

Spiro[4.4] and spiro[4.5] lactones from phthaloyl chloride and 1,4- and 1,5-bis-nucleophiles

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Phthaloyl chloride reacts with the 1,4-bis-nucleophiles **3** to give spiro[4.4] lactones **7** and **9** and with the 1,5-bis-nucleophiles **10** to give spiro[4.5] lactones **12**, as proved by X-ray crystallography, and not the 8- and 9-membered heterocyclic systems previously claimed.

4,5-Dichloro-1,2,3-dithiazolium chloride ('Appel Salt') **1** is a remarkably versatile reagent in organic synthesis.¹⁻⁴ When treated with primary aromatic amines followed by secondary aliphatic amines it gives the dithiazoles **2** which can be hydrolysed to the amidino thioamides **3**.² As reactive 1,4-bis-nucleophiles compounds **3** are useful in heterocyclic synthesis, particularly when treated with 1,1-bis-electrophiles to give five-membered rings **4** (X = CS, CNPh, SO and SO₂) (Scheme 1),³ and with 1,2-bis-electrophiles to give six-membered rings.⁴ A more unusual application was the reported reaction of compound **3** with the 1,4-bis-electrophile, phthaloyl chloride, in CH₂Cl₂ containing pyridine at room temperature to give the 8-membered ring compounds, 2,5-benzothiazocine-1,6-diones **5** (Scheme 2). Nine examples, selected from R = Pr, Bu and Ar = 4-XC₆H₄ (X = Cl, Br, Me, MeO, NO₂) and 3-O₂NC₆H₄, were reported in 45–83% yield.³

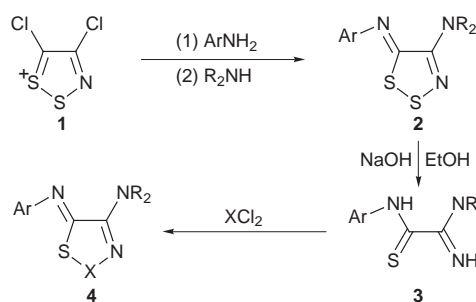
These unusual 2,5-benzothiazocines were unknown, and if valid, this route would render them readily available. However displacement of the second chlorine in phthaloyl chloride to form a highly unsaturated 8-membered ring seems questionable on mechanistic grounds; furthermore it overlooks the possibility of a lower energy process involving interaction between the two acid chloride groups, typified by the long-known isomerisation of phthaloyl chloride into 3,3-dichlorophthalide.⁵ It occurred to us that attack of the second carbonyl group could be through the first, as shown in **6** for example, to give the strain-free spiro[4,4]

lactones **7** (or **9**) rather than the 8-membered ring (Scheme 3). This we have now shown to be the case.

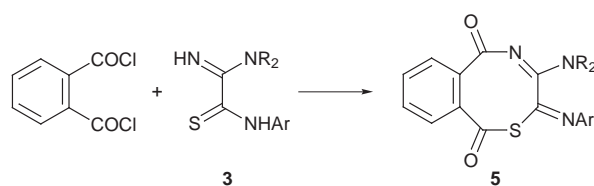
We repeated the preparation of the amidino thioamides **3** (R = Pr, Ar = 4-O₂NC₆H₄, 4-MeOC₆H₄), and treated them with phthaloyl chloride and pyridine, exactly as reported,³ to obtain 1 : 1 adducts (44 and 47% yield, respectively). By spectroscopic comparison these were clearly the same products as described in the literature.³ Careful chromatography and slow crystallisation from Pr₂O–hexane gave the 4-nitrophenyl product as yellow crystals, mp 229–231 °C, suitable for X-ray crystallography† which revealed the structure to be the racemic spiro lactone **9** (R = Pr, Ar = 4-O₂NC₆H₄). It is clear from their IR, ¹H and ¹³C NMR and mass spectra that all the claimed benzothiazocines **5** are structurally very similar and thus we deduce that they are all spiro compounds **9**; indeed this structure is in better agreement with the spectroscopic data than the benzothiazocine **5**, which remains unknown.

The X-ray structure of **9** (R = Pr, Ar = 4-O₂NC₆H₄) is illustrated in Fig. 1. There are only minor differences in the geometries of the four independent molecules: small changes in the conformations of the NPr₂ groups and in the twist angle between the planes of the imidazole and nitrophenyl ring systems. The only other structural features of note are a pronounced double bond character for N(3)–C(4) and delocalisation within the thioamide [N(1)–C(5)–S(5)].

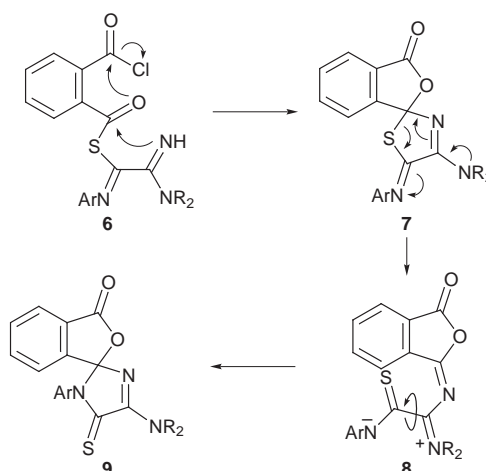
In the reaction of the amidino thioamides **3** with phthaloyl chloride there are various possibilities for the order of nucleophilic attack. Because of the high nucleophilicity of sulfur we consider **6** to be the more likely first intermediate and this would result in the formation of **7** rather than **9**. It is possible that **7** is the kinetic product which then undergoes a Dimroth type rearrangement to the more stable thioamide structure **9**, through the stabilised ring-opened intermediate **8**. This view was strongly supported by studying the reactions of phthaloyl



Scheme 1



Scheme 2



Scheme 3

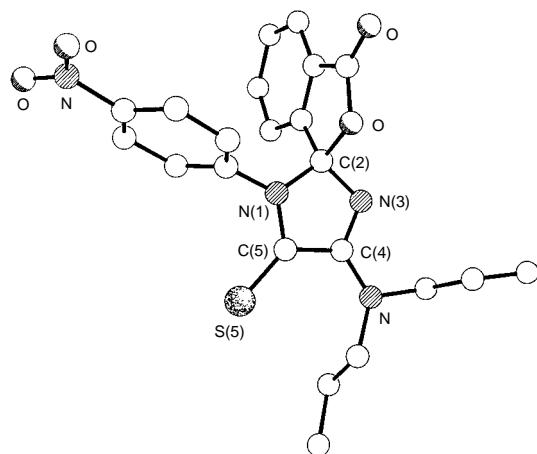
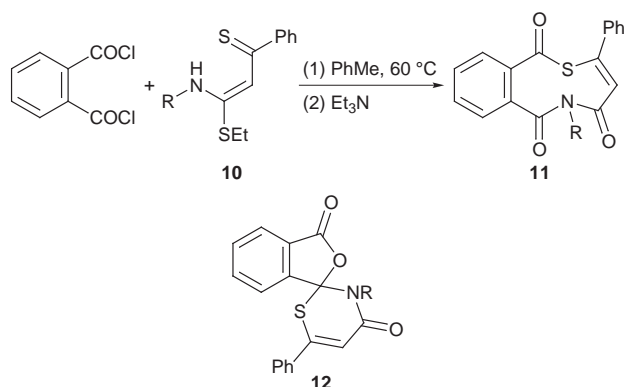


Fig. 1 The structure of one of the four crystallographically independent molecules of **9** (R = Pr, Ar = 4-O₂NC₆H₄). Selected bond lengths (Å) [averaged over the four molecules]; N(3)–C(4) 1.29(2), N(1)–C(5) 1.35(2), C(5)–S(5) 1.622(13).

chloride with the amidino thioamides **3** (R = Pr, Ar = 2,6-Me₂C₆H₃ and R = Pr, Ar = 2,4,6-Me₃C₆H₂) where the bulkier *N*-aryl groups should favour the less congested structure **7** over **9**. From each of these reactions two isomeric products were isolated and shown spectroscopically to be **7** (62%) and **9** (32%) for the dimethyl and **7** (65%) and **9** (28%) for the trimethyl compounds. The products **7** in the dimethyl and trimethyl series are labile and isomerise slowly to **9** on standing in CH₂Cl₂ at room temperature; this rearrangement is markedly catalysed by acid (HCl in CDCl₃). In view of the possible formation of structural isomers in the cyclisation of compound **3**, the five-membered ring structures **4**, proposed above,³ should also be treated with caution and isomeric thioamide structures be considered.

In similar vein the condensation of phthaloyl chloride with the 1,5-bis-nucleophiles **10** has been reported to give the equally striking 9-membered ring system, 2,6-benzothiazinone-1,5,7-trione **11**.⁶ Eleven such products (R = Me, Et, allyl, cyclohexyl, Bn, substituted benzyl) were obtained as colourless solids, mostly in very high yields, and all exhibit very similar spectroscopic properties.⁶ If correct this would provide an attractive route to this new ring system, but again it seemed likely that the 1,5-bis-nucleophiles **10** could be reacting by the same general mechanism as the 1,4-bis-nucleophiles **3**, to give the analogous spiro[4,5] lactones **12**.



We therefore prepared the thione **10** (R = Et) and treated this with phthaloyl chloride as reported,⁶ to give a colourless crystalline product, mp 132–133 °C (61%). X-Ray crystallography reveals a spiro junction between the phthalide and thiazinone ring systems, thus confirming the alternative structure **12** (Fig. 2). The thiazinone ring has a half-chair conformation with the spiro centre C(2) lying 0.64 Å out of the plane of the remaining atoms—which are co-planar to within 0.04 Å.

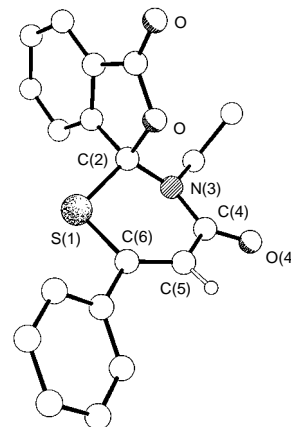


Fig. 2 The molecular structure of **12**, (R = Et). Selected bond lengths (Å); S(1)–C(6) 1.738(3), C(6)–C(5) 1.343(4), N(3)–C(4) 1.373(4), C(4)–O(4) 1.226(4), C(4)–C(5) 1.466(4).

The spectroscopic data for **12** (R = Et) agreed well with the spiro structure and with the data reported for the other products, indicating that these too are all spiro compounds, and that the nine-membered ring of **11** is still unknown. A similar spiro lactone structure has been assigned to the product from phthaloyl chloride and 2-(dihydroimidazol-2-yl)thiophenol, on the basis of its ¹³C NMR spectrum which agreed well with that of our product.⁷

It follows from these results that spiro lactone (phthalide) structures should always be considered for the products of condensation of phthaloyl chloride, and related 1,2-bis-carboxylic acid halides, with 1,4 and higher bis-nucleophiles.

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Notes and References

† *Crystal data for 9* (R = Pr, Ar = 4-O₂NC₆H₄): C₂₂H₂₂N₄O₄S, *M* = 438.5, monoclinic, *Pc* (no. 7), *a* = 12.699(3), *b* = 20.079(3), *c* = 18.900(3) Å, β = 109.03(1)°, *V* = 4555(1) Å³, *Z* = 8 (there are four crystallographically independent molecules in the asymmetric unit), *D*_c = 1.279 g cm⁻³, μ(Mo-Kα) = 1.78 cm⁻¹, *F*(000) = 1840. A yellow block of dimensions 0.77 × 0.50 × 0.20 mm was used. For **12** (R = Et): C₁₉H₁₅NO₃S, *M* = 337.4, monoclinic, *P2₁/n* (no. 14), *a* = 10.159(1), *b* = 8.330(1), *c* = 19.638(1) Å, β = 101.33(1)°, *V* = 1629.4(2) Å³, *Z* = 4, *D*_c = 1.375 g cm⁻³, μ(Cu-Kα) = 19.1 cm⁻¹, *F*(000) = 704. A thin clear plate of dimensions 0.40 × 0.27 × 0.02 mm was used. 8304 (1940) independent reflections were measured on Siemens P4/PC diffractometers with Mo-Kα (Cu-Kα) radiation using ω-scans for **9** (**12**) respectively. The structures were solved by direct methods and all of the major occupancy non-hydrogen atoms were refined anisotropically using full-matrix least-squares based on *F*² to give *R*₁ = 0.073 (0.036), *wR*₂ = 0.183 (0.089) for 4269 (1616) independent observed (and absorption corrected for **12**) reflections [*I*(*F*_o) > 4σ(*F*_o)], 2θ ≤ 50° (125°)] and 1117 (218) parameters for **9**, (**12**) respectively. The polarity of **9** could not be reliably determined, probably due to the presence of a non-crystallographic inversion centre at 0.878, 0.393, 0.580. CCDC 182/884.

- R. Appel, H. Janssen, M. Siray and F. Knoch, *Chem. Ber.*, 1985, **118**, 1632; J. J. Folmer and S. M. Weinreb, *Tetrahedron Lett.*, 1993, **34**, 2737; T. Besson and C. W. Rees, *J. Chem. Soc., Perkin Trans. 1*, 1996, 2857; R. F. English, O. A. Rakin, C. W. Rees and O. G. Vlasova, *J. Chem. Soc., Perkin Trans. 1*, 1997, 201 and references cited therein.
- H. Lee, K. Kim, D. Whang and K. Kim, *J. Org. Chem.*, 1994, **59**, 6179.
- S.-H. Choi and K. Kim, *Tetrahedron*, 1996, **52**, 8413.
- M.-K. Jeon and K. Kim, *Tetrahedron*, 1998, **54**, 2459.
- D. V. Banthorpe and B. V. Smith, in *The Chemistry of Acyl Halides*, ed. S. Patai, Interscience, London, 1972, ch. 8; P. R. Jones, *Chem. Rev.*, 1963, **63**, 461.
- S. H. Kim and K. Kim, *Heteroatom Chem.*, 1995, **6**, 387.
- W. Reid and A. von der Eltz, *Liebigs Ann. Chem.*, 1988, 599.

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