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Synthesis and antimicrobial activity of 1-benzamido-5-hydroxyindole derivatives

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Abstract. 1-Benzamido-2-methyl-3-carbethoxy-5-hydroxyindole and 1-benzamido-2-methyl-3-carbethoxy-5-hydroxybenz[*g*]indole were synthesized by adopting the Nenitzescu reaction. These new 5-hydroxyindoles were reacted with methyl iodide to obtain O- and N-methylated products. All the newly synthesized compounds were characterized by their IR, NMR and mass spectra and were also screened for their antimicrobial activity.

Keywords. 1-Benzamido-5-hydroxyindole derivatives; mass spectra; antimicrobial activity.

1. Introduction

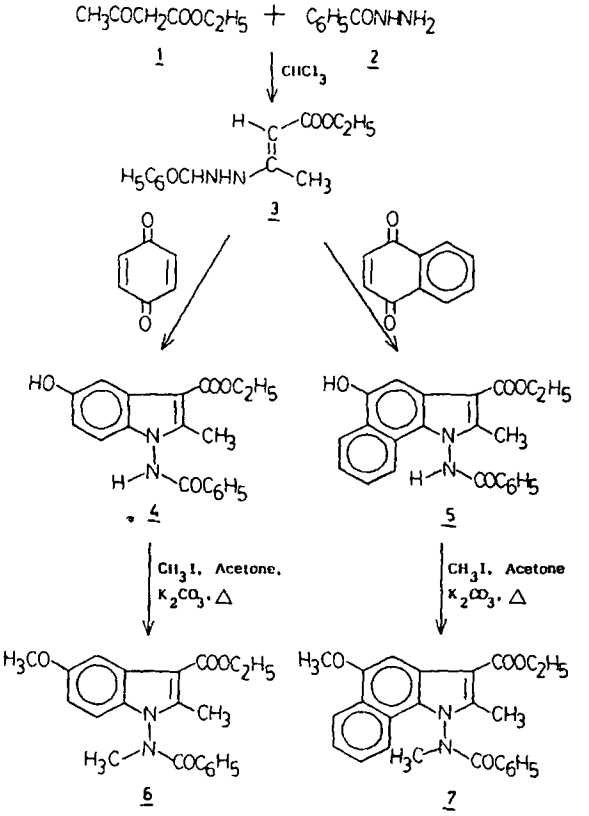
Heterocycles bearing functional group(s) are important synthons in organic syntheses. The presence of amino group on biologically active heterocycles would be quite rewarding from synthetic and biological aspects. The antiserotonin (Woolley and Shaw 1953, 1956, 1957; Gaddum *et al* 1955; Hiremath and Siddappa 1964–65), antitumour (Eakin *et al* 1984), antidepressant (Schatz *et al* 1975), antibacterial and antifungal (Schatz *et al* 1975; Chauhan and Parikh 1989) activities of various aminoindoles have been well documented in literature. However, relatively little work has been done on indoles with an amino group directly attached to the indole ring, particularly, to the ring nitrogen. Synthesis of indole derivatives carrying both amino and hydroxy functions has not been reported so far. It was therefore planned to introduce simultaneously both amino and hydroxy functions on the indole ring by adopting the Nenitzescu method (Nenitzescu 1929) leading to the synthesis of substituted 1-amino-5-hydroxyindole derivatives.

2. Results and discussion

The required precursor viz. ethyl β-(N'-benzoyl-N-hydrazino)crotonate (3) was prepared by condensing ethyl acetoacetate (1) with benzoic hydrazide (2) in chloroform. This crotonate (3) on reaction with 1,4-benzoquinone and 1,4-naphthoquinone under Nenitzescu condition (Nenitzescu 1929) afforded the desired 1-benzamido-2-methyl-3-carbethoxy-5-hydroxyindole (4) and 1-benzamido-2-methyl-3-carbethoxy-5-hydroxybenz[*g*]indole (5) respectively. Further, these 5-hydroxyin-

*For correspondence

doles (4) and (5) were reacted with methyl iodide in dry acetone in the presence of anhydrous potassium carbonate and catalytic amount of potassium iodide to produce the O- and N-methylated products viz. 1-(N-methylbenzamido)-2-methyl-3-carbethoxy-5-methoxyindole (6) and 1-(N-methylbenzamido)-2-methyl-3-carbethoxy-5-methoxybenz[*g*]-indole (7) in good yields (scheme 1).



Scheme 1.

The IR, PMR and mass spectral data of these new compounds were consistent with the structures assigned. The mass spectrum of 1-benzamido-2-methyl-3-carbethoxy-5-hydroxyindole (4) showed a molecular ion peak M^+ at *m/z* 338. The loss of $C_{12}H_{13}N_2O_3$ from M^+ resulted in a benzoyl fragment at *m/z* 105 (base peak) which on further fragmentation gave a phenyl cation at *m/z* 77. The mass spectrum of 1-(N-methylbenzamido)-2-methyl-3-carbethoxy-5-methoxyindole (6) exhibited a characteristic molecular ion peak at *m/z* 366 and a base peak at *m/z* 105 due to a benzoyl fragment. The other prominent peaks observed were at *m/z* 321, 261 and 232 due to the loss of OC_2H_5, C_6H_5CO and $H_3C{-}N{-}COC_6H_5$ respectively from the molecular ion.

3. Experimental

Melting points were determined in open capillary tubes and are uncorrected. IR spectra were obtained on a Perkin-Elmer 881. PMR spectra were recorded on a GE NMR-300 MHz and mass spectra on an Autospec EI spectrometer.

3.1 *Ethyl β-(N'-benzoyl-N-hydrazino)crotonate (3)*

To a stirred solution of benzoic hydrazide (2) (13·6 g, 0·1 mol) in chloroform (100 ml), were added ethyl acetoacetate (1) (13·0 g, 0·1 mol) and conc. HCl (2 drops). The reaction mixture was stirred at room temperature for 12 h. The organic layer was washed with water (3 × 50 ml), dried over anhydrous sodium sulphate and the chloroform then removed under reduced pressure. The residual crotonate was taken to the next step without any further purification.

3.2 *1-Benzamido-2-methyl-3-carbethoxy-5-hydroxyindole (4)*

A mixture of 1,4-benzoquinone (5·94 g, 0.055 mol) and ethyl β-(N'-benzoyl-N-hydrazino)crotonate (3) (12·40 g, 0·05 mol) in chloroform (100 ml) was heated at reflux for 2 hours. The solvent was removed under reduced pressure, the residue treated with ethanol and left overnight at room temperature. It was filtered, washed with ethanol and recrystallized from dioxan; m.p. 278–80°C (26·4% yield).

Analysis calcd. for $C_{19}H_{18}N_2O_4$: C, 67·44; H, 5·36; N, 8·28;
found: C, 67.58; H, 5·38; N, 8·38%.
IR: νcm^{-1}: 3310 (OH); 3190 (NH); 1671 (ester carbonyl); 1635 (amide carbonyl).
PMR (DMSO-d_6/TMS): δ: 1·36(*t*, $J = 7·5$ Hz, 3H, C-3 $COOCH_2\underline{CH}_3$); 2·55(*s*, 3H, C-2 CH_3); 4·32(*q*, $J = 7·5$ Hz, 2H, C-3 $COO\underline{CH}_2CH_3$); 6·5–8·2(*m*, 9H, ArH and C-5 OH); 9·03(*s*, 1H, $>N\underline{H}$).
Mass: *m/z* (%): 338($[M]^{+\cdot}$ 26); 105($[M-C_{12}H_{13}N_2O_3]^+$, 100); 77($[M-C_{13}H_{13}N_2O_4]^+$, 43).

3.3 *1-Benzamido-2-methyl-3-carbethoxy-5-hydroxybenz[g]-indole (5)*

To ethyl β-(N'-benzoyl-N-hydrazino)crotonate (3) (12·40 g, 0·05 mol) in glacial acetic acid (100 ml) was added 1,4-naphthoquinone (8·69 g, 0·055 mol) in small portions with stirring. The mixture was heated at 50–60° for 5 hours and left overnight at room temperature. The separated solid was collected by filtration, washed with acetic acid, dried and recrystallized from dioxan. m.p. 275–6°C (35·8% yield).

Analysis calcd. for $C_{23}H_{20}N_2O_4$; C, 71·11; H, 5·19; N, 7·21;
Found C, 71·26; H, 5·29; N, 7·38%.
IR: νcm^{-1}: 3300(OH/NH); 1665(ester carbonyl); 1648 (amide carbonyl).
PMR (DMSO-d_6/TMS): δ: 1·49(*t*, $J = 7$ Hz, 3H, C-3 $COOCH_2\underline{CH}_3$); 2·65(*s*, 3H, C-2 CH_3); 4·40(*q*, $J = 7$ Hz, 2H, C-3 $COO\underline{CH}_2CH_3$); 7·4–8·5(*m*, 10H, ArH); 9·98(*s*, 1H, $>N\underline{H}$); 12·43(*s*, 1H, C-5 OH).
Mass: *m/z* (%): 388($[M]^{+\cdot}$, 94); 315($[M-C_3H_5O_2]^+$, 12); 283($[M-C_7H_5O]^+$, 16); 267($[M-C_7H_7NO]^{+\cdot}$, 31); 255($[M-C_8H_5O_2]^+$, 10); 239($[M-C_8H_7NO_2]^{+\cdot}$, 17); 222($[M-C_9H_{12}NO_2]^+$, 22); 195($[M-C_{10}H_{11}NO_3]^{+\cdot}$, 10); 105($[M-C_{16}H_{15}N_2O_3]^+$, 100); 77($[M-C_{17}H_{15}N_2O_4]^+$, 48).

3.4 *1-(N-methylbenzamido)-2-methyl-3-carbethoxy-5-methoxyindole (6)*

To 1-benzamido-2-methyl-3-carbethoxy-5-hydroxyindole (4) (0·338 g, 0·001 mol) in dry acetone (50 ml) were added methyl iodide (0·568 g, 0·004 mol), anhydrous K_2CO_3 (1 g) and potassium iodide (0·1 g). The reaction mixture was heated at reflux for 30

hours and it was then filtered while hot. The solvent was removed under reduced pressure and the residue was crystallized from ethanol. m.p. 128–9°C (61·4% yield).

Analysis calcd. for $C_{21}H_{22}N_2O_4$:C, 68·83; H, 6·05; N, 7·64;
Found:C, 68·81; H, 6·13; N, 7·84%.
IR:νcm^{-1}:1704 (ester carbonyl); 1674 (amide carbonyl).
PMR ($CDCl_3$/TMS):δ:1·42(*t*, $J = 7$ Hz, 3H, C-3 $COOCH_2\underline{CH}_3$); 2·5(*s*, 3H, C-2 CH_3); 3·48(*s*, 3H, $>N-CH_3$); 3·88(*s*, 3H, C-5 OCH_3); 4·36(*q*, $J = 7$ Hz, 2H, C-3 $COO\underline{CH}_2CH_3$); 6·96(*dd*, $J = 8·5$ Hz & 2·5 Hz, 1H, C-6 H); 7·64(*d*, $J = 2·5$ Hz, 1H, C-4 H); 7·10–7·40 (*m*, 6H, ArH).
Mass: *m/z* (%): 366($[M]^+$, 78); 321($[M-C_2H_5O)]^+$, 15); 261($[M-C_7H_5O]^+$, 61); 232($[M-C_8H_8NO]^+$, 54); 215($[M-C_9H_{11}O_2]^+$, 16); 187($[M-C_{10}H_{13}NO_2]^+$, 32); 172($[M-C_{10}H_{16}NO_2]^+$, 22); 105($[M-C_{14}H_{17}N_2O_3]^+$, 100); 77($[M-C_{15}H_{17}N_2O_4]^+$, 76).

3.5 *1-(N-methylbenzamido)-2-methyl-3-carbethoxy-5-methoxybenz[g]indole* (7)

A mixture of 1-benzamido-2-methyl-3-carbethoxy-5-hydroxybenz[*g*]indole (5) (0·388 g, 0·001 mol) in dry acetone (50 ml), methyl iodide (0·568 g, 0·004 mol), anhydrous potassium carbonate (1 g) and potassium iodide (0·1 g) was heated at reflux for 30 hours. It was filtered hot and the solvent was removed under reduced pressure. The residue was collected and crystallized from ethanol. m.p. 160–1°C (72% yield).

Analysis calcd. for $C_{25}H_{24}N_2O_4$:C, 72·10; H, 5·81; N, 6·73;
Found:C, 72·25; H, 5·80; N, 6·96%.
IR:νcm^{-1}:1695 (ester carbonyl); 1665 (amide carbonyl).
PMR ($CDCl_3$/TMS):δ:1·43(*t*, $J = 7$ Hz, 3H, C-3 $COOCH_2\underline{CH}_3$); 2·5(*s*, 3H, C-2 CH_3); 3·59(*s*, 3H, N–CH_3); 4·08(*s*, 3H, C-5 OCH_3); 4·38(*q*, $J = 7$ Hz, 2H, C-5 $COO\underline{CH}_2CH_3$); 7·0–8·5(*m*, 10H, ArH).
Mass: *m/z* (%):416($[M]^+$, 91); 401($[M-CH_3]^+$, 12); 311($[M-C_7H_5O]^+$, 18); 282($[M-C_8H_8NO]^+$, 30); 268($[M-C_9H_{10}NO]^+$, 6); 236($[M-C_{10}H_{14}NO_2]^+$, 38); 209($[M-C_{11}H_{13}NO_3]^+$, 16); 105($[M-C_{18}H_{19}N_2O_3]^+$, 100); 77($[M-C_{19}H_{19}N_2O_4]^+$, 41).

4. Antimicrobial activity

The newly synthesized indole derivatives were screened for their antibacterial activity against *E. coli* and *B. cirroflagellosus* using Norfloxocin as standard and for their antifungal activity against *C. albicans* and *A. niger* using griseofulvin as standard. The culture medium was nutrient agar and the method employed was the cup-plate method (Kavanagh 1963; Seeley and Van Demark 1975). The compound (6) showed moderate inhibition against *E. coli*, weak inhibition against *B. cirroflagellosus* and *A. niger* and zero inhibition against *C. albicans*. The remaining compounds (4) (5) and (7) showed weak activity against all the four microbes.

5. Conclusion

The procedure adopted in the synthesis of the title compounds has a wide scope and allows straightforward synthesis of various biologically significant indole and benz[*g*]indole derivatives carrying amino and hydroxy functional groups.

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