

Pyrrole and *C*-Acetyl-*N*-phenylnitrilimine

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The addition reaction of *C*-acetyl-*N*-phenylnitrilimine to pyrrole has been investigated. The products obtained show that the reaction proceeds *via* two distinct pathways. The 1,3-addition reaction leads to the non-cyclic-adduct III, whereas the 1,3-cycloaddition reaction gives a mixture of regioisomeric Δ_2 -pyrroline IV and V, and Δ_1 -pyrroline VI and VII mono-cycloadducts. These latter compounds cannot be isolated because they undergo a further 1,3-cycloaddition reaction leading to the *N*-substituted *bis*-adducts X and XI, and to the *bis*-adducts XII and XIII. The stereochemical assignment for X, XI, XII and XIII is provided by nmr data which suggest also that in X and XI the rotation around the exocyclic N-C bond is relatively slow on the instrument time scale.

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As a result of our interest in the addition reactions of pyrrole derivatives (1,2), in this paper we report the behaviour of pyrrole itself (I) toward *C*-acetyl-*N*-phenylnitrilimine (II). Treating I with II at room temperature, we obtained compounds III (12.3%), X (1.2%), XI (2.6%), XII (5%), XIII (2.4%), XIV (2.2%) and XVI (2.1%) (3). The structures of the above mentioned compounds have been assigned on the basis of chemical and/or spectroscopic properties.

Compound III shows infrared bands due to NH and C=O groups. Its nmr spectrum, measured in the presence of deuterium oxide, shows *inter alia* a spin system AMX with three coupling constants, which are in agreement with the reported values for the 2-substituted pyrrole derivatives (4), and appear to exclude the isomeric 3-substituted structure.

In accordance with our previous observations on the chemical behaviour of similar compounds (1,2), compounds X and XI dissolved in ethanol and then treated with concentrated hydrochloric acid yielded 4,4'-dipyrazole XIV and 4,5'-dipyrazole XV, together with α -amino- α -(*N*-phenylhydrazone)acetone (XVI). We have also observed that compound X yielded XIV and XVI when it was allowed to remain in various organic solvents over an extended period of time. This fact can explain the presence of XIV and XVI in the reaction mixture, derived from I and II, and the different yields observed for X in different experiments.

In the course of elucidating the structures of X and XI by nmr, we have observed spectral patterns which suggest that rotation around the exocyclic N-C bond is relatively slow on the instrument time scale. The spectrum of X revealed in fact four doublet resonances due to protons 3a, 3b, 7a and 6a, as a consequence of the non-equivalence of protons at the bridge-heads (in the corresponding *N*-methyl-derivative (1), the same protons are equivalent in pairs). The nmr spectrum of X also shows a singlet at δ 1.75 (3H); this value is somewhat

unusual for a methyl group on a C=O, and might be rationalized by the fact that methyl protons of the group linked to the pyrrolidine ring are lying in the shielding region of the phenyl ring at N₁ or N₆. On the other hand, the nmr spectrum of XI suggest the existence in solution of two conformers in the ratio 75:25. The nmr spectrum in fact revealed in the region of δ 4.32-6.38, four doublet resonances due to the 3a, 4a, 7a and 7b protons of the major conformer. The resonances due to the pyrrolidine methine protons of the minor conformer consisted of two doublets (H_{4a} and H_{7a}) and an apparent singlet (H_{3a} and H_{7b}), which appeared as AB q at 14°. No assignment can be made at this point concerning the preferred conformer.

The nmr spectra of XII and XIII show *inter alia* an ABMPX system for the pyrrolidine protons, which can be analyzed on an approximate first-order basis (see Table I). A check of multiplet assignments was made for XII by decoupling experiments (see Table II) which showed also that the signal relative to the H_X proton is overlapped by those of the aromatic protons at δ 7.12. Chemical shifts of H_A, H_B and H_P are comparable in XII and XIII, indicating the presence of the *Z*-moiety in both compounds. On the other hand, in the *bis*-adduct XII, *ortho* protons of the phenyl group at N₅ are shifted downfield due to deshielding effect of the carbonyl group at C₃. This effect, absent in XIII, and the observed chemical shifts of H_M and H_X, which are at higher and lower field, respectively, than the corresponding protons of XIII, provide evidence for the junction of the two heterocyclic rings in the *W*-moiety.

An examination of the products obtained from I and II shows that the initial addition of the nitrilimine to pyrrole gives rise to different kinds of reactions. The 1,3-addition reaction leads to the non-cyclic-adduct III, whereas a 1,3-cycloaddition reaction gives cyclic regioisomeric Δ_2 -pyrroline monoadducts IV and V, which are in equilibrium (5) with Δ_1 -pyrrolinones VI and VII. All mono-cyclic

Table II
Double Irradiation Experiments for Compound XII

Proton Irradiated	Irradiation at δ	Lines Collapsed		Measured Remaining Coupling (J Hz)	
		Original Form	Final Form		
H _A	1.98	3.70 td	dd	MX 10.1	MB 1.2
		5.46 dd	d	PB 5.2	
H _M	3.70	1.98 ddd	dd	AB 13.5	AP 9.0
		2.60 ddd (a)	dd (a)	BP 5.2	
H _P	5.46	1.98 ddd	dd	AM 10.1	AB 13.5
		2.60 ddd (a)	dd (a)	BM 1.2	
H _X	7.12	3.70 td	dd	AM 10.1	BM 1.2

(a) Partially obscured by those of methyl protons.

bis-cycloadducts.

The stereochemical assignment for X and XI is provided by the absence of coupling between the adjacent protons 3a and 3b in X, and 7a and 7b in XI, which agree with the dihedral angles of the proposed structures. Although the observed coupling constants seem to not agree with the *anti*-structures proposed for XII and XIII, in that $J_{\text{trans}} \text{H}_P\text{-H}_A > J_{\text{cis}} \text{H}_P\text{-H}_B$, they could be explained assuming that the partially sp^2 -hybridized-N₄ makes the proton H_P pseudo-axial, thus substantially varying the dihedral angles. Moreover, an examination of molecular models of the *sin*-structures corresponding to XII and XIII points out a strong interaction between the two acetyl groups or the phenyl and acetyl group at positions 3 and 5.

EXPERIMENTAL

Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. Infrared spectra (Nujol mull) were obtained with a Perkin-Elmer Infracord 137. Nmr spectra (deuteriochloroform unless otherwise stated) were measured using tetramethylsilane as internal standard with a Jeol C-60 spectrometer. Uv spectra (95% ethanol) were recorded on a Beckmann DB spectrometer.

Reaction of Pyrrole I with Nitrilimine II.

Pyrrole (I) (3 g.) and α -chloro- α -(*N*-phenylhydrazono)acetone (18.8 g.), dissolved in dry THF (150 ml.), were treated with triethylamine (17.6 ml.). After standing at room temperature 30 days the precipitated triethylamine hydrochloride was filtered off and the solvent was evaporated under reduced pressure. The residue was repeatedly chromatographed on a Woelm neutral alumina column with cyclohexane-ethyl acetate mixtures as eluents yielding the unreacted pyrrole (1.2 g., 40%), the 3,6-diacetyl-1,4-dihydro-2,4-diazepine (6) (1 g., 14%), and the following compounds in order of elution.

2-Pyruvoylpyrrole-2¹-(phenylhydrazono) (III).

This compound was obtained in 12.3% yield (1.25 g.), m.p. 96-98° (cyclohexane); ir: 3280 (NH) and 1654 cm^{-1} (C=O); nmr: δ 2.52 (s, 3H, COCH₃), 6.40 (m, 1H, H₄), 6.67 (m, 1H, H₃), 6.98 (m, 1H, H₅), 7.00-7.65 (m, 5H, Ar-H), 9.25 (s, 1H,

NH), 10.5 (br s, 1H, NH, Pyr.); after deuterium oxide added: δ 6.40 (dd, 1H, H₄, $J_{3,4} = 3.7$ and $J_{4,5} = 3.0$ Hz), 6.67 (dd, 1H, H₃, $J_{3,4} = 3.7$ and $J_{3,5} = 1.2$ Hz), 6.98 (dd, 1H, H₅, $J_{3,5} = 1.2$ and $J_{4,5} = 3.0$ Hz); uv: λ max nm (log ϵ) 241 (4.05), 286-292 (3.66), 372 (4.22).

Anal. Calcd. for C₁₃H₁₃N₃O: C, 68.70; H, 5.77; N, 18.49. Found: C, 68.90; H, 5.81; N, 18.45.

3,7-Diacetyl-1,4a,5,7a,8,8a-hexahydro-1,5-diphenylpyrazolo[4',3':4,5]pyrrolo[2,1-c]-s-triazole (XII).

This compound was obtained in 5% yield (0.86 g.), m.p. 198-200° (ethanol); ir: 1654 and 1670 cm^{-1} (C=O); nmr: δ 2.47 and 2.52 (2s, 2 x 3H, 2 x COCH₃), 6.70-7.45 (m, 9H, Ar-H and H_X), 7.60-7.85 (m, 2H, *ortho* Ar-H at position 5), for other signals see Table I; uv: λ max nm (log ϵ) 241 (4.32), 285 (3.46), 294 (3.51), 364 (4.42).

Anal. Calcd. for C₂₂H₂₁N₅O₂: C, 68.20; H, 5.46; N, 18.08. Found: C, 68.23; H, 5.72; N, 18.07.

3,7-Diacetyl-3a,4,4a,5,7a,7b-hexahydro-1,5-diphenyl-4-pyruvoyl-1H-pyrrolo[2,3-c:4,5-c']dipyrzole-4¹-(phenylhydrazono) (XI).

This compound was obtained in 2.6% yield (0.64 g.), m.p. 230-232° (ethanol); ir: 3258 cm^{-1} (NH), 1650 and 1662 cm^{-1} (C=O); nmr: δ 2.00, 2.17, 2.32, 2.52 and 2.62 (5s, 25% 3H, 75% 3H, 3H, 25% 3H, and 75% 3H, 3 x COCH₃), 4.43 and 4.48 (2d overlapping, 1H, H_{7a} maj. and H_{7a} min., $J_{4a-7a} = 8.2$ Hz), 5.01 (d, 75% 1H, H_{3a} or H_{7b} maj., $J_{3a-7b} = 9.0$ Hz), 5.37 (s, 25% 2H, H_{3a} and H_{7b} min.), 5.52 (d, 75% 1H, H_{7b} or H_{3a} maj., $J_{3a-7b} = 9.0$ Hz), 6.10 and 6.23 (2d, 1H, H_{4a} min. and H_{4a} maj., $J_{4a-7a} = 8.2$ Hz), 6.75-7.75 (m, 13H, and 25% 1H, Ar-H and NH min.), 7.80-8.10 (m, 2H, *ortho* Ar-H at position 1), 8.60 (s, 75% 1H, NH maj.); at 14° the singlet at δ 5.37 appeared as AB q ($\Delta\nu = 6.8$ Hz, $J = 9.0$ Hz); (DMSO-d₆): δ 9.86 and 10.20 (2s brs, 75% and 25%, NH); uv: λ max nm (log ϵ) 239 (4.42), 298 s (3.00), 355 (4.69).

Anal. Calcd. for C₃₁H₂₉N₇O₃: C, 67.99; H, 5.34; N, 17.91. Found: C, 67.80; H, 5.15; N, 18.05.

3,3'-Diacetyl-1,1'-diphenyl-4,4'-dipyrzole (XIV).

This compound was obtained in 2.2% yield (0.36 g.), m.p. 208° (ethanol) (lit. m.p. (1) 208°).

α -Amino- α -(*N*-phenylhydrazono)acetone (XVI).

This compound was obtained in 2.1% yield (0.17 g.), m.p. 184° (ethanol) (lit. m.p. (7) 183°).

3,5-Diacetyl-1,3a,7,7a,8,8a-hexahydro-1,7-diphenylpyrazolo[3',4':4,5]pyrrolo[2,1-c]-s-triazole (XIII).

This compound was obtained in 2.4% yield (0.41 g.), m.p. 228° (ethanol); ir: 1655 and 1668 cm^{-1} (C=O); nmr: δ 2.48 and 2.50 (2s, 6H, 2 x COCH_3), 6.75-7.50 (m, 10H, Ar-H), for other signals see Table I; uv: λ max nm (log ϵ) 242 (4.12), 298 (3.20), 364 (4.34).

Anal. Calcd. for $\text{C}_{22}\text{H}_{21}\text{N}_5\text{O}_2$: C, 68.20; H, 5.46; N, 18.08. Found: C, 67.88; H, 5.40; N, 18.00.

3,4-Diacetyl-3a,3b,6,6a,7,7a-hexahydro-1,6-diphenyl-7-pyruvoyl-1H-pyrrolo[2,3-c:5,4-c']dipyrzolo-7¹-(phenylhydrazone) (X).

This compound was obtained in 1.2% yield (0.29 g.), m.p. 240-242° (ethanol); ir: 3250 cm^{-1} (NH), 1650 and 1668 cm^{-1} (C=O); nmr: δ 1.75 (s, 3H, COCH_3), 2.60 (s, 6H, 2 x COCH_3), 4.79 (d, 1H, H_{3a} , $J_{3a-7a} = 7.5$ Hz), 5.01 (d, 1H, H_{3b} , $J_{3b-6a} = 8.2$ Hz), 5.96 (d, 1H, H_{6a} , $J_{3b-6a} = 8.2$ Hz), 6.40 (d, 1H, H_{7a} , $J_{3a-7a} = 7.5$ Hz), 6.70-7.50 (m, 15H, Ar-H), 8.33 (s, 1H, NH).

Anal. Calcd. for $\text{C}_{31}\text{H}_{29}\text{N}_7\text{O}_3$: C, 67.99; H, 5.34; N, 17.91. Found: C, 68.02; H, 5.34; N, 18.13.

Cleavage of the Adducts X and XI.

A solution of adduct X (0.1 g.) in ethanol (10 ml.) was treated with a catalytic amount of concentrated hydrochloric acid and the solution was left at room temperature for 1 hour. After evaporation of the solvent, crystallization of the residue from ethanol afforded XIV in quantitative yield, m.p. 208° (lit. m.p. (1) 208°).

A solution of adduct XI (0.1 g.) in ethanol (10 ml.) and a catalytic amount of concentrated hydrochloric acid was refluxed for 4 hours. After evaporation of the solvent, crystallization of the residue from ethanol afforded XV in quantitative yield, m.p. 169° (lit. m.p. (1) 169°).

In the mother liquors of X and XI, the presence of XVI was confirmed by tlc.

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