View Article Online / Journal Homepage / Table of Contents for this issue

Published on 01 January 1983. Downloaded by Monash University on 25/10/2014 10:34:17.

A Simple Ring-expansion of 1,4-Benzothiazines to give 1,5-Benzothiazepines

Yoshifumi Maki,*[a] Magoichi Sako,[a] Naomichi Mitsumori,[b] Sadayuki Maeda,[b] and Masahiro Takaya*[b]

[a] *Gifu College of Pharmacy, 6-1, Mitahora-higashi 5 chome, Gifu, 502, Japan*
[b] *Research Laboratory, Hamari Chemicals Ltd., 4-29-1, Kunijima, Higashiyodogawa, Osaka, 533, Japan*

A new ring-expansion of 2-phenylmethylene-2*H*-1,4-benzothiazin-3(4*H*)-ones (**1**) to give 2,3-dihydro-3-oxo-2-phenyl-1,5-benzothiazepin-4(5*H*)-ones (**3**) has been developed; an episulphonium ion intermediate could be involved.

Only a few examples of the ring-expansion of 1,4-benzothiazines into 1,5-benzothiazepines have been reported.[1,2] The juxtaposition of the *exo*-methylene grouping to the sulphur in the 2-phenylmethylene-2*H*-1,4-benzothiazin-3(4*H*)-one system prompted us to explore a new route to the corresponding 1,5-benzothiazepine system.

This paper describes a simple conversion of the 1,4-benzothiazines into the 1,5-benzothiazepines which appears to involve an episulphonium ion intermediate. The ring-expansion proceeds under mild conditions and gives high yields. In principle it is widely applicable to the preparation of the thiazepine system.

The 4-methyl-2-phenylmethylene-2*H*-1,4-benzothiazin-3-(4*H*)-one derivatives (**1a**—**c**) were prepared easily by condensation of the parent 2*H*-1,4-benzothiazin-3(4*H*)-one with the corresponding benzaldehydes followed by methylation.[3,4] Trimethylsilyl chloride (6 mmol) was added to a solution of the 1,4-benzothiazine (**1a**) (2 mmol) in tetrahydrofuran and this was followed by the addition of 30% hydrogen peroxide (7.5 mmol) at −10 °C in portions.[5] After stirring at −10 °C

View Article Online

Published on 01 January 1983. Downloaded by Monash University on 25/10/2014 10:34:17.

for 4 h, the reaction mixture was worked up in the usual way and the chlorohydrin (**2a**) was isolated in 90% yield. The structure of (**2a**) was confirmed by spectral data,† mass spectrum *m/z* 320 (M^+); ^{1}H n.m.r. ($CDCl_3$, δ) 6.60 (1H, **s**, =C*H*Cl); i.r. (Nujol, cm^{-1}) 3300 (OH). The reaction of (**1a**) with trimethylsilyl hydroperoxide,[5] which was generated *in situ* from trimethylsilyl chloride and hydrogen peroxide, was the most convenient method of obtaining the chlorohydrin (**2a**), presumably *via* an epoxide intermediate.

Treatment of the chlorohydrin (**2a**) (1.5 mmol) with silver carbonate (2.0 mmol) in tetrahydrofuran for 30 min at 0 °C gave 2,3-dihydro-5-methyl-3-oxo-2-phenyl-1,5-benzothiazepin-4(5*H*)-one (**3a**) in 88% yield. The formation of an enol acetate and phenylhydrazone and the spectral data, *e.g.* i.r. (neat, cm^{-1}) 1720, 1670 (C=O); ^{1}H n.m.r. ($CDCl_3$, δ) 5.42 (1H, s, SC*H*CO), are consistent with the 1,5-benzothiazepine structure (**3a**). In order to eliminate the alternative 1,4-benzothiazine structure, 2-benzoyl-4-methyl-2*H*-1,4-benzothiazin-3(4*H*)-one (**7**) was prepared by the condensation of 4-methyl-2*H*-1,4-benzothiazin-3(4*H*)-one with methyl benzoate in the presence of sodium hydride in dimethyl sulphoxide.[6] The spectral data of (**3a**) were clearly different from those of (**7**) and therefore the 1,5-benzothiazepine structure (**3a**) was confirmed. Analogously, the 1,4-benzothiazines (**1b,c**) were converted into the 1,5-benzothiazepines (**3b,c**) respectively in high yields.

Treatment of (**1a**) (5 mmol) in toluene containing acetic acid with lead tetra-acetate (6 mmol) resulted in the formation of the diacetoxy derivative (**4**) in 76% yield. Compound (**4**) could be formed as shown by (A). The diacetoxy derivative (**4**) was partially hydrolysed with 10% hydrochloric acid to give the monoacetoxy derivative (**5**) (80%) which was identical in every respect with a sample obtained in 30% yield from the reaction of (**1a**) with hydrogen peroxide–acetic anhydride.[6] Further treatment of (**5**) with 10% sodium hydroxide gave the dihydroxy derivative (**6**) approximately quantitatively. The dihydroxy derivative (**6**) was obtained directly from (**4**) on hydrolysis with 10% sodium hydroxide. Ring-expansion to form (**3a**) was also achieved, in 75% yield, by the treatment of (**6**) with thionyl chloride in tetrahydrofuran.

The ring-expansion of (**2**) to give (**3**) can be reasonably explained by the intermediacy of an episulphonium ion as shown by (B). The thionyl chloride catalysed conversion of (**6**) into (**3a**) could also involve the episulphonium ion (B) as a key intermediate. It has been proposed that the ring-contraction of pyrimido-1,5-benzothiazepines to pyrimido-1,4-benzothiazines proceeds *via* an episulphonium ion intermediate.[7] An episulphonium ion intermediate has been considered for a number of ring-contractions and ring-expansions of sulphur-containing heterocycles.[8] In contrast to previous examples, this work provides a novel example of the ready ring-expansion which may arise from an episulphonium ion intermediate possessing a tertiary hydroxy group in the bridgehead.

Received, 31st January 1983; Com. 137

† All new compounds gave satisfactory microanalytical results and spectral data consistent with their proposed structures.

References

1 Y. Maki and T. Hiramitsu, *Chem. Pharm. Bull. (Tokyo)*, 1977, **25**, 292.
2 M. Hori, T. Kataoka, H. Shimizu, and N. Ueda, *Tetrahedron Lett.*, 1981, 1701.
3 V. Baliah and T. Rangarajan, *J. Chem. Soc.*, 1960, 4703.
4 J. Krapcho and C. F. Turk, *J. Med. Chem.*, 1973, **16**, 776.
5 T-L. Ho, *Synth. Commun.*, 1979, **9**, 37.
6 F. Eiden and F. Meinel, *Arch. Pharm.*, 1979, **312**, 302.
7 T. Hiramitsu, Y. Maki, and S. Senda, *J. Chem. Soc., Perkin Trans.* 1, 1978, 716.
8 H. C. Van der Plas, 'Ring Transformation of Heterocycles,' vol. 2, Academic Press, London and New York, 1973, p. 50.