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4H-1,4-BENZOTHIAZINE DERIVATIVES VIA A NOVEL LEAD TETRAACETATE INDUCED RING CONTRACTION.

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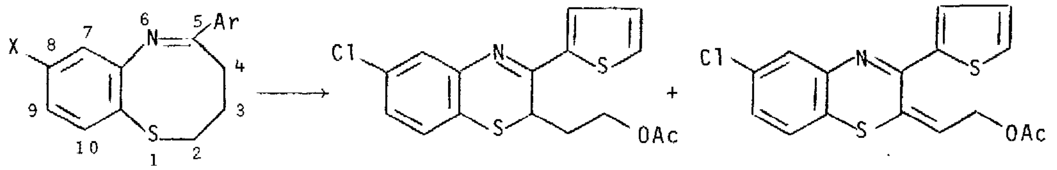
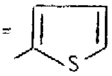
Abstract - 8-Chloro-3,4-dihydro-5-(2-thienyl)-2H-1,6-benzothiazocine underwent a facile lead tetraacetate induced ring contraction forming several 3-(2-thienyl)-4H-1,4-benzothiazine derivatives.

During the course of investigating the synthesis and chemistry of various 5-aryl-2H-1,6-benzothiazocine derivatives (1), several unexpected reactions were discovered.[1] In particular, when 8-Chloro-3,4-dihydro-5-(2-thienyl)-2H-1,6-benzothiazocine (1a) was treated with lead tetraacetate, a facile bond reorganization occurred leading to the novel formation of benzothiazine derivatives 2 and 3. Other derivatives of 1 (Ar=phenyl and/or X=H) reacted similarly[1].



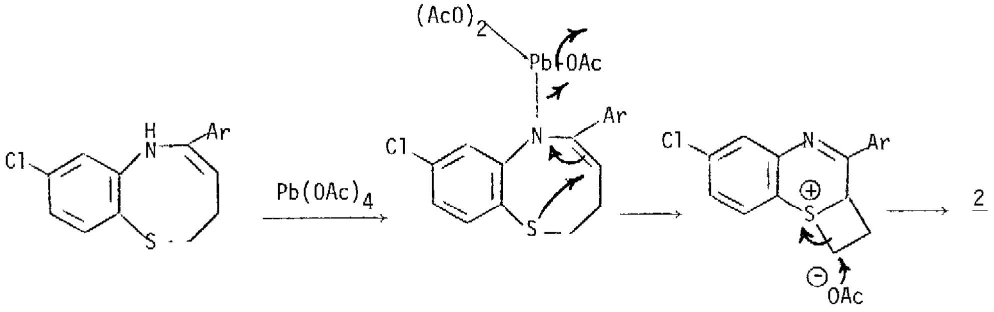
1 2 3

1a, Ar=  , X=Cl

Benzothiazocine 1a[2] was dissolved in glacial acetic acid, treated with 1.1 equivalents of lead tetraacetate and the resulting solution was warmed to 70° C for five hours (at which time TLC analysis revealed complete disappearance of 1a and the formation of two products). Typical extractive work-up procedures gave the product mixture (84% yield) of 2 and 3 in a ratio of 1.4:1 as evidenced by ^{1}H NMR analysis[3,4]. If a larger proportion of lead tetraacetate was used, 1a was consumed more rapidly and 3 became the preponderant component of the product mixture.

Both 2 and 3 were separated and isolated using preparative layer chromatography. Structural assignment was made based upon spectral data[3,4], mechanistic considerations and ultimately x-ray analysis of 3 (*vide infra*).

A possible mechanism[5] for the formation of 2 and 3 involves the coordination of lead tetraacetate with 4 (the enamine tautomer of 1a) to form 5. Subsequent transannular sulfur migration to C-4 and loss of lead diacetate and acetate ion leads to 6. Acetate attack on 6 leads directly to the formation of 2. Oxidation of 2 by either the oxidant or air leads to 3. The possible involvement of a sulfoxide intermediate has been precluded by its independent synthesis[6] and subsequent exposure to the reaction conditions which does not result in the formation of 2 and 3. Attempts to use a deuterium label to further elucidate the mechanism failed to provide any useful insight into the course of rearrangement.



4 5 6

Crystals of 3 grown from hexane are orthorhombic, space group Pbca, Z=8, a=8.057(2), b=22.476(6), C=17.419(4) Å. The measured density is 1.474 g Cm^{-3} (by flotation in aqueous KI solution) which agrees with the calculated value 1.470 g Cm^{-3} based on one molecule, $C_{16}H_{12}NO_2S_2Cl$, in the asymmetric unit. A crystal 0.61 x 0.23 x 0.06 mm was used for three dimensional data collection on an Enraf-Nonius computer-controlled diffractometer. The $\theta/2\theta$ scan method was used with Ni-filtered Cukα radiation. In the range $3 < \theta < 60$, 2343 independent reflections were measured of which 1739 were classified as observed ($I > 2.0\sigma(I)$); empirical absorption corrections were applied. Both the trial structure containing all non-hydrogen atoms[7] and further refinement[8] were straightforward with all hydrogen atoms located and the non-hydrogens refined anisotropically to give a final discrepancy factor of R=0.067.[9]

The molecule obtained is shown as the ORTEP drawing, Figure 1. Planarity of the rings in 3 was examined by computing appropriate least squares planes. The benzothiazine system is essentially planar except for the carbon adjacent to the sulfur atom which deviates by 0.53Å from the plane of the aromatic ring. For the chlorine, nitrogen and sulfur atoms, the deviations are -0.07Å. -0.15Å and -0.05Å respectively. The five membered ring is planar within experimental error; the torsion angle around the connecting bond is -22°. A survey of intramolecular distances did not reveal any close contacts; packing of molecules in this structure may be attributed, therefore, to Van der Waals forces.

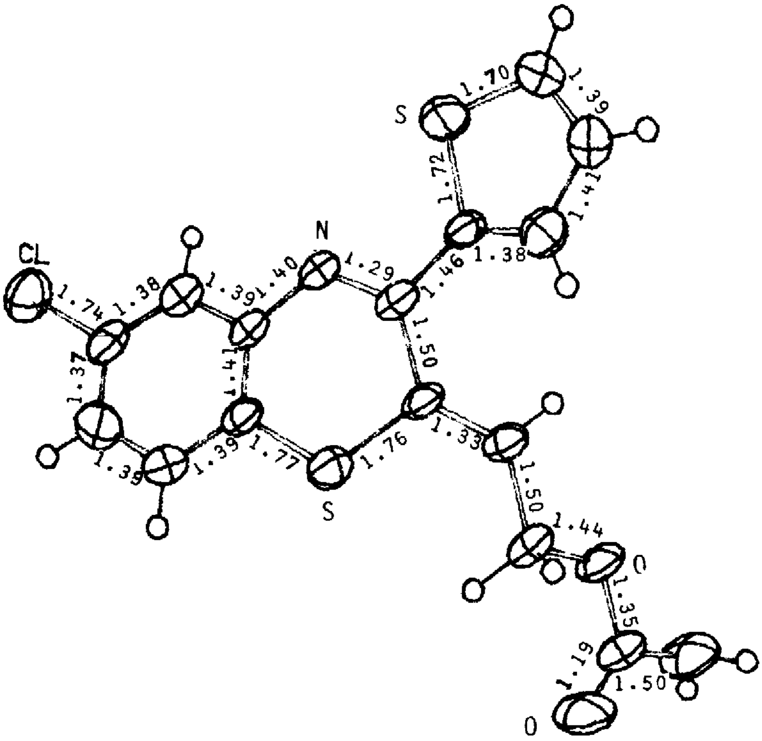


Figure 1

Acknowledgements

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References and Footnotes

1. A complete report of the chemistry of these systems is the subject of a future report from these laboratories. J. B. Press and N. H. Eudy, manuscript in preparation.
2. Data for 1a: mp 133-134° C. IR(KBr) 1629 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ 7.56 (m, 3H), 7.02 (m, 3H, aromatic and thiophene H), 3.06 (m, 2H, S-CH$_2$), 2.20 (m, 2H, N=C-CH$_2$), 1.78 (m, 2H, C-CH$_2$-C). MS 293 (M$^+$). Anal Calcd for $C_{14}H_{12}NS_2Cl$: C, 57.22; H, 4.12; N, 4.77; S, 21.83. Found C, 57.11; H, 4.17; N, 4.67; S, 22.03.
3. Data for 2: IR (neat) 1742 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ 7.5 (m, 3H), 7.10 (m, 3H, aromatic and thiophene H), 4.14 (m, 3H, S-C-H and CH$_2$O), 2.06 (s, 3H, COCH$_3$), 1.84 (m, 2H, CH$_2$). Double irradiation of the signal at δ 1.84 caused the collapse of the signals at δ 4.14. MS (calcd for $C_{16}H_{14}NO_2S_2Cl$: 351.0154) 351.0160.
4. Data for 3: mp 102-104° C. IR(KBr) 1739 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ 7.5 (m, 3H), 7.08 (m, 3H,

aromatic and thiophene H), 6.68 (t, J=7Hz, 1H, =C-H), 4.86 (d, J=7Hz, 2H, CH_2), 2.08 (s, 3H, $COCH_3$). MS (calcd for $C_{16}H_{12}NO_2S_2Cl$: 348.9998) 348.9993. Anal Calcd C, 54.92; H, 3.46; N, 4.01; S, 18.34; Cl, 10.14. Found C, 54.38; H, 3.52; N, 3.93; S, 18.35; Cl, 10.15.

5. An alternate mechanism could be envisioned via a coordination of lead to both nitrogen and sulfur atoms of 4 leading to an activated intermediate whose crown shaped conformation might easily account for the facility of ring contraction.
6. The sulfoxide of 1a was prepared using 1.1 equivalents of sodium meta periodate in methanol and was a white crystalline solid, 99% yield, mp 152-153° C. IR(KBr) 1613 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.85 (d, J=8.5Hz, 1H, H at C-10), 7.80 (m, 2H, thiophene H), 7.48 (dd, J=8.5, 2.0Hz, 1H, H at C-9), 7.21 (m, 1H, thiophene H), 7.10 (d, J=2.0Hz, 1H, H at C-7), 3.10 (m, 2H, S(O)-CH_2), 2.20 (m, 4H, CH_2). Anal Calcd for $C_{14}H_{12}NOS_2Cl$: C, 54.27; H, 3.91; N, 4.52; S, 20.70; Cl 11.44. Found C, 54.17; H, 4.20; N, 4.55; S, 20.23; Cl, 11.73.
7. Trial structure was determined using the MULTAN direct phase determination program cf. G. Germain, P. Main and M. M. Woolfson, Acta Cryst., A27, 368(1971).
8. All calculations were made on a DEC-10 computer using the X-RAY SYSTEM (1976) system of programs (Technical Report TR-446, The Computer Science Center, University of Maryland, College Park, Maryland). The atomic scattering factors were taken from International Tables for Crystallography (1968), Vol. III Birmingham: Kynoch Press.
9. Final atomic coordinates and a list of structure factors may be obtained from the authors.

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