Addition Reactions of Heterocycles. VI. (1) Reactions of 1,2-Dimethylpyrrole and 1-Methyl-2-carbomethoxypyrrole with Nitrilimines.

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Addition reactions of 1,2-dimethylpyrrole and 1-methyl-2-carbomethoxypyrrole with *C*-acetyl-*N*-phenylnitrilimine, have been investigated. 1,2-Dimethylpyrrole gives three different types of adducts: *i.e.* bis-cycloadducts (Vc) and (VIc), spirocycloadduct (IX), and non cyclic bis-adduct (XII). On the other hand, 1-methyl-2-carbomethoxypyrrole gives the bis-cycloadduct (VIb) only. Compound XII arises probably through a double 1,3-addition reaction, whereas the formation of cycloadducts Vc, VIc, and IX depends on the substituents present at C_2 of the pyrrole ring and consequentially on the intermediary occurence of mono-cycloadduct (IIIc), its methylenic tautomer VII, VIc, and XI. The behaviour of the cycloadducts towards heating or acidic treatment showed a termal cleavage of the pyrazoline ring and acidic cleavage of the pyrrolidine ring.

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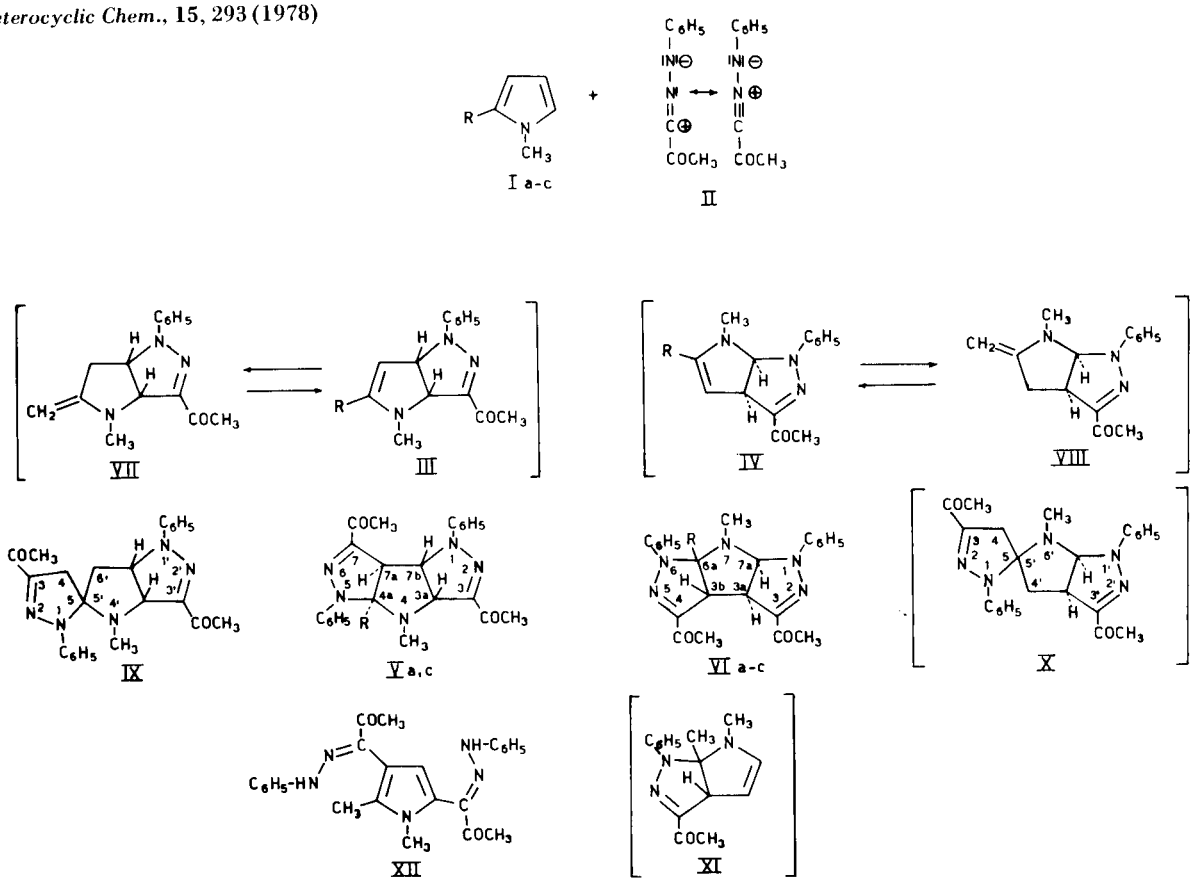
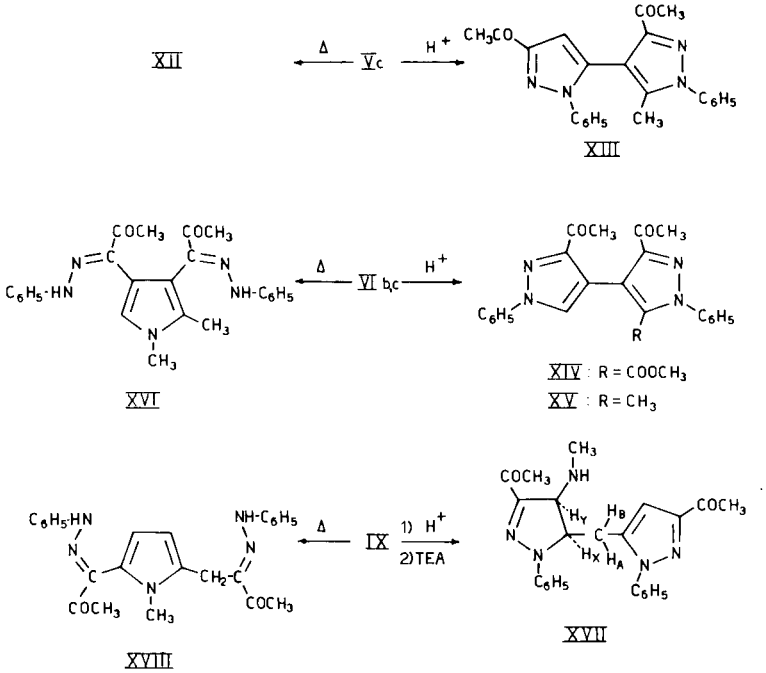


Scheme 1

Previously (2) we have reported that *N*-methylpyrrole (Ia) reacts with dipole (II), generated *in situ*, to give double cycloaddition products Va, and VIa. Formation of bis-cycloadducts demonstrates that, in the first 1,3-cycloaddition of the dipole II to pyrrole ring, both regioisomeric mono-cycloadducts IIIa and IVa are formed; these non isolable intermediates subsequently act as dipolarophiles regiospecifically.

Aimed to ascertain the role of 2-substituents in determining the orientation of the cycloaddition leading



to 1:1 adducts, our investigations were extended to examine the behaviour of 1-methyl-2-carbomethoxypyrrole (Ib) and 1,2-dimethylpyrrole (Ic). To establish the reactivity of Ic is of some interest since the hypothetical pyrrolidine mono-cycloadducts IIIc and IVc, in their tautomeric form (3) VII and VIII, might be envisaged to undergo also [3+2] cycloaddition with dipole II hence yielding bis-cycloadducts which differ from those isolated from *N*-methylpyrrole (see Scheme 1).

We find that while 1-methyl-2-carbomethoxypyrrole (Ib) reacts with dipole II to give the bis-cycloadduct (VIb, 20%), 1,2-dimethylpyrrole (Ic) gave a complex reaction mixture from which compounds Vc, (40%), VIc, (3%), IX, (10%), and XII, (11%) were isolated.

The structures of the compounds Vc and VIb-c were elucidated by spectroscopic and chemical data, which were similar to those reported for Va (2) and VIa (2). The uv spectra were consistent with condensed 1-phenyl-substituted-Δ^2-pyrazolines and ir spectra fail to show any signal in the range 3500-3300 cm^{-1}. The low δ value of the $-CH_3$ protons resonance, as compared with the resonance of the same protons in the starting pyrrole derivatives, indicates absence of ring current. In the bis-cycloadduct (Vc) the *ortho* protons of the phenyl group at N_1 are shifted downfield, due to deshielding effect of the carbonyl group at C_7. This effect, already observed for Va, but not for VIa-c, provides evidence for asymmetrical or symmetrical location of the pyrazoline rings.

By comparing the chemical shifts of the *7a* proton of Vc and of the *3b* protons of VIb-c with those of the same protons of Va (2,4) and VIa (2), respectively, we have observed that these protons are shielded by a methyl group and deshielded by a carbomethoxy group. The observed effect on the shift induced by substituents on neighbouring *cis* protons is in agreement with the findings on a series of cycloadducts of indole derivatives (5) with dipole II and 1,3-diphenyl-pyrazoline derivatives (6). Although the flexibility of the pyrrolidine ring does not allow generality in stereochemical assignements (7), the observed coupling constant for *7a-7b* protons (0 in Va and Vc) and for *3a-3b* protons (0 in VIa-b, 1 in VIc), agrees with dihedral angles in the assigned structures.

Adduct Vc, when dissolved in hot ethanol and refluxed in the presence of hydrogen chloride, yields 4,5′-dipyrazole derivative XIII, whereas compounds VIb-c yield 4,4′-dipyrazole derivatives XIV and XV, along with methylamine.

By heating at 170° adduct Vc, one obtains bis-phenylhydrazone XII, identical with the product isolated from reaction mixture of Ic and II, whereas adduct VIc gave XVI. The structures proposed for XII and XVI are consistent with our uv, ir and nmr spectra.

Structure IX was confirmed by examining the products arising from the mentioned reaction. Spirocycloadduct IX, at reflux in ethanol containing concentrated hydrochloric acid gave the hydrochloride of XVII which, treated with triethylamine, yielded the free base. As expected compound XVII shows NH and C=O absorption in the ir spectrum and a ABXY pattern for pyrazoline and metilene protons in the nmr spectrum (see Experimental). Spiro cycloadduct IX was found to be labile also in organic solvent solutions; *i.e.*, slow conversion of IX into XVII is observed in chloroform, carbon tetrachloride or benzene. As a consequence the nmr spectrum does not provide definitive confirmation for the structure IX.

The results obtained are in agreement with the predicted electronic effect of substituents in the cycloaddition reaction. In fact in the case of 1-methyl-2-carbomethoxypyrrole (Ib) a diminished cycloaddition reactivity is observed. The yield of the only cycloadduct isolated (VIb) is far from quantitative, and the large amount of unreacted Ib present in the reaction mixture indicates that the conversion of Ib into VIb is slow. The nature of bis-cycloadduct VIb suggest that the influence of carbomethoxy group at C_2 strongly affects the regioselectivity of the first cycloaddition, suppressing formation of IIIb and hence of the asymmetric bis-cycloadduct Vb.

Assuming compound XII arising through a double 1,3-addition reaction, the yield of the compounds Vc, VIc, and IX, suggest that 1,2-dimethylpyrrole is first converted mainly into IIIc, which results from a favorable orientation of the dipole toward the 5,4 ring positions. The novel type adduct IX arises as result of tendency of the mono-cycloadduct IIIc to react also from its tautomeric form VII, thus making feasible the alternative reaction path involving attack of the dipole II to dipolarophile $-C=CH_2$; this yields to formation of the spirocycloadduct IX. We have been unable to isolate the spirocycloadduct X and this fact suggest the intermediary occurrence of mono-cycloadduct XI rather than IVc in the formation of the bis-cycloadduct VIc, which is in agreement with the directing effect of the methyl group at C_2 of the pyrrole ring in the electrophilic substitution (8).

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 were determined in deuteriochloroform using tetramethylsilane as internal standard on a Jeol C-60H spectrometer. Uv spectra (95% ethanol) were recorded on a Beckman DB spectrometer.

Reaction of 1-Methyl-2-carbomethoxypyrrole (Ib) with Nitrilimine (II).

Compound Ib (1 g.) and α-chloro-α-(*N*-phenylhydrazone)-acetone (1.53 g.), dissolved in dry THF (25 ml.), were treated with triethylamine (3.6 ml.). After 20 days, triethylamine hydrochloride (1.05 g.) was filtered off and the solvent evaporated under reduced pressure. The residue dissolved in benzene was chromatographed over neutral Woelm alumina. The first benzene fractions (2.5 l.) were evaporated and the residue crystallized from cyclohexane to yield 0.36 g. (20%) of 3,4-diacetyl-3a,3b,6,-6a,7,7a-hexahydro-6a-carbomethoxy-7-methyl-1,6-diphenyl-1*H*-pyrrolo[2,3-c:5,4-c']dipyrazole (VIb), m.p. 188-190°; ir: 1748 and 1666 cm^{-1} (C=O); uv: nm (log ε) 238 (4.34), 290s (3.92), 299s (3.97), 350 (4.47); nmr: δ 2.39, 2.44 and 2.51 (3s, 3 x 3H, NCH_3 and 2 x $COCH_3$), 3.64 (s, 3H, $COOCH_3$), 4.56 (d, 1H, H_{3a}, $J_{3a\text{-}7a}$ = 7.2 Hz), 4.80 (s, 1H, H_{3b}), 5.67 (d, 1H, H_{7a}, $J_{3a\text{-}7a}$ = 7.2 Hz), 6.8-7.5 (m, 10H, ArH).

Anal. Calcd. for $C_{25}H_{25}N_5O_4$: C, 65.35; H, 5.48; N, 15.24. Found: C, 65.38; H, 5.51; N, 15.19.

Further elution gave unreacted Ib and few amounts of unidentified products.

Reaction of 1,2-Dimethylpyrrole (Ic) with Nitrilimine (II).

Compound Ic (2 g.) and α-chloro-α-(*N*-phenylhydrazone)-acetone (4.13 g.), dissolved in dry THF (25 ml.), were treated with triethylamine (8.4 mL). After 20 days, triethylamine hydrochloride (2.8 g.) was filtered off and the solvent evaporated under reduced pressure and at room temperature. The oily residue, taken up with methanol (20 ml.), gave a solid product, which was recrystallized from methanol to yield 1.75 g. (40%) of 3,7-diacetyl-3a,4,4a,5,7a,7b-hexahydro-4,4a-dimethyl-1,5-diphenyl-1*H*-pyrrolo-[2,3-c:4,5-c']dipyrazole (Vc), m.p. 152-154° with transformation; ir: 1661 and 1639 cm^{-1} (C=O); uv: nm (log ε) 238 (4.25), 300s (3.98), 344 (4.44); nmr: δ 1.54 (s, 3H, CH_3), 2.12 (s, 3H, NCH_3), 2.44 and 2.50 (2s, 6H, 2 x $COCH_3$), 3.96 (s, 1H, H_{7a}), 4.71 (d, 1H, H_{3a}, $J_{3a\text{-}7b}$ = 8.2 Hz), 5.17 (d, 1H, H_{7b}, $J_{3a\text{-}7b}$ = 8.2 Hz) 6.85-7.60 (m, 8H, ArH), 7.71-8.0 (m, 2H, *ortho* Ar-H at position *1*).

Anal. Calcd. for $C_{24}H_{25}N_5O_2$: C, 69.38; H, 6.07; N, 16.86. Found: C, 69.41; H, 6.05; N, 16.87.

The methanolic solution combined were concentrated under reduced pressure to a sirup. The residual sirup taken up with methanol gave another solid product, which purified by repeated crystallization from methanol, yield 0.44 g. (10%) of 3,3'-diacetyl-3'a,4',6',6'a-tetrahydro-4'-methyl-1,1'-diphenylspiro[2-pyrazoline-5,5'(1'H)pyrrolo[3,2-c]pyrazole] (IX), m.p. 158-159°; ir: 1656 cm^{-1} (C=O); uv: nm (log ε) 239 (4.31), 289s (3.63), 300s (3.75), 360 (4.31).

Anal. Calcd. for $C_{24}H_{25}N_5O_2$: C, 69.38; H, 6.07; N, 16.86. Found: C, 69.37; H, 6.06; N, 16.84.

Again the mother methanolic solution was concentrated under reduced pressure, residual sirup taken up with methanol and the crystalline precipitate removed by filtration. Recrystallization from cyclohexane yielded 0.48 g. (11%) of 1,1'-(1,2-dimethylpyrrole-3,5-diyl)-di-1,2-propanedione-1,1'-bis(phenylhydrazone) (XII), m.p. 183°; ir: 3210 cm^{-1} (NH), 1760 and 1634 cm^{-1} (C=O); uv: nm (log ε) 236 (4.45), 286s (3.92), 295 (3.99), 353 (4.59); nmr: δ 2.06 (s, 3H, CH_3), 2.58 (s, 6H, 2 x $COCH_3$), 3.32 (s, 3H, NCH_3), 6.11 (s, 1H, pyrrole-H), 6.75-7.45 (m, 10H, ArH), 8.55-9.10 (2s, br, 2H, 2 x NH).

Anal. Calcd. for $C_{24}H_{25}N_5O_2$: C, 69.38; H, 6.07; N, 16.86. Found: C, 69.35; H, 5.94; N, 16.68.

With the same procedure after removal of methanol *in vacuo*, ethanol (20 ml.) was added, the solid precipitate was removed by filtration and after several recrystallizations from ethanol, 0.14 g. (3%) of 3,4-diacetyl-3a,3b,6,6a,7,7a-hexahydro-6a,7-dimethyl-1,6-diphenyl-1*H*-pyrrolo[2,3-c:5,4-c']dipyrazole (VIc) contaminated with IX (nmr and tlc) were obtained, m.p. 142°; ir: 1659 cm^{-1} (C=O); nmr: δ 1.52 (s, 3H, CH_3), 2.07 (s, 3H, NCH_3), 2.45 and 2.55 (2s, 2 x 3H, 2 x $COCH_3$), 4.11 (d, 1H, H_{3b}, $J_{3a\text{-}3b}$ = 1 Hz), 4.49 (dd, 1H, H_{3a}, $J_{3a\text{-}7a}$ = 7.5 Hz and $J_{3a\text{-}3b}$ = 1 Hz), 5.58 (d, 1H, H_{7a}, $J_{3a\text{-}7a}$ = 7.5 Hz), 6.70-7.65 (m, 10H, ArH).

Thermal Rearrangements of Vc, VIc, and IX into XII, XVI, and XVIII, Respectively.

The cyclic adduct (0.1 g.) was heated in a test tube above its melting point (oil bath) for 5 minutes. After cooling, the rearrangement product was obtained with high yield from Vc. Compound XII was obtained, m.p. 183° from cyclohexane. From VIc, 1,1'-(1,2-dimethylpyrrole-3,4-diyl)di-1,2-propanedione-1,1'-bis(phenylhydrazone) (XVI) was obtained, m.p. 106-108° from ethanol; ir: 3260 cm^{-1} (NH) and 1655 cm^{-1} (C=O); uv: nm (log ε) 234 (4.38), 287s (3.84), 294 (3.98), 347 (4.48); nmr: δ 2.02 (s, 3H, CH_3), 2.37 and 2.39 (2s, 2 x 3H, 2 x $COCH_3$), 3.61 (s, 3H, NCH_3), 6.62 (s, 1H, pyrrole-H), 6.7-7.5 (m, 10H, Ar-H), 8.54 (s, br, 2H, 2 x NH).

From IX, 1-(1-methyl-5-pyruvoylpyrrol-2-yl)2,3-butanedione-

2,5-bis(phenylhydrazone) (XVIII) was obtained, m.p. 162° from methanol; ir: 3225 and 3175 cm^{-1} (NH), 1654 and 1645 cm^{-1} (C=O); uv: nm (log ϵ) 235 (4.39), 284 (3.95), 292 (4.02), 343 (4.49); nmr: δ 2.51 and 2.54 (2s, 2 x 3H, 2 x $COCH_3$), 3.23 (s, 3H, NCH_3), 3.91 (s, br, 2H, CH_2), 5.99 (d, br, 1H, pyrrole-H at position *3*), 6.11 (d, 1H, pyrrole-H at position *4*, J_{3-4} = 3.8 Hz), 6.8-7.5 (m, 10H, Ar-H), 8.65 and 8.72 (2s, brs, 2H, 2 x NH).

Anal. Calcd. for $C_{24}H_{25}N_5O_2$: C, 69.38; H, 6.07; N, 16.86. Found: C, 69.41; H, 6.06; N, 16.83.

Transformation of Cyclic Adducts Vc, VIb, VIc, and IX into XIII, XIV, XV, and XVII, Respectively by Acid Treatment. General Procedure.

A solution of cyclic adduct (0.1 g.) in hot ethanol (10 ml.) was treated with two drops of concentrated hydrochloric acid and heated under reflux for six hours. After cooling, the solvent was removed under reduced pressure and the residue was crystallized.

From Vc, 3,3'-diacetyl-5-methyl-1,1'-diphenyl-4,5'-dipyrazole (XIII) was obtained, m.p. 148° from ethanol; ir: 1672 cm^{-1} (C=O); uv: nm (log ϵ) 232 (4.46), 252s (4.37); nmr: δ 2.12 (s, 3H, CH_3), 2.33 and 2.65 (2s, 2 x 3H, 2 x $COCH_3$), 6.86 (s, 1H, pyrazole-H), 7.25 and 7.42 (2s, 2 x 5H, Ar-H).

Anal. Calcd. for $C_{23}H_{20}N_4O_2$: C, 71.86; H, 5.24; N, 14.58. Found: C, 71.83; H, 5.26; N, 14.54.

From VIb, 3,3'-diacetyl-5-carbomethoxy-1,1'-diphenyl-4,4'-dipyrazole (XIV) was obtained, m.p. 185-186° from ethanol; ir: 1726 and 1686 cm^{-1} (C=O); uv: nm (log ϵ) 232 (4.48), 267-273s (4.32); nmr: δ 2.57 and 2.59 (2s, 2 x 3H, 2 x $COCH_3$), 3.51 (s, 3H, $COOCH_3$), 7.1-7.6 (m, 8H, Ar-H), 7.6-7.9 (m, 2H, *ortho* Ar-H at positon *1'*), 8.14 (s, 1H-pyrazole-H).

Anal. Calcd. for $C_{24}H_{20}N_4O_4$: C, 67.27; H, 4.70; N, 13.08. Found: C, 67.31; H, 4.75; N, 13.01.

From VIc, 3,3'-diacetyl-5-methyl-1,1'-diphenyl-4,4'-dipyrazole (XV) was obtained, m.p. 198-200° from ethanol; ir: 1672 cm^{-1}; uv: nm (log ϵ) 242 (4.55), 276s (4.25); nmr: δ 2.18 (s, 3H, CH_3), 2.60 and 2.67 (2s, 2 x 3H, 2 x $COCH_3$), 7.25-7.77 (m, 8H, Ar-H), 7.75-8.00 (m, 2H, *ortho* Ar-H at position *1'*), 8.06 (s, 1H, pyrazole-H).

Anal. Calcd. for $C_{23}H_{20}N_4O_2$: C, 71.86; H, 5.24; N, 14.58. Found: C, 71.92; H, 5.30; N, 14.49.

From IX, 3-acetyl-5-[(3-acetyl-1-phenylpyrazol-5-yl)methyl]-4-(methylamino)-1-phenyl-2-pyrazoline hydrochloride was obtained, m.p. 185°; this upon treatment with a chloroform solution of triethylamine was chromatographed on silica gel column (eluent chloroform). The free base XVII so obtained was crystallized from ethanol; m.p. 133-135°; ir: 3295 cm^{-1} (NH), 1690 and 1652 cm^{-1} (C=O); uv: nm (log ϵ) 241 (4.36), 360 (4.31); nmr: δ 2.08 (s, 3H, NCH_3), 2.41 and 2.58 (2s, 2 x 3H, 2 x $COCH_3$), 2.88 (dd, 1H, H_A, J_{A-B} = 15.5 Hz, J_{A-X} = 3 Hz), 3.35 (dd, 1H, H_B, J_{AB} = 15.5 Hz, J_{B-X} = 8.2 Hz); 4.46 (m, 1H, H_X), 4.22 (d, 1H, H_Y, J_{X-Y} = 10.2 Hz), 6.79 (s, 1H-pyrazole-H), 6.8-7.5 (m, 10H, Ar-H).

Anal. Calcd. for $C_{24}H_{25}N_5O_2$: C, 69.38; H, 6.07; N, 16.86. Found: C, 69.39; H, 6.10; N, 16.90.

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