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Chemistry of O- and C-adducts derived from 1,4-diazinium salts: the use of tetrahydropyrazines in the synthesis of condensed systems

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1-Ethyl-2,3-dicyano-5-nitromethyl-6-methoxy-1,4,5,6-tetrahydropyrazine reacts with *N*-methylquinoxalinium iodide in the presence of triethylamine to form octahydro-2,4a,5,10-tetraazabenzo[*b*]fluorene-3,4-dicarbonitrile, while our attempts to obtain similar polycyclic products from stereoisomeric 5-(*S*)- and 5-(*R*)-(1′-nitroprop-1′-yl)-6-methoxy-1,4,5,6-tetrahydropyrazines derived from the reaction of 1-nitropropane with 2,3-dicyano-5,6-dimethoxy-1-ethyl-1,4,5,6-tetrahydropyrazine were unsuccessful.

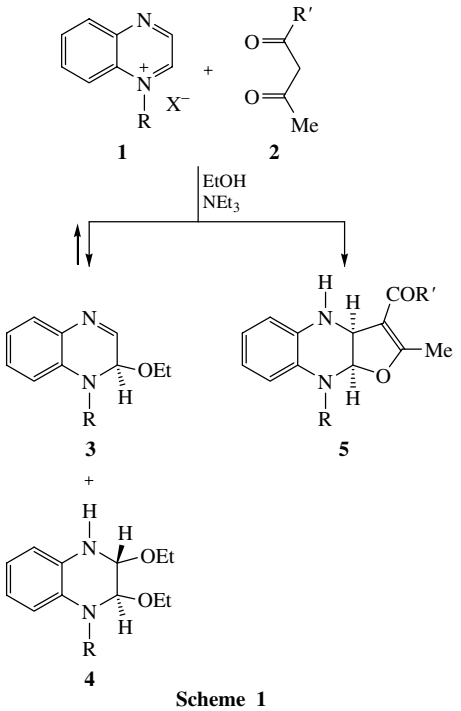
It is well-known that 1,4-diazines (pyrazines, quinoxalines and pteridines),[1–5] 1,2,4-triazines[3,6–8] and their cationic forms have a profound tendency to add mono- and bifunctional nucleophilic reagents at the two neighbouring carbons thus giving rise to mono- or di-σ^H-adducts or condensed heterocyclic systems in which the tetrahydropyrazine (1,2,4-triazine) ring is fused with five- or six-membered heterocycles.[1–8] Concurrent formation of mono- and diadducts, as well as stereochemical features for annelation of five- and six-membered heterocycles to 1,4-diazines, have been established.[1,4,5] In particular, quinoxalinium salts **1** react with β-ketoesters **2** in alcohols at –20 °C in the presence of triethylamine to form mono- and dialkoxy adducts **3** and **4** in addition to cyclization products **5** (Scheme 1).[1]

Contrary to σ^H-adducts **3** and **4**, which were detected only in solutions by NMR spectroscopy, 3a,4,9,9a-tetrahydrofuro[2,3-*b*]-quinoxalines **5** are stable to be isolated in a crystalline state. However, the role of **3** and **4** in the formation of furoquinoxalines **5**, and stereochemical features of these transformations remain unknown.

We reported the X-ray data for *trans*-dialkoxy adducts **8** derived from the reaction of 2,3-dicyanopyrazinium tetrafluoroborate **6** with alcohols in the presence of triethylamine.[9] When reacting with acetoacetone or ethyl acetoacetate, *trans*-dialkoxy-adducts **8** are transformed into *cis*-tetrahydrofuro[2,3-*b*]pyrazines **10**, while the reactions of **8** with nitroalkanes afford corresponding tetrahydropyrazines **11** (Scheme 2).[9]

Here we report the ability of tetrahydropyrazines **11** to act as 1,3-N,C-bifunctional nucleophiles. Indeed, we found that 1-ethyl-2,3-dicyano-6-methoxy-5-nitromethyl-1,4,5,6-tetrahydropyrazine **11a** reacts smoothly with *N*-methylquinoxalinium iodide **1a** at room temperature in the presence of triethylamine to form the condensed system of octahydro-2,4a,5,10-tetraazabenzo[*b*]fluorene-3,4-dicarbonitrile **13**,† as evidenced by X-ray crystallography data (Scheme 3, Figure 1).‡

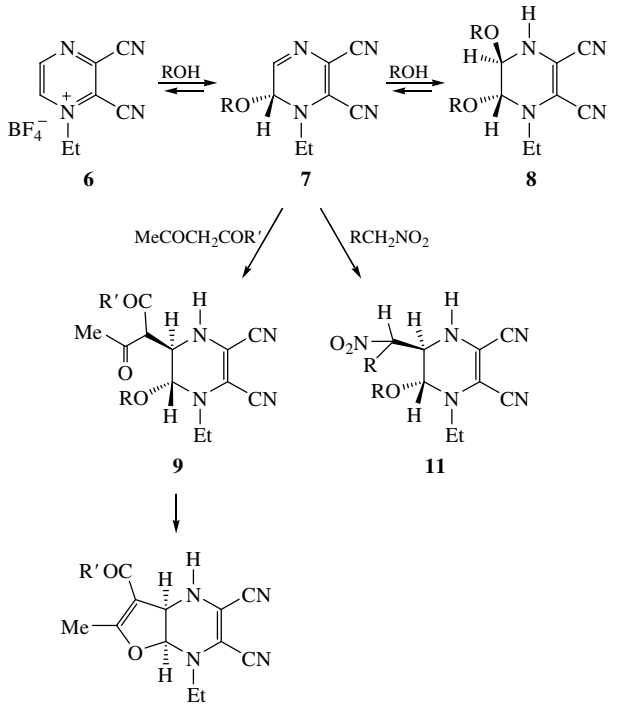
In order to elucidate whether substituents at the CH active centre and their stereo configurations are affecting the formation of polycyclic systems, 2,3-dicyano-5,6-dimethoxy-1-ethyl-1,4,5,6-tetrahydropyrazine **8a** was reacted with 1-nitropropane bearing the prochiral C(1) carbon centre. The reaction occurred in THF in the presence of triethylamine, thus resulting in the formation of a 1:1 mixture of two stereoisomeric products. The compounds were identified as 2,3-dicyano-1-ethyl-5-(1′-nitroprop-1′-yl)-6-methoxy-1,4,5,6-tetrahydropyrazine **14** with different configurations of the *exo*-cyclic carbon C(10) chiral centre



Scheme 1

(Scheme 4). Compounds **14A** and **14B** with (5*R**,6*R**,10*R**)- and (5*R**,6*R**,10*S**)-configurations were separated by chromatography† and characterised by X-ray crystallography (Figures 2 and 3).‡ The X-ray data indicate unequivocally that the addition of nitropropane at the C(5) of intermediate **7a** takes place at the *trans*-position relative to the position of the methoxy group at C(6) (Scheme 3). Transformation of dimethoxy adduct **8a** into stereoisomers **14A** and **14B** is supposed to proceed according to Scheme 4.

Analysis of ^{1}H NMR spectra, including COSY and NOESY experiments, shows that there are spectral features enabling one to distinguish (*R**,*R**,*R**)- and (*R**,*R**,*S**)-stereoisomers. In particular, a cross-peak between C(6)H and CH_2 group protons in the ^{1}H NMR NOESY spectrum of **14B** and a strong upfield shift for the resonance signal of the CH_α proton of



Scheme 2

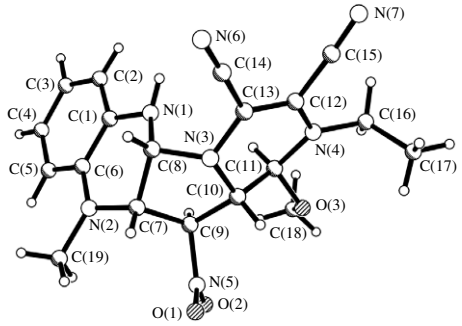


Figure 1 X-ray structure of the condensed system of **13**.

† ^{1}H NMR spectra were recorded on a Bruker DRX-400 spectrometer.

*1-Methoxy-2-ethyl-10-methyl-11-nitro-1,2,4b,5,10,10a,11,11a-octahydro-2,4a,5,10-tetraazabenzo[*b*]fluorene-3,4-dicarbonitrile* **13**. Triethylamine (56 μl, 0.4 mmol) was added at an ambient temperature to a suspension of 2,3-dicyano-6-methoxy-5-nitromethyl-1,4,5,6-tetrahydropyrazine **11a** (100 mg, 0.4 mmol) and 1-methylquinoxalinium iodide **1a** (104 mg, 0.4 mmol) in 2 ml of methanol with stirring. The precipitate obtained after stirring for 6 h was filtered off and recrystallised from a methanol–butanol mixture (1:1) to give 79 mg (51%) of compound **13** with mp 163–164 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 6.62 (m, 4H, Ar), 6.49 (s, 1H, NH), 5.00 [dd, 1H, $NO_2C(11)H$, $J_{11,11a}$ 4.4 Hz, J 1.0 Hz], 4.90 [m, 2H, C(10a)H, C(4b)H], 3.88 [d, 1H, OC(1)H, $J_{1,11a}$ 6.9 Hz], 3.68 [dd, 1H, C(11a)H, $J_{1,11a}$ 6.9 Hz, $J_{H(11)H(11a)}$ 4.4 Hz], ~3.35 (m, 2H, NCH_2), 3.26 (s, 3H, OMe), 2.86 (s, 3H, NMe), 1.10 (t, 3H, Me, ^3J 7.2 Hz). MS, *m*/*z* (I, %): 395 (15.38, M^+), 251(1.14), 146 (100.00), 131 (39.21). Found (%): C, 57.70; H, 5.38; N, 24.86. Calc. for $C_{19}H_{21}N_7O_3$ (%): C, 57.71; H, 5.35; N, 24.79.

2,3-Dicyano-1-ethyl-5-(1'-nitroprop-1'-yl)-6-methoxy-1,4,5,6-tetrahydropyrazines **14A** *and* **14B**. 2,3-Dicyano-5,6-dimethoxy-1-ethyl-1,4,5,6-tetrahydropyrazine **8a** (222 mg, 1 mmol) was added to a solution of 1-nitropropane (89 μl, 1 mmol) and NEt_3 (279 μl, 2 mmol) in 3 ml of MeCN. After two days, the solvent was evaporated, the residue was washed with water and purified by chromatography on silica gel (eluent: MeCOOEt–hexane, 1:3). Recrystallization from MeOH gave 90 mg (32%) of **14A** (yellow crystals, mp 153–155 °C) and 79 mg (29%) of **14B** (yellow crystals, mp 148–149 °C). For **14A** found (%): C, 51.68; H, 6.26; N, 25.17. Calc. for $C_{12}H_{17}N_5O_3$ (%): C, 51.60; H, 6.14; N, 25.07.

‡ *Crystallographic data for* **13**, **14A** *and* **14B.** X-ray diffraction experiments were carried out on an Enraf-Nonius CAD-4 diffractometer ($\omega/2\theta$-scanning, MoKα radiation, graphite monochromator).

Crystals of **13** belong to the monoclinic system, space group $P2_1/c$, unit cell parameters: a = 12.426(3), b = 17.140(4) and c = 9.419(2) Å, β = 104.22(2)°. The structure was solved by the direct method using the SHELXS-97 program[10] and refined by the SHELXL-97 program[10] using the least-squares method in the anisotropic (isotropic for H atoms) approximation to R = 0.034 [$wR(F^2)$ = 0.093] for 2216 reflections with $F_0 > 4\sigma(F_0)$.

Crystals of **14A** belong to the triclinic system, space group $P\bar{1}$, unit cell parameters: a = 8.710(4), b = 9.209(2) and c = 10.336(4) Å, α = = 65.25(2)°, β = 88.53(3)°, γ = 83.86(3)°, V = 748.4(5) Å^3, Z = 2, d_{calc} = = 1.24 g cm^{-3}. The structure was solved by the direct method using the SHELXS-97 program[10] and refined by the SHELXL-97 program[10] using the least-squares method in the anisotropic (isotropic for H atoms) approximation to R = 0.039 [$wR(F^2)$ = 0.108] for 2247 reflections with $F_0 > 4\sigma(F_0)$. Hydrogen atoms were localised from difference syntheses.

Crystals of **14B** belong to the triclinic system, space group $P\bar{1}$, unit cell parameters: a = 8.790(1), b = 11.962(2) and c = 13.724(3) Å, α = 86.27(2)°, β = 88.66(2)°, γ = 78.62(2)°, V = 1411.6(4) Å^3, Z = 4, d_{calc} = 1.31 g cm^{-3}. The structure was solved by the direct method using the SHELXS-97 program[10] and refined by the SHELXL-97 program[10] using the least-squares method in the anisotropic (isotropic for H atoms) approximation to R = 0.034 [$wR(F^2)$ = 0.090] for 4317 reflections with $F_0 > 4\sigma(F_0)$. Hydrogen atoms were localised from difference syntheses.

Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). These data can be obtained free of charge *via* www.ccdc.cam.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk). Any request to the CCDC for data should quote the full literature citation and CCDC reference numbers 295880, 295881 and 296240 for **14A**, **14B** and **13**, respectively. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2006.

Table 1 ^{1}H NMR chemical shifts (δ/ppm) and coupling constants (Hz) for isomers **14A** and **14B**.

Fragment		$CDCl_3$		$(CD_3)_2SO$	
		14A	**14B**	**14A**	**14B**
O–C(6)H–N(1)		4.32 (d, 1H, ^3J 2.0 Hz)	4.48 (d, 1H, ^3J 2.0 Hz)	4.53 (d, 1H, ^3J 1.9 Hz)	4.88 (d, 1H, ^3J 2.0 Hz)
C–C(5)H–N(4)		3.88 (ddd, 1H, ^3J 10.2 Hz, ^3J 7.6 Hz, ^3J 2.0 Hz)	3.95 (ddd, 1H, ^3J 10.1 Hz, ^3J 6.6 Hz, ^3J 2.0 Hz)	3.86 (ddd, 1H, ^3J 9.8 Hz, ^3J 6.7 Hz, ^3J 1.9 Hz)	3.83 (ddd, 1H, ^3J 9.9 Hz, ^3J 6.6 Hz, ^3J 2.0 Hz)
O_2NCH		4.00 (ddd, 1H, ^3J 10.2 Hz, ^3J 10.2 Hz, ^3J 3.2 Hz)	4.02 (ddd, 1H, ^3J 10.1 Hz, ^3J 10.1 Hz, ^3J 3.2 Hz)	4.29 (ddd, 1H, ^3J 10.1 Hz, ^3J 9.8 Hz, ^3J 3.3 Hz)	4.10 (ddd, 1H, ^3J 9.9 Hz, ^3J 8.5 Hz, ^3J 3.3 Hz)
OMe		3.31 (s, 3H)	3.35 (s, 3H)	3.22 (s, 3H)	3.26 (s, 3H)
N(4)H		3.95 (s, 1H)	4.00 (s, 1H)	7.30 (d, 1H, ^3J 6.7 Hz)	7.11 (d, 1H, ^3J 6.6 Hz)
CCH_2Me		0.98 (t, 3H, ^3J 7.4 Hz)	1.00 (t, 3H, ^3J 7.4 Hz)	0.85 (t, 3H, ^3J 7.4 Hz)	0.84 (t, 3H, ^3J 7.4 Hz)
$N(1)CH_2Me$		1.31 (t, 3H, ^3J 7.2 Hz)	1.27 (t, 3H, ^3J 7.2 Hz)	1.17 (t, 3H, ^3J 7.2 Hz)	1.16 (t, 3H, ^3J 7.2 Hz)
$N(1)CH_2$	H_α	3.59 (dq, 1H, ^2J 14.4 Hz, ^3J 7.2 Hz)	3.59 (dq, 1H, ^2J 14.4 Hz, ^3J 7.2 Hz)	3.41 (m, 2H)	3.47 (dq, 1H, ^2J 14.7 Hz, ^3J 7.2 Hz)
	H_β	3.41 (dq, 1H, ^3J 7.2 Hz, ^2J 14.4 Hz)	3.41 (dq, 1H, ^3J 7.2 Hz, ^2J 14.4 Hz)		3.39 (dq, 1H, ^2J 14.7 Hz, ^3J 7.2 Hz)
CH_2Me	H_α	2.11 (ddq, 1H, ^2J 14.8 Hz, ^3J 7.4 Hz, ^3J 3.2 Hz)	1.75 (ddq, 1H, ^2J 15.0 Hz, ^3J 7.5 Hz, ^3J 3.2 Hz)	1.96 (ddq, 1H, ^2J 14.6 Hz, ^3J 7.4 Hz, ^3J 3.3 Hz)	1.91 (m, 2H)
	H_β	1.91 (ddq, 1H, ^2J 14.8 Hz, ^3J 10.2 Hz, ^3J 7.4 Hz)	1.97 (ddq, 1H, ^2J 15.0 Hz, ^3J 10.1 Hz, ^3J 7.5 Hz)	1.77 (ddq, 1H, ^2J 14.6 Hz, ^3J 10.1 Hz, ^3J 7.4 Hz)	

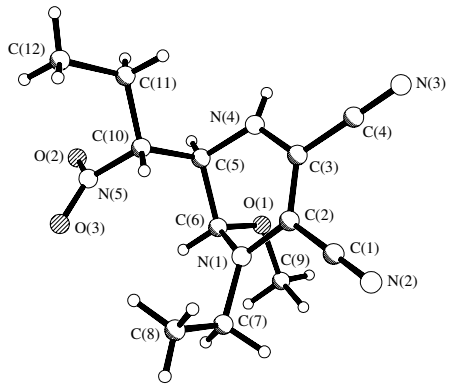


Figure 2 X-ray structure of (5*R**,6*R**,10*R**)-2,3-dicyano-1-ethyl-5-(1′-nitroprop-1′-yl)-6-methoxy-1,4,5,6-tetrahydropyrazine **14A**.

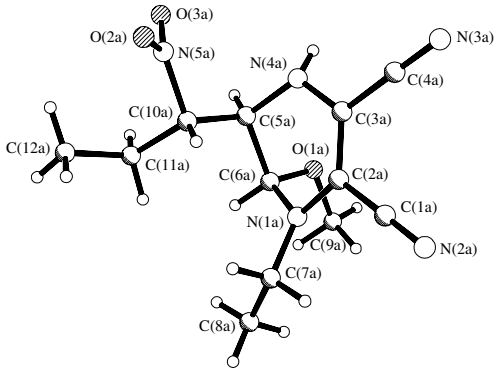


Figure 3 X-ray structure of (5*R**,6*R**,10*S**)-2,3-dicyano-1-ethyl-5-(1′-nitroprop-1′-yl)-6-methoxy-1,4,5,6-tetrahydropyrazine **14B**.

the $CH(NO_2)CH_2Me$ group (Table 1) are the most indicative characteristics (Figure 2, Scheme 4). Chemical shifts (ppm) and coupling constants (Hz) in the ^{1}H NMR spectra of stereoisomeric adducts **14A** and **14B** are consistent with their structures (Table 1).

Unfortunately, we failed to obtain condensed systems by a reaction of *N*-methylquinoxalinium iodide **1a** with both stereoisomeric adducts **14A** and **14B**, which shows that the formation of polycyclic systems is very sensitive to substituents at the *exo*-cyclic carbon centre.

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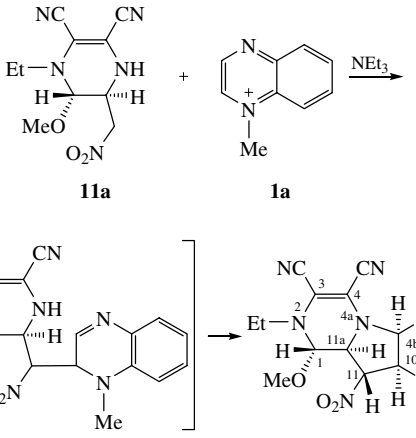
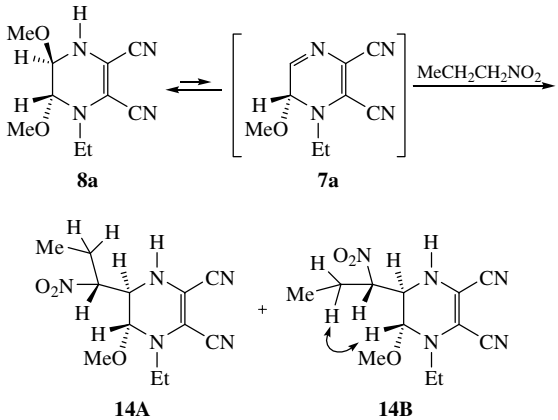


Scheme 3



Scheme 4

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