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Short Communication

Synthesis, characterization and pharmacological activities of 5,6,11,12-tetrahydroindolo[2,3-*a*]carbazole derivatives

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Abstract

A series of new 5,6,11,12-tetrahydroindolo[2,3-*a*]carbazole derivatives (**3a**–**h**) was synthesized. Treatment of 8-methyl-1-oxo-1,2,3,4-tetrahydrocarbazole (**1a**) with phenylhydrazine hydrochloride in ethanol furnished the title compound (**3a**) in poor yield along with 8-methyl-1-phenylhydrazono-1,2,3,4-tetrahydrocarbazole (**2a**). Better yields were obtained when **1a**–**h** were treated with phenylhydrazine in glacial acetic acid. All the newly synthesized compounds were characterized on the basis of IR, NMR, mass-spectra and elemental analysis and screened for pharmacological activities.

Keywords: Phenylhydrazine; Indolocarbazole derivatives; Glacial acetic acid; Pharmacological activity

1. Introduction

The therapeutic importance of carbazole derivatives are well established [1–10]. The discovery of tetracyclic pyridocarbazoles and their anticancer properties [11–14] has provoked much interest in their synthesis. The antitumour [5,6], anti-inflammatory [15], antibacterial [16,17] and antifungal [18] activities of heterocyclic compounds containing indole moiety are also well documented; but only very few reports are available on pentacyclic carbazole derivatives [19–22]. In this connection, we recently reported a simple synthesis of quinocarbazoles [23] and herein we report a convenient one-pot synthesis of indolocarbazole derivatives and their pharmacological properties.

2. Chemistry

To realize our objective, an equimolar mixture of 8-methyl-1-oxo-1,2,3,4-tetrahydrocarbazole (**1a**) [6,7] and phenylhydrazine hydrochloride in absolute ethanol was refluxed for 4 h. This yielded a mixture of two products, which were separated and characterized on the basis of IR, ^{1}H-NMR, mass spectra and elemental analysis data (Scheme 1).

The major product was obtained in the 2% petroleum ether–ethyl acetate fraction. It melted at 105°C and exhibited IR absorptions at 3473, 3344 and 1600 cm^{-1}, which were ascribable to two –NH stretching vibrations and a –C=N stretching vibration, respectively. The ^{1}H-NMR spectrum of the product displayed a multiplet at δ 2.15–2.32 for two protons, a three-proton singlet at δ 2.47, two triplets at δ 2.66 and 3.01 each of two-proton intensity, and an aromatic multiplet at δ 6.97–7.95 for eight protons. Its mass spectrum exhibited a molecular ion peak at m/z 289 (32%) and the base peak at m/z 288 ($M^+ - H$). Further, the elemental analysis (C, 78.71; H, 6.48 and N, 14.37%) agreed well with the molecular formula $C_{19}H_{19}N_3$. Based on the above spectral evidence, the product was assigned as 8-methyl-1-phenylhydrazono-1,2,3,4-tetrahydrocarbazole (**2a**).

The other product, of minor yield, was obtained in the 5% petroleum ether–ethyl acetate fraction. It melted at 175°C and showed strong IR absorptions at 3300 and 1649 cm^{-1} corresponding to the –NH and –C=C stretching vibrations, respectively. In its ^{1}H-

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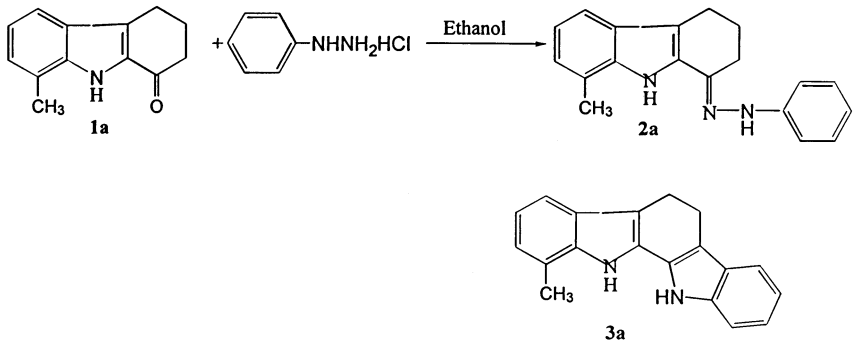


Scheme 1.

NMR spectrum, two multiplets at δ 2.46 and 2.84 corresponded to two CH_2 groups, a sharp singlet at δ 2.52 was due to $-CH_3$ protons, an aromatic envelope at δ 6.89–7.30 was consistent with seven aromatic protons and a broad singlet at δ 8.42 for the –NH proton. The mass spectrum and elemental analysis (C, 83.69; H, 5.78 and N, 10.17%) were in good agreement with the molecular formula $C_{19}H_{16}N_2$. The molecular ion appeared at m/z 272 (24%) and the base peak at m/z 270 ($M^+ - H_2$). On the basis of the above-mentioned spectral evidence, the product was assigned as 1-methyl-5,6,11,12-tetrahydroindolo[2,3-*a*]carbazole (**3a**).

Table 1
Characterization data of **2a** and 5,6,11,12-tetrahydroindolo [2,3-*a*] carbazoles (**3**) [a]

Compound no.	Molecular formula	Yield (%)	m.p. (°C)
2a	$C_{19}H_{19}N_3$	63	105
3a	$C_{19}H_{16}N_2$	70	175
3b	$C_{19}H_{16}N_2$	71	170
3c	$C_{19}H_{16}N_2$	67	118–120
3d	$C_{18}H_{13}N_2C1$	65	145–147
3e	$C_{18}H_{14}N_2$	69	Decomposed >310
3f	$C_{18}H_{13}N_2Br$	60	190–191
3g	$C_{20}H_{16}N_2O_2$	62	160–162
3h	$C_{19}H_{19}N_3O$	65	227–228

[a] IR (ν cm^{-1}): **2a**, 3473 (N–H), 3344 (N–H), 1600 (C=N); **3a**, 3300 (N–H), 1649 (C=C); **3b**, 3257 (N–H), 1626 (C=C); **3c**, 3273 (N–H), 1643 (C=C); **3d**, 3280 (N–H), 1635 (C=C); **3e**, 3292 (N–H), 1599 (C=C); **3f**, 3310 (N–H), 1620 (C=C); **3g**, 3250 (N–H), 1680 (C=O), 1635 (C=C); **3h**, 3270 (N–H), 1610 (C=C). ^{1}H-NMR (400 MHz, $CHCl_3$-*d*, δ ppm): **2a**, 6.97–7.93 (m, 8H, aryl H), 3.01 (t, 2H, C_4–CH_2), 2.66 (t, 2H, C_2–CH_2), 2.47 (s, 3H, CH_3), 2.15–2.32 (m, 2H, C_3–CH_2); **3a**, 8.42 (b s, 1H, NH), 6.89–7.30 (m, 7H, aryl H), 2.84 (m, 2H, C_6–CH_2), 2.52 (s, 3H, CH_3), 2.46 (m, 2H, C_5–CH_2); **3b**, 8.75 (b s, 1H, –NH), 7.18–7.42 (m, 7H, aryl H), 2.97 (t, 2H, C_6–CH_2), 2.63 (t, 2H, C_5–CH_2), 2.44 (s, 3H, CH_3); **3c**, 8.78 (b s, 1H, –NH), 6.99–7.54 (m, 7H, aryl H), 2.98 (t, 2H, C_6–CH_2), 2.63 (t, 2H, C_5–CH_2), 2.47 (s, 3H, CH_3); **3d**, 8.67 (b s, 1H, –NH), 7.19–7.47 (m, 7H, aryl H), 3.02 (t, 2H, C_6–CH_2) 2.65 (t, 2H, C_5–CH_2); **3e**, 9.42 (b s, 1H, –NH) 7.25–7.50 (m, 8H, aryl H), 3.01 (t, 2H, C_6–CH_2), 2.65 (t, 2H, C_5–CH_2); **3f**, 9.00 (b s, 1H, –NH), 6.88–7.91 (m, 7H, aryl H), 2.96 (t, 2H, C_6–CH_2), 2.64 (t, 2H, C_5–CH_2); **3g**, 6.99–7.94 (m, 7H, aryl H), 4.01 (s, 3H, $COOCH_3$), 3.04 (t, 2H, C_5–CH_2), 2.72 (t, 2H, C_5–CH_2); **3h**, 8.95 (b s, 1H, –NH), 6.87–7.92 (m, 7H, aryl H), 3.82 (s, 3H, OCH_3), 3.03 (t, 2H, C_5–CH_2), 2.70 (t, 2H, C_5–CH_2).

Both **2a** and **3a** were tested for their antibacterial, antifungal and antitubercular activities. Compound **3a** was found to be more potent compared to **2a** (Table 2). In order to increase the yield of the active compound **3a**, an equimolar mixture of **la** and phenylhydrazine was refluxed in glacial acetic acid for 3 h. This yielded a single product. The product was found to be **3a** by means of mixed melting point, superimposable IR spectra and elemental analysis. Here, the reaction commenced via the formation of the corresponding hydrazone which loses a nitrogen molecule and undergoes cyclization as in Fischer indole synthesis [24,25].

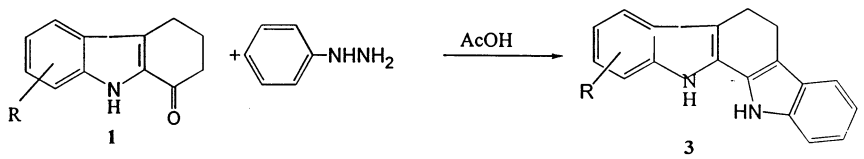
A similar series of compounds, **3b**–**h**, was obtained from **1b**–**h** (Table 1 and Scheme 2).

3. Experimental

Melting points were determined on a Mettler FP5 and are uncorrected. The IR spectra (in KBr pellets) were recorded on a Shimadzu FT-IR 8201 (PC) spectrophotometer. ^{1}H-NMR spectra were recorded in $CHCl_3$-*d* either on an AMX 400 MHz or FX 90Q (90 MHz) spectrometer using TMS as internal standard. The mass spectra were recorded on a JEOL-D 300 spectrometer operating at 70 eV. The purity of the compounds was checked by thin layer chromatography on a silica gel plate.

*3.1. Reaction of 8-methyl-1-oxo-1,2,3,4-tetrahydrocarbazole (**1a**) with phenylhydrazine hydrochloride*

A mixture of 8-methyl-1-oxo-1,2,3,4-tetrahydrocarbazole (**1a**, 0.002 mol) and phenylhydrazine hydrochloride (0.002 mol) in dry ethanol (20 ml) was refluxed for 4 h. The ethanol was distilled off, poured into ice water



1a R = 8 CH_3
1b R = 7 CH_3
1c R = 6 CH_3
1d R = 6 Cl
1e R = H
1f R = 6 Br
1g R = 8 $COOCH_3$
1h R = 8 OCH_3

3a R = 1 CH_3
3b R = 2 CH_3
3c R = 3 CH_3
3d R = 3 Cl
3e R = H
3f R = 3 Br
3g R = 1 $COOCH_3$
3h R = 1 OCH_3

Scheme 2.

Table 2
Antibacterial activity data of **2a** and 5,6,11,12-tetrahydroindolo[2,3-*a*] carbazoles (**3**)

Compound no.	Minimum inhibitory concentration (μg/ml)			
	Escherischia coli	*Staphylococcus aureus*	*Pseudomonas aeruginosa*	*Bacillus subtilis*
2a	12.5	12.5	25	12.5
3a	12.5	12.5	12.5	6
3b	12.5	12.5	12.5	6
3c	6	12.5	12.5	6
3d	3	12.5	6	6
3e	12.5	12.5	25	12.5
3f	12.5	12.5	12.5	6
3g	12.5	12.5	25	12.5
3h	6	12.5	6	25
Furacin (standard)	6	12.5	12.5	12.5

and extracted with chloroform. The excess solvent was evaporated to give a brown residue, which was chromatographed over a column packed with silica gel. The column was eluted with 2 and 5% petroleum ether–ethyl acetate mixture to yield two different products, **2a** and **3a**. The products thus obtained were recrystallized using the respective solvent mixture.

*3.2. Reaction of 1-oxo-1,2,3,4-tetrahydrocarbazoles (**1a–h**) with phenylhydrazine*

An equimolar mixture of the respective 1-oxo-1,2,3,4-teterahydrocarbazole (**1a–h**, 0.002 mol) and phenylhydrazine (0.002 mol) in glacial acetic acid (10 ml) was refluxed for 3 h. The reaction mixture was cooled, poured into ice water, extracted with chloroform and dried over anhydrous Na_2SO_4. The excess solvent was evaporated. The resulting residue was purified by passing through a column packed with silica gel and eluted with 5% petroleum ether–ethyl acetate mixture to yield the title compounds **3a–h**. The product thus obtained was recrystallized by using the same solvent mixture.

4. Pharmacological activities

All the newly synthesized compounds, **2a** and **3a–h**, were screened for their in vitro antibacterial activities against *Escherischia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Bacillus subtilis*, and antifungal activities against *Candida albicans*, *Trichophyton rubrum* and *Aspergillus niger* according to the disc diffusion method [26]. The minimal inhibitory concentrations values were determined by the serial dilution method. Furacin was used as a standard drug for comparison in antibacterial screening studies. The results are tabulated in Tables 2 and 3.

The antibacterial screening indicates that compound **3d** carrying a chloro group showed excellent antibacterial activity against *E. coli*, *P. aeruginosa* and *B. subtilis*. Compounds **3a**, **3b** and **3c** also possessed good antibacterial activities against *B. subtilis*. The antibacterial activities of the remaining compounds were comparable with that of furacin, especially against *S. aureus* and *B. subtilis*. The antifungal studies indicate that **3d** exhibited good antifungal activity against all the fungi tested. Also, **3h** with a methoxy group showed excellent activity against *A. niger*.

Table 3
Antifungal and antitubercular activity data of **2a** and 5,6,11,12-tetrahydroindolo[2,3-*a*]carbazoles (**3**)

Compound no.	Minimum inhibitory concentration (μg/ml)			
	Candida albicans	*Trichophyton rubrum*	*Aspergillus niger*	*Mycobacterium tuberculosis*
2a	200	200	150	200
3a	150	200	150	150
3b	200	150	50	150
3c	150	150	200	150
3d	50	75	50	50
3e	150	150	200	200
3f	150	100	150	100
3g	200	200	150	200
3h	150	200	50	75

All the newly synthesized compounds were also tested for their tuberculostatic activity against the $H_{37}R_v$ strain of *Mycobacterium tuberculosis* using Kricheneris medium by the tube dilution method. Compounds **3d** and **3g** showed moderate activity (Table 3). It was concluded that compound **3d** deserves further pharmacological investigation as it exhibited good antibacterial, antifungal and antitubercular activities.

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