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Thermolysis of 4-(2-azido-3-nitrophenyl)-1,4-dihydropyridines as source of β-carboline derivatives and some related compounds

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Abstract—Thermolysis in refluxing xylene of 4-(2-azido-3-nitrophenyl)-1,4-dihydropyridines was investigated. β-Carboline derivatives and related compounds were obtained in various yields, according to the nature of the substituents in the 1,4-dihydropyridine ring. © 2001 Published by Elsevier Science Ltd.

Our continuing interest in the pharmacochemistry of the furoxan system led us to investigate 1,4-dihydropyridines (1,4-DHPs) bearing at the 4-position benzofuroxanyl and benzofurazanyl moieties.[1–3] For the preparation of 4-[benzofuroxan-4(7)-yl] derivative **1** (Fig. 1), a synthetic route we explored involves, as starting materials, the appropriate 1,4-DHPs 4-substituted with the 2-azido-3-nitrophenyl moiety (**2**, Scheme 1).

In fact, it is known that photolysis and thermolysis of *o*-nitrophenyl azides are a general method to synthesize the benzofuroxan system.[4] Irradiation of methyl 1,4-dihydro-2,6-dimethyl-5-nitro-4-(2-azido-3-nitrophenyl)-pyridine-3-carboxylate (**2**) dissolved in THF with a medium-pressure Hg lamp afforded, as principal product, the expected DHP **1**.[3] Herein, we report the preliminary results of a study of thermolysis of **2** and of related 1,4-DHPs **4** and **5**.

These latter compounds were easily obtained by a modified Hantzsch approach. The condensation of β-aminocrotonitrile, methyl β-aminocrotonate and aldehyde **3** to give **4** (yield 67%), was achieved in refluxing ethanol, while the reaction of methyl β-aminocrotonate with **3** to give **5** (yield 65%) was carried out in ethanol in the presence of trifluoroacetic acid at 0°C (Scheme 1).[†]

Thermolysis of **2** in boiling xylene over 6 h gave a complex mixture of products. Compounds with $R_f = 0.3$ (yield 25%) and $R_f = 0.4$ (yield 20%), respectively, were separated by flash chromatography (eluent CH_2Cl_2 9.5/EtOAc 0.5). Analytical data and the mass spectrum of the second eluted were in keeping with the molecular formula $C_{15}H_{13}N_3O_4$. ^1H and ^{13}C NMR spectra still showed the presence of the two initial methyl groups and of the carboxymethyl function. All other signals indicated the presence of an aromatic structure. On this basis, we suggest the structure **6** for this compound. This reaction represents a new and interesting pathway to functionalized β-carbolines. Analytical data and the mass spectrum of the first eluted were in keeping with the molecular formula $C_{15}H_{14}N_4O_6$. ^1H and ^{13}C NMR

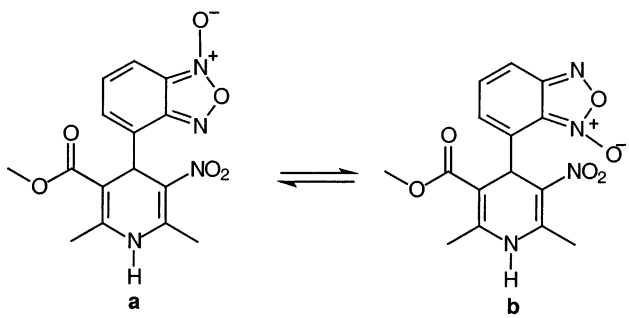

Figure 1.

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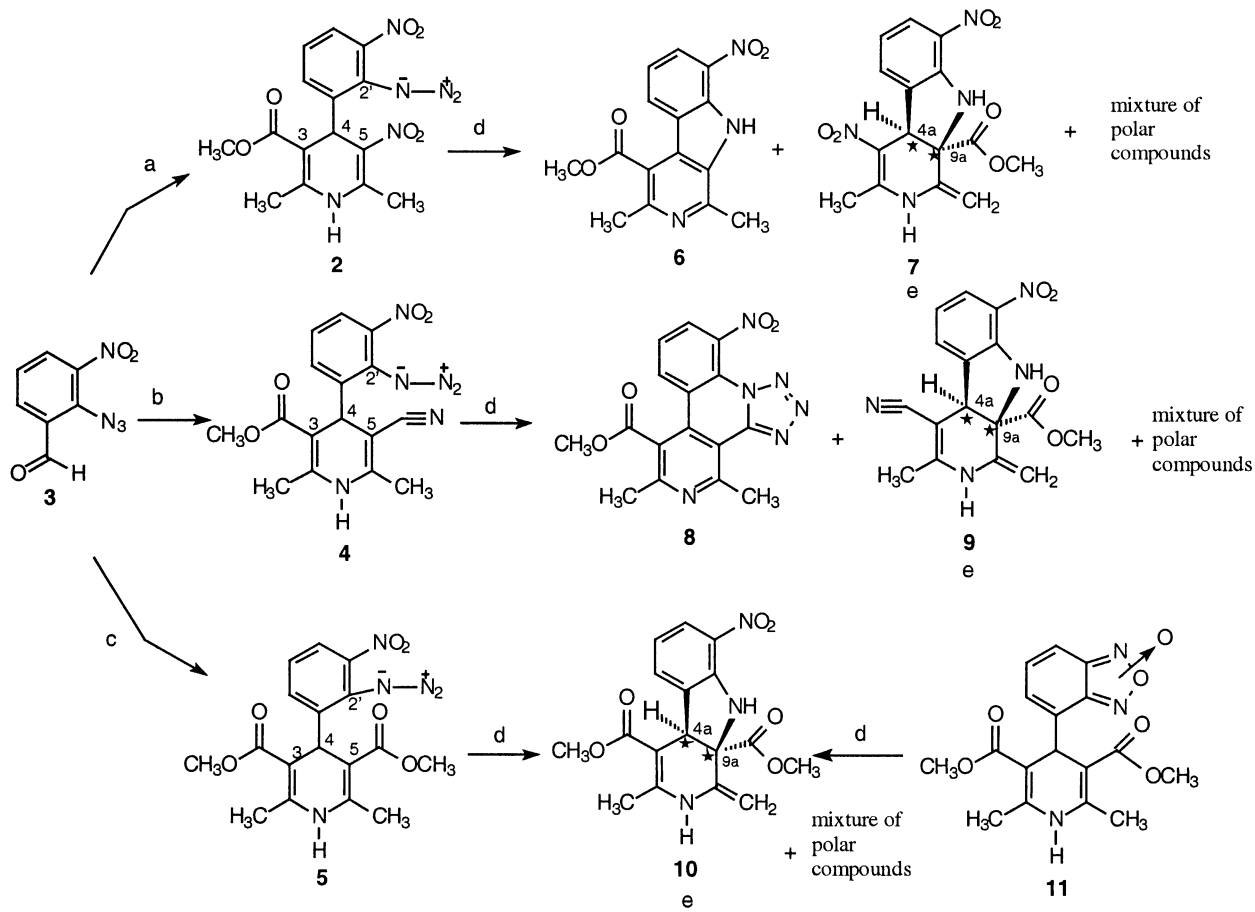


Scheme 1. *Reagents and conditions*: (a) methyl β-aminocrotonate, nitroacetone, *i*-PrOH, reflux over 6 h; (b) β-aminocrotonitrile, methyl β-aminocrotonate, EtOH, reflux over 6 h; (c) methyl β-aminocrotonate, CF_3COOH, EtOH, 0°C; (d) xylene, reflux over 6 h; (e) the products were obtained as racemic mixture. In the scheme, the stereoisomers 4a*S*, 9a*R*; 4a*R*, 9a*R*; 4a*R*, 9a*R*, respectively, are represented for compounds **7**, **9** and **10**.

spectra agree with the proposed structure **7** (Table 1). In particular, the two singlets at 5.22 and 4.89 ppm, respectively (two doublets in acetone at 5.15 and 4.90 ppm, respectively, $J^2 = 1.95$ Hz), in the proton spectrum are diagnostic for the presence of the exocyclic methylene, as well as the ^{13}C NMR signal at 99.1 ppm, which appears as a triplet in the proton-coupled ^{13}C NMR spectrum, and as a negative peak in the DEPT-^{13}C spectrum. Compound **7** was obtained with a diastereoselectivity in favor of a *cis*-fusion between the

† All the compounds were purified by flash chromatography using CH_2Cl_2 9.5/EtOAc 0.5.

Selected data for compounds **4**–**10**:

Compound **4**: 70% yield of an orange solid, mp 189–191°C (dec.), darkening at 185°C (EtOAc/PE); *m*/*z* (EI): 354 (M^+, <1%), 326 (M^+–28, 7%). ^1H NMR (DMSO-d_6): δ 2.02, 2.34 (2s, 6H, $C_{2,6}$-CH_3); 3.46 (s, 3H, OCH_3); 5.14 (s, 1H, C4-H); 7.50–8.06 (m, 3H, Ph.); 9.38 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 17.6, 18.7 ($C_{2,6}$-CH_3); 36.1 (C4); 51.1 (OCH_3); 83.3 (C3); 98.5 (C5); 119.5 (CN); 125.0, 127.5, 129.3, 135.0, 143.4, 143.6, 147.4, 147.6 (Ph and C2, C6); 166.7 (CO). ν_{max} (KBr): 2100 (N_3); 2210 (CN); 1700 (CO) cm^{-1}. Anal. ($C_{16}H_{14}N_6O_4$) C, H, N.

Compound **5**: 65% yield of a yellow solid, mp 157–158°C (MeOH); *m*/*z* (EI): 387 (M^+, <0.1%), 359 (M^+–28, 3%). ^1H NMR (DMSO-d_6): δ 2.38 (s, 6H, $C_{2,6}$-CH_3); 3.64 (s, 6H, 2×OCH_3); 5.43 (s, 1H, C4-H); 7.52–7.96 (m, 3H, Ph); 9.12 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 18.4 ($C_{2,6}$-CH_3); 35.8 (C4); 50.9 (OCH_3); 101.3 (C3, C5); 123.8, 126.9, 128.9, 135.5, 143.7, 146.2, 146.5 (Ph and C2, C6); 167.1 (CO). ν_{max} (KBr): 2100 (N_3); 1700 (CO) cm^{-1}. Anal. ($C_{17}H_{17}N_5O_6$) C, H, N.

Compound **6**: 25% yield of a yellow solid, mp 221–222°C (EtOAc/PE); *m*/*z* (EI): 299 (M^+). ^1H NMR (DMSO-d_6): δ 2.61, 2.92 (2s, 6H, 2×CH_3); 4.09 (s, 3H, OCH_3); 7.43 (t, 1H), 8.48 (d, 1H), 8.36 (d, 1H) (Ph); 11.78 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 21.3, 22.3 (2×CH_3); 52.9 (OCH_3); 117.7, 119.6, 123.9, 124.3, 125.0, 130.9, 133.0, 133.4, 133.9, 145.3, 145.4 (arom.); 168.4 (CO). Anal. ($C_{15}H_{13}N_3O_4$) C, H, N.

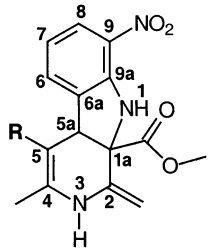
Compound **7**: 20% yield of a yellow solid, mp 206–207°C (dec.) (EtOAc/PE); *m*/*z* (EI): 346 (M^+). Anal. ($C_{15}H_{14}N_4O_6$) C, H, N (for NMR data see Table 1).

Compound **8**: 6% yield of an orange solid, mp 244–245°C (dec.), darkening at 140°C (EtOAc/PE); *m*/*z* (EI): 352 (M^+). ^1H NMR (DMSO-d_6): δ 2.70, 3.30 (2s, 6H, 2×CH_3); 4.09 (s, 3H, OCH_3); 8.07 (t, 1H), 8.34 (d, 1H), 8.57 (d, 1H) (Ph). ^{13}C NMR (DMSO-d_6): δ 23.2, 26.8 (2×CH_3); 54.0 (OCH_3); 111.7, 121.3, 121.8, 121.9, 126.9, 129.4, 124.5, 133.3, 141.3, 147.6, 156.5, 159.2 (arom.); 169.6 (CO). Anal. ($C_{16}H_{12}N_6O_4$) C, H, N.

Compound **9**: 30% yield of a yellow solid, mp 194–195°C (dec.) (EtOAc/PE); *m*/*z* (EI): 326 (M^+); Anal. ($C_{16}H_{14}N_4O_4 \cdot 0.15H_2O$) C, H, N (for NMR data see Table 1).

Compound **10**: 30–60% yield of a yellow solid, mp 186–188°C (EtOAc/PE); *m*/*z* (EI): 359 (M^+). Anal. ($C_{17}H_{17}N_3O_6$) C, H, N (for NMR data see Table 1).

Table 1. ^1H and ^{13}C NMR chemical shifts (ppm) of the exomethylene structures **7**, **9** and **10** (DMSO-d_6, TMS)



	7		**9**		**10**	
	R = NO_2		R = CN		R = $COOCH_3$	
	^1H	^{13}C	^1H	^{13}C	^1H	^{13}C
1	10.37[a] (1H, s, br)	–	9.56[a] (1H, s, br)	–	9.30[a] (1H, s, br)	–
1a	–	67.9	–	68.7	–	67.9
2	–	139.6	–	138.8	–	140.9
3	8.68[a] (1H, s, br)	–	8.18[a] (1H, s, br)	–	8.48[a] (1H, s, br)	–
4	–	150.7	–	149.2	–	149.1
5	–	117.7	–	71.8	–	89.4
5a	5.09 (1H, s)	44.8[d]	4.35 (1H, s)	42.6[d]	4.56 (1H, s)	44.6[d]
6	7.22 (1H, d)	130.7[d]	7.47 (1H, d)	129.9[d]	7.13 (1H, d)	130.0[d]
6a	–	129.5	–	129.4	–	129.2
7	6.73 (1H, dd)	118.2[d]	6.83 (1H, dd)	118.4[d]	6.70 (1H, dd)	118.0[d]
8	7.81 (1H, d)	123.0[d]	7.84 (1H, d)	123.1[d]	7.76 (1H, d)	122.4[d]
9	–	133.4	–	133.8	–	136.0
9a	–	144.5	–	144.2	–	144.6
CO	–	169.5	–	170.8	–	170.2, 167.4
OCH_3	3.77 (3H, s)	53.4[d]	3.74 (3H, s)	53.4[d]	3.74, 3.67 (6H, 2s)	53.1,[d] 50.7[d]
CH_2	5.22, 4.89[b] (2H, 2s)	99.1[d]	4.68, 4.64 (2H, 2s)	94.6[d]	4.82, 4.56[c] (2H, 2s)	93.2[d]
4-CH_3	2.58 (3H, s)	21.3[d]	2.08 (3H, s)	18.5[d]	2.32 (3H, s)	19.4[d]
CN	–	–	–	121.0	–	–

[a] Tentatively assigned.
[b] 5.15 (1H, d), 4.90 (1H, d) $J^2 = 1.95$ Hz in acetone.
[c] 4.78 (1H, d), 4.60 (1H, d) $J^2 = 1.50$ Hz in acetone.
[d] Signals observed by DEPT-sequence.

hydrogenated pyridine and pyrroline. The appropriate conformation for such a reaction is easily attained from the stable antiperiplanar position of the azidic group with respect to the hydrogen of the 4-chiral carbon by rotation of the phenyl group around the sp^2–sp^3 bond in the same quadrant.

Thermolysis of **4** in boiling xylene over 6 h again gave a complex mixture of compounds. Products with $R_f = 0.5$ (yield 30%) and $R_f = 0.4$ (yield 6%) were easily separated from the other polar reaction products by flash chromatography (eluent CH_2Cl_2 9.5/EtOAc 0.5). Analytical data and the mass spectrum of the second to be eluted were in keeping with the molecular formula $C_{16}H_{12}N_6O_4$. On the basis of ^1H and ^{13}C NMR spectra, as well as the absence of N_3 and CN in IR absorption, we suggest for this compound the structure **8**. Intramolecular uncatalyzed addition of an azido group to nitrile and subsequent aromatization by air oxidation rationalizes its formation. Analytical data and the mass spectrum of the first eluted were in keeping with the molecular formula $C_{16}H_{14}N_4O_4$. ^1H and ^{13}C NMR spectra (Table 1) again suggest for this compound the exomethylene structure **9**. Good quality crystals obtained by slow evaporation of an ethanolic solution allowed confirmation of the proposed structure by X-ray analysis (Fig. 2).

Finally, a product with molecular formula $C_{17}H_{17}N_3O_6$ was separated by flash chromatography from the com-

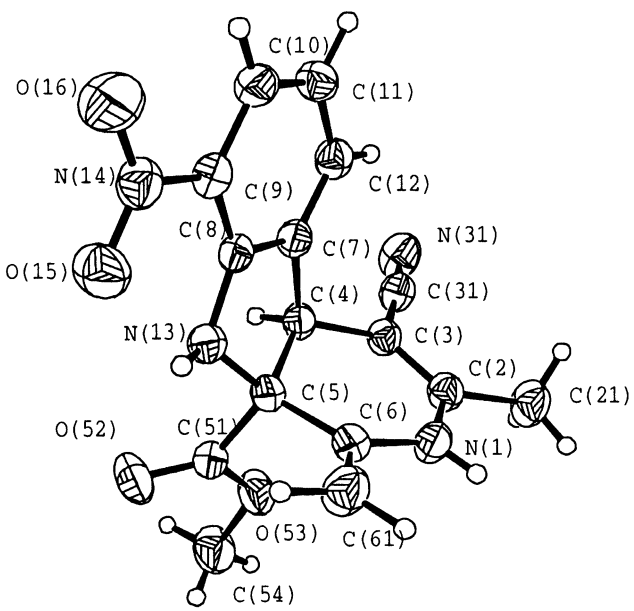


Figure 2.

plex mixture of polar compounds obtained by thermolysis of **5** in boiling xylene (6 h). The yields for this product were erratic (30–60% range) and this could be due to its partial decomposition during the chromatographic separation. The exocyclic methylene structure **10** was confirmed for this compound through NMR spectroscopy (Table 1). As for compound **7**, derivatives **9** and **10** were obtained as a single pair of enantiomers.

It is interesting that thermolysis of the benzofuroxan 1,4-DHP **11**, under the same conditions, affords **10** in a similar yield. Brief heating (30 min) in refluxing xylene of **5** generates a product which, analyzed by HPLC, appears principally as a mixture of the unchanged azide **5** and **10**. Attempts to isolate the benzofuroxan **11** under these conditions failed. These findings suggests that, if one of the possible mechanisms for the transformation **5**→**10** passes through **11**, then the rearrangement **11**→**10** must be rapid compared with the azide decomposition.

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