Pergamon

Tetrahedron 54 (1998) 6565–6570

TETRAHEDRON

Reactions of cephalosporin sulphones 2. Rearrangement of 2α-bromocephem sulphones to pyrroles[1]

Tamás E. Gunda* and Gabriella N. Szőke‡

Research Group for Antibiotics, Hungarian Academy of Sciences, P.O.Box 70, H-4010 Debrecen, Hungary

Received 8 January 1998; revised 3 April 1998; accepted 7 April 1998

Abstract: 2α-Bromocephem sulphones exhibit two different rearrangements in acetonitrile solution: first, the tendency for elimination of the bromine as a bromonium ion leads to its formal movement to the para position of the 7ß-aromatic ring. Secondly, a bromopyrrole derivative may also form, which can possibly be attributed to an unusual Ramberg-Bäcklund-like rearrangement followed by bromination.

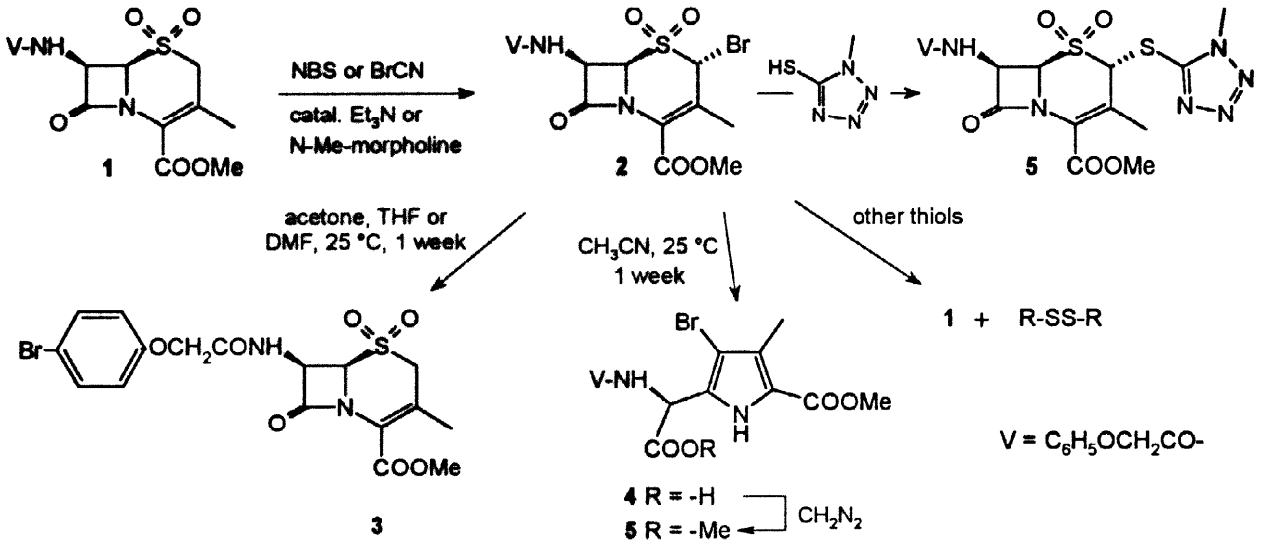
The use of 2-halogenocephalosporins represents an attractive route for obtaining multifariously substituted cephalosporins. Surprisingly, only a small number of papers are dealing with these compounds. The reason for this could be, that halogens in the immediate vicinity of sulphur, sulphoxides or sulphones often exhibit diverse activities in nucleophilic reactions. The first investigations of 2-halogenocephems were connected with the allylic halogenation of the 3-methyl-group of the cephems, when they were obtained as undesired byproducts. In the recent years especially Alpegiani *et al.* probed into the investigation of cephalosporin sulphones; their investigations led to the discovery of 2-mercaptoheteroaryl-cephem sulphones with high leucocyte elastase inhibiting properties.[2] Our aim was the systematic investigation and comparison of the behavior of cephem sulphides, sulphoxides and sulphones with different halogenation agents, and their reactivity under various conditions. In the course of this work we encountered two new interesting rearrangements of 2-bromocephem sulphones.

Discussion

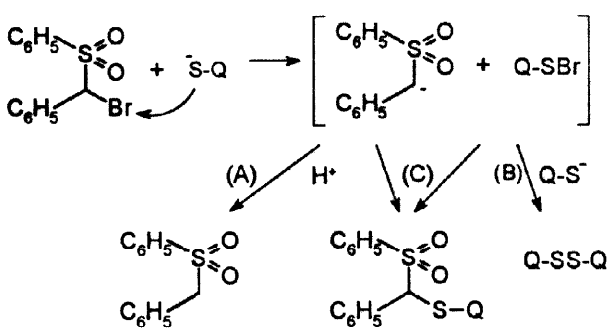
In default of a good process for the preparation of 2-bromocephem sulphones we have developed a process using the *in limbo* bromination agent cyanogen bromide, catalysed by a strong base.[3] The attempted nucleophilic displacement reaction of **2** with different thiolates led to the same result already described by others.[2,4,5] For example, among the thiols investigated only 4-mercapto-1-methyltetrazole was able to take part in a normal nucleophilic process, leading to the formation of 2-mercaptocephem derivative **5**. In contrast, only the reduced precursor **1** and the corresponding disulphides were isolated with other thiols like alkylmercaptanes, thiophenol, mercaptopyridines.

‡ **Present address:** Department of Clinical Chemistry, School of Medicine, University of Debrecen, Debrecen, Hungary

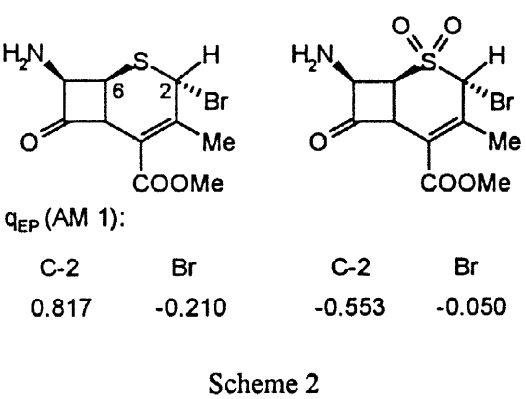
0040-4020/98/$19.00
PII: S0040-4020(98)00316-0



When **2** was allowed to stay in different solvents without any reaction partner for a longer time at room temperature, the slow formation of two new compounds was observed. In THF, acetone or DMF solution the main product **3**, came from the para bromination of the aromatic ring, together with varying amount of **1**. When the acetonitrile solution of **2** was allowed to evaporate slowly in the air, the result was an about 1:1 mixture of **1** and the bromopyrrole derivative **4**. We ascribe all of these phenomena to the inverse polarity of the C-2–Br bond, or in other words, the bromine atom in the 2-bromocephem sulphones is relatively positively charged compared to the carbon. This may cause the nucleophilic partner to attack the bromine instead of the carbon as pointed out by Bordell and Jarvis,[5] and outlined in Scheme 1. This gives rise to the formation of a sulfenyl



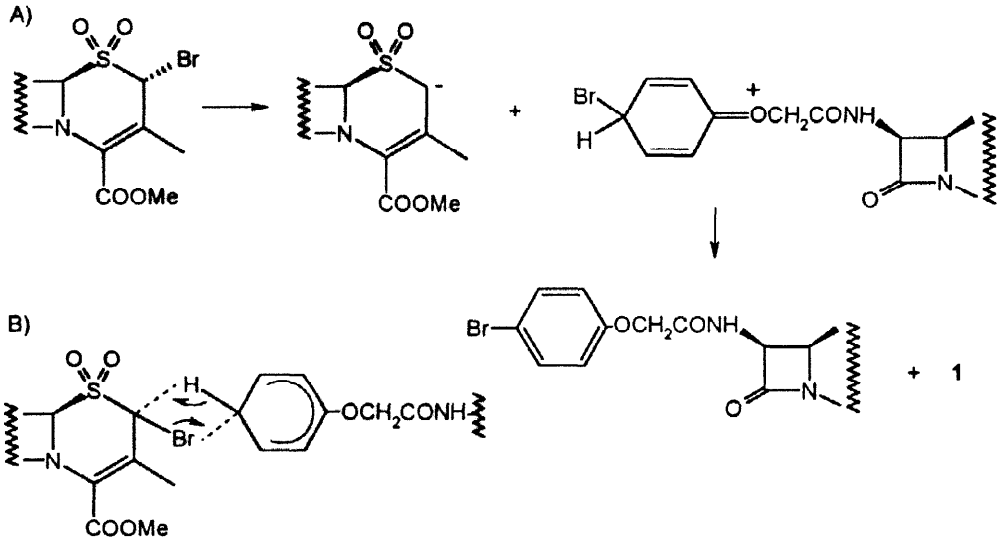
Scheme 1



Scheme 2

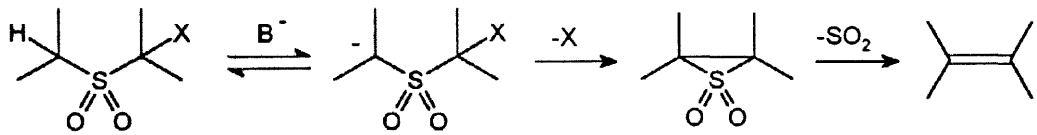
bromide and an anion, which, in turn, yield to the reduced starting material (route A), the disulfide (route B) and varying amount of the substituted product. In this latter substitution process the anion plays formally the role of the nucleophilic reagent and attacks the sulfenyl bromide. Because the anion does not retain its configuration, in our case the α-face stereoselectivity of the reaction can be attributed to a reagent approach control. We found that simple semiempirical charge calculations can add quantitative support to this mechanism: in Scheme 2, the calculated EP charges at C-2 and the bromine atom in a sulphide and its sulphone can be seen. It is noteworthy that the bromine atom is more positive than the carbon, so the polarization of the C-2–Br bond is reversed in the sulphone.

In our opinion this reversed charge relation is the cause of the two rearrangements. Thus, the formation of 3 can be explained as follows: the formal heterolytic splitting of the C-2 – Br bond leads to a bromonium ion. The benzene ring of a neighbour molecule may form a π-complex with the bromine and this may enhance the initial polarization of this bond. A subsequent electrophilic bromination process can lead to the brominated end product (Scheme 3A). We can speculate that these steps are not necessarily fully separated and no free bromonium ion forms, the interchange of the bromine and proton may occure via a more or less cyclic (but concerted) transition state as depicted in Scheme 3 B.



Scheme 3.

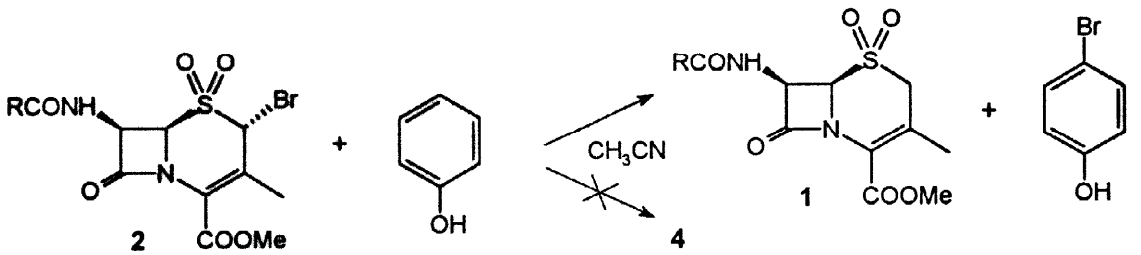
It is more difficult to find an acceptable mechanism for the formation of 4. In the key step a sulphur dioxide eliminates from the thiazine ring accompanied with the simultanous formation of a new double bond. This step is formally very similar to the classical Ramberg – Bäcklund rearrangement.[6] In this process α-halogeno sulphones are capable of an intramolecular 1,3-elimination under alkaline conditions. The carbanion mechanism as outlined in Scheme 4 has generally been accepted. Halogenated products have never been found to form in the rearrangement, however, there is a so called Meyers variation of this rearrangement,[7] where the initial



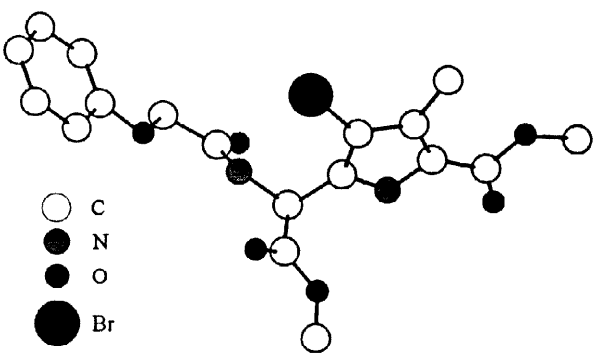
Scheme 4.

halogen derivative is generated *in situ* and more or less halogenated byproducts also form. According to our knowledge no investigations were done to elucidate whether this type of Ramberg – Bäcklund rearrangement starts from a dihalogen derivative or halogenation occurs afterwards. In our case there are no basic reaction conditions which could lead to the elimination of a proton from position 6. On the other hand, the rearrangement is connected with the leaving of the bromine atom and the formation of bromonium ion. This was also witnessed in the experiment when 2 was allowed to stay in acetonitrile solution in the presence of ten

times excess phenol; no formation of **4** was observed but the presences of 4-bromophenol and the starting **1** were easily detected and identified by chromatography.



Also it is interesting that among the investigated solvents the formation of **4** was observed only in acetonitrile solution: SO_2 and HBr elimination instead of electrophilic bromination. In our opinion a reason for this may lie in the interaction of acetonitrile and the bromonium ion: acetonitrile may interact with the ion and stabilize it to some extent with the aid of its C≡N π-bonds or the lone pair of the nitrogen. This may decrease the reactivity of bromonium ion toward the aromatic ring. The resulting **2a** ionic transition product (Scheme 5) may initiate an "inverse-way" Ramberg-Bäcklund rearrangement: instead of the usual replacement of the halogen by a β-carbanion, now the anion having resulted from the halogenium loss would expel the β-hydrogen. In such a process the hydrogen should leave in the form of a hydride ion, which should be considered to very unlikely *per se*. However, the Br^+-CH_3CN complex could facilitate the expelling of the C-6 hydrogen, leading to **2c**. Thus, formally a HBr 1,3-elimination takes place as depicted by **2b**. After the SO_2 elimination the highly strained ring system of **2d** splits very easily yielding to **2e**, which, in turn, is brominated by **2** to the endproduct **4**, by the analogy of the reaction **2** → **3** previously discussed. This is supported by the fact that nearly an 1:1 mixture of **2** and **4** forms, and, in turn, pyrrole is extremely susceptible to electrophilic attack owing to its π-electron excessive character and reacts readily with electrophiles.[8]



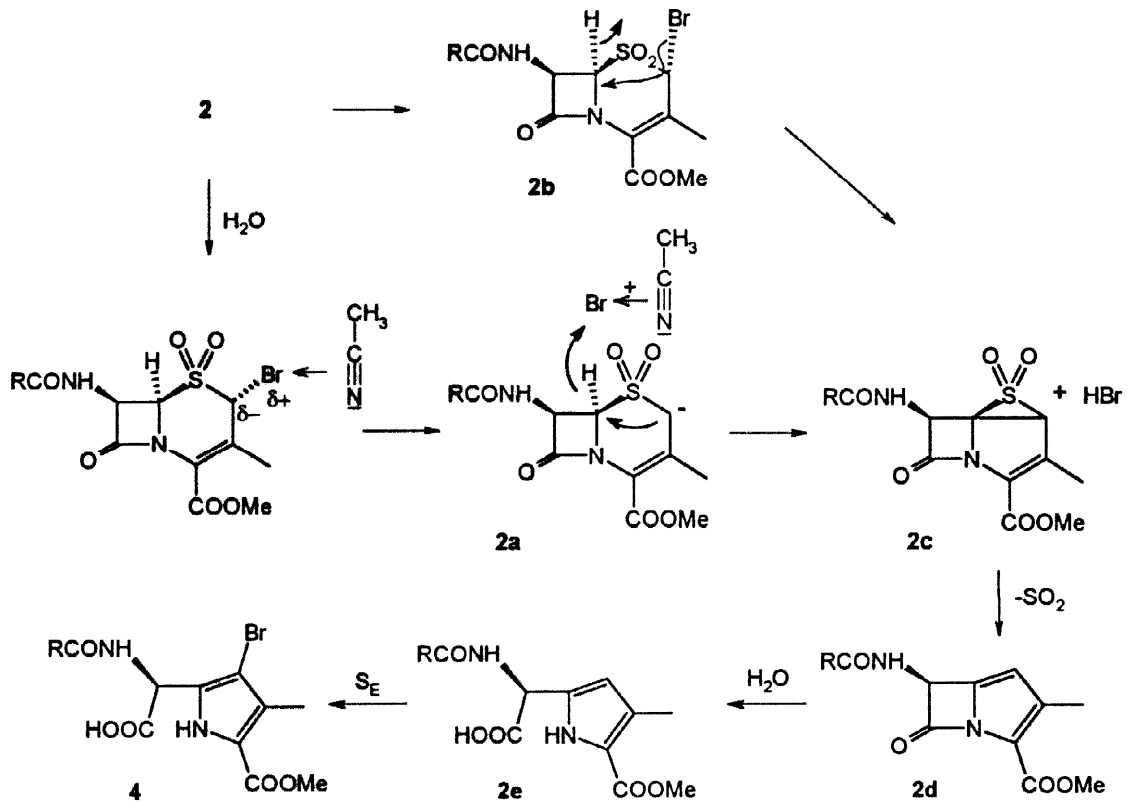
X-Ray structure of **5**.

Acknowledgement

This work was funded by the grant of the Hungarian National Science Fund OTKA T 23592. We thank Dr Attila Bényei for the X-ray structure analysis.

Experimental

Melting points were determined on a Koffler-type hot-stage apparatus. IR spectra were recorded on a Perkin-Elmer 283B spectrophotometer in KBr pellets. The ^1H NMR spectra were recorded on a Bruker WP-SY-200 instrument, with Me_4Si as internal standard. The X-ray data were collected with an Enraf-Nonius Mach3 diffractometer.



Scheme 5.

The starting **methyl 1,1-dioxo-2α-bromo-3-methyl-7-phenoxyacetamido-cephem-4-carboxylate (2)** was prepared from **1** with cyanogen bromide[3] in CH_2Cl_2, and after evaporation of the solvent it was used immediately for the next reactions.

Methyl 1,1-dioxo-3-methyl-7-(4-bromo-phenoxyacetamido)-cephem-4-carboxylate (3): **2** (prepared from 0.43 g of **1**) was dissolved in 20 ml of acetone, THF or DMF, and was allowed to stand at room temperature. The reaction was followed with thin layer chromatography (silicagel, toluene-EtOAc-AcOH 7:3:1). After 6 days no more changes were observed, and the reaction mixture consisted of an about 1:1 mixture of **1** and **3**. The latter compound, possessing somewhat higher R_f value, was separated and purified by column chromatography yielding 0.17 g of **3** (33 % from **1**). M.p.: 223-5 °C; ^{1}H NMR (DMSO-d_6) δ 1.98 (s, 3H), 3.77 (s, 3H), 4.17 - 4.31 (ABq, 2H), 4.56 - 4.75 (ABq, 2H), 5.31 (d, H, J = 5.2 Hz), 5.00 (dd, H, J = 5.2 and 9.2 Hz), 6.84-7.45 (AA'BB', 4H, characteristic of para-disubstituted benzene, J = 8.8 Hz); IR (KBr) ν 1798, 1732, 1700, 1488, 1330, 1232 cm^{-1}; MS (EI) ($C_{17}H_{17}N_2O_7SBr$, 473.30) m/e: 472 (1.1%, M), 155 (71%, $BrC_6H_4^+$); analysis for $C_{17}H_{17}N_2O_7SBr$ calc./found %: C 43.14/42.88, H 3.62/3.58, N 5.92/5.99, Br 16.88/17.07

Methyl 4-bromo-5-[carboxy-(2-phenoxyacetamido)-methyl]-3-methyl-1H-pyrrole-2-carboxylate (4): When the previous reaction was carried out in acetonitrile at room temperature, slow crystallization started after 2 days. The reaction mixture was allowed to evaporate slowly to 20% of its original volume. The precipitate was filtered and recrystallized from acetonitrile. 0.12 g (23 % from **1**), m.p.: 229-221 °C; $[\alpha]_D^{20}$ 48.7

(0.318, MeOH); ^{1}H NMR (DMSO-d_6) δ: 2.09 (s, 3H), 3.68 (s, 3H), 4.48 (s, 2H), 5.71 (d, H, J = 8.9 Hz), 6.85-7.25 (m, 5H), 8.53 (d, H, J = 8.9 Hz), 11.9 (s, H); ^{13}C NMR (DMSO-d_6) δ: 11.3 (CH_3), 47.7 (CH), 51.2 (OCH_3), 66.9 (CH_2), 100.2 (C), 114.9 (CH), 118.1 (C), 121.5 (CH), 125.2 (C), 129.5 (CH), 129.7 (C), 157.5 (C), 160.5 (CO), 167.4 (CO), 169.5 (CO); analysis for $C_{17}H_{17}N_2O_6Br$ calc./found %: Br 18.79/18.22, S 0.0/0.08

Methyl 4-bromo-5-[carbomethoxy-(2-phenoxyacetamido)-methyl]-3-methyl-1H-pyrrole-2-carboxylate (5). This compound was prepared by adding diazomethane to the methanol solution of **4** until the disappearance of the starting material. The obtained ester was recrystallized twice from methanol – ether, m.p. 160-3 °C. Crystall data: $C_{18}H_{18}BrN_2O_6$, M = 438.25, triclinic P1$^-$, a = 7,414(2), b =11.647(3), c = 11.815(3) Å, α = 104.98(2)°, β = 93.91(1)°, γ = 97.19(2)°, V = 926.6(4) Å^3, Z = 2, T = 293 K, μ = 2,256 mm^{-1}; wR(F^2) = 0,1962 (244 parameters). The data collection was performed with an Enraf-Nonius Mach3 diffractometer, the collection, calculation and refinement of the data were made by the programs CAD-4 Express, SIR-92 and SHELXL93

References

1) First part: Gunda, T. E.; Tamás, L.and Sályi, S. *Tetrahedron Lett.* **1998**, *39*, 3061
2) a) Alpegiani, M.; Bissolino, P.; Borghi, D.; Sbraletta, D.; Tonani, R. and Perrone, E. *Heterocycles* **1993**, *36*, 1747; b) Alpegiani, M.; Bissolino, P.; Corigli, R.; Del Nero, S.; Perrone, E.; Rizzo, V.; Sacchi, N., Cassinelli, G.; Franceschi, G. *J. Med. Chem.* **1994**, *37*, 4003
3) Gunda, T. E. and Szőke, G. N. *Synth. Commun.* **1997**, *27*, 3395
4) Botta, M.; Crucianelli, M.; Saladino, R. and Nicoletti, R. *Heterocycles* **1992**, *34*, 1375
5) Bordwell, F. G. and Jarvis, B. B. *J. Org. Chem.* **1968**, *33*, 1182
6) Review article *Paquette, L. A.*: "The Ramberg-Bäcklund Rearrangement", *Org. Reactions* **1977**, *25*, 1
7) a) Cusy, G. and Taylor, J. K. *Tetrahedron* **1989**, *45*, 455; b) Kaltemberg, J.; de Waard, E. R. and Huisman, H. O. *Tetr. Letters* **1973**, 1482
8) Jones, R. A.: "Pyrroles and their Benzo-derivatives: Reactivity" in "Comprehensive Heterocyclic Chemistry" (Bird, C. W. and Cheeseman, G. W. H., eds.), vol 4., p 201. Pergamon Press, **1984**.
9) The referee suggested an interesting alternative mechanism for the formation of **4**: the dibromo derivative **A** could form via a disproportionation, which, in turn, could hydrolytically cleave to intermediate **B**. Subsequent cyclisation and elimination results in **4**: