An Elegant Synthetic Route to 3-Cyano-5,6-dihydro-2-ethoxy-4-phenyl-pyrido[2,3-*a*]carbazoles

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Z. Naturforsch. **59b,** 106 – 108 (2004); received August 4, 2003

2-Benzylidene-1-oxo-1,2,3,4-tetrahydrocarbazoles (**1a – e**) obtained from the corresponding 1-oxo-1,2,3,4-tetrahydrocarbazoles on reaction with malononitrile in dry benzene with sodium hydride afforded 3-cyano-5,6-dihydro-2-ethoxy-4-phenyl-pyrido[2,3-*a*]carbazoles (**2a – e**) in good yields. A plausible mechanism for the formation of the title compound has been proposed and all the compounds were characterised by IR, NMR, mass spectral methods and elemental analysis.

Key words: 1-Oxo-1,2,3,4-tetrahydrocarbazoles, 2-Benzylidene-1-oxo-1,2,3,4-tetrahydrocarbazoles, Aldol Condensation, Malononitrile, Sodium Hydride

Since the discovery of the promising anti-tumor properties and antineoplastic activity of the alkaloid ellipticine (5,11-dimethyl-6*H*-pyrido[3,4-*b*]carbazole), tetracyclic compounds of the pyridocarbazole type have stimulated considerable interest in the field of condensed systems [1, 2]. Recently, 7*H*-pyrido[4,3-*c*]carbazole derivatives were found to elicit anti-HIV properties [3]. Many derivatives of ellipticine have been synthesised in an attempt to improve the antitumor properties and 9-hydroxy-ellipticine is undergoing extensive clinical trials for the treatment of metastatic breast cancer, mycloblastic leukemia and some solid tumors [4 – 8]. So far, [*b*]- and [*c*]-pyridocarbazoles have been reported. Due to the prominence in their pharmacological activity and lack of reports on *a*-fused pyridocarbazole derivatives it was felt challenging and worthwhile to device a simple route for the synthesis of pyrido[2,3-*a*]carbazoles, which can be expected to exhibit anticancer properties.

In this connection, 2-benzylidene-1-oxo-1,2,3,4-tetrahydrocarbazoles (**1a – e**) obtained from the corresponding 1-oxo-1,2,3,4-tetrahydrocarbazoles [9] in dry ethanol were reacted with malononitrile in dry benzene with sodium hydride to afford the *a*-fused pyridocarbazoles.

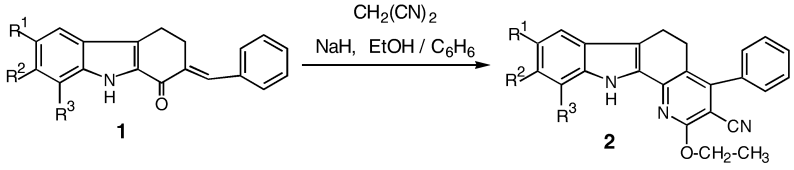
2-Benzylidene-8-methyl-1-oxo-1,2,3,4-tetrahydrocarbazole (**1a**) [10] dissolved in dry ethanol on reaction with malononitrile in the presence of sodium hydride in dry benzene gave a single product. It showed IR absorptions at 3338 and 1552 cm^{-1} corresponding to NH and C=N stretching vibrations. The presence of a cyano group was inferred from a sharp band at 2218 cm^{-1}. The ^{1}H NMR spectrum showed a three-proton singlet at δ 2.58, which corresponds to the methyl protons at C-10. An unresolved multiplet of four proton intensity at δ 2.83 to δ 2.95 corresponds to 5-H_2 and 6-H_2 protons. The methylene protons of the ethoxy group at C-2, appeared as a quartet at δ 4.65 with $J = 7.0$ Hz and this downfield shift was attributed to the presence of the cyano group *ortho* to the OEt group. The methyl protons of the ethoxy group at C-2 appeared as a triplet at δ 1.52 with $J = 7.0$ Hz. The aromatic protons at C-7, C-9 position appeared as doublets at δ 7.47 with $J = 7.6$ Hz and δ 7.15 with $J = 7.8$ Hz, respectively. The 8-H appeared as a triplet at δ 7.07 with $J = 7.2$ Hz. The protons of the phenyl ring at C-4 appeared as an unresolved multiplet in the region δ 7.34 – 7.44. A broad singlet at δ 8.58 was due to the carbazole NH proton. The elemental analysis and the molecular ion peak at $m/z = 379$ (100%) agreed well with the molecular formula, $C_{25}H_{21}N_3O$. Based on the given spectral data and elemental analysis, the product formed was identified as 2-cyano-5,6-dihydro-3-ethoxy-4-phenyl-10-methylpyrido[2,3-*a*]carbazole (**2a**). A similar series of compounds **2b – e** were realized from **1b**, **1c**, **1d** and **1e**, respectively (Scheme 1).

A plausible mechanism for the formation of product **2** may be the following. First, the carbanion intermediate generated from the malononitrile under ba-

Table 1. Physical and spectral data of 3-cyano-5,6-dihydro-2-ethoxy-4-phenyl-pyrido[2,3-*a*]carbazole derivatives (**2**).

Compound	M.p. (°C) (solvent)[a]	Yield (%)	IR (ν, cm^{-1})	Molecular formula (MS)	Analysis (%) calcd.	found	^{1}H NMR (δ ppm, $CDCl_3$)
2a	176 (PE-EA)	78	3388 (NH) 2218 (C≡N) 1552 (C=N)	$C_{25}H_{21}N_3O$ (379)	C 79.17 H 5.54 N 11.07	79.14 5.59 11.10	1.52 (t, J = 7.0 Hz, 3H, 2-OCH$_2$-*Me*), 2.58 (s, 3 H, 10-*Me*), 2.83 – 2.95 (m, 4 H, 5-H$_2$, 6-H$_2$), 4.65 (q, J = 7.0 Hz, 2H, 2-OC*H*$_2$-Me), 7.07 (t, J = 7.2 Hz, 1H, 8-H), 7.15 (d, J = 7.8 Hz, 1H, 9-H), 7.34 – 7.44 (m, 5H, 2'-H to 6'-H), 7.47 (d, J = 7.6 Hz, 1H, 7-H), 8.58 (b s, 1H, carbazole-N*H*).
2b	208 (PE-EA)	75	3329 (NH) 2214 (C≡N) 1546 (C=N)	$C_{25}H_{21}N_3O$ (379)	C 79.17 H 5.54 N 11.07	79.19 5.56 11.02	1.51 (t, J = 7.0 Hz, 3H, 2-OCH$_2$-*Me*), 2.49 (s, 3H, 9-*Me*), 2.65 – 3.20 (m, 4H, 5-H$_2$, 6-H$_2$), 4.63 (q, J = 7.0 Hz, 2H, 2-OC*H*$_2$-Me), 6.97 (t, J = 8.0 Hz, 1H, 8-H), 7.13 – 7.35 (m, 5H, 2'-H to 6'-H), 7.45 (d, J = 8.0 Hz, 1H, 7-H), 7.51 (s, 1H, 10-H), 8.66 (b s, 1H, carbazole-N*H*).
2c	230 (PE-EA)	79	3349 (NH) 2214 (C≡N) 1557 (C=N)	$C_{25}H_{21}N_3O$ (379)	C 79.17 H 5.54 N 11.07	79.16 5.52 11.05	1.51 (t, J = 7.0 Hz, 3H, 2-OCH$_2$-*Me*), 2.45 (s, 3H, 8-*Me*), 2.82 – 2.94 (m, 4H, 5-H$_2$, 6-H$_2$), 4.63 (q, J = 7.0 Hz, 2H, 2-OC*H*$_2$-Me), 7.11 – 7.32 (m, 5H, 2'-H to 6'-H), 7.35 – 7.54 (m, 3H, 7-H, 9-H, 10-H), 8.69 (b s, 1H, carbazole-N*H*).
2d	245 (PE-EA)	75	3370 (NH) 2224 (C≡N) 1556 (C=N)	$C_{24}H_{18}N_3OCl$ (399)	C 72.12 H 4.50 N 10.51	72.15 4.48 10.54	1.51 (t, J = 7.0 Hz, 3H, 2-OCH$_2$-*Me*), 2.83 – 2.93 (m, 4H, 5-H$_2$, 6-H$_2$), 4.62 (q, J = 7.0 Hz, 2H, 2-OC*H*$_2$-Me), 7.21 – 7.50 (m, 5H, 2'-H to 6'-H), 7.52 (s, 1H, 7-H), 7.58 (d, J = 8.7 Hz, 1H, 9-H), 7.93 (d, J = 8.7 Hz, 1H, 10-H), 8.81 (b s, 1H, carbazole-N*H*).
2e	213 (PE-EA)	80	3390 (NH) 2218 (C≡N) 1560 (C=N)	$C_{24}H_{19}N_3O$ (365)	C 78.92 H 5.20 N 11.50	78.90 5.23 11.52	1.51 (t, J = 7.0 Hz, 3H, 2-OCH$_2$-*Me*), 2.82 – 2.96 (m, 4H, 5-H$_2$, 6-H$_2$), 4.63 (q, J = 7.0 Hz, 2H, 2-OC*H*$_2$-Me), 7.16 (t, J = 7.1 Hz, 1H, 8-H), 7.27 (t, J = 7.2 Hz, 1H, 9-H), 7.28 – 7.48 (m, 5H, 2'-H to 6'-H), 7.44 (d, J = 7.8 Hz, 1H, 7-H), 7.57 (d, J = 7.8 Hz, 1H, 10-H), 8.79 (b s, 1H, carbazole-N*H*).

[a] PE-EA: Petroleum ether - Ethyl acetate.



1, 2 **a** : R^3 = CH_3, R^1 = R^2 = H; **b** : R^2 = CH_3, R^1 = R^3 = H; **c** : R^1 = CH_3, R^2 = R^3 = H; **d** : R^1 = Cl, R^2 = R^3 = H; **e** : R^1 = R^2 = R^3 = H

Scheme 1. Synthesis of 3-cyano-5,6-dihydro-2-ethoxy-4-phenyl-pyrido[2,3-*a*]carbazoles.

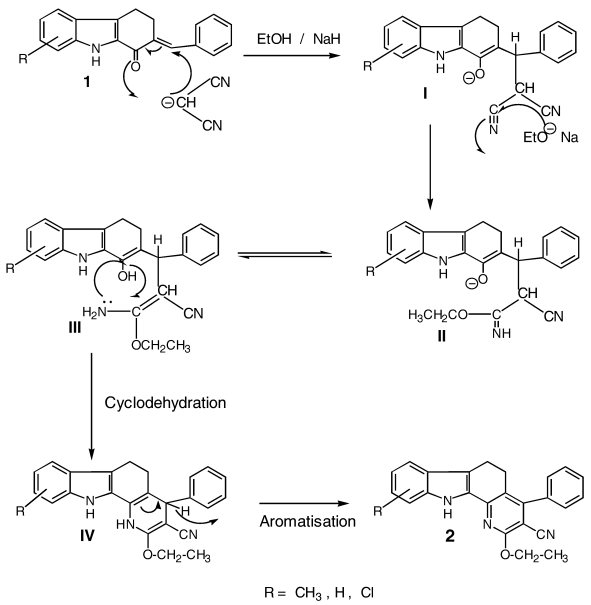
sic conditions, on 1,4-Michael type addition with α,β-unsaturated carbonyl substrate **1** yields the dinitrile intermediate **I**. One of the two symmetric CN-carbon is attacked by the ethoxide ion to give the imino intermediate **II**, which tautomerises to amino intermediate **III**. This amino form on cyclodehydration followed by aromatization affords the final product **2** (Scheme 2).

Experimental Section

General: Thin layer chromatography was used to access the purity of the products. Melting points were determined by using a Mettler FP 51 melting point apparatus and are uncorrected. IR spectra were recorded using KBr discs on a Shimadzu FTIR-8201 PC Infrared Spectrophotometer and ^{1}H NMR on a Varian AMX 400 FT-NMR spectrometer using TMS as internal reference in $CDCl_3$. The chemical shifts are quoted in parts per million. Mass spectra were recorded on a Joel JMS-D 300 mass spectrometer. Satisfactory microanalyses were obtained with Carlo Erba 1106 and Perkin Elmer Model 240 CHN analyzers.

General procedure for the synthesis of 3-cyano-5,6-dihydro-2-ethoxy-4-phenyl-pyrido[2,3-a]carbazoles (**2**)

To 1.00 g of sodium hydride (degreased with petroleum ether) in dry benzene (10 ml), a solution of the



Scheme 2. Mechanism for the formation of **2**.

respective 2-benzylidene-1-oxo-1,2,3,4-tetrahydrocarbazole (**1**, 0.001 mol) in dry ethanol (20 ml) was added in ice-cold condition. To this mixture, malononitrile (0.005 mol) was added and refluxed on a water bath for five hours. Then, the excess of solvent was removed by distillation and poured into ice-water. The reaction mixture was then neutralised with ice-cold HCl (1:1) and extracted with ethyl acetate (3×50 ml). The organic layer was thoroughly washed with water and dried over anhydrous sodium sulphate. On removal of the solvent a brown crude mixture was obtained. It was purified by column chromatography over silica gel using a petroleum ether ethyl acetate (95:5) mixture as eluant to afford a yellow crystalline product.

Experimental data of **2a – e** thus produced are collected in Table 1.

Acknowledgements

The authors thank SIF, IISc, Bangalore for the ^{1}H NMR spectral analysis and the Head, RSIC, CDRI, Lucknow for the mass spectral data.

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