

SYNTHESIS OF TETRAHYDROAZOCINES AND DIHYDRO-2H-THIOCINS VIA RING ENLARGEMENT

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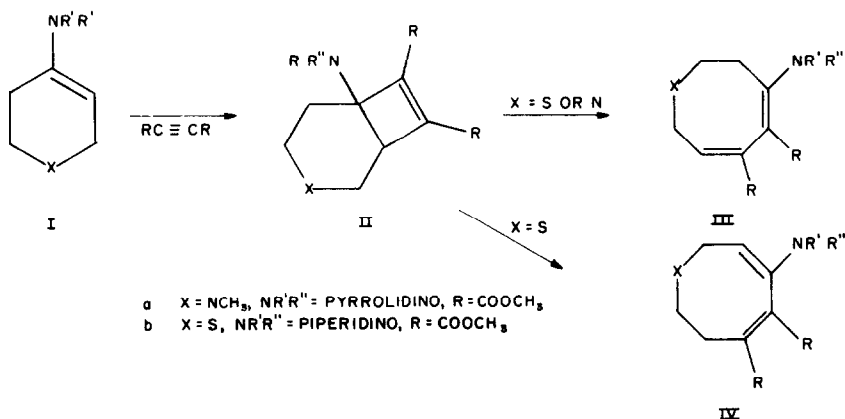
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Previously we described the synthesis of thiepins from 3-pyrrolidinothiophenes via ring enlargement by two carbon atoms<sup>1,2</sup>. Recent papers on the preparation of eight-membered heterocycles<sup>3</sup> and reactions of enamines with cyclopropanones<sup>4</sup> prompted us to report our findings in this field.

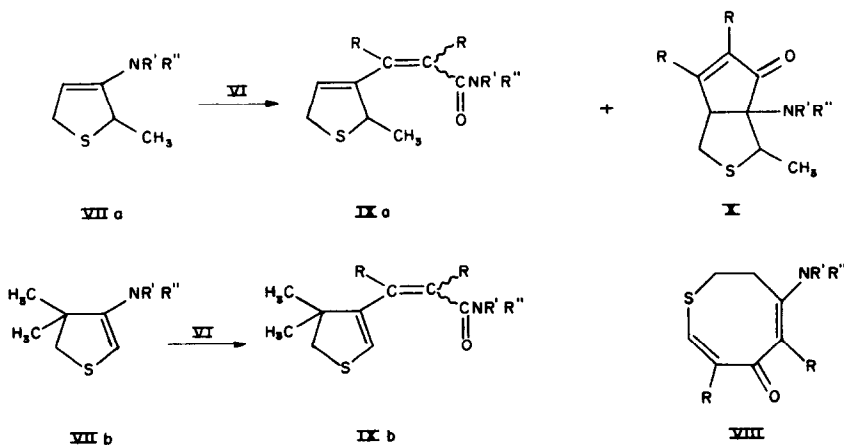
The synthesis of the compounds dealt with here — tetrahydroazocines and dihydro-2H-thiocins — was approached in two different ways, viz. via ring enlargement of enamines of six-membered heterocyclic ketones by two carbon atoms and via the reaction of enamines of five-membered ring ketones with cyclopropanones<sup>5</sup>.

4-Methyl-1-pyrrolidino-4-azacyclohex-1-ene (Ia)<sup>6</sup> and 1-piperidino-4-thiacyclohex-1-ene (Ib)<sup>7</sup> reacted with one equivalent of dimethyl acetylenedicarboxylate at room temperature to yield the corresponding 3-heterobicyclo[4.2.0]-oct-7-enes (II) via a [2+2] cycloaddition. Without being isolated these compounds were converted at 100 °C (2 h/dioxane) into their monocyclic isomers. Compound IIa, the 7,8-bis(methoxycarbonyl)-3-methyl-6-pyrrolidino-3-azabicyclo[4.2.0]oct-7-ene, afforded a 1,2,3,8-tetrahydroazocine derivative [IIIa, m p. 124-125.5 °C,  $\delta_{H_T}$  6.57 (dd,  $J_1 = 7.5$  Hz and  $J_2 = 8.5$  Hz)], formed by ring opening of the cyclobutene moiety, in 50% overall yield. Compound IIb gave two isomeric 3,8-dihydro-2H-thiocins, IIIb [m p. 184-185 °C,  $\delta_{H_T}$  6.76 ppm (dd,  $J_1 = 6$  Hz and  $J_2 = 8$  Hz)] and IV [m p. 101-102 °C,  $\delta_{H_T}$  4.95 ppm (dd,  $J_1 = 7.5$  Hz and  $J_2 = 8.5$  Hz)], in overall yields of 20 and 40%, respectively. A separate experiment showed that these two isomers were not interconvertible under the prevailing reaction conditions. Therefore, we conclude that IV is formed by a 1,5-hydrogen shift concurrent with the ring opening step<sup>8</sup>.

Upon acid-catalysed hydrolysis the two different 3,8-dihydro-2H-thiocins yielded the same product V (IIIb, OH replaces NR'R''). Obviously, under these conditions IV, or the corresponding enol, isomerizes to the thermodynamically more stable isomer



Our second approach to thiocin derivatives was based on the [2+2] reaction of simple enamines with diphenylcyclopropenone (VI), as reported by Ciabattoni and Berchtold<sup>5</sup> Under the conditions described in reference 5 (refluxing benzene/16 h) 2-methyl-3-pyrrolidino-2,5-dihydrothiophene (VIIa) reacted with one equivalent of VI to yield a mixture of three (1:1) addition products 3,3-Dimethyl-pyrrolidino-2,3-dihydrothiophene (VIIb) reacted far more readily (at room temperature/16 h) giving single 1:1 adduct in 90 % yield

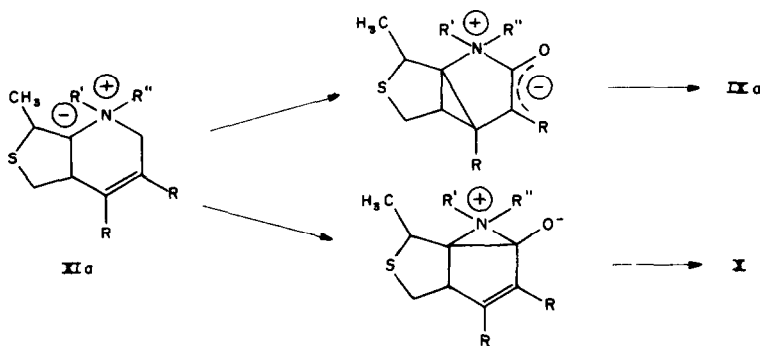


$\text{NR}'\text{R}'' = \text{PYRROLIDINO AND R} = \text{C}_6\text{H}_5$

Surprisingly, none of the reaction products were thiocins. This was concluded from their stability in acidic solutions. In compounds of type VIII the 1,4-dienamine-3-one group would hydrolyse rapidly<sup>9</sup>. On the basis of spectral data we finally assigned structure IX to the major products<sup>10</sup> and structure X to the by-products formed in the reaction with VIIa<sup>11</sup>. The conversion of VII into IX can be rationalized as an insertion of the cyclopropanone into the C-N bond of the enamine, a reaction type that had not been reported so far for enamines.

While this work was in progress Dreiding et al.<sup>4a</sup> showed that the original structural assignments for the adducts of cyclopropanones with enamines were incorrect. They, too, found that cyclopropanone had been inserted into the C-N bond of the enamine. Their suggestion that the reaction proceeds via a [3+3] cycloaddition to give an "acylide" which subsequently rearranges to an amide found support when Eicher and Bohm<sup>4b</sup> succeeded in isolating such an "acylide".

We assume that the reactions of the type reported here also involve the formation of an "acylide" e.g. XIa in the reaction between VI and VIIa. Subsequent rearrangement of XI in two different ways explains the formation of both IXa and X.



NR'R'' = PYRROLIDINO AND R = C<sub>6</sub>H<sub>5</sub>

The high reactivity of VIIb compared to that of VIIa can now be attributed to the larger electron density at C<sub>2</sub>, resulting from the stabilization of the partly negative charge by the adjacent sulfur atom. A similar difference in reactivity was observed in the reactions of VIIa and b with acetylenes<sup>1</sup>.

R E F E R E N C E S  
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- 8 Only in one other case has the formation of such an "abnormal" reaction product been observed viz in the ring opening of a 1-morpholinobenzo[c]bicyclo[3 2 0]hept-7-ene [G.A Berchtold and G.F. Uhlig, J Org Chem 28, 1459 (1963)].
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- 10 IXa m.p 197-198 °C, yield 15 %,  $\delta_{\text{H}_{\text{vinyl}}}$  5.78 ppm (s),  $\nu_{\text{C=O}}$  1615  $\text{cm}^{-1}$ , M,M-70 and M-98  
IXb m.p 155-157 °C, yield 90 %,  $\delta_{\text{H}_{\text{vinyl}}}$  5.91 ppm (s),  $\nu_{\text{C=O}}$  1620  $\text{cm}^{-1}$ , M,M-70 and M-98
- 11 Xa m.p 115-116.5 °C, yield 5 %,  $\nu_{\text{C=O}}$  1695  $\text{cm}^{-1}$ ,  $\delta_{\text{H}_4}$  3.90 and 3.50 ppm ( $J_{\text{AB}} = 9$  Hz),  $\delta_{\text{H}_5}$  2.48 ppm ( $J_{\text{BC}} = 12$  Hz)  
Xb m.p 113-115 °C, yield 2 %,  $\nu_{\text{C=O}}$  1692  $\text{cm}^{-1}$ ,  $\delta_{\text{H}_4}$  4.07 and 3.10 ppm ( $J_{\text{AB}} = 6.5$  Hz),  $\delta_{\text{H}_5}$  2.54 ppm ( $J_{\text{BC}} = 12$  Hz)