Synthesis of Monocyclic Thiepins

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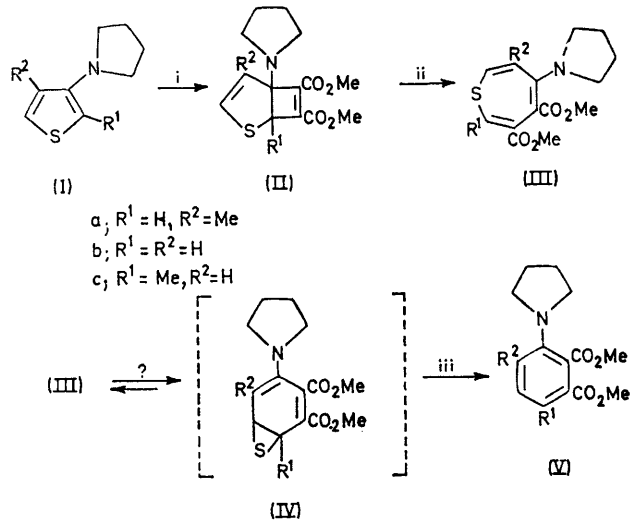
Summary 3,4-Dimethoxycarbonyl-5-pyrrolidin-1-ylthiepins (III) can be synthesized by cycloaddition of (substituted) 3-pyrrolidin-1-ylthiophens (I) and dimethyl acetylenedicarboxylate; the reaction proceeds *via* 2-thiabicyclo[3,2,0]hepta-3,6-diene intermediates (II).

BICYCLIC compounds containing a thiepin ring have recently been prepared.[1–3] However, in contrast to other 8π-electron heterocycles, *e.g.* oxepins and azepines,[4] monocyclic thiepins have not been synthesized so far. The failure of attempts to prepare such compounds is attributed to the anti-aromatic character of the ring system; a negative resonance energy was calculated by Dewar and Trinajstić.[5,6] Thiepins have been suggested as transient intermediates in the formation of the corresponding benzene derivatives but no experimental evidence for their existence has so far been presented.[5]

We describe here the first synthesis of a monocyclic thiepin, based on the 'enamine-like' reaction of *N*-heteroarylpyrrolidines and activated acetylenes.[3] 3-Methyl-4-pyrrolidin-1-ylthiophen (Ia)[7] was treated in deuteriochloroform at −30 °C with dimethyl acetylenedicarboxylate. Cycloaddition proceeded rather slowly at this temperature, giving the thiabicycloheptadiene (IIa) whose structure was proved by its i.r. and ^{1}H n.m.r. spectra [ν(C=C) 1643 cm^{-1}; δ 4·48 (s, 1-H), 5·76 (s, 3-H), 2·60 (CH_2N) p.p.m.] which are in good agreement with those for 2-thiabicyclo[3,2,0]hept-6-enes.[8]

The cycloadduct (IIa) rearranged, *via* ring opening of the cyclobutene fragment, into the pyrrolidinylthiepin (IIIa) δ 7·30 (s, 2-H), 6·76 (7-H), and 3·10 p.p.m. (CH_2N)]. The chemical shift of 2-H is in line with that of 7-H in the corresponding 2,3-dihydrothiepins (7·1—7·2 p.p.m.[8]) and that of 2-H (δ 7·00 p.p.m.) in benzo[*b*]thiepins.[3]

At the reaction temperature (−30 °C) sulphur is extruded slowly from this thiepin, possibly *via* the valence isomer of (IIIa), the thianorcaradiene (IV), to give a benzene derivative (V) [δ 7·18 (5-H) and 7·66 (ABq, J 8 Hz, 6-H) p.p.m.].† The rates of cycloaddition (i), rearrangement (ii), and sulphur extrusion (iii) are of the same order of magnitude at −30 °C; after 80 h the optimum yield of thiepin (IIIa) was reached.



The other 3-pyrrolidinylthiophens (Ib) and (Ic) reacted similarly with dimethyl acetylenedicarboxylate. The rates of cycloaddition with (Ia) and (Ib) are approximately the same at −30 °C. Compound (Ic) reacted only at room temperature and as desulphurization proceeded rather

† The structure of compound (Va), m.p. 66—67°, was further proved by a correct elemental analysis and a parent peak at m/e = 277.

bridged *trans*-cycloheptene derivative rather than by invoking Bredt's rule.[7] It is especially noteworthy that the solvolysis of (**1**) does not lead to a similar fragmentation process. Attempts to trap (**7**) as a bicyclic adduct have so far been unsuccessful.

The Ag^+-promoted hydrolysis of (**9**) was also found to proceed rapidly at 20° under the above conditions and 6-bromomethylenecyclonon-3-en-1-one (**11**) (50%) was obtained as the major product. It seems likely that this reaction also proceeds *via* an intermediate bicyclo[4,3,1]-dec-1(10)-ene derivative (**10**). It would appear to follow from the sharpness of the bromomethylene proton resonances in their n.m.r. spectra that (**6**) and (**11**) are both pure geometrical isomers and thus that the fragmentation reaction is stereospecific.

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