PREPARACIÓN SIMPLE DE NUEVAS *N*-ARIL-*N*-(3-INDOLMETIL) ACETAMIDAS Y SU ANÁLISIS ESPECTROSCÓPICO

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RESUMEN

La síntesis de nuevas N-aril-N-(3-indolmetil)acetamidas, basada en un paso inicial de la reacción de iminozación del indol-3-carboaldehído, ha sido reportada. Las estructuras de los indoles C-3 sustituidos fueron confirmadas por los estudios de ^{1}H-RMN, ^{13}C-RMN y experimentos de 2D-RMN.

Palabras clave: derivados de indol, reacción de acetilación chemo-selectiva.

SIMPLE PREPARATION OF NEW *N*-ARYL-*N*-(3-INDOLMETHYL) ACETAMIDES AND THEIR SPECTROSCOPIC ANALYSIS

ABSTRACT

The synthesis of new *N*-aryl-*N*-(3-indolmethyl)acetamides based on first step iminozation reaction of indol-3-carbaldehyde is reported. The structures of the C-3 substituted indoles were confirmed by ^{1}H-NMR and ^{13}C-NMR studies supported by inverse-detected 2D NMR experiments.

Key words: indole derivatives, chemo-selective acetylation reaction.

INTRODUCTION

The research of the indol chemistry has been and still is one of the most active areas of heterocyclic chemistry. In recent years, much interest has been attracted to the preparation of substituted indoles due to their numerous biologically significant activities.[1] The 3-indolylmethanamine derivatives **1** were the important intermediates of the natural and natural-like products, such as hydro-? -carboline and pyrido[4,3-*b*]indole derivatives.[2] This 3-indolyl methanamine motif is also embedded in numerous indole alkaloids from simple alkaloid gramine **2** to complex aspidospermine alkaloid **3**[3] (figure 1).

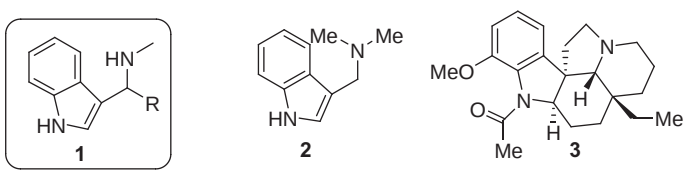

Figure 1. Relevant natural alkaloids derived from the 3-indolylmethanamine system

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As a result of their biological and synthetic importance, a variety of methods have been reported for the preparation of 3-substituted indoles, using indol or 3-indolcarboxyaldehyde as starting materials. Generally, the Mannich reaction[4] and the catalyzed Friedel-Crafts alkylation reactions of indoles[5] are considered as a powerful carbon-carbon bond process to afford the 3-indolylmethanamine derivatives **1**. However, another synthetic route to these compounds by using 3-indolcarboxyaldehyde, via its imino derivatives formation, is valid. This route has been employed by our laboratory, which recently started an own medicinal program directed to small molecules for drug delivery. We were particularly interested in 3-indolylmethanamine derivatives molecules that could serve as useful precursors to many drug-like indolic compounds in our quest for compounds with antiparasitic properties.[6] To the best of our knowledge, a simple preparation of new (3-indolmethyl)acetamide and (1-acetylindolmethyl-3)acetamide regulating only a solvent nature has not been described. The results of our investigation on preparation, spectral and structural characterization of new two acetamides based on 3-indolyl methanamine motif are reported in this work.

EXPERIMENTAL

All reagents were purchased from Aldrich, commercial grade. The purity of the products and the composition of the reaction mixtures were monitored by thin layer chromatography over Silufol UV_{254} 0,25 mm-thick chromatoplates. Product isolation and purification were performed by column chromatography over silica gel, using ethyl acetate-petroleum ether mixtures as eluents. The IR spectra were measured with a LUMEX INFRALUM FT-02 spectrophotometer in KBr. The ^{1}H-NMR spectra were acquired Bruker Advance AM-400 spectrometers using $CDCl_3$ as a solvent and TMS as internal reference. The mass spectra were obtained on an HP 5890A series II gas chromatograph interfaced to an HP 5972 mass selective detector that used electron impact ionization (70 eV).

N-(3-Indolyden)-2-cyanoaniline (6)

A mixture of the indol-3-carbaldehyde (figure 2) **4** (1,18 g, 8,14 mmol), the 2-cyanoaniline **5** (1,15 g, 9,77 mmol), and the glacial AcOH (7,40 mL) was prepared in dry toluene (50 mL). The reaction mixture was stirred and refluxed for 8 hours with a Dean-Stark trap. Once the reaction mixture was allowed to room temperature, the precipitated solid was filtered and washed with petroleum ether. Then, it was dried to vacuum to obtain 1,90 g (7,76 mmol, 95%) of clean white and stable solid product **6**. R_f: 0,44 (2:1 petroleum ether/ethyl acetate). Mp. 207-208 ºC. Anal. calcd for $C_{16}H_{11}N_3$: C, 78,35; H, 4,52; N, 17,13. M = 245,10. Found: C, 78,16; H, 4,67; N, 17,18. GC-MS: R_t = 29,34 min; *m/z* (%): 245 ($M^{+\cdot}$, 100), 218 (12), 190 (8), 142 (18), 116 (19), 89 (14). IR (KBr): 3386 $\nu_{(NH)}$, 2222 $\nu_{(CN)}$, 1612 $\nu_{(C=N)}$, 1423 $\nu_{(C=C),}$ 1338 $\nu_{(C-N)}$ cm^{-1}.

2-*N*-[(1*H*-Indol-3-ylmethyl]aminobenzonitrile (7)

To an ethanol solution (100 mL) of 2,00 g (8,16 mmol) of the *N*-(3-indolyden)-2-cyanoaniline **6**, 1,54 g (40,7 mmol) of $NaBH_4$ in small proportions were slowly added to the reaction mixture. After the addition of the reductive agent, the reaction mixture was refluxed for 90 min. The reaction mixture was allowed to room temperature and diluted with 100 mL of distillated water to give the white precipitated solid, which was filtered and vacuum dried to obtain 1,40 g (5,97 mmol, 70%) of the product **7**. R_f 0,43 (3:1 petroleum ether/ethyl acetate).

Mp. 148-149 ºC. Anal. calcd for $C_{16}H_{13}N_3$: C, 77,71; H, 5,30; N, 16,99. M = 247,11. Found: C, 77,53; H, 5,57; N, 16,90. GC-MS: R_t = 26,42 min; *m/z* (%): 247 ($M^{+\cdot}$, 7), 207 (8), 149 (9), 130 (100), 118 (36), 102 (23), 91 (18). IR (KBr): 3402 $\nu_{(NH),}$ 3352 $\nu_{(NH\text{-}indol)}$, 2218 $\nu_{(CN)}$, 1605 $\nu_{(NH)}$, 1419 $\nu_{(C=C),}$ 1335 $\nu_{(C\text{-}N)}$ cm^{-1}; ^{1}H NMR (400 MHz): ä 8,12 (1H, br.s, H-N), 7,63 (1H, d, *J* = 7,8 Hz, 4-H_{indol}), 7,22 (1H, dd, *J* = 8,8, 6.1 Hz, 5'-H_{Ar}), 7,40-7,36 (3H, m, 2,5,6-H_{indol}), 7,17-7,3 (2H, m, 7-H_{indol}, 3'-H_{Ar}), 6,81 (1H, d, *J* = 8,3 Hz, 6'-H_{Ar}), 6,68 (1H, t, *J* = 7,5 Hz, 4'-H_{Ar}), 4,84 (1H, br.s, H-N), 4,56 (2H, d, *J* = 4,9 Hz, -CH_2) ppm. ^{13}C NMR (100 MHz): ä 150,2, 136,3, 134,6 (+), 132,3 (+), 126,5, 122,7 (+), 122,5 (+), 119,9 (+) 118,6 (+), 117,1, 116,1 (+), 112,3, 111,3 (+), 110,9 (+), 95,6, 39,4 (-) ppm.

_N_-(2-Cyanophenyl)-_N_-(1_H_-indol-3-ylmethyl)acetamide (8)

A mixture of the amine **7** (1,00 g, 4,05 mmol), acetic anhydride (1,65 g, 16,20 mmol), and Et_3N (1,22 g, 12,10 mmol) was prepared in dry toluene (20 mL). The reaction mixture was heated to 70 ºC for 3 hours. The reaction mixture was allowed to room temperature and treated with 30 mL of aqueous Na_2CO_3 and extracted with ethyl acetate (3 x 30mL). The organic layer was dried over Na_2SO_4 and after, concentrated in vacuum. The crude product was purified through silica gel preparative chromatography with petroleum ether / ethyl acetate (10:1) to obtain a white solid acetamide **8** 0,50 g (1,73 mmol, 43%). R_f 0,43 (3:1 petroleum ether/ethyl acetate). Mp. 144-145 ºC. Anal. calcd for $C_{18}H_{15}N_3O$: C, 74,72; H, 5,23; N, 14,52. M = 289,33. Found: C, 74,64; H, 5,49; N, 14,37. GC-MS: R_t = 27,94 min; *m/z* (%): 289 ($M^{+\cdot}$, 12), 246 (3), 190 (8), 172 (23), 130 (100), 118 (22), 102 (11), 77 (9). IR (KBr): 3342 $\nu_{(NH)}$, 2211 $\nu_{(CN)}$, 1701 $\nu_{(NC=O),}$ 1674 $\nu_{(N\text{-}H)}$, 1450 $\nu_{(C=C),}$ 1371 $\nu_{(C\text{-}N)}$ cm^{-1}; ^{1}H NMR (400 MHz): ä 8,44 (1H, d, *J* = 8,0 Hz, 6'-H_{Ar}); 7,57 (1H, ddd, *J* = 7,7; 7,3; 1,1 Hz, 4-H_{indol}); 7,40-7,35 (4H, m, 5,7-H_{indol}, 4',5'-H_{Ar}); 7,31 (ddd, *J* = 7,7; 7,3; 1,1 Hz, 6-H_{indol}); 6,76-6,71 (2H, m, 2-H_{indol}, 3'-H_{Ar}); 4,95 (1H, br.s, H-N); 4,55 (2H, s, CH_2); 2,58 (3H, s, Me) ppm. ^{13}C NMR (100 MHz): ä 168,6; 149,2; 136,2; 134,1 (+); 132,8 (+); 128,9; 125,7 (+); 123,8 (+); 123 (+); 118,9 (+); 118,7 (+), 117,7; 117,2 (+), 116,4; 111,5 (+), 96,2; 39,3 (+); 23,9 (-) ppm.

_N_-(1-Acethyl-1_H_-indol-3-ylmethyl)-_N_-(2-cyanophenyl)acetamide (9)

A mixture of the amine **7** (0,50 g, 2,02 mmol), acetic anhydride (10,80 g, 98 mmol), and Et_3N (0,44 g, 4,30 mmol) was heated to 100 ºC for 3 hours. Then, the reaction mixture was allowed to room temperature and treated with 50 mL of aqueous NaOH and extracted with ethyl acetate (3 x 30 mL). The organic layer was dried over Na_2SO_4 and later dried in vacuum. Silica gel preparative chromatography (petroleum ether / ethyl acetate, 2:1) of the crude product afforded diacetamide **9** (0,53 g, 80%) as a white and stable solid. R_f 0,50 (petroleum ether/ethyl acetate, 1:1). Mp. 124-125 ºC. Anal. Calcd for $C_{20}H_{17}N_3O_2$: C, 72,49; H, 5,17; N, 12,68. M = 331,13. Found: C, 72,23; H, 5,33; N, 12,35. GC-MS: R_t = 28,52 min; *m/z* (%): 331 ($M^{+\cdot}$, 12), 289 (7), 246 (7), 172 (9), 130 (100), 118 (10), 102 (7), 77 (7). IR (KBr): 2229 $\nu_{(CN)}$, 1704 $\nu_{(NC=O),}$ 1654 $\nu_{(NC=O),}$ 1658 $\nu_{(N\text{-}H)}$, 1454 $\nu_{(C=C),}$ 1348 $\nu_{(C\text{-}N)}$ cm^{-1}. ^{13}C NMR (100 MHz): ä 169,4, 168,5, 144,7, 135,6, 134,4 (+), 133,9, 130,3 (+), 129,3, 128,8 (+), 125,4 (+), 123,7 (+), 118,9 (+), 117,3; 116,5 (+), 115,8; 113,1; 42,8 (-), 23,9 (+), 22,4 (+) ppm.

RESULTS AND DISCUSSION

Aldimines are valuable starting materials, not only for different N-containing heterocycles but also to diverse secondary heteroaromatic amines,[7] which represent good candidates for bio-screening with diverse types of activities.[8,9] Thus, the *N*-aryl- imine **6**, the main starting material in this research, was prepared from commercially available 3-indolaldehyde (**4**) and 2-cyanoaniline (**5**), according to published methods.[10,11] This aldimine was obtained in 95 % as a white and stable solid. Since the reduction of aldimines with an excess of $NaBH_4$ in methanol is still the reaction of choice to produce the secondary amines in reasonably good yield, we employed this method in our work. Thus, *N*-(2-cianophenyl)-*N*-(3-indolylmethyl)amine (**7**) was prepared as a white solid in 70 % yields after purification through recrystallization (figure 2). This amine has interesting structural elements to use in the synthesis of different indolic heterocycles. So, we studied its acetylation reaction with acetic anhydride. First, to a stirred solution of amine **7** in toluene as solvent and in the presence of Et_3N, excessive acetic anhydride is added and refluxed for appropriate time to allow the *N*-(2-cianophenyl)-*N*-(3-indolmethyl)acetamide (**8**) synthesis in acceptable yields (45-50 %). Then, acetylating reaction between the amine and excess acetic anhydride in the presence of Et_3N at 100 °C without organic solvent (toluene) was performed. After usual workup, diacetylated indole **9** was obtained in good yields (80-85 %). So, a simple change in the reaction conditions could afford different acetamides based on the 3-indolyl methanamine motif (figure 2). This developed selective process represents a good protocol to the synthetic organic chemistry, especially within those processes requiring a particular position protection.

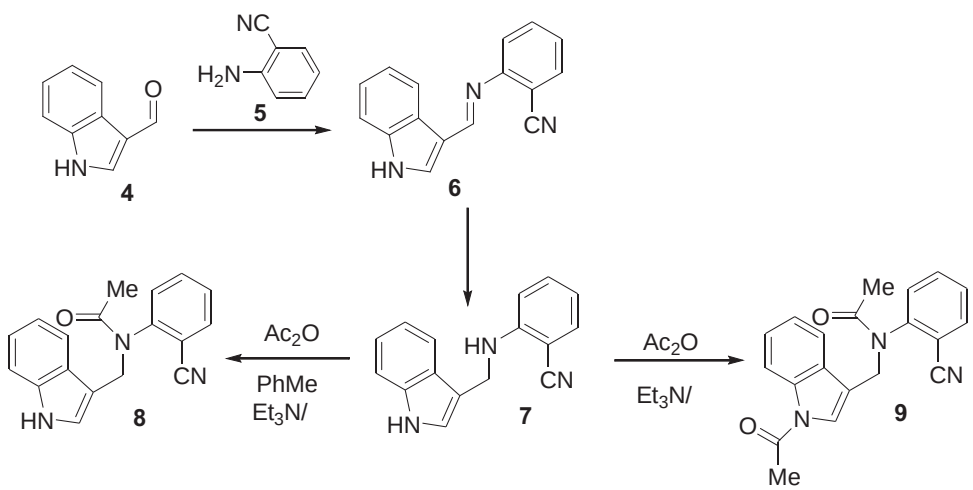

Figure 2. Preparation of *N*-aryl-*N*-(3-indolmethyl)acetamides

The structures of the C-3 substituted indoles **7-9** were confirmed on the basis of analytical and spectral data and were supported by inverse-detected 2D NMR experiments. The compound **7** ir spectrum characteristic absorption bands were observed at 3402 and 3352 cm^{-1}, assignable to tension vibrations CH_2-N-H and N-H_{indol}, respectively. Its ^{1}H NMR spectrum displays a duplet at 4,56 ppm (J = 4,9 Hz) ppm corresponding to two protons coupling with the neighbor N-H proton (br. s, 4,84 ppm), which suggest the presence of the methylenic unit linked to the N-H function. The peaks at 7,17-7,3 (H-7); 7,36-7,40; 7,40-736 (H-5, H-2, H-6), and 7,63 (H-4) ppm showed the presence of aromatic protons of the indole moiety. The ^{13}C NMR spectra, also shows all expected characteristic peaks at 39,4 (CH_2), 117 (CN), and 95,6-150,2 (aromatic carbons).

The compound **8** gave a molecular ion peak $M^{+\cdot}$, at *m*/*z* 289, suggesting the molecular formula $C_{18}H_{15}N_3O$, and indicating the acetyl group coupling with **7**. The acetamide **8** displayed characteristic infrared absorption bands with a single amine absorption band at 3342 cm^{-1} and with a carbonyl sign at 1701 cm^{-1} suggesting the acetylation reaction involvement of the CH_2-N; this is the band appearing at high wave number of the corresponding N-H_{indol} vibration tension in the IR spectrum. Its ^{1}H NMR spectra analysis showed a singlet at 2,58 ppm corresponding to three protons which belong to the acetyl group and another singlet at 4,55 ppm due to the presence of the methylenic 3-CH_2-N indolic protons. This signal's multiplicity is explained by assuming the proton N-H next to it, substituted now for the acetyl group, which leaves no possibility to H,H coupling, while it does happen with the amine **7**. The ^{13}C NMR spectrum of **8** displayed characteristic carbonyl signal at 168 ppm, this is strong evidence to an acetyl group bonded to the molecule; in addition to a signal at 39,3 and 23,9 ppm, showing the presence of CH_2 and CH_3 in the molecule. Introduction of an acetyl group into the molecule affects the H-6' chemical shift from the aromatic moiety, this is 116 ppm to the compound **7** an 123 ppm to the acetamide **8**. The signal at 39,3 ppm for CH_2-N has been distinguished on the basis of the DEPT-135 experiment. On the basis of these spectral studies, compound **8** was characterized as the *N*-(2-cyanophenyl)-*N*-(1*H*-indol-3-ylmethyl)acetamide.

The new compound **9** gave a molecular ion peak at *m*/*z* 331, corresponding to the molecular formula $C_{20}H_{17}N_3O_2$ as indicated by its EI-MS. The loss of 43 units (one acetyl group) generates the same mass spectrum as the acetamide **8**. The IR spectrum shows bands at 1704 and 1654 cm^{-1}, assignable to two carbonyl groups. The N-H absorption bands were not observed in the region of 3300-3400 cm^{-1}. The ^{1}H NMR spectrum showed, as expected, two singlets at 22,4 and 23,9 ppm, which integrated three protons each. To the methylenic protons case, they appeared to be diasterotopic resonating at the high field frequencies 4,75 and 5,46 ppm with a coupling constant J = 15 Hz, usual constant value to a germinal coupling. Of course, the aromatic protons were also assigned. The ^{13}C NMR spectrum showed all expected characteristic peaks at 169,4 (ArN-CO-), 168,5 (Ar_{indol}N-CO-) ppm, in addition to a signal at 117,3 ppm showing the presence of CN in the molecule. Besides, methyl carbons at 23,9 (Ar_{indol}NCO-CH_3) and 22.4 (ArNCO-CH_3) ppm and the methylene carbon at 42,8 ppm were also displayed in the ^{13}C NMR.

CONCLUSSIONS

N-aryl-*N*-(3-indolmethyl)acetamides incorporating the indolic core, structural analogues of some natural alkaloids. The acylation method is worth as a regioselective process because the conditions variations lead to the mono- or di-acetamide. The compounds characterization through different techniques gives evidence enough and strong support with regard to the success of the proposed scheme.

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REFERENCES

1. Sundberg R.J. **The Chemistry of Indoles**; Academic Press: San Diego, 1996.
2. a) Wynne J.H, Stalick W.M. J. Org. Chem. 67, 5850, (2002); b) Molina. P, Alcantara. J, Lopez-Leonardo. C. *Tetrahedron* 1996; 52: 5833.
3. **Phytochemical Dictionary. A Handbook of Bioactive Compounds from Plant***s*, Ed. Harborne J.B., Baxter H. Taylor & Francis: London-Washington DC, 1993; p. 164.
4. a) Snyder H.R, Smith C.W, Sterwart. J.M. *J. Am. Chem.* Soc. 1944; 66: 200; b) Brehm W.J, Lindwall H.G. *J. Org. Chem.* 1950; 15: 685; c) Dai H.-G, Li J.-T, Li T.-S. *Synth. Commun.* 2006; 36: 1829.
5. a) Ke B, Qin Y, He Q, Huang Z, Wang F. *Tetrahedron Lett.* 2005; 46: 1751; b) Zhao J.-L, Liu L, Zhang H.-B, Wu Y.-C, Wang D, Chen Y.-J Synlett. 2006; 96; c) Jiang B, Huang Z.-G, Synthesis 2005; 2198; d) Shirakawa S, Kobayashi S. *Org. Lett.* 2006; 8: 4939.
6. a) Kouznetsov V.V, Vargas Méndez L.Y, Tibaduiz B, Ochoa C, Montero Pereira D, Nogal Ruiz J.J, Portillo C.F, Gómez A.B, Bahsas A, Amaro-Luis *J. Archiv der Pharmazie* 2004; 337: 127; b) Kouznetsov V, Rodríguez W, Stashenko E, Ochoa C, Vega C, Rolón M, Montero Pereira D, Escario J. A, Gómez Barrio A. *J. Heterocycl. Chem.* 2004; 41: 995; c) Vargas M.L.Y, Castelli M.V, Kouznetsov V.V, Urbina G.J.M, López S.N, Sortino M, Enriz R.D, Ribas J.C, Zacchino S.A. Bioorg. *Med. Chem.* 2003; 11: 1531.
7. Hutchins R.O, Hutchins M.K. **Comprehensive Organic Synthesis,** Pergamon Press: Oxford, 1991. p. 25-78.
8. Kleemann A, Engel J. **Pharmaceutical Substances,** Thieme: New York, 1999.
9. Evers A, Hessler G, Matter H, Klabunde T. *J. Med. Chem.* 2005; 48: 5448.
10. Billman J.H, Diesing A.C. *J. Org. Chem.* 1957; 22: 1068.
11. Layer R.W. *Chem. Rev.* 1963; 63: 489.