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NON-STEREOSPECIFIC RING EXPANSIONS OF BENZOTHIAZOLINE SULFOXIDES[1)]

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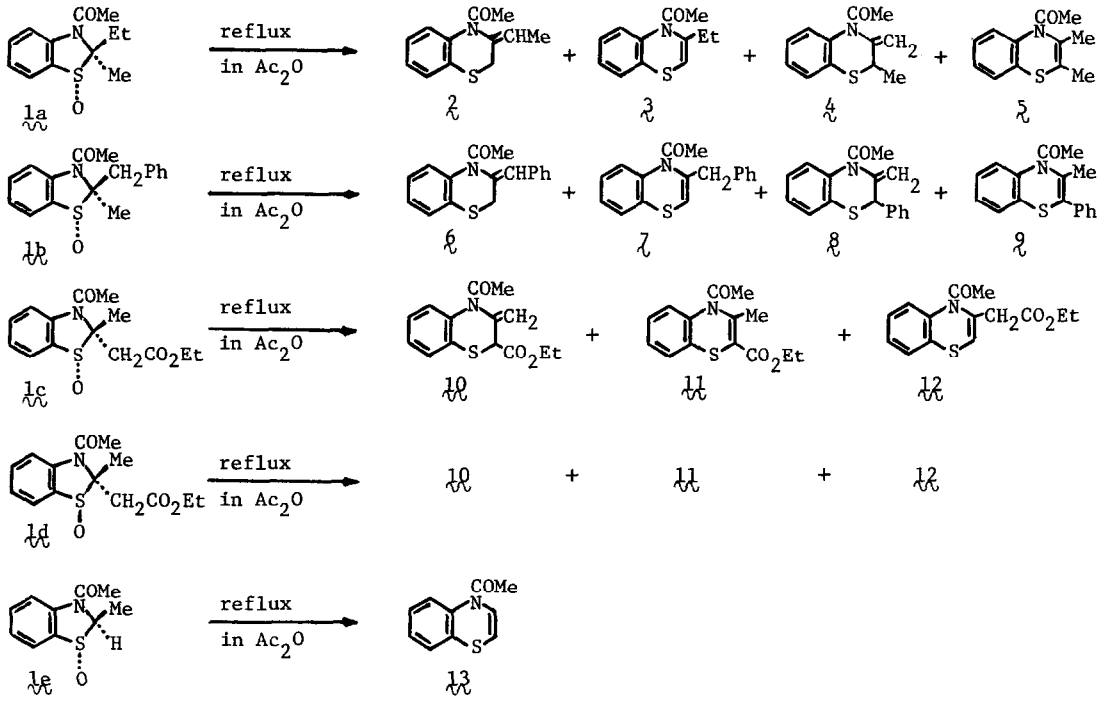
Summary: Non-stereospecific ring expansions of 3-acetylbenzothiazoline sulfoxides to benzothiazines from the reaction with acetic anhydride are reported.

In our earier papers[2)], we reported a novel ring expansion of benzothiazoline sulfoxides to benzothiazines from the reaction with acetic anhydride and that the reaction proves to be widely applicable for the preparation of 1,4-benzothiazines. Now, in order to investigate the stereospecificity of this novel ring expansion we carried out the ring expansion of some benzothiazoline sulfoxides having two different substituents at 2-position[3,4)] with acetic anhydride and found that the reaction is non-stereospecific and quite different from the well-known ring expansion of penicillin sulfoxides to cephalosporins (Morin rearrangement[5)]).

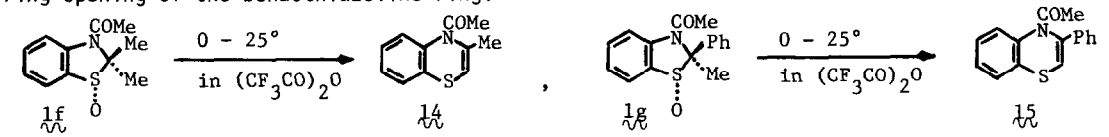
The reaction results are shown in Scheme I. Refluxing trans-3-acetyl-2-ethyl-2-methylbenzothiazoline 1-oxide (1a) in acetic anhydride for 1.5 hr produced four benzothiazines 2, 3, 4 and 5 in yields of 29, 15, 25 and 7 %, respectively. From the reaction of trans-3-acetyl-2-benzyl-2-methylbenzothiazoline 1-oxide (1b), the similar results were obtained, affording four ring expansion products 6, 7, 8 and 9 in yields of 35, 5, 23 and 9 %, respectively. Compounds 2, 3, 6 and 7 are the products expanded in the direction of the substituents (methyl group of 1a and 1b) cis to the sulfoxide moiety. On the contrary, compounds 4, 5, 8 and 9 are the products expanded in the direction of the trans substituents (ethyl group of 1a; benzyl group of 1b) to the sulfoxide oxygen. The ratio of the products expanded in the two directions is about 4 : 3 in both sulfoxides 1a and 1b. These results indicate that the ring expansions proceeded equally with either the cis or the trans sulfoxide, and therefore the reactions are non-stereospecific. Although cis-3-acetyl-2-ethoxycarbonylmethyl-2-methylbenzothiazoline 1-oxide (1c) gave 10 and 11 which were expanded in the direction of cis ethoxycarbonylmethyl group in total yield of 84 %, together with 12 expanded in the opposite direction in only 3 % yield, the trans isomer (1d) gave 10 and 11 mainly (total yield of 49 %) which are the products expanded in the trans direction, and 17 % yield of 12 expanded in the cis direction. This result shows that the ring expansion proceeds in the direction of the substituent having more acidic protons if the acidity of protons between the two substituents is remarkably different. trans-3-Acetyl-2-methylbenzothiazoline 1-oxide (1e) also afforded a ring expanded product 13 in 39 % yield. We attempted to detect, in the course of the reaction, another isomer of the sulfoxide which might be formed by epimerization under the reaction conditions by thin-layer chromatography (TLC) and NMR spectral analysis, but we could not observe any isomers.

We next tried the ring expansion of the sulfoxides with trifluoroacetic anhydride at 0 -



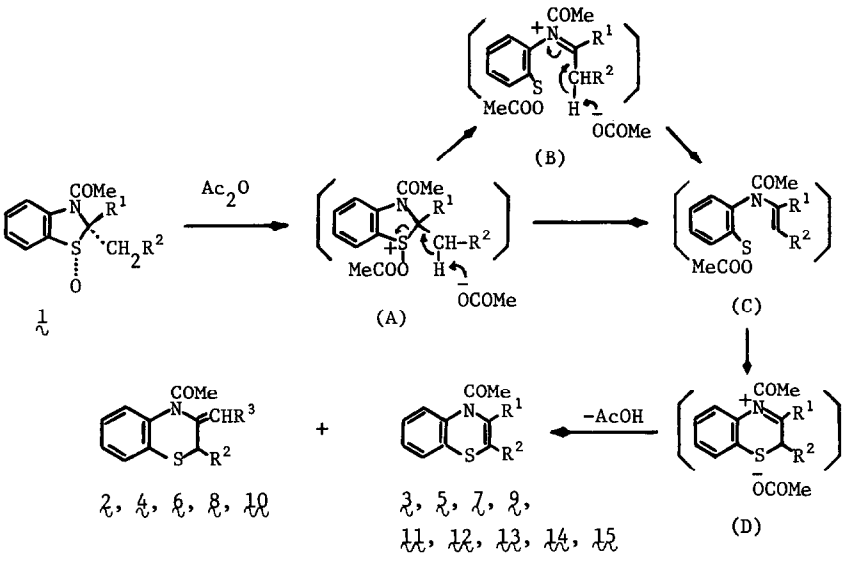
Scheme I

25°, under whose conditions thermally induced epimerization or reaction of the sulfoxides may not occur. Treatment of 3-acetyl-2,2-dimethyl-(1f) or trans-3-acetyl-2-methyl-2-phenylbenzothiazoline 1-oxide (1g) with trifluoroacetic anhydride at 0 - 25° caused ring expansion to afford 14 or 15 in 32 or 38 % yield, respectively (Scheme II). Moreover, stirring 1c in trifluoroacetic anhydride yielded two ring expansion products 11 and 12 in yields of 26 and 16 %, respectively. This indicates that acid anhydrides strongly act as reaction initiators for the ring opening of the benzothiazoline ring.



Scheme II

Based on the above results, it became obvious that the ring expansion of benzothiazoline sulfoxides to benzothiazines with acid anhydrides is non-stereospecific, different from the similar ring expansion of penicillin sulfoxides to cephalosporins which is stereospecific.[5] The reaction pathway may be explained by the mechanism depicted in Scheme III. The mechanism involves initial acetylation of oxygen atom of the sulfoxide with acetic anhydride, forming an intermediate (A), followed by S-C_2 bond cleavage with β-hydrogen abstraction to give sulfenic anhydride (C) or by direct S-C_2 bond cleavage due to the participation of the lone pair on the nitrogen atom at 3-position to form an intermediate (B) which leads to the intermediate (C).



Scheme III

Sulfenic anhydride (C) gives the immonium ion (D) by recyclization with the loss of acetate anion. Collapse of the immonium ion (D) leads to the observed products. In the intermediate (A), the stereochemistry of the sulfoxide may be lost by pyramidal inversion of the sulfonium center, and the intermediate (B) apparently loses the stereochemistry of the sulfoxide because of direct ring opening, clearly explaining the non-stereospecificity of the ring expansion.

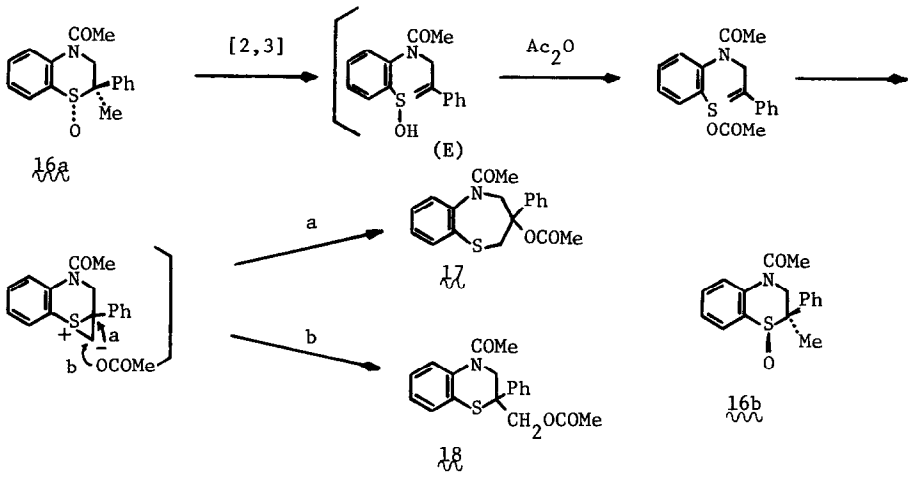
It is more reasonable to consider that this non-stereospecificity may result from easy cleavage[6] of C_2-S bond in thiazoline ring by the participation of the lone pair on the nitrogen atom at 3-position of benzothiazoline 1-oxide. This assumption was verified by the stereospecific ring expansion of 1,4-benzothiazine sulfoxides, in which direct electronic effects of nitrogen atom for the cleavage of C_2-S bond leading to the ring expansion are blocked since one methylene linkage is introduced between sulfur and nitrogen atoms. Refluxing of trans-4-acetyl-2-methyl-2-phenyl-2,3-dihydro-4H-1,4-benzothiazine 1-oxide (16a[7] having methyl group cis to the sulfoxide oxygen) with acetic anhydride for 1.5 hr afforded ring expansion product 17[8] in 26 % yield together with 18[8] in 52 % yield (see Scheme IV). On the contrary, the cis isomeric sulfoxide (16b[7] having methyl group trans to the sulfoxide) was unaffected under the same reaction conditions. This stereospecific reaction result is explained by the mechanism postulating the sulfenic acid (E) resulted from thermal 2,3-sigmatropic rearrangement of 16a as a first intermediate as shown in Scheme IV.

REFERENCES AND FOOTNOTES

1) A part of this work was presented at the ACS/CSJ Chemical Congress, Honolulu, Hawaii, April 1979, Abstracts, ORGN-163.

2) a) M. Hori, T. Kataoka, H. Shimizu, and Y. Imai, Heterocycles, 1978, 10, 17; b) Idem, Chem. Pharm. Bull. (Tokyo), 1979, 27, 1973.

3) The 2,2-disubstituted benzothiazoline sulfoxides, required in the present study, were pre-



Scheme IV

pared by conventional method reported in our previous paper.[2b] The separation of cis and trans isomers was carried out by preparative TLC on silica gel with appropriate solvents. The configurational assignments of cis-trans stereoisomers of the sulfoxides were performed by NMR spectral analysis according to the previous paper.[2b]

4) The IR, NMR and mass spectra, and also the elemental analyses fully support the structures assigned to all new compounds.

5) E. H. Flynm, "Cephalosporins and Penicillins", Academic Press, Inc., New York, 1972, p.183; P. G. Sammes, Chem. Revs., 1976, 76, 113.

6) This kind of easy cleavage of thiazoline ring was observed by us as seen in the following reactions: 1,2,2,3-tetramethylbenzothiazolinium iodide formed in situ by methylation of 2,2,3-trimethylbenzothiazoline with methyl iodide easily underwent ring opening to give N-methyl-N-(o-methylthiophenyl)-N-isopropylideneiminium iodide (M. Hori, T. Kataoka, H. Shimizu, and Y. Imai, Chem. Pharm. Bull. (Tokyo), 1979, 25, 1482). Treatment of the sulfoxide 1g with methyl iodide in the presence of silver perchlorate gave acetophenone in quantitative yield (unpublished data).

7) The sulfoxide 16 was prepared through four steps from 2-phenyl-3-oxo-2,3-dihydro-4H-1,4-benzothiazine synthesized by the reaction of o-aminobenzenethiol with α-bromophenylacetic acid. The separation of the cis (16b) and trans isomers (16a) was successfully achieved by preparative TLC on silica gel using hexane-ethyl acetate (2:1). The configurational assignments of cis-trans stereoisomers were performed by NMR spectral analysis. The details will be reported in a full paper.

16a: mp 141-142°; IR(KBr)νmax cm^{-1} 1660(CO), 1050(SO); NMR($CDCl_3$)δ 1.63(3H,s,CH_3), 2.15(3H,s,$COCH_3$), 3.81(1H,d,J=14.5Hz,CH_2), 4.87(1H,d,J=14.5Hz,CH_2), 7.08-7.78(9H,m,ArH). 16b: mp 133-134°; IR(KBr)νmax cm^{-1} 1660(CO), 1050(SO); NMR($CDCl_3$)δ 1.86(3H,s,CH_3), 2.29(3H,s,$COCH_3$), 4.32(2H,ABq,J=14.5Hz,CH_2), 6.92-7.54(9H,m,ArH).

8) 17: mp 160-161.5°; IR(KBr)νmax cm^{-1} 1740(ester), 1660(CO); NMR($CDCl_3$)δ 1.82(3H,s,$OCOCH_3$), 2.13(3H,s,$COCH_3$), 2.69(1H,d,J=15Hz,C_2-H), 3.12(1H,d,J=15Hz,C_4-H), 4.09(1H,d.d,J=15, 2Hz, C_4-H), 5.33(1H,d.d,J=15, 2Hz,C_2-H), 7.00-7.80(9H,m,ArH); MS(m/e) 341(M^+), 281($M^+-CH_3CO_2H$). 18: oil; IR(neat)νmax cm^{-1} 1750(ester), 1660(CO); NMR($CDCl_3$)δ 1.97(3H,s,CH_3), 2.15(3H,s,CH_3), 3.62(1H,d,J=13Hz,CH_2), 4.54(2H,ABq,J=11.5Hz,CH_2), 4.99(1H,d,J=13Hz,CH_2), 6.96-7.62(9H,m,ArH); MS(m/e) 341(M^+).

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