Synthesis of α-alkyl- and α,α-dialkyl-β-phenyltryptamines

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A new method was developed for the synthesis of α-alkyl- and α,α-dialkyl-β-phenyltryptamines based on alkylation of nitroalkanes with α-phenyl-*nor*-gramine.

Key words: α-phenyl-*nor*-gramine, nitroalkanes, tryptamines.

The chemistry and pharmacology of tryptamines attract steady interest even within 50 year after the discovery of serotonine (1948).[1] Tryptamines possess a broad spectrum of physiological activities, *viz.*, antitumor, antiradiation, and psychotropic activities.[2] The synthesis as well as the adrenoblocking and antioxidase activities of α-methyltryptamine (indopan) have been described in the literature.[3,4] The present study was aimed at developing a convenient procedure for the synthesis of α-alkyl- and α,α′-dialkyl-β-phenyltryptamines, which is necesary for studying these compounds in more detail.

Several methods for the synthesis of tryptamines are presently available. These procedures can be arbitrarily divided into two groups, *viz.*, the formation of the indole ring starting from compounds containing the ethylamine chain and the formation of the ethylamine chain based on compounds of the indole series. We chose the latter alternative taking into account that the target compounds can be prepared from the readily accessible starting compounds in two steps.

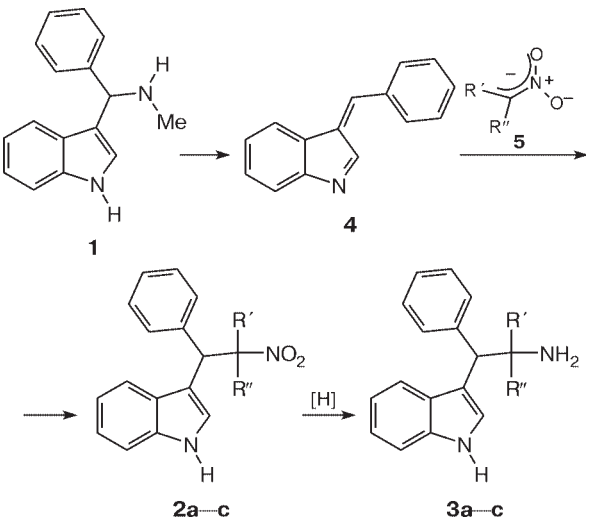
In the present study, we describe for the first time alkylation of nitroalkanes with α-phenyl-*nor*-gramine[5] (**1**) followed by reduction of the resulting 3-(2-nitro-1-phenylalkyl)indoles **2** to the corresponding tryptamines **3**.

The reactions of compound **1** with nitroethane, 1-nitropropane, and 2-nitropropane in EtOH in the presence of bases afforded 3-(2-nitro-1-phenylpropyl)-1*H*-indole (**2a**), 3-(2-methyl-2-nitro-1-phenylpropyl)-1*H*-indole (**2b**), and 3-(2-nitro-1-phenylbutyl)-1*H*-indole (**2c**), respectively, in good yields. The reactions proceeded, apparently, through the formation of 3-[(*Z*)-phenylmethylidene]-3*H*-indole (**4**) followed by the attack with the potassium salt of the aci form of nitroalkanes **5** (Scheme 1).

We prepared for the first time tryptamines **3a—c** in high yields by reducing compounds **2a—c**, respectively, with hydrazine hydrate in the presence of Raney nickel.

According to the ^{1}H NMR spectroscopic data, compounds **2a**,**c** and **3a**,**c** were obtained as mixtures of diastereomers in a ratio of 50 : 50. Since the diastereotopic

Scheme 1



2, 3: R′ = H; R″ = Me (**a**); R′ = R″ = Me (**b**); R′ = H; R″ = Et (**c**)

methyl groups in compounds **2b** and **3b** are magnetically nonequivalent, their NMR spectra have signals of two methyl groups. Interestingly, compound **3a** is a structural analog simultaneously of phenamine and indopan.

Experimental

The ^{1}H NMR spectra were recorded on a Bruker WM-250 spectrometer with Me_4Si as the internal standard. The mass spectra (EI) were measured on an SSQ-710 (Finnigan MAT) spectrometer; the energy of ionizing electrons was 70 eV.

Nitroalkanes were purchased from Fluka.

3-(2-Nitro-1-phenylalkyl)indoles 2 (general procedure). A solution of K_2CO_3 (0.1 g, 0.07 mmol) in H_2O (1 mL) and nitroalkane (0.625 mmol) were added to a boiling solution of α-phenyl-*nor*-gramine (**1**) (1.0 g, 0.42 mmol) in 95% EtOH (10 mL). The reaction mixture was heated at the boiling temperature under a stream of an inert gas until the starting com-

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pound was consumed. The course of the reaction was monitored by TLC (Silufol UV-254, the EtOAc—CCl_4 system, 1 : 4). The reaction mixture was cooled to ~20 °C. The precipitate that formed was filtered off and recrystallized from 95% EtOH.

3-(2-Nitro-1-phenylpropyl)-1*H*-indole (2a). The yield was 63%. M.p. 150.5—151 °C. ^{1}H NMR ($CDCl_3$), δ: 8.18 (br.s, 1 H, NH); 7.64 (m, 1 H, $H(4)_{Ind}$); 7.38 (m, 3 H, $H(7)_{Ind}$, *o*-Ph); 7.26 (m, 2 H, *m*-Ph); 7.20 (m, 1 H, *p*-Ph); 7.13—7.20 (m, 2 H, $H(5)_{Ind}$, $H(6)_{Ind}$); 7.10 (d, 1 H, $H(2)_{Ind}$, J = 2.1 Hz); 5.44 (dd, 1 H, CHMe, J_{CH-CH} = 10.7 Hz, J_{CH-Me} = 6.4 Hz); 4.77 (d, 1 H, IndCHPh); 1.62 (d, 3 H, Me). MS, *m/z* (I_{rel} (%)): 280 $[M]^+$ (14), 206 $[IndCHPh]^+$ (100). Found (%): C, 72.64; H, 5.65; N, 9.81. $C_{17}H_{16}N_2O_2$. Calculated (%): C, 72.84; H, 5.75; N, 9.99.

3-(2-Methyl-2-nitro-1-phenylpropyl)-1*H*-indole (2b). The yield was 69%. M.p. 146—148 °C. ^{1}H NMR ($CDCl_3$), δ: 9.40 (br.s, 1 H, NH); 7.49 (m, 1 H, $H(2)_{Ind}$); 7.47 (m, 1 H, $H(4)_{Ind}$); 7.44 (m, 2 H, *o*-Ph); 7.39 (m, 1 H, $H(7)_{Ind}$); 7.3 (m, 3 H, *p*- and *m*-Ph); 7.11 (m, 1 H, $H(6)_{Ind}$); 7.00 (m, 1 H, $H(5)_{Ind}$); 5.16 (s, 1 H, CH); 1.71 (s, 3 H, Me); 1.70 (s, 3 H, Me). MS, *m/z* (I_{rel} (%)): 294 $[M]^+$ (34), 206 $[IndCHPh]^+$ (100). Found (%): C, 73.04; H, 5.94; N, 9.71. $C_{18}H_{18}N_2O_2$. Calculated (%): C, 73.45; H, 6.16; N, 9.52.

3-(2-Nitro-1-phenylbutyl)-1*H*-indole (2c). The yield was 60%. Viscous oil. ^{1}H NMR (CD_3CN), δ: 9.27—9.35 (m, 1 H, NH); 7.67—7.00 (m, 10 H, Ph, Ind); 5.38—5.41 (m, 1 H, $CHNO_2$); 4.76—4.81 (m, 1 H, IndCHPh); 1.66 (m, 2 H, CH_2); 0.89—0.91 (m, 3 H, Me, both diastereomers). MS, *m/z* (I_{rel} (%)): 294 $[M]^+$ (11), 206 $[IndCHPh]^+$ (100). Found (%): C, 73.24; H, 5.85; N, 10.01. $C_{18}H_{18}N_2O_2$. Calculated (%): C, 73.45; H, 6.16; N, 9.52.

3-(2-Amino-1-phenylalkyl)indoles 3 (general procedure). Raney nickel (0.1 g) was added to a solution of compounds **2a—c** (0.42 mmol) in 95% EtOH (10 mL). Then a 20% hydrazine hydrate solution in ethanol, which was prepared by mixing hydrazine hydrate (20 g) with 95% EtOH (80 mL), was added portionwise with intense stirring. The reaction mixture was heated and then refluxed with stirring under a stream of inert gas until the starting compound was consumed. The course of the reaction was monitored by TLC (Silufol UV-254, the EtOAc—CCl_4 system, 1 : 4). The reaction mixture was cooled to ~20 °C, an insoluble precipitate was filtered off, and the solvent was distilled off on a rotary evaporator.

1-(1*H*-Indol-3-yl)-1-phenyl-2-propylamine (3a). The yield was 90%, the compound sublimed without melting. ^{1}H NMR (DMSO-d_6), δ: 10.85—10.93 (m, 1 H, NH); 7.53 (m, 1 H, $H(2)_{Ind}$); 7.51 (m, 1 H, $H(4)_{Ind}$); 7.42 (m, 2 H, *o*-Ph); 7.40 (m, 1 H, $H(7)_{Ind}$); 7.26 (m, 2 H, *m*-Ph); 7.13 (m, 2 H, *p*-Ph); 7.03 (m, 1 H, $H(6)_{Ind}$); 6.92 (m, 1 H, $H(5)_{Ind}$); 3.92—3.95 (both d, 1 H, PhCHCHMe, J = 8.77, both diastereomers); 3.72 (m, 1 H, CHMe); 0.94—1.05 (both d, 3 H, Me, J = 5.85, both diastereomers). MS, *m/z* (I_{rel} (%)): 250 $[M]^+$ (11). Found (%): C, 81.24; H, 7.14; N, 10.83. $C_{17}H_{18}N_2$. Calculated (%): C, 81.56; H, 7.25; N, 11.19.

1-(1*H*-Indol-3-yl)-2-methyl-1-phenyl-2-propylamine (3b). The yield was 90%. M.p. 122—124 °C. ^{1}H NMR ($CDCl_3$), δ: 8.14 (br.s, 1 H, NH); 7.59 (m, 1 H, $H(4)_{Ind}$); 7.52 (d, 1 H, $H(2)_{Ind}$, J = 2.14 Hz); 7.48 (m, 2 H, *o*-Ph); 7.30 (m, 1 H, $H(7)_{Ind}$); 7.30 (m, 3 H, *p*- and *m*-Ph); 7.14 (m, 1 H, $H(6)_{Ind}$); 7.06 (m, 1 H, $H(5)_{Ind}$); 4.26 (s, 1 H, CH); 1.23 (s, 3 H, Me); 1.20 (s, 3 H, Me). ^{1}H NMR (CD_3CN), δ: 9.30 (br.s, 1 H, NH); 7.62 (d, 1 H, $H(2)_{Ind}$, J = 2.1 Hz); 7.57 (m, 1 H, $H(4)_{Ind}$); 7.53 (m, 2 H, *o*-Ph); 7.36 (m, 1 H, $H(7)_{Ind}$); 7.25 (m, 2 H, *m*-Ph); 7.15 (m, 1 H, *p*-Ph); 7.08 (m, 1 H, $H(6)_{Ind}$); 6.99 (m, 1 H, $H(5)_{Ind}$); 4.29 (s, 1 H, CH); 1.16 (s, 3 H, Me); 1.13 (s, 3 H, Me). MS, *m/z* (I_{rel} (%)): 264 $[M]^+$ (13), 206 $[IndCHPh]^+$ (100). Found (%): C, 81.54; H, 7.34; N, 10.31. $C_{18}H_{20}N_2$. Calculated (%): C, 81.78; H, 7.63; N, 10.60.

1-(1*H*-Indol-3-yl)-1-phenyl-but-2-ylamine (3c). The yield was 90%, m.p. 118—120 °C. ^{1}H NMR (DMF-d_6), δ: 11.17 (br.s, 1 H, NH); 7.68 (m, 1 H, $H(2)_{Ind}$); 7.66 (m, 1 H, $H(4)_{Ind}$); 7.52 (m, 2 H, *o*-Ph); 7.49 (m, 1 H, $H(7)_{Ind}$); 7.29 (m, 2 H, *m*-Ph); 7.16 (m, 2 H, *p*-Ph); 7.08 (m, 1 H, $H(6)_{Ind}$); 6.97 (m, 1 H, $H(5)_{Ind}$); 4.38 (d, 1 H, IndCHPh, J = 9.9 Hz); 3.88 (m, 1 H, CHEt); 1.42—1.61 (m, 2 H, CH_2); 1.40 (t, 3 H, Me, J = 7.3 Hz). ^{1}H NMR (CD_3CN+TFA), δ: 7.68 (m, 1 H, $H(4)_{Ind}$); 7.48 (m, 1 H, $H(2)_{Ind}$); 7.48 (m, 2 H, *o*-Ph); 7.48 (m, 1 H, $H(7)_{Ind}$); 7.35 (m, 2 H, *m*-Ph); 7.23 (m, 1 H, *p*-Ph); 7.19 (m, 1 H, $H(6)_{Ind}$); 7.10 (m, 1 H, $H(5)_{Ind}$); 4.47 (d, 1 H, IndCHPh, J = 11.6 Hz); 4.15 (m, 1 H, CHEt); 1.63—1.76 (m, 2 H, CH_2); 1.40 (t, 3 H, Me, J = 7.7 Hz). MS, *m/z* (I_{rel} (%)): 264 $[M]^+$ (13). Found (%): C, 81.44; H, 7.27; N, 10.43. $C_{18}H_{20}N_2$. Calculated (%): C, 81.78; H, 7.63; N, 10.60.

References

1. M. Rappoport and A. Green, *Science*, 1948, **108**, 329.
2. N. N. Suvorov and V. S. Shashko, *Khimiya i farmakologiya sredstv profilaktiki radiatsionnykh porazhenii* [*Chemistry and Pharmacology of Drugs for Prophylaxis of Radiation Affections*], Atomizdat, Moscow, 1975, 98 (in Russian).
3. D. Nichols, D. Lloyd, M. Johnson, and A. Hoffman, *J. Med. Chem.*, 1988, **31**, 1406.
4. D. Repke and W. Ferguson, *J. Heterocycl. Chem.*, 1976, **13**, 775.
5. B. B. Semenov and Yu. I. Smushkevich, *Izv. Akad. Nauk, Ser. Khim.*, 2001, 521 [*Russ. Chem. Bull., Int. Ed.*, 2001, **50**, 543].

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