

STUDIES ON PYRIDAZINE COMPOUNDS, XIV¹

CYCLIZATION OF PYRIDAZINYLDRAZONES

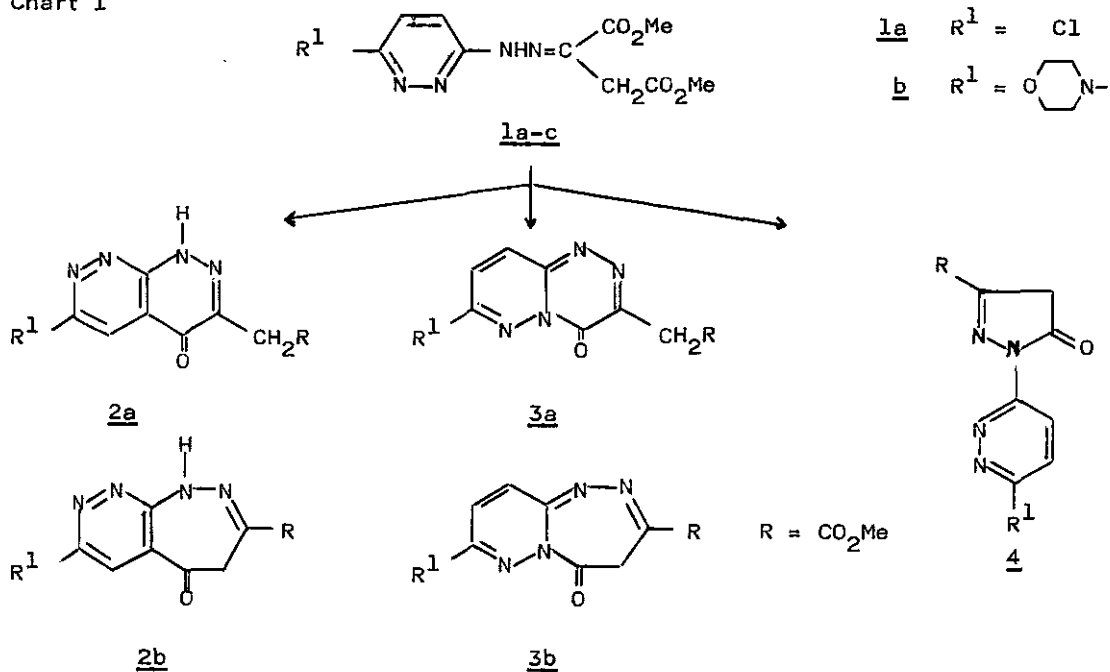
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Abstract - Under suitable thermal or basic conditions pyridazinyldrazones are transformed to the desmotropic pyridazinyldrazolinones, the structure of which was proven by alkylation and acylation.

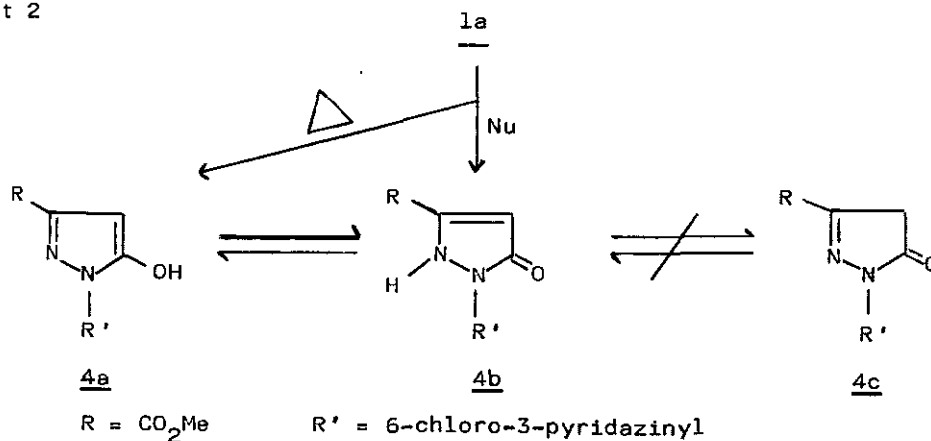
In a previous work² we described cyclization of pyridazinyldrazones prepared from aliphatic oxoesters. Further studies have now shown that cyclization of pyridazinyldrazones of type 1³ obtained from dialkyl acetylenedicarboxylates proceeded differently, depending on the reaction conditions (thermal or basic). Theoretically, the alternative formation of the C-condensed 2, N-condensed 3 and the substituted 4 systems (with the possible formation of the corresponding tautomers and seven-membered ring isomers, too) should be taken into consideration. With the knowledge of the known cyclization of heterocyclidrazones⁴ to compounds of type 3 or the easy endo N-acylations of pyridazinyldrazones⁵, the formation of 2a,b and 3a,b could surprisingly be excluded on the basis of spectral data.

Chart 1



These data revealed, however, the appearance of desmotropes which have only rarely been reported^{4,6} - especially cases involving $\text{C}=\text{C} \rightarrow \text{C}=\text{N}$ tautomerism. The kinetically controlled thermal cyclization⁷ of 1a resulted in 4a OH-tautomer (mp 157-159°C in 35-50 % yield) - however, the thermodynamically controlled reaction under basic conditions⁸ led to the 4b NH-tautomer (mp 188-189°C in 90-95 % yield).

Chart 2

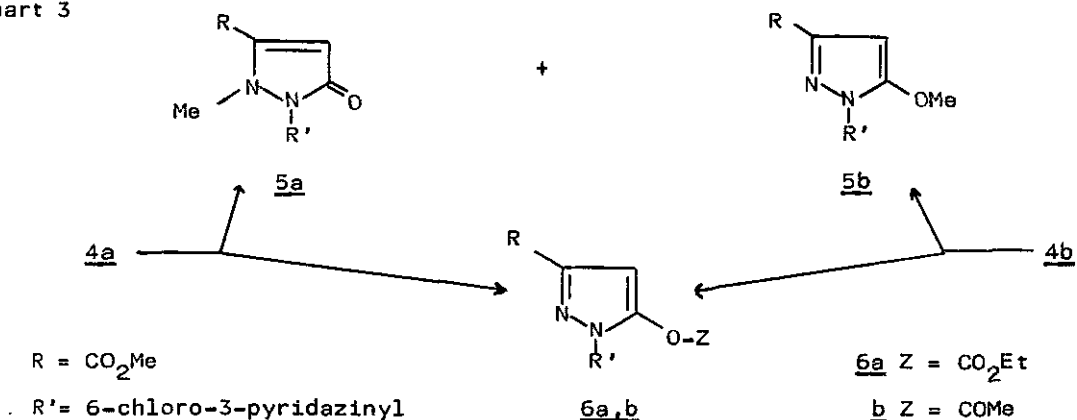


In accordance with our former investigations⁹, no CH-tautomer 4c was found either in solid phase or in DMSO-d₆ solution.

Structures 4a and 4b were confirmed by elemental analysis, as well as UV, IR and ¹H-NMR measurements. Primary evidence for structure 4a was afforded by the IR-bands (in KBr) : ν_{OH} 2700-3200 (broad and diffuse) and $\nu_{C=O}$ (ester) 1745 cm⁻¹ and by the ¹H-NMR spectrum (in DMSO-d₆) in which the characteristic singlet of the heteroaromatic pyrazolyl proton (in position 4) appeared at 5.21 ppm, the position of the signal due to the -OH is \sim 9 ppm (broad). The IR-spectrum of 4b showed the characteristic bands of a NH-tautomer (in KBr) : ν_{NH} 3280 cm⁻¹ (very strong), $\nu_{C=O}$ (ester) 1735 cm⁻¹ and $\nu_{C=O}$ (carbonyl) 1720 cm⁻¹. The ¹H-NMR spectrum showed a vinyl signal (of the pyrazolyl C₄-proton) appearing as a singlet at 5.03 ppm (in DMSO-d₆), the position of the signal due to the -NH is \sim 3-4 ppm (broad). The chemical shift of the pyridazinyl H-4 is also characteristic of the desmotropes: 8.05 ppm for 4a (the pyrazolyl N-2 is an amine nitrogen and can be protonated) and 8.8 ppm for 4b (the pyrazolyl N-2 is an amide nitrogen and can not be protonated). Finally, the ¹H-NMR spectrum of the mixture (4a + 4b) in trifluoroacetic acid proved the desmotropic structures.

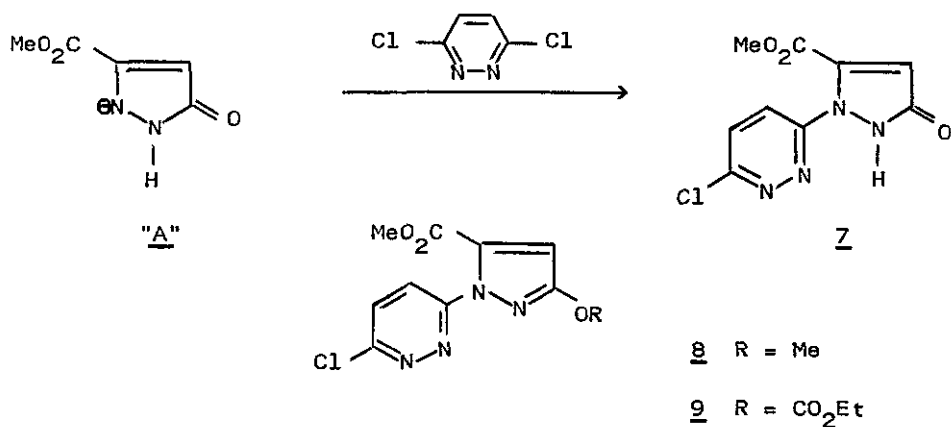
When heated over its melting point 4a was converted into the more stable NH-tautomer 4b. This process could not be observed in DMSO solution at 130°C. Further interesting results have been provided by alkylation and acylation of both desmotropes (4a and 4b) - by the aid of diazomethane, methyl sulfate and methyl iodide, respectively - and on the other hand, by diethyl pyrocarbonate, acetyl chloride and acetic anhydride, respectively¹⁰ - because of the ambident character of the molecule 4. The alkylations led to the N- and O-methylated derivatives (5a¹¹ and 5b¹²), with diazomethane predominantly to 5a (the ratio of 5a to 5b was about 5 to 1), while in a (5:1) ratio for 5b with other alkylating agents. The acylations exclusively resulted in the O-acylated derivatives 6a,b¹³ in good yields¹⁴.

Chart 3



Another possibility for the synthesis of 4 could have been the alkylation of 3(5)-methoxycarbonyl-5(3)-pyrazolinone with 3,6-dichloropyridazine¹⁵. In a striking contrast, the reaction led only to the isomeric 2-alkylated pyrazolinone 7¹⁶. This can be explained by the effect of the methoxycarbonyl group in the alpha position which can stabilize the anion "A". The compound 7 could be converted into the O-methyl derivative 8¹⁷ and into the O-acyl derivative 9¹⁸, respectively.

Chart 4



It is interesting to note that in the case of the 3-methylpyrazolinone derivative of 4 no difference existed in the tautomeric forms obtained under basic or thermal reaction conditions, i.e. the alkylation of 3-methyl-5-pyrazolinone by 3,6-dichloropyridazine led to 1-alkylated pyrazolinone.

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7. The thermal reaction was carried out in Dowtherm (5-10 volumes as a solvent) at 240-250°C for 5 min.
8. The hydrazone la was reacted in an aliphatic alcohol containing sodium methoxide or in aqueous ammonium hydroxyde solution at room temperature.
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10. The methylation was carried out by diazomethane (in alcoholic solution at room temperature), by methyl sulfate (in acetone in the presence of potassium carbonate at reflux temperature for 2-10 h), or by methyl iodide (in dimethylformamide in the presence of potassium carbonate at 70°C for 15 h), while the ethoxycarbonylation was reached by heating with diethyl pyrocarbonate (at 130°C for 2-4 h), or by ethyl chloroformate (in dioxane in the presence of pyridine at room temperature for 2-4 h) and the acetylation by acetic anhydride (at 150°C for 10 min) or by acetyl chloride (in dioxane in the presence of pyridine at room temperature for 2 h).

11. 5a: mp 202-204°C, ν 1740 cm^{-1} (ester C=O), 1680 cm^{-1} (C=O); δ 3.5 (N-Me,s), 6.15 (4-CH, pyrazole,s).
12. 5b: mp 138-139°C; ν 1740 cm^{-1} (C=O ester); δ 4.05 (O-Me,s), and 6.53 (4-CH, pyrazole,s) and δ 90.6 in C^{13} -NMR (C^4 -pyrazole).
13. 6a: mp 96-97°C; ν 1740 (C=O ester), 1770 cm^{-1} (R-O-C=O); δ 1.37 (CH_3 -ester,t), 4.37 (CH_2 -ester,q) and 6.98 (4-CH, pyrazole,s) in DMSO-d_6 .
- 6b: mp 136-137°C; ν 1790 (R-O-C=O); 1745 cm^{-1} (C=O ester); δ 2.40 (CH_3 -acetyl,s), 3.92 (CH_3 -methoxy,s) and 6.96 (4-CH, pyrazole,s) in DMSO-d_6 .
14. Analogously, the same results were obtained in the reaction of 1b: NH-tautomer mp 208-210°C, OH- tautomer mp 168-171°C, O-Me deriv. mp 77-78°C, N-Me deriv. mp 203-205°C, O-CO₂Et deriv. mp 117-118°C.
15. The alkylation was carried out in DMSO/NaH system at 60°C for 10 h.
16. 7: mp 158-160°C, (30 %); ν 3310 cm^{-1} (NH), 1725 cm^{-1} (ester + C=O); δ 6.73 (4-CH, pyrazole,s).
17. 8: mp 109-111°C (64 %); ν 1740 cm^{-1} (C=O ester); δ 6.73 (4-CH, pyrazole,s) and 4.10 (OMe).
18. 9: mp 113-114°C (78 %); ν 1790 cm^{-1} (R-O-C=O), 1745 cm^{-1} (ester); 6.93 (4-CH, pyrazole,s).

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