206. Rearrangement of Cephem Bromohydrins to Thiazepine Derivatives

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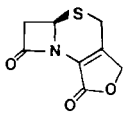
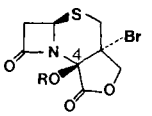
Summary

A new rearrangement of cephem bromohydrins **2–5** to thiazepine derivatives **7–8** is described. The structure of the rearragement product is established by an independent synthesis. The probable mechanism of the above rearrangement is discussed.

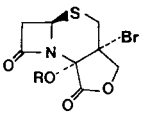
During our work [1] on the synthesis of 7-deamidocephalosporin lactone **1**, we have reported the isolation of two isomeric cephem bromohydrins **2** and **4** as intermediates and have shown by equilibration experiments that they differ only in the configuration at C(4). The relative configuration of bromine and hydroxyl groups in compound **4** was recently and unambiguously shown to be *cis*, by an X-ray crystal structure determination [2], thus in turn establishing compound **2** as *trans* bromohydrin.



1[a])



2 R = H
3 R = $COCH_3$



4 R = H
5 R = $COCH_3$

[a]) For the sake of clarity only one isomer is depicted here. All the compounds in fact are racemic.

In the present communication we report a facile rearrangement of these bromohydrins to thiazepine derivatives. This transformation closely resembles that of 6-α-chloropenicillanic acid to thiazine **6** reported by *Stoodley et al.* [3].

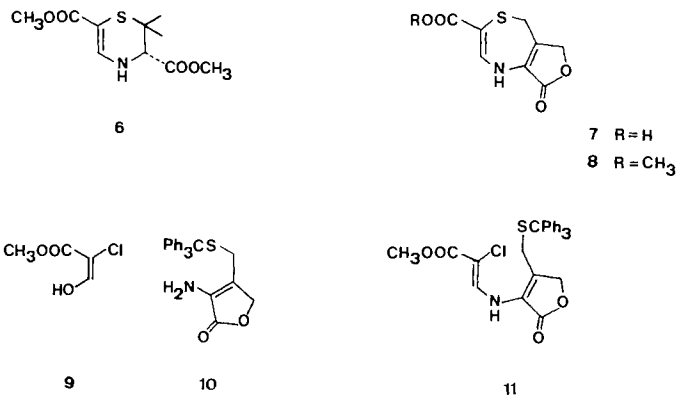
The *trans* bromohydrin **2** was found to be unstable, decomposing slowly on storage, with liberation of HBr. The corresponding acetate **3** decomposes even faster than the parent compound. After 120 hours of storage, we could isolate the decomposition product **7**, m.p. 222–224° in 82% yield. Compound **7** analysed for $C_8H_7NO_4S$, IR. (KBr): 3440 br., 1770, 1650, 1600; MS. (*m/e*): 213 M^+. NMR. showed only four signals, at 9.29 (*d*, $J = 7$ Hz, 1H, NH, exchangeable with D_2O), 7.79 (*d*, $J = 7$ Hz, 1H), 4.84 (*s*, 2H, lactone CH_2) and 3.58 (*s*, 2H, SCH_2) and the characteristic β-lactam protons are missing in the spectrum. Based on the above data the thiazepine structure **7** was proposed for the product. The chemical shift found for the vinylic hydrogen atom and the coupling constant with the adjacent NH group compares well with the value reported for a similar proton in compound **6** (7.76, *d*, $J = 7$ Hz) [3]. Compound **7**, on treatment with diazomethane afforded, as expected, the methyl ester **8** and all the data on this compound are in complete agreement with the proposed structure.

The *cis* bromohydrin **4** and its acetate **5** were found to be stable under normal conditions, however, they rearranged readily to the thiazepine **7** on warming in dioxane with few drops of 1N HCl. Both the bromohydrins **2** and **4** and their acetates **3** and **5**, on refluxing in methanolic HCl-solution gave the methyl ester **8** in high yield.

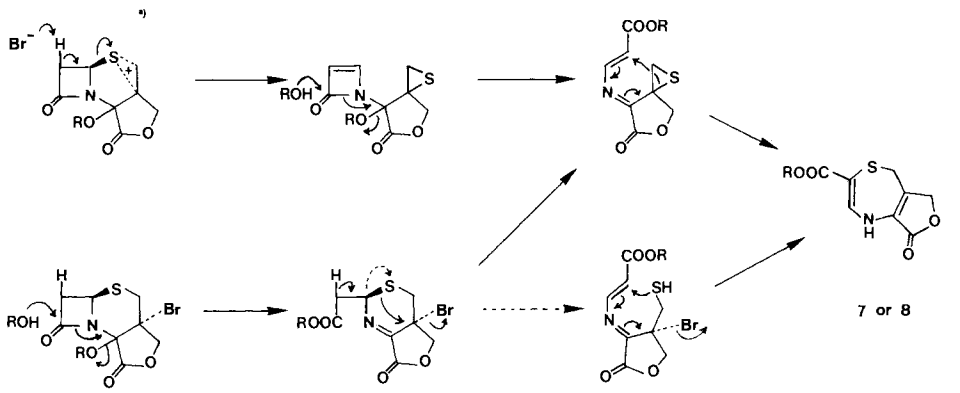
The structure of compound **8** was conclusively established by an unambiguous synthesis. Condensation of methyl 2-chloro-3-oxopropionate (**9**) [4] [5] with the aminofuranone **10** [6], yielded compound **11** in 90% yield. Removal of the trityl protecting group [7] and cyclization to compound **8** was achieved in one step by treating compound **11** with dry HCl in dry nitromethane. The thiazepine **8** thus obtained was identical in all respects with the one isolated earlier.

Regarding the mechanism of formation of these thiazepines **7** and **8** from cephems **2**, **3**, **4**. and **5**, nothing is known at present, and obviously it shall be a complex

Scheme 1



Scheme 2



a) The sulfonium ion postulated here is analogous to the one proposed for the interconversion of penicillins and cephalosporins [8].

process involving the formation of several intermediates. Two probable mechanisms, which we think worth considering, are shown in *Scheme 2*. Decomposition of compounds **2** and **3** by a radical process is not ruled out.

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Experimental part

General remarks. Preparative chromatography was carried out on silica gel (*Merck*, 0.05–0.20 mm). Melting points are not corrected. UV. spectra: λ_{max} in nm, log ε in parentheses. IR. spectra: $\tilde{\nu}_{max}$ in cm^{-1}, abbreviations: *s* = strong, *m* = medium, *w* = weak. NMR. spectra: internal standard tetramethyl silane ($\delta = 0$ ppm), abbreviations: *s* = singlet, *d* = doublet, br. = broad, *J* = spin-spin coupling constant (Hz). Mass spectra (MS): *m/e*, relative peak intensity in parentheses.

8-Oxo-1,4,5,6-tetrahydro-furo[3,4-e][1,4]thiazepine-3-carboxylic acid (**7**). a) *From acetate* **3**. 400 mg (1.13 mmol) of **3** was allowed to stand for 120 h without protection from atmosphere. The resulting brown material on recrystallization from methanol yielded compound **7** as pale yellow crystalline solid, 196 mg (82%), m.p. 222–224°, Rf ($CHCl_3$/MeOH 9:1) = 0.1. – IR. (KBr): 3440*s*, 3250*m*, 1770*s*, 1650*s*, 1600*s*, 1550*s*, 1430*m*, 1340*s*, 1280*s*, 1260*s*, 1220*s*, 1190*m*, 1160*s*, 1085*m*, 1060*s*, 1030*m*, 1000*s*, 945*m*, 900*m*, 850*m*, 800*w*, 770*m* and 690*w*. – NMR. (DMSO-d_6): 9.29 (*d*, *J* = 7 Hz, 1 H, NH); 7.79 (*d*, *J* = 7 Hz, 1 H, vinylic H); 4.84 (*s*, 2 H, lactone CH_2); 3.58 (*s*, 2 H, SCH_2). – MS. (140°): 213 (0.1, M^+), 183 (100), 169 (8), 168 (12), 152 (10), 124 (8), 116 (21), 59 (15), 57 (28), 45 (11), 28 (18).

$C_8H_7NO_4S$	Calc.	C 45.08	H 3.31	N 6.57	S 15.02%
(213.14)	Found	„ 44.87	„ 3.38	„ 6.42	„ 14.91%

b) *From bromhydrin* **4**. 293 mg (1 mmol) of **4** was dissolved in 20 ml of dioxane containing few drops of 1 N HCl and the reaction mixture was warmed at 80° for 45 min. The pale yellow compound, which seperated from the reaction mixture on addition of few drops of water, was recrystallized from methanol and was found to be identical in all respects with compound **7** isolated in the earlier experiment.

Compounds **2**, **3** and **5** on similar treatment as above yielded compound **7**.

Methyl-8-oxo-1,4,5,6-tetrahydrofuro[3,4-e][1,4]thiazepine-3-carboxylate (**8**). a) *From compound* **7**. 75 mg (0.35 mmol) of acid **7** was suspended in 50 ml of acetonitrile followed by the addition of ethereal diazomethane until the persistence of the yellow colour and the reaction mixture was taken to dryness. The residual oil thus obtained was purified by preparative TLC. with CH_2Cl_2 as solvent. Recrystallization from ether gave compound **8** as colourless crystalline solid, 74 mg (90%), m.p. 229°, Rf ($CHCl_3$/MeOH 9:1) = 0.86. – UV. (EtOH): 283 (4160), 352 (5370). – IR. (KBr): 3420*m*, 3075*w*, 2950*w*, 1755*s*, 1670*s*, 1600*s*, 1535*s*, 1435*m*, 1355*m*, 1250*m*, 1245*s*, 1190*m*, 1160*m*, 1095*m*, 1070*s*, 1000*s*, 770*m*, 760*m*, 650*w*. – NMR. (DMSO-d_6): 9.45 (*d*, *J* = 7 Hz, 1 H, NH); 7.79 (*d*, *J* = 7 Hz, 1 H, vinylic H); 4.84 (*s*, 2 H, lactone CH_2); 3.64 (*s*, 3 H, $COOCH_3$); 3.60 (*s*, 2 H, SCH_2). – MS. (100°): 227 (57, M^+), 198 (14), 183 (100), 170 (10), 169 (13), 168 (18), 152 (12), 124 (9), 116 (11), 59 (10), 57 (12), 45 (12), 28 (107).

$C_9H_9NO_4S$	Calc.	C 47.57	H 3.99	N 6.16	S 14.11%
(227.17)	Found	„ 47.68	„ 4.09	„ 6.03	„ 14.07%

b) *From bromohydrin* **4**. 200 mg (0.68 mmol) of **4** was dissolved in 25 ml of dry methanol and the solution was saturated with dry HCl. The reaction mixture was refluxed for 1 h, evaporated to dryness and the residue was chromatographed on a column of silica gel using $CHCl_3$ as an eluent. First fractions gave compound **8** and was recrystallized from ether as colourless crystalline solid, 131 mg (85%), identical in all respects with the compound obtained earlier.

Compound **2**, **3** and **5** on similar treatment with dry methanol and HCl yielded compound **8**.

3-(N-β-carbomethoxy-β-chloro-vinylamino)-4-[(triphenylmethylthio)methyl]-2,5-dihydrofuran-2-one (**11**). 1.93 g (5 mmol) of amine **10** [5] and 0.68 g (5 mmol) of methyl-2-chloro-3-oxopropionate (**9**) [4] were dissolved in 200 ml of dry benzene. After the addition of catalytic amount of *p*-toluene sulfonic acid, the reaction mixture was refluxed for 1 h and the water was removed with a *Dean Stark* trap.

The yellow solution thus obtained was evaporated and the residue was filtered through a column containing 30 g of silica gel using CH_2Cl_2 as an eluent. The oil thus obtained, on recrystallization from ether/light petroleum yielded compound **11** as pale yellow crystalline solid, 2.25 g (90%), m.p. 117°, Rf ($CHCl_3$/MeOH 97:3) = 0.37. – UV. (EtOH): 261 1530), 311 (3660). – IR. ($CHCl_3$): 3450*w*, 3090–2840*w*, 1765*s*, 1710*s*, 1680*s*, 1640*s*, 1490*m*, 1440*m*, 1430*m*, 1350*w*, 1305*w*, 1255–1195*s*, 1140*w*, 1105*m*, 1060*m*, 1030*w*, 995*w*. – NMR. ($CDCl_3$): 8.36 (*d*, J = 12 Hz, 1H, vinylic H); 7.50–7.20 (*m*, 15H, triphenyl); 6.43 (br. *d*, J = 12 Hz, 1H, NH); 4.50 (*s*, 2H, lactone CH_2); 3.78 (*s*, 3H, $COOCH_3$); 3.20 (*s*, 2H, SCH_2). – MS. (105°): 243 (100), 228 (11), 215 (10), 193 (9), 167 (24), 166 (20), 165 (90), 60 (15).

$C_{28}H_{24}ClNO_4S$	Calc.	C 66.45	H 4.78	H 2.77	S 6.34	Cl 7.01%
(506.34)	Found	„ 66.75	„ 4.96	„ 2.64	„ 6.18	„ 7.25%

Methyl-8-oxo-1,4,5,6-tetrahydro-furo[3,4-e][1,4]thiazepine-3-carboxylate (**8**). *From compound* **11**. 2.00 g (3.96 mmol) of **11** was dissolved in 250 ml of dry nitromethane and was cooled on ice to 0°. Dry HCl was passed through the solution for 30 min and the reaction mixture was allowed to stand at room temperature for 72 h with stirring. The reaction mixture was diluted with 200 ml of chloroform and was evaporated to dryness and recrystallized from methanol by cooling at 0° for 24 h. The colourless crystalline solid, 540 mg thus obtained was identical with compound **8** isolated earlier in all respects.

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207. Kreuzkonjugierte Cyanine und Merocyanine aus Salzen des 1-substituierten 2,3-Dimethylchinoxalins (Vinyloge von Indigo-imiden mit cyclisch eingebauter Imidfunktion)

Vorläufige Mitteilung[1])

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(25. VII. 77)

Crossed conjugated Cyanines and Merocyanines, obtained from Salts of 1-substituted 2,3-Dimethylquinoxalines. (A second type of vinylogous Indigo-imides.) Preliminary Communication.

Summary

On dissolving quaternary salts of 2,3-dimethylquinoxaline in dimethylformamide or dimethylsulfoxide, a spontaneous reaction takes place: the title compounds are isolated from the reaction mixtures; they are easily oxidized, *e.g.* by MnO_2. Mechanistic aspects are discussed.

[1]) Eine ausführliche Mitteilung soll später in dieser Zeitschrift erscheinen.