A Short Synthesis of Prodigiosin Analogues

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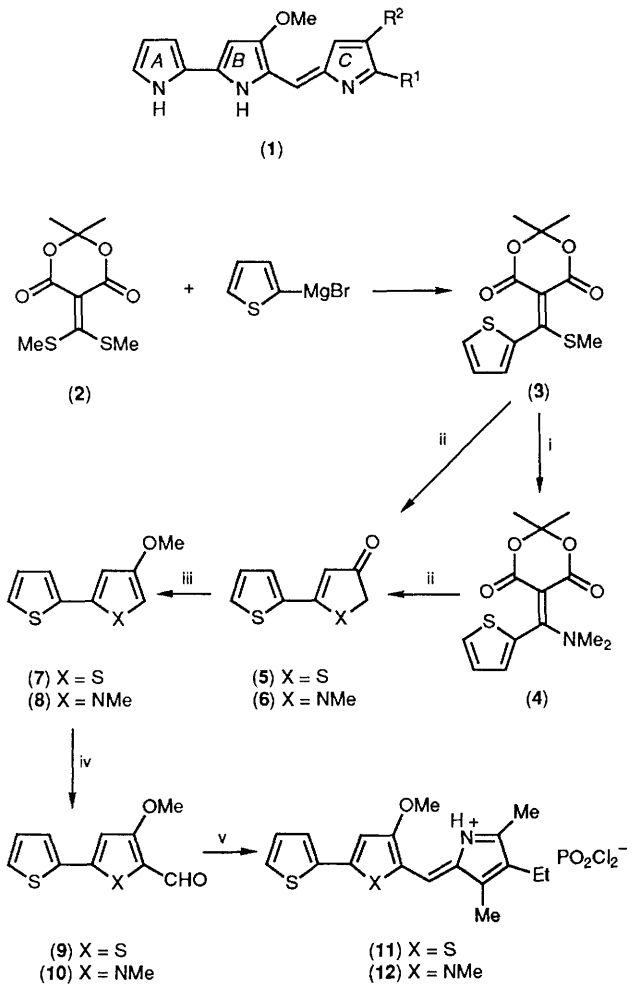
A convenient synthetic route to three-ring systems (**11**) and (**12**) related to those found in prodigiosin antibiotics is described: the *X*-ray crystal structure of (**12**) shows that the exocyclic double bond has a *Z*-configuration, which allows hydrogen bonding between the methoxy group and the pyrrole NH of ring *C*.

Two total syntheses of the prodigiosin series of antibiotics (**1**) have appeared in the last three years.[1,2] Both have employed a novel multi-step methodology to solve the problems inherent in the synthesis of the highly sensitive oxygenated pyrrole ring. We have overcome such problems by a two-step gas-phase method[3] based on the pyrolysis of aminomethylene Meldrum's acid derivatives, and we have recently shown that analogous thiophenes can be obtained by a similar procedure.[4] In this communication, we show how these early studies can be readily extended to the synthesis of analogues of the prodigiosin ring system, and report the *X*-ray crystal structure of one such derivative.



Scheme 1. *Reagents and conditions:* i, Me_2NH; ii, FVP (600 °C, 10^{-3} Torr); iii, MeOTs, NaH, DMI; iv, $POCl_3$, dimethylformamide; v, kryptopyrrole, $POCl_3$.

Thus, treatment of the ketene dithioacetal (**2**)[5] with 2-thienylmagnesium bromide in tetrahydrofuran[6] gives (**3**; 80%),† which can be transformed into the dimethylaminomethylene derivative (**4**; 65%) (Scheme 1). Flash vacuum pyrolysis of (**3**) or (**4**) gives the thiophenone (**5**; 76%) or the pyrrolone (**6**; 70%), respectively: the instability of the latter compound either neat or in solution is testimony to the convenience and efficiency of the pyrolysis method of generating these ring systems. Transformation into the ethers (**7**) and (**8**) requires specific *O*-alkylation of the enolates obtained by treatment of (**5**) or (**6**) with base.[10] The combination of a hard alkylating agent (methyl toluene-*p*-sulphonate) and a highly polar solvent, dimethylimidazolidinone (DMI), gave the required products (**7**) and (**8**) in 90% yield with no trace of *C*-alkylated derivatives. Vilsmeier formylation occurs specifically in the 2-position, due to activation by both the heteroatom and the methoxy group; both (**9**) and (**10**) were obtained in 75% yield. The final

† All new compounds were characterised by their spectra and by elemental analysis (solids) or accurate mass measurement (liquids).

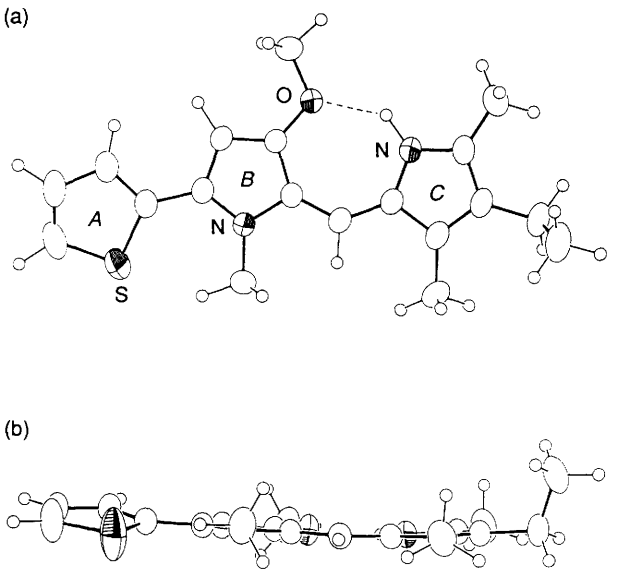


Figure 1. (a) General view of the cation (**12**). (b) Orthogonal view of the cation (**12**).

coupling reactions were carried out under standard conditions[11] using kryptopyrrole (2,4-dimethyl-3-ethylpyrrole) as a model α-unsubstituted pyrrole derivative, to give the three-ring systems (**11**; 72%) and (**12**; 68%). The overall yields for the five to six steps from (**2**) are therefore 30 and 17%, respectively.

The results of an *X*-ray crystal structure determination of the prodigiosin analogue (**12**)‡ are shown in Figure 1. The three rings are almost coplanar (despite possible *peri*-interactions between rings *A* and *B*). The configuration of the methoxy group is particularly noteworthy, allowing a seven-membered ring hydrogen bond with the pyrrole NH of ring *C*. It is possible that the configuration of the rings defined by hydrogen bonding in this way may be associated with the biological activity of prodigiosins, which is known[12] to be dependent on the presence of the ring *B* methoxy group.

Work is in progress to adapt the synthetic route shown in Scheme 1 to other members of the prodigiosin family, including the natural products.[13]

† *Crystal data* for: $C_{19}H_{23}N_2OS^+ \cdot PCl_2O_2^-$, M = 461.33, triclinic, space group $P\bar{1}$, a = 10.0286(18), b = 10.0913(14), c = 12.5266(22) Å, α = 109.770(9), β = 92.232(9), γ = 111.054(6)°, U = 1094.6 Å^3 [from 2θ values of 57 reflections measured at ±ω (2θ = 21—35°, $\bar{\lambda}$ = 0.71073 Å), T = 298 K], Z = 2, D_c = 1.399 g cm^{-3}, μ(Mo-K_α) = 0.481 mm^{-1}. A dark red columnar crystal (0.37 × 0.42 × 1.08 mm) was mounted on a Stöe STADI-4 four-circle diffractometer. Data collection using Mo-K_α *X*-radiation ($\bar{\lambda}$ = 0.71073 Å), ω–2θ scans, and the learnt-profile method[7] gave 4031 reflections ($2\theta_{max.}$ 50°), 3735 unique ($R_{int.}$ 0.028), of which 3433 with $F \geq 6\sigma(F)$ were used in all calculations. Following solution by automatic direct methods,[8] the structure was refined by full-matrix least-squares (on F), with anisotropic thermal parameters for all non-H atoms: H atoms were included in fixed, calculated positions except for those in methyl groups bound to sp^2 centres where each Me was treated as a rigid group.[9] At final convergence, R = 0.0488, R_w = 0.0798, S = 1.387 for 259 parameters, and the final ΔF synthesis showed no feature above 0.56 e Å^{-3}. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

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