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A NOVEL TRANSFORMATION OF 2-DICHLORACETAMIDO-1-METHYL-5-NITROIMIDAZOLE TO 5-DICHLOROACETYLIMINO-TETRAHYDROIMIDAZO (4,5-c) PYRAZOLES.[1]

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Summary : 2-Dichloracetamido-1-methyl-5-nitroimidazole undergoes novel cycloaddition with diazomethane to form 5-dichloracetylimino-tetrahydroimidazopyrazoles via 2-dichloracetylimino-1,3-dimethyl-5-nitroimidazoline.

1,3-Dipolar cycloaddition reactions of diazomethane to α,β-unsaturated nitro compounds as dipolarophiles are well documented in literature[2]. But studies on the dipolarophilic activities of five membered heterocyclic systems such as imidazoles and thiazoles[3] are quite limited, since heterocycles are reluctant to undergo addition reactions and prefer to give substitution reactions which preserve their aromatic character. We report here an unusual cycloaddition of diazomethane to the C-4 - C-5 double bond of a nitroimidazole, due to the formation of an intermediate II with disrupted aromaticity.

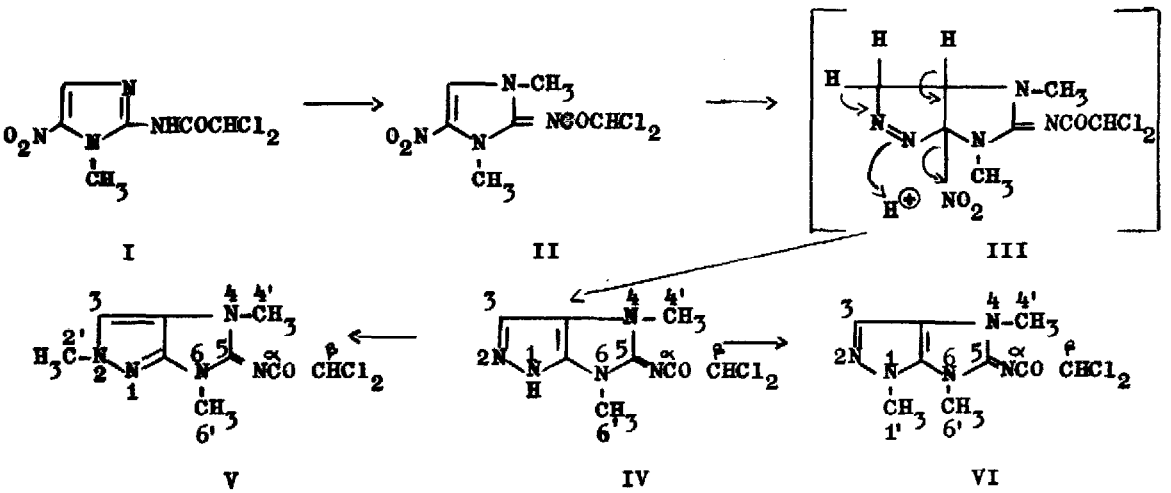
Reaction of 2-dichloracetamido-1-methyl-5-nitroimidazole I (available from an antiprotozoic programme) in methanol with ethereal diazomethane yielded a mixture from which II and the imidazopyrazoles IV-VI were isolated in about 10% yield each by silica gel chromatography and crystallised from methylene chloride-ether. Elemental analysis and spectral, in particular ^{13}C NMR data (Table 1) helped to arrive at the structures. II, m.p. 120°, $C_7H_8Cl_2N_4O_3$ (M^+ at m/e 266) had the following NMR spectral features: ^1H :δ3.66, 3.88 (3H each, s, N-CH_3), 6.11 (1H, s, -$CHCl_2$) and 8.03 ppm (1H, s, C-4H); ^{13}C :δ168.1 (C=O, d, $^2J_{CH}$ = 2 Hz), 122.8 (C-4, octet, $^1J_{CH}$ = 208 Hz, $^3J_{CH}$ = 3.5 Hz), 70.4 (CO$\underline{C}$H, d, $^1J_{CH}$ = 181 Hz), 34.6 (N-$\underline{C}H_3$, octet, $^1J_{CH}$ = 143 Hz, $^3J_{CH}$ = 2 Hz), 33.2 ppm (N-$\underline{C}H_3$, q, $^1J_{CH}$ = 145 Hz).

V, also formed from II with diazomethane, m.p.157°, $C_9H_{11}Cl_2N_5O$ (M^+ at m/e 275) had ^1H NMR signals at δ 3.53, 3.6 and 4.0 (3H each, s, N-$\underline{C}H_3$), 6.2 (1H, s, -$C\underline{H}Cl_2$) and 7.3 ppm (1H, s, C-3H) and its isomer, VI, m.p. 100° (M^+ at m/e 275), at δ 3.53, 3.72 and 4.07 (3H each, s, N-$C\underline{H}_3$), 6.15 (1H, s, $C\underline{H}Cl_2$) and 7.3 ppm (1H, s, C-3 H). V and VI were easily differentiated by the fact that the signal due to C-3 in ^{13}C NMR spectrum in the former at 111.6 ppm was composed

of two quartets, $^{1}J_{CH}$ = 194 Hz and $^{3}J_{CH}$ = 1.5 Hz, with the fine splitting contributed by a three bond coupling with the methyl protons at position 2. The large doublet from C-3 in VI lacked this fine structure.

IV, m.p. 156°, $C_8H_9Cl_2N_5O$ (M^+ at m/e 261) exhibiting proton signals at δ3.6 (6H, s, 2 N-CH_3), 6.25 (1H, s, $C\underline{H}Cl_2$) and 7.5 ppm (1H, s, C-3 H) was clearly the desmethyl derivative of V and VI and the common precursor.

We have also observed similar series of products with other 2-amido and 2-sulphonamido-5-nitroimidazoles and thiazoles and are exploring the scope of our novel observation. Significantly we find that nitroimidazoles like 1,2-dimethyl and 1-methyl-2-dimethylamino-5-nitroimidazoles fail to undergo cycloaddition with diazomethane, emphasising the role of the nitroimidazoline intermediate II in the chain of events which we postulate to go through the adduct III as follows:



I II III

V IV VI

Table 1: ^{13}C NMR Spectral Data of Imidazopyrazoles IV - VI[4]

	C-3	C-1'	C-2'	C-4'	C-6'	C-α	C-β
IV	110.4(d)	-	-	32.4 (q)	30.4 (q)	167.4	70.8 (d)
V	111.6(o)	-	40 (q)	32.9 (q)	30.7 (q)	169.0	70.6 (d)
VI	120 (d)	36.7 (q)	-	32.7 (q)	31.2 (q)	169.4	70.6 (d)

References

1. Contribution No.592 from CIBA-GEIGY Research Centre.
2. R. Huisgen, Angew. Chem. (Int. Edn.), 2, 565 (1963).
3. A. Dondoni, A. Medici, C. Venturoli, L. Forlani and V. Bertolasi, J. Org. Chem., 45, 621 (1980).
4. Chemical shifts in ppm downfield from TMS : d = doublet; q = quartet; o = octet.

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