Tetrahedron Letters,Vol.22,No.50,pp 5077-5078,1981
Printed in Great Britain

0040-4039/81/505077-02$02.00/0

SYNTHESIS OF 4,5-DIHYDRO-1,4-BENZOTHIAZEPINE DERIVATIVES VIA RING EXPANSION[1]

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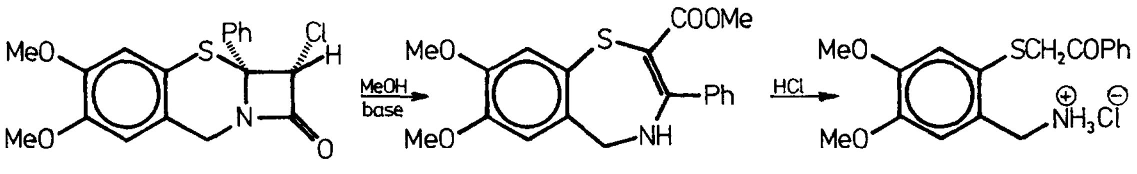
Summary: Basic treatment in methanol of a chloro-β-lactam fused with dihydrobenzothiazine led to the corresponding 1,4-benzothiazepine derivative via a new ring expansion. The structure of the product, deduced from IR and ^{1}H NMR data, was confirmed by X-ray measurements.

In methanol in the presence of bases, 6α-phenyl-7α-chloro-2,3(2',3'-dimethoxybenzo)-1-thiaoctem (**1**). prepared by us recently[2], yielded 2-carbomethoxy-3-phenyl-7,8-dimethoxy-4,5-dihydrobenzothiazepine (**2**, mp 170-2 °C) via ring expansion in a new type of reaction. The rate of the reaction depends on the base applied. 100% yield was achieved with 1 mole t-BuOK in 0,5 h or with 1 mole Et_3N in 24 h.

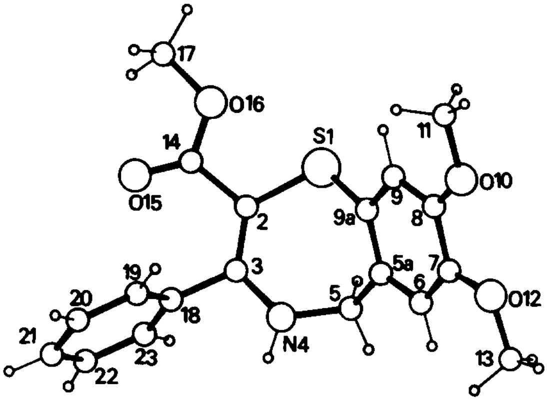


1 **2** **3**

The IR[3] and ^{1}H-NMR spectral data[4] proved the presence of a/ a CH_2-NH group: νNH: 3320 (KBr) and 3420 cm^{-1} ($CHCl_3$); δCH_2L 4.90 ppm, d (6Hz); δNH: 4.60 ppm, t (6Hz); b/ a tetrasubstituted benzene ring bearing two methoxy groups: δOCH_3: 3.85 and 3.90 ppm, 2xs (2x3H); δArH 6.70 and 7.15 ppm, 2xs (2x1H); c/ a carbonyl group in a conjugated ester of amide moiety, but not in a β-lactam ring: νC=O: 1640 cm^{-1} (KBr) and 1675 cm^{-1} ($CHCl_3$); d/ a third methoxy substituent: 3.45 ppm, s (3H); and e/ a phenyl ring: $C_{Ar}H$: 765 cm^{-1}; $\gamma C_{Ar}C_{Ar}$: 705 cm^{-1}; δArH:∿7.3 ppm, ∿s (5H).

Of the possible structure in accordance with all these spectral data, structure **2** was proved by X-ray measurements. Crystal data: $C_{19}H_{19}O_4NS$, M: 357.4,

$a = 18.190(2)$, $b = 7.266(3)$, $c = 13.194(3)$ Å, $\beta = 101.88(2)^\circ$, $V = 1706.5(1.4)$ Å,[5] μ(Mo-K_α, $\lambda = 0.71073$ Å) = 2.15 cm^{-1}, $D_X = 1.391$ gcm^{-3}, $Z = 4$, space group $P2_1/c$, 2372 non-zero intensities were collected on an Enraf-Nonius CAD4 computer-controlled, four-circle, single-crystal diffractometer, with monochromated Mo radiation. The structure was solved by direct methods using the MULTAN program.[6] 1369 reflexions [$I \geq \sigma(I)$] were used in a full matrix anisotropic least-squares refinement. Hydrogen atoms were located in difference maps and were refined in two isotropic least-squares cycles. The final R is 0.053 for observes and 0.119 for all reflexions. The structure is shown in Fig. 1 with the numbering used in the X-ray structure determination (bare numbers denote carbon atoms).[5]



Hydrolysis of **2** with 10% HCl led to 2-benzoylmethylthio-4,5-dimethoxybenzylamine hydrochloride (**3**, mp 184-5 °C, 96%)[7] via splitting of the N-C(sp^2) bond, followed by the decarboxylation of the ß-ketocarboxylic acid derivative formed by hydrolysis of the ester group. Compound **3** was also synthesized independently, from 2-mercapto-4,5-dimethoxybenzylamine hydrochloride[8] with phenacyl bromide in methanol: dimethylformamide (3:1) solution (yield 76%).

References and Notes

1. Saturated heterocycles, Part 26. Part 25: G. Bernâth, F. Fülöp, Gy. Argay, A. Kálmán, P. Sohár: Tetrahedron Letters, Accepted for publication.
2. L. Fodor, J. Szabó and P. Sohár: Tetrahedron, 37, 963 (1981).
3. Further IR data (Perkin Elmer 325 spectrometer, cm^{-1}) of **2**: νC=C (conjugated with the phenyl ring): 1500 (KBr), νC-O (conj. ester): 1290, 1055 (KBr) and 1290, 1055 ($CHCl_3$).
4. The ^1H NMR spectrum of **2** was recorded in $DCDl_3$ at room temperature with a Varian XL-100 FT spectrometer at 100 MHz, using TMS as internal standard.
5. Relevant data are deposited with the C. C. D. C /cf. Tetrahedron Lett. **22** No. 18 (1981).
6. G. Germain, P. Main, M. M. Woolfson, Acta Cryst., **A27**, 368 (1971).
7. IR (KBr, cm^{-1}) and ^1H NMR data (Varian EM-360 spectrometer, in DMSO-d_6, at 60 MHz, δppm) of **3**: NH_3^+: 3500-2500, νC=O: 1665, νC-C (methoxy): 1275, 1260, 1040, $\gamma C_{Ar}H$(phenyl): 730, 720, $\gamma C_{Ar}C_{Ar}$(phenyl): 658, δNCH_2: 4.2 gy (2H) δSCH_2: 4.60 s, (2H), δOCH_3: 3.80 and 3.85 2xs (2x3H), δArH: 7.10 and 7.40 2xs (2x1H), δNH_3^+: 8.65 t(3H), νArH (m- and p-phenyl): 440-465 Hz, m(3H) and νArH (o-phenyl): 470-490 Hz, m(2H)
8. J. Szabó, E. Vinkler, I. Varga: Acta Chim. Acad. Sci. Hung., **58**, 179 (1968).

(Received in UK 21 September 1981)