New Synthesis of Pyrrolobenzothiazine and Pyrrolobenzoxazine Ring Systems

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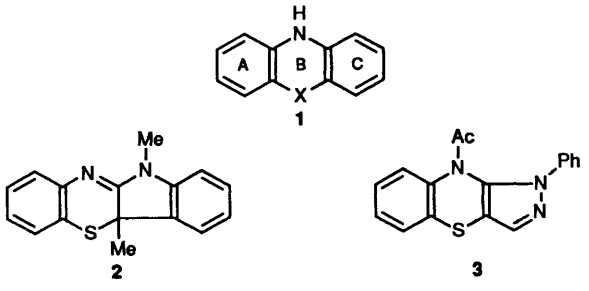
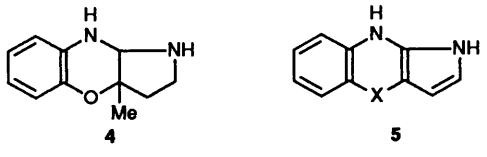
A new and simple synthesis of pyrrolobenzothiazine and pyrrolobenzoxazine ring sytems is described. Thus, 2-aminophenol and 2-aminothiophenol reacted with maleic anhydride at room temperature to give the acids **7** which were converted into their acid chlorides **9** and then their amides **10**. Subsequent pyrolysis of the latter in polyphosphoric acid for 15 h gave the title compounds in good yield. [1,4]Benzothiazino[2,3-*d*][1,6]benzothiazocin-6-(7*H*)-one, a new type of phenothiazine heterocycle, was also isolated.

Smiles rearrangement of diaryl amines and sulfides[1–7] and the pyrolytic condensation of suitably substituted diarylamines and sulfides[8–14] are established routes to phenothiazines **1** (X = S) and phenoxazines **1** (X = O) together with their aza analogues.[15–17] These methods, however, failed when applied to certain modified rings of this type. While all the four isomeric systems[12] in which ring A or C of phenothiazine is replaced with pyridine have been made, such replacements with pyrrole are rare, only compounds **2**[18] and **3**[19] having been reported.

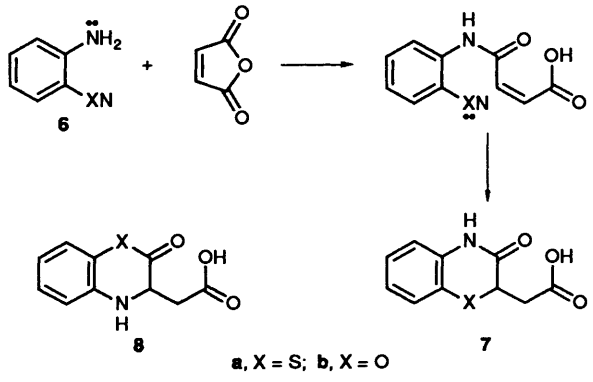


In the phenoxazine series,[20,21] the situation is similar, only compound **4**[22] having been reported by Methylene Blue-sensitized photooxygenation of tryptamine hydrochloride. We have now successfully prepared new pyrrolobenzo-thiazine and -oxazine ring systems **5** by a new and simple mehod.

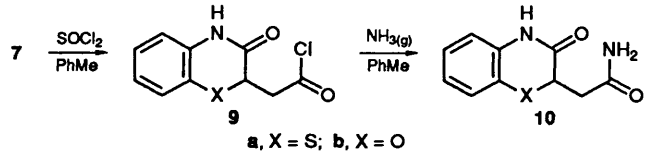


The reaction of 2-aminothiophenol **6a** with maleic anhydride at 28 °C gave an addition product identified as the acid **7a** (94%) on the basis of elemental analysis and spectroscopy. Strong IR absorption at 1680 and 1265 cm^{-1}, characteristic of cyclic secondary amides (6-membered lactams),[24] support the assigned structure **7a** rather than the cyclic thioester (δ-thiolactone, **8a**) which would show thioester carbonyl stretching near 1695 cm^{-1}.[25,26] Similar products were obtained with 2-aminophenol **6b**. If the product were a δ-lactone **8b** the ester carbonyl stretching band would have appeared at 1750–1735[25] rather than 1704 cm^{-1}.

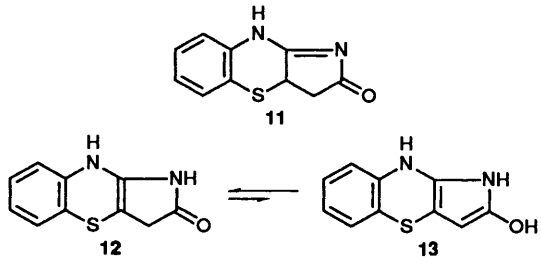
Product **7a** was probably formed by initial nucleophilic attack on the carbonyl carbon of maleic anhydride by the amino group of compound **6a**, a reaction leading to ring-opening of the maleic anhydride and cyclic addition of the mercapto group to the olefinic bond to give the thiazine ring. Formation of compound **7b** was similarly rationalized.



Product **7a** with thionyl chloride in refluxing toluene gave the acid chloride **9a** and this as a suspension in toluene upon passage of ammonia gas at room temperature afforded the corresponding amide **10a** (89%). Analogous reactions were carried out for the oxygen analogues starting with 2-aminophenol **6b**. Microanalysis, IR, UV and NMR spectroscopic results agree with the assigned structures.

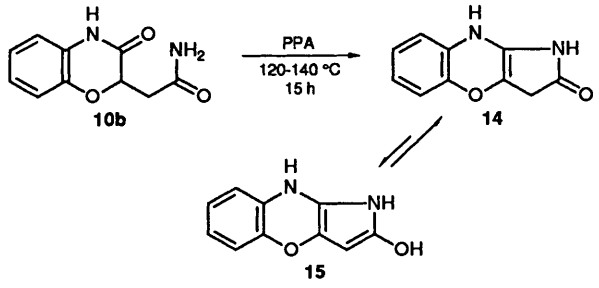


The amide **10a** when heated in polyphosphoric acid (PPA) at 120–130 °C for 15 h gave a yellowish brown solid upon work-up, the IR spectrum of which showed the absence of amide NH_2 absorption at 3240 cm^{-1} and the appearance of peaks at 440 and 476 nm characteristic of a highly conjugated system. These properties agree with both isomeric structures **11** and **12**.



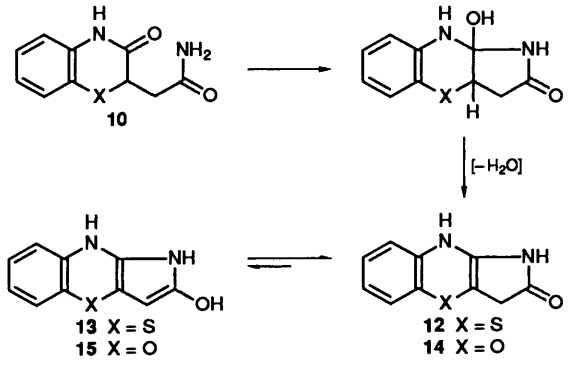
However, the absence in the NMR spectrum of two aliphatic CH signals in the range δ 4.0–1.50 rule out structure **11** whilst the appearance of a single signal at δ 3.25 (OH) is in agreement with structure **12** for this product. The intense colour of the product coupled with strong IR absorption at 1680 cm^{-1} (CO) together with the broad band at 3550–3200 cm^{-1} (OH) suggest the existence of keto–enol tautomerism in which the former predominates. Evidence that this is so comes from the NMR spectra of compounds **12** and **13** in which the peak area of the broad enolic OH band of the latter is $\geqslant \frac{1}{2}$ that of the 3-CH_2 band of structure **12** (peak areas are 5.16 for CH_2 band in structure **12** and 0.32 for the enolic OH band of structure **13**).

Cyclic condensation of compound **10b** in polyphosphoric acid at 120–140 °C gave a yellowish brown solid (46%) whose structure was rationalized as product **14**.

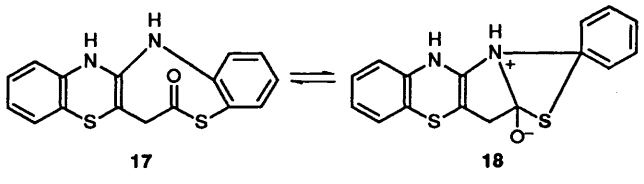


As with the sulfur analogue, **12**, product **14** is in tautomeric equilibrium with its enol form **15**, the former predominating.

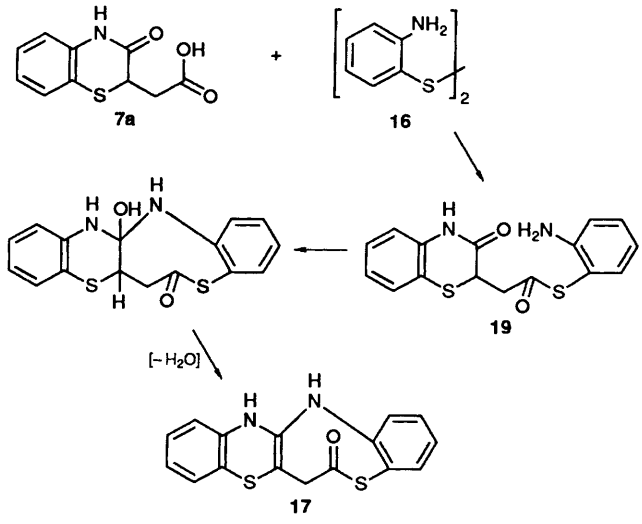
These cyclization reactions probably occurred by nucleophilic attack of the amido nitrogen on the benzo-thiazine and -oxazine carbonyl carbons followed by the elimination of water.



Reaction of the acid **7a** with disulfide **16** in dimethyl sulfoxide at 140–145 °C for 5.5 h gave a yellow solid identified as compound **17** from its analysis and IR and NMR spectra. The IR absorption at 1680 cm^{-1} (**17**) is in agreement with an 8-membered ring structure, earlier reports of such low-frequency bands having been recorded for 8-, 9- and 10-membered ring systems where trans-annular nitrogen-carbonyl interactions are possible.[27–30]



A second product was obtained as a brown oil and identified as the thioester, **19**, the precursor of product **17**. Its identity was further confirmed by conversion into the product **17** by pyrolysis. Thus, product **17**, was probably formed by esterification of the acid, **7a**, with the disulfide **16** followed by cyclic condensation of the resulting amino keto ester **19** to compound **17**.



Experimental

M.p.s were determined with a Fisher–Johns apparatus and are uncorrected. UV and visible spectra were recorded on a Pye Unicam SP 8000 spectrophotometer using matched 1 cm quartz cells. The solvent was dimethylacetamide (DMAC) and absorption maxima are given in units of nm, figures in parentheses are ε values in units of mol^{-1} dm^3 cm^{-1}. IR spectra were obtained with a Perkin-Elmer 137 spectrophotometer and some on a Digilab FTS-40 (FT-IR) instrument using KBr discs. ^1H NMR spectra were determined on a Bruker AM 360 spectrophotometer; the solvent was [$^2H_6$]dimethyl sulfoxide unless otherwise stated. Chemical shifts were reported on the δ scale relative to tetramethylsilane (TMS) used as the internal standard. All reactions were followed up by TLC monitoring using silica gel as adsorbent. All products were purified by column chromatography on aluminium oxide 90 (Merck, 70–230 mesh ASTM) using DMF or DMAC as the eluting solvent unless otherwise stated.

3,4-*Dihydro*-3-*oxo*-2H-1,4-*benzothiazin*-2-*ylacetic Acid* **7a**.—To a stirred solution of maleic anhydride (4.90 g, 50 mmol) in toluene (30 cm^3) was added 2-aminothiophenol (6.25 g, 50 mmol) in toluene (30 cm^3). The mixture was stirred at room temperature (28 °C) to give within a few minutes a yellowish white solid. At the end of 3 h the solid was filtered off, purified by column chromatography and recrystallized from ethanol, after treatment with activated charcoal, to give white crystals of compound **7a** (10.51 g, 94%), m.p. 179–180 °C; λ_{max}(DMAC)/nm 280 (4138); ν_{max}(KBr)/cm^{-1} 3440–3240 (OH), 3220 (NH), 1704 (C=O), 1680 (NHCO) and 1265 (NH of cyclic NHCO); δ_H($CDCl_3$) 10.65 (1 H, br, exchangeable with D_2O, CO_2H), 8.03 (1 H, NH), 6.82–7.45 (m, 4 H, ArH), 3.98 (t, 1 H, 2-CH, *J* 7.2), 3.15 (dd, 1 H, 9-CH_a of CH_2, *J* 7.2), 2.65 (dd, 1 H, 9-CH_b of CH_2, *J* 7.2) (Found: C, 54.0; H, 4.0; N, 6.2; S, 14.5. $C_{10}H_9NO_3S$ requires C, 53.81; H, 4.04; N, 6.28; S, 14.35).

3,4-*Dihydro*-3-*oxo*-2H-1,4-*benzoxazin*-2-*ylacetic Acid* **7b**.—This compound was prepared as was described for compound **7a**. 2-Aminophenol (10.90 g, 100 mmol) and maleic anhydride (9.8 g, 100 mmol) gave compound **7b** as a yellow crystalline solid (20.11 g, 97% yield); m.p. 175–176 °C; λ_{max}(DMAC)/nm 275 (6454) and 300 (8086); ν_{max}(KBr)/cm^{-1} 3450–3340br (OH), 3250 (NH) and 1710 (C=O) 1260 (NH of cyclic NHCO) (Found:

C, 58.1; H, 4.3; N, 6.9. $C_{10}H_9NO_4$ requires C, 57.97; H, 4.35; N, 6.76).

3,4-*Dihydro*-3-*oxo*-2H-1,4-*benzothiazin*-2-*ylacetamide* **10a**.—To a suspension of compound **7a** (4.46 g, 20 mmol) in toluene (75 cm^3) was added freshly distilled thionyl chloride (8.0 cm^3, 67 mmol). The mixture was refluxed for 3 h on a water-bath until the evolution of hydrogen chloride gas ceased. Excess of thionyl chloride and toluene were distilled off under reduced pressure to leave **9a** as a brown viscous oil which solidified on cooling. It was immediately suspended in toluene and freshly generated ammonia gas was bubbled into it for 2 h to give **10a** as a yellow-brown solid. This was filtered off by suction and recrystallized from aqueous *N*,*N*-dimethylformamide to afford the product (3.49 g, 89%), m.p. 230 °C; λ_{max}(DMAC)/nm 276 (4387) and 352 (6769); ν_{max}(KBr)/cm^{-1} 3400, 3240 (NH, NH_2) and 1690 (CO); δ_H($CDCl_3$–[$^2H_6$]-Me_2SO) 6.70–7.10 (5 H, m, ArH, NH), 6.13 (2 H, s, br, NH_2), 3.82 (1 H, t, 2-CH), 2.46 (2 H, d, CH_2CONH_2) (Found: C, 53.9; H, 4.7; N, 12.5; S, 14.6. $C_{10}H_{10}N_2O_2S$ requires C, 54.05; H, 4.50; N, 12.61; S, 14.41).

3,4-*Dihydro*-3-*oxo*-2H-1,4-*benzoxazin*-2-*ylacetamide* **10b**.—The acid **9b** (4.0 g, 20 mmol) was converted into compound **10b** (2.6 g, 63%) as reported for compound **10a**. The product was a yellow–brown solid, m.p. 213–215 °C; λ_{max}(DMAC)/nm 297 (8891) and 307 (9270); ν_{max}(KBr)/cm^{-1} 3430 (NH), 3240 (d, NH_2) and 1700 (CO); δ_H([$^2H_6$]-Me_2CO) 7.12–7.65 (5 H, m, ArH, NH), 6.22 (2 H, s, br, NH_2), 3.80 (1 H, 2-CH), and 2.38 (2 H, CH_2) (Found: C, 58.1; H, 5.0; N, 13.6. $C_{10}H_{10}N_2O_3$ requires C, 58.25; H, 4.85; N, 13.59%).

1H,9H-*Pyrrolo*[3,2-b][1,4]*benzothiazin*-2(3H)-*one* **12**.—Compound **10a** (4.00 g, 18 mmol) and orthophosphoric acid (5 cm^3) were stirred and heated at 120–130 °C for 15 h to give a dark syrup liquid on cooling. This was treated with water (50 cm^3) and the mixture stirred and filtered *in vacuo*. The residue taken up in a minimum volume of *N*,*N*-dimethylacetamide (DMAC) was boiled, filtered after treatment with activated charcoal, and allowed to cool to give compound **12** (2.52 g, 69%) as brown crystalline material; m.p. >285 °C (decomp.); λ_{max}(DMAC)/nm 295 (5992), 350 (4627), 440 (3641) and 476 (2996); ν_{max}(KBr)/cm^{-1}, 3550–3200 (enol OH, NH), 1680 (C=O); δ_H([$^2H_6$]-Me_2SO) 10.80 (0.25 H, area ratio 0.32, enol OH), 8.10 (2 H, br, NH), 6.80–7.60 (4 H, m, ArH), 3.25 (2 H, area ratio 5.16, s, CH_2) (Found: C, 58.6; H, 4.0; N, 13.6; S, 15.65. $C_{10}H_8N_2OS$ requires C, 58.82; H, 3.92; N, 13.73; S, 15.69%).

1H,9H-*Pyrrolo*[3,2-b][1,4]*benzoxazin*-2(3H)-*one* **14**.—Compound **14**, prepared from compound **10b** (1.00 g, 4.9 mmol) in a similar fashion to compound **12** except that the reflux temperature was 120–140 °C, was isolated as a brown powder (0.42 g, 46%), m.p. 265 °C; λ_{max}(DMAC)/nm 280 (3310), 350 (2779), 460 (1390) and 496 (12 226); ν_{max}(KBr)/cm^{-1} 3520–3380 (enol OH, NH) and 1720 (C=O); δ_H([$^2H_6$]-Me_2SO) 9.60 (enol OH), 7.90–6.50 (6 H, m, NH, ArH) and 3.32 (2 H, CH_2) (Found: C, 64.0; H, 4.1; N, 14.6. $C_{10}H_8N_2O_2$ requires C, 63.83; H, 4.26; N, 14.89).

13H,14H-[1,4]*Benzothiazino*[2,3-d][1,6]*benzothiazocin*-6(7-H)-*one* **17**.—Compound **7a** (2.23 g, 10 mmol), compound **16** (1.25 g, 5 mmol) and dimethyl sulfoxide (50 cm^3) were stirred and heated under reflux on an oil-bath at 140–145 °C for 5.5 h. Solvent was distilled off *in vacuo* to leave a maldorous greenish brown oil which, when cool, was treated with ethanol (20 cm^3) to give a greenish yellow solid. This was filtered off and recrystallized from toluene to give yellow crystals of compound **17** (1.72 g, 55%), m.p. 293–294 °C; λ_{max}(DMAC)/nm 345 (21.840) and 480 (3.343); ν_{max}(KBr)/cm^{-1} 3430 (v br, OH, NH) and 1680 (C=O); δ_H([$^2H_6$]-Me_2SO) 8.30–7.52 (8 H, m, ArH), 7.30 (1 H, br, 13-NH), 7.21 (1 H, br, 14-NH), 3.16 (2 H, s, 7-CH_2) (Found: C, 61.4; H, 4.0; N, 9.1; S, 20.5. $C_{16}H_{12}N_2S_2O$ requires C, 61.54; H, 3.85; N, 8.97; S, 20.51%).

The ethanolic mother liquor gave a further brown oil which was chromatographed on alumina with chloroform as eluent; the product, as a pure brown oil [ν_{max}(KBr)/cm^{-1} 3440 (br, NH) and 1680 (d, s, C=O)], gave further compound **17** when heated in DMSO at 140–150 °C for 5 h.

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