

CYCLOADDITIONS IN THE PYRROLE SERIES

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Besides the typical reactions of heteroaromatic electrophilic substitution, some pyrrole derivatives are known to undergo also $[4 + 2]$ and $[2 + 1]$ cycloaddition reactions (1), which allowed to focus the diene character of pyrrole with respect to dienophiles (2) and to carbenes or carbenoids (3).

Within the investigations on addition reactions in the heterocyclic series (4), we now report the first example of cycloaddition between a compound with 1,3-dipolar character and a pyrrole derivative.

N-methylpyrrole I, when treated with N-phenylpyruvonnitrileimide prepared in situ (5), yields a complex reaction mixture from which double addition products III and IV, with a 3:1 ratio, have been isolated.

Structures III and IV have been attributed on the basis of the following spectroscopic and chemical evidences. Compound III, m.p. 204°C; UV λ_{\max} 238, 288, 297, 352 nm (log ϵ 4.40, 3.91, 3.94, 4.51, respectively); IR 1650 cm^{-1} (C=O); NMR δ 2.41 (s, 3H, N-CH₃), 2.51 (s, 6H, 2 x COCH₃), 4.53 (d, J = 6.8 Hz, 2H, 3a-H and 3b-H), 5.50 (d, J = 6.8 Hz, 2H, 6a-H and 7a-H), 6.8-7.45 (m, 10H, Ar-H). Compound IV: m.p. 187°C; UV λ_{\max} 237, 289(s), 299(s), 352 nm (log ϵ 4.38, 3.85, 3.88, 4.53, respectively); IR 1650-1655 cm^{-1} (C=O); NMR δ 2.52 and 2.58 (2 s, 6H, 3H, 2 x COCH₃, N-CH₃), 4.32 (d, J = 7.5 Hz, 1H, 3a-H), 4.65 (d, J = 8.2 Hz, 1H, 6a-H), 5.28 (d, J = 8.2 Hz, 1H, 3b-H), 5.55 (d, J = 7.5 Hz, 1H, 7a-H), 6.9-8.05 (m, 10H, Ar-H).

a) The UV spectra of III and IV are very alike, thus indicating that the same chromophores are present in both molecules; moreover, they are consistent with condensed N-phenyl substituted Δ_2 -pyrazolines.

b) The IR spectra of III and IV do not show any signal in the range 3500-3300 cm^{-1} .

c) The low δ value of N-CH₃ protons (2.41 and 2.52 or 2.58 for III and IV, respectively), compared with that of the same protons of N-methyl-pyrrole (3.50 δ) (7), indicates absence of ring current, both in III and IV.

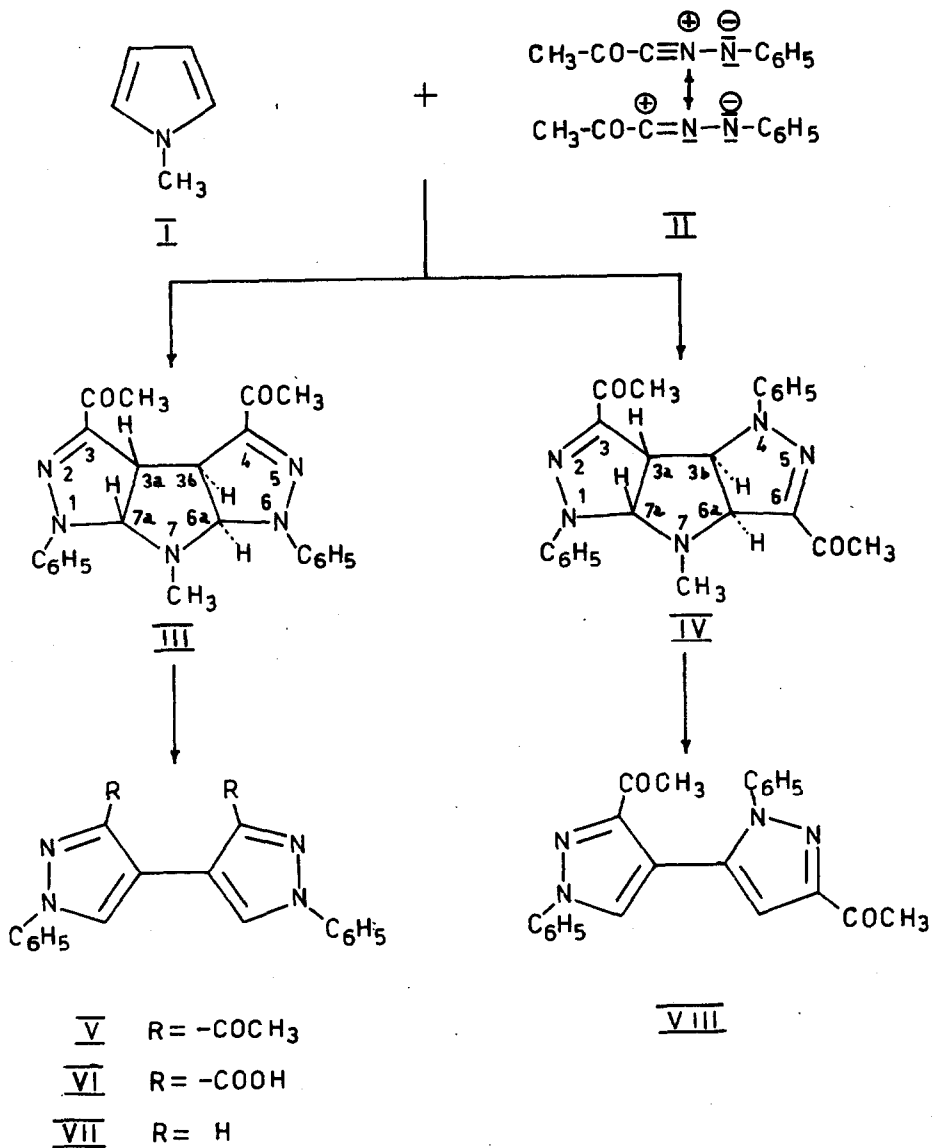
d) The protons at the rings junction of III are equivalent in pairs, whereas those of IV show no equivalence.

e) III (1 g) dissolved by heating in ethanol (100 ml) and treated with conc. HCl (1 equivalent) yields methylamine and 4,4'-dipyrazole V. Quantitative yield: m.p. 208°C; UV λ_{max} 249, 276(s) nm (log ϵ 4.59, 4.37, respectively); IR 1686 cm^{-1} (C=O); NMR δ 2.73 (s, 6H, 2 x COCH₃), 7.15-8.0 (m, 10H, Ar-H), 8.70 (s, 2H, 5,5'-Heter-H). V, by oxidation with Br₂ and NaOH in water-dioxane mixture, yields acid VI. Yield 80%; m.p. 270°C dec.; UV λ_{max} 245(s), 270 nm (log ϵ 4.38, 4.46, respectively); IR 2400-3200 cm^{-1} (OH), 1678 cm^{-1} (C=O); NMR (DMSO) δ 7.2-8.15 (m, 10H, Ar-H), 8.74 (s, 2H, 5,5'-Heter-H). Compound VI, after heating above its melting point (5 minutes), decarboxylates to give VII. Yield 85%; m.p. 212°C; UV λ_{max} 280 nm (log ϵ 4.44); NMR δ 7.0-7.8 (m, 10H, Ar-H), 7.80 (d, $J < 1$, 2H, 3,3'-Heter-H), 7.98 (d, $J < 1$, 2H, 5,5'-Heter-H). Compound VII has been identified by comparing its properties (m.p., UV, and NMR spectra) with those of an authentic specimen (8). On the contrary, compound IV yields VIII only when boiled for a long time in conc. HCl (8 hrs.). Quantitative yield: m.p. 169-170°C; UV λ_{max} 242, 267(s) nm (log ϵ 4.55, 4.47); IR 1675 cm^{-1} (C=O); NMR δ 2.46 (s, 3H, COCH₃), 2.71 (s, 3H, COCH₃), 7.13 (s, 1H, Heter-4-H), 7.25-8.0 (m, 10H, Ar-H), 8.03 (s, 1H, Heter-5'-H).

The above results prove that in the initial $[2+3]$ cycloaddition the electrophilic centre of dipole II attacks both α - and β -positions of N-methyl-pyrrole I. The resulting cyclic monoadducts (which cannot be isolated) control electronically and sterically the dipole II orientation in the subsequent $[2+3]$ cyclization because of their particular structure. Therefore, when assuming a cis-junction, configurations III and IV (and their enantiomers) seem to be the correct ones and in good agreement with NMR data (IV, in particular).

The reaction here investigated (9), which seems to be without precedent in the pyrrole series, is also interesting with regard to synthesis. In fact, for the first time it allowed the synthesis of the polycondensed heterocycles

3a3b6a7a-tetrahydropyrrole[2,3c:4,5c]-dipyrazole and 3a3b6a7a-tetrahydropyrrole[2,3c:5,4c]-dipyrazole. These compounds (which alone may have a pharmaceutical interest) are good substrates to obtain 4,4'-dipyrazoles and 4,5'-dipyrazoles, the few known examples of which have been prepared by long and complicated methods (10).



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UV spectra (ethanol) have been carried out by an automatic DB spectrophotometer. IR spectra (nujol) have been obtained by an Infracord 137 Perkin Elmer spectrophotometer. NMR spectra (CDCl_3) have been recorded by a Jeol C-60 spectrograph, using TMS as internal standard.

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5. 12.2 mmoles of N-methylpyrrole I and 12.2 mmoles of α -chloro- α -(N-phenylhydrazono)acetone have been dissolved in 25 ml THF and 35 mmoles of triethylamine have been added. After keeping them at room temperature for 15 days, triethylamine chloride (12.2 mmoles) has been filtered, the solvent removed at reduced pressure, and the remaining ethanol (15 ml) has been added. The precipitate thus obtained yields III (0.6 g) and IV (0.2 g) by fractionated crystallization from ethanol.
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