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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

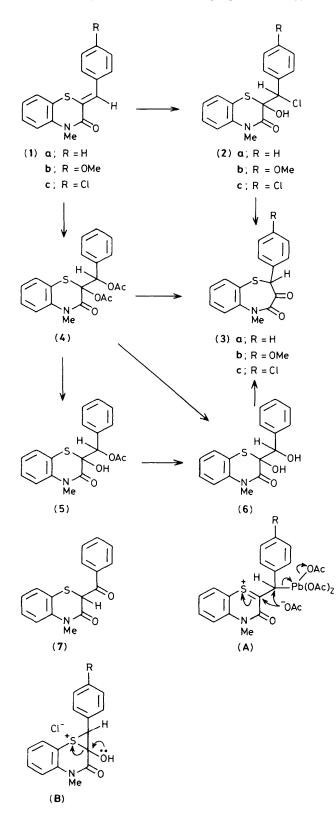
ª Gifu College of Pharmacy, 6-1, Mitahora-higashi 5 chome, Gifu, 502, Japan ^b Research Laboratory, Hamari Chemicals Ltd., 4-29-1, Kunijima, Higashiyodogawa, Osaka, 533, Japan

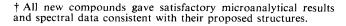
A new ring-expansion of 2-phenylmethylene-2H-1,4-benzothiazin-3(4H)-ones (1) to give 2,3-dihydro-3-oxo-2-phenyl-1,5-benzothiazepin-4(5H)-ones (3) has been developed; an episulphonium ion intermediate could be involved.

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-2H-1,4-benzothiazin-3(4H)-one system prompted us to explore a new route to the corresponding 1,5-benzothiazepine system.

This paper describes a simple conversion of the 1,4benzothiazines into the 1,5-benzothiazepines which appears to involve an episulphonium ion intermediate. The ringexpansion 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 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^+) ; ¹H n.m.r. (CDCl₃, δ) 6.60 (1H, s, =CHCl); 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(5H)-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); ¹H n.m.r. (CDCl₃, δ) 5.42 (1H, s, SCHCO), are consistent with the 1,5-benzothiazepine structure (3a). In order to eliminate the alternative 1,4benzothiazine structure, 2-benzoyl-4-methyl-2H-1,4-benzothiazin-3(4H)-one (7) was prepared by the condensation of 4-methyl-2H-1,4-benzothiazin-3(4H)-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 sulphurcontaining 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.

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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.