H. Land, "Heterocyclic Compounds", Vol. 5, R.C. Elderfield Ed., Wiley, New York, N.Y., 1957, Chapter 8, p. 653.

f) K. Hirai, T. Ishiba, and K. Inazu, Chem. Pharm. Bull. (Tokyo), 1974, 22, 1940.

15. a) C. Kawasaki, I. Tomita, and T. Motoyama, Vitamins (Kyoto), 1957, 13, 57.

b) see ref. 5 above.

c) C. Kawasaki and I. Tomita, Yakugaku Zasshi, 1958, 78, 1160, 1163.

d) C. Kawasaki and I. Tomita, Yakugaku Zasshi, 1959, 79, 295.

16. A. Takamizawa, K. Hirai, and T. Ishiba, Tetrahedron Letters, 1970, 437, 441.

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