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INSERTION OF ISOPRENE UNITS INTO INDOLE AND 3-SUBSTITUTED INDOLES IN AQUEOUS SYSTEMS

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Abstract—Indole (**1**) and 3 - methylbut - 2 - enyl bromide (**2**) were reacted in aqueous solution over a wide range of pH, in absence of Lewis catalysts, leading to 3 - (3' - methylbut - 2' - enyl) indole (**3**), 2,3 - di - (3' - methylbut - 2 - enyl) indole (**4**) and to 2 - (3 - indolyl) - 3,3 - di - (3' - methylbut - 2' - enyl) - 2,3 - dihydroindole (**6**) in acidic buffer, whereas compound **6** was not formed at basic pH. Both the reactivity and the selectivity of the reaction appear to be influenced by the acidity of the medium. The reaction extended to biologically significant 3-substituted indoles gave a series of new products. 3-Substituted indoles bearing a basic group at their β-position (**7**, **11**, **12** and **13**) in acetic buffer (pH = 3) gave mainly cyclization to dihydrofurano or dihydropyrrolo [2.3-b] indoles (**15**, **16**, **20**, **21** and **23**), whereas those with the basic group at the γ-position (**9**, **10**) gave the 2 - (3 - methylbut - 2 - enyl) indole derivatives (**18**, **19**) only.

Alkylation with alkyl halides and related alkylating agents was extensively studied in aprotic media either on indole or on indole salts.[1] The tightness of the ion pair metal cation/indole anion was shown to affect strongly the reactivity and the selectivity of the reaction (C vs N alkylation).[2] In the presence of Friedel–Krafts catalysts, electrophilic substitution at the 3-position mainly occurs although with scarce yields, presumably because of the tendency of both the starting material and the product towards polialkylation and polimerization under acidic conditions.[3] Particular attention was also paid to the reaction in protic acidic media with benzyl halides with the purpose of obtaining a selective attack at the tryptophan moiety of a peptide or protein chain (Koshland reaction).[4]

However, no report has been made, as far as we know, on the direct alkylation of indole with allyl derivatives in protic media. The problem is of particular interest in connection with the biosynthesis of important classes of natural products (Ergot alkaloids,[5] echinulin,[6] neoechinulins,[7] etc.) and may provide a useful tool for the selective modification of tryptophan-containing proteins.

From preliminary tests, we observed that indole was scarcely reactive towards allyl alcohols and allyl halides at pH 3 (acetic buffer),† as well as at higher pHs. Among the reagents which gave positive results, i.e. the alkyl-substituted allyl halides, such as crotyl, prenyl and geranyl bromides, 3 - methylbut - 2 - enyl bromide appeared to be the most suitable to our study for its reactivity and for its similarity with the corresponding pyrophosphate, the natural prenylating agent.[8]

In a homogeneous and buffered medium (acetic acid/sodium acetate pH = 3) indole (**1**) reacted with 3 - methylbut - 2 - enyl bromide (**2**) (molar ratio 1:1) and gave the 3 - (3' - methylbut - 2' - enyl) indole as expected, and two byproducts: the 2,3 - di - (3' - methylbut - 2' - enyl) indole (**4**) and the 2 - (3 - indolyl) - 3,3 - (3' - methylbut - 2' - enyl) - 2,3 - dihydro indole (**6**) (which could be obtained and separated in a better yield by using a higher prenyl bromide:indole molar ratio), and traces of other monosubstituted indoles (total yield <5%). The relative yields of the products were obtained by combined GLC and NMR analyses. Compound **3** was already known,[9] compound **4** was identified, after hydrogenation to 2,3 - di - (3' - methylbutyl) indole (**4'**), by comparison with an authentic specimen otherwise synthesized (Experimental); the structure of **6** was elucidated by chemical and spectral methods.

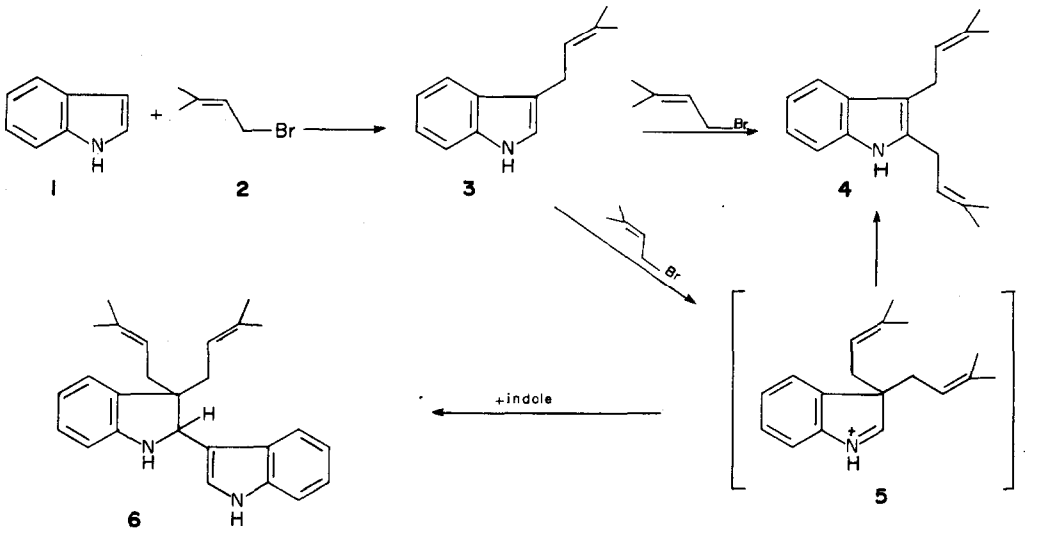
The following mechanism may account for the results obtained: the initially formed 3 - methylbut - 2 - enyl indole (**3**) reacts competitively with the alkylating agent, either directly at the 2-position[10] leading to **4** or at the 3-position leading to the corresponding indolenine (**5**). Under the above reaction conditions the (at least partially) protonated indolenine may either rearrange[11] to **4** or give an electrophilic attack onto an electron-rich substrate such as the unreacted indole, affording the indoline (**6**). The capability of 3,3-dialkylindolenines to act as electrophilic agents was verified by reacting 3,3 - dimethyl-indolenine with a series of electron-rich aromatic systems (indoles, pyrroles, phenols), and obtaining the corresponding 2 - aryl- (or heteroraryl) - 3,3 - dimethyl - 2,3 - dihydro indoles.[12] The reaction was developed synthetically to provide a simple, though general, method for the indolinylization of aromatic systems.

On the base of the above reported results, the following general scheme for indole alkylation in protic acid medium may be outlined (see Scheme 1).

Indeed, the reaction was influenced by the pH of the medium (indole conversion at pH = 3 61%; at pH = 5 49%; at pH = 10 43%). Prenylation occurred more extensively as the acidity of the buffer increased, probably on account of the decreased nucleophilicity of the medium and of the increased electrophilicity of the prenylating agent, due to the greater solvation of the leaving group.

The selectivity of the reaction appears strongly affected by the pH: in the basic buffer (pH = 10) the unprotonated intermediate indolenine cannot give the electrophilic attack at indole and therefore the indoline (**6**) is not formed. The scarce, though detectable amount (2%) of 2,3 - di - (3' - methylbut - 2' - enyl) indole (**4**) may

†For buffer composition see Experimental.



Scheme 1.

rather derive from a direct attack at the 2-position of the 3-substituted indole.

However, practically only C-attacks were observed (at the 3- or 2-position) whereas N-prenyl derivatives were not obtained, as expected on account of the shielding effect exerted by the cation H^+ and by the solvent on the nitrogen.

Actually, a prevalent N-attack (64%) by the same reagent was observed in strongly basic medium in the presence of quaternary ammonium salts.[13]

The reaction (at pH 3) was then extended to biologically significant 3-substituted indoles in order to develop biogenetic-type syntheses.

When a basic group was present at the β-position of the 3-substituent, (**7**, **11**, **12**, **13**) cyclic derivatives (dihydrofurano or pyrrolo[2,3-b]indoles) were mainly obtained (**15**, **16**, **20**, **21**) by intramolecular nucleophilic attack onto the 2 position of the protonated indolenine, together with a lesser amount of the 2-substituted derivatives (**14**, **22**). Apparently, the propionic acid methyl ester (**10**) was not sufficiently basic to give the cyclization.

In contrast, when the basic group was located at the γ-position of the 3-substituent (**9**, **10**), no cyclization products, but only 2-prenyl derivatives were obtained (**18**, **19**) (see Table 1).

With the available cyclo - L - alanyl - L - tryptophyl (**13**), known precursor in the biosynthesis of echinulin[14] and neoechinulins,[15] compound **23** was obtained as major product. This structure may be connected with brevianamide E.[16]

EXPERIMENTAL

All m.ps were determined on a Büchi apparatus and are uncorrected. UV spectra for solns in 95% EtOH were determined using a Cary 17 spectrometer. IR spectra (KBr) were determined using a Perkin–Elmer 457 spectrometer. NMR spectra were obtained with Varian XL 100 and Jeol C 60 HL spectrometers, using $CDCl_3$ solns and TMS as internal standard (the chemical shifts are expressed in ppm). Mass spectra were determined on a Varian-MAT CH 5 spectrometer, using direct insertion probe (70 eV). GLC was performed on a Varian 1400 Aerograph, flame ionization detector, with a 10 ft × 0.125 XE 60 5% (60–80 mesh) Chromosorb G column. TLC experiments were carried out on Merck silica gel GF_{254} plates. Preparative TLC was carried out on 1 mm thick layers. All the compounds described gave satisfactory C, H, N, microanalyses.

Buffers composition. The following solns were used: acetic (sodium acetate:acetic acid:water, 8 g:100 ml:20 ml-pH 2.7); citric (citric acid:2 N NaOH:EtOH, 21 g:120 ml:120 ml-pH 5.6); carbonate (sat hydro-alcoholic (1:1) solution of Na_2CO_3-pH 11.8). The buffer capacities of the three solutions were verified by titration with a standard solution of 1 N HCl.

Reactions of indole (**1**) *with* 3 - *methylbut* - 2 - *enyl bromide* (**2**) *in acetic buffer.* To a stirred soln of indole (0.0037 mol) in 25 ml of buffer soln 3 - methylbut - 2 - enyl bromide (0.0037 mol) was added under N_2 at room temp.

After 5 hr the mixture was diluted with water (100 ml), neutralized with sat $NaHCO_3$ aq, and extracted with ethyl ether. The combined extracts were reduced to small bulk and separated by preparative TLC (hexane:EtOAc, 8:2). Compounds **3** and **6** were thus separated and identified: compound **3** was already known;[9] compound **6** was identified as follows: ν_{max} 3450 (indole NH), 3300 sh (indoline NH) cm^{-1}; λ_{max} 220 sh (4.48), 278 (4.03), 288 (3.97) nm: δ 1.04 (3H, s), 1.51 (3H, s), 1.58 (3H, s), 1.67 (3H, s), 2–2.6 (4H, m), 3.65 (1H, broad s, indoline NH), 4.94 (1H, t, J = 7 Hz), 5.07 (1H, s), 5.18 (1H, t, J = 7 Hz), 6.4–7.5 (9H, m, aromatics), 8 (1H, s, indole NH); *m/e* 370 (M^+), 301, 232; (Found: C, 84.05; H, 7.58; N, 7.47; $C_{26}H_{30}N_2$ requires: C, 84.28; H, 8.16; N, 7.56%). 2,3 - Di - (3' - Methylbut - 2' - enyl) indole (**4**): *m/e* 253 (M^+), 238, 184, 182, 168, 130, 117, could not be isolated in good yield for spectral analysis because of its easy oxydability. It could be identified only after hydrogenation with Pd/C (5%) at room temp. and by comparison with an authentic sample otherwise synthesized (see below).

The composition of the mixture was evaluated by GLC (programmed temp. from 100° to 240° at a 6°/min rate, using indole as internal standard and by NMR; yields: unreacted indole (**1**) 39%; **3** 30%; **4** 11%; **6** 17%.

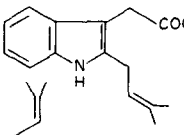
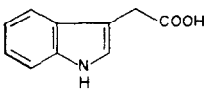
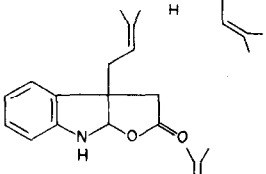
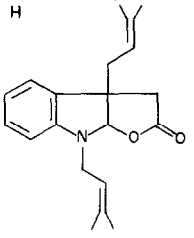
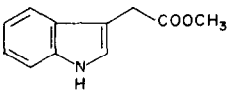
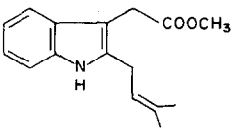
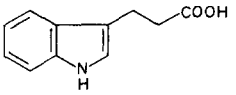
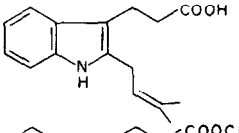
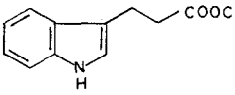
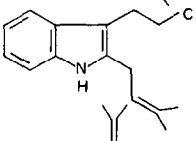
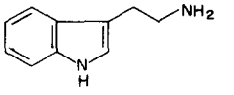
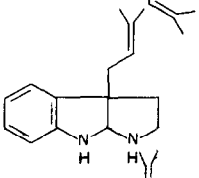
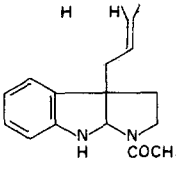
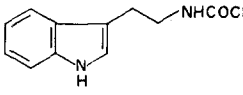
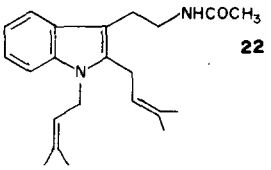
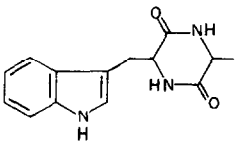
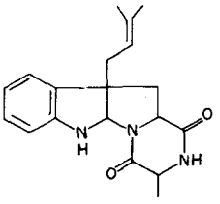
In citric buffer. The same procedure was used as for the acetic buffer, except for the neutralization with $NaHCO_3$; yields: **1** 51%; **3** 21%; **4** 5%; **6** 10%.

In carbonate buffer. As for the citric buffer; yields: **1** 57%; **3** 20%; **4** 2%.

2,3 - *Di* - (3' - *methylbutyl*) *indole* (**4'**). Compound **3** (0.002 mol) in acetic buffer was reacted with 3 - methylbut - 2 - enyl bromide (0.003 mol) for 24 hr at room temp. under N_2. The mixture was neutralized with $NaHCO_3$, extracted with ether, evaporated to dryness, and hydrogenated in EtOH with Pt/PtO_2 at room temp. for 3 hr. The product was purified by TLC (hexane:EtOAc, 9:1); yield 80%; *m/e* 257 (M^+), 200, 144, 130; δ 0.87 (3H, s), 1.0 (3H, s), 1.2–1.8 (6H, m), 2.60 (2H, t, J = 7 Hz), 2.7 (2H, t, J = 7 Hz), 6.8–7.5 (4H, m aromatic H), 7.8 (1H, broad s, NH); (Found: C, 83.60; H, 10.51; N, 5.35. $C_{18}H_{27}N$ requires: C, 83.98; H, 10.57; N, 5.44%).

Reaction of 3 - *methylbut* - 2 - *enyl bromide with* 3-*substituted indoles* (**7–13**) *in acetic buffer.* To a stirred soln of 3-substituted indoles (0.002 mol) in acetic buffer (40 ml) 3 - methylbut - 2 - enyl

Table 1. Reaction of 3-substituted indole derivatives with 3-methylbut-2-enyl bromide in acetic buffer

	Substrates	Molar ratio[a]	Products[b]		Yield
				14	42%[c]
7		1 : 4		15	37.1%
				16	12.6%
8		1 : 4		17	64%
9		1 : 4		18	63%
10		1 : 4[d]		19	64%
11		1 : 3		20	72%
				21	65%
12		1 : 4		22	15%
13		1 : 1		23	15%

[a] Molar ratios were all >1 because of the less reactive substrates.

[b] Only the most relevant products were isolated and characterized; however the difference to 100 is mostly unreacted starting material.

[c] Unreacted starting material 14.8%.

[d] With a ratio of 1:10 the yield of **19** was 89%.

bromide (0.008 mol) was added dropwise under N_2, at room temp. After 5 hr the mixture was poured into water (200 ml) and extracted with ethyl ether. The combined ethereal extracts were washed several times with a sat $NaHCO_3$ aq soln, which was subsequently acidified with dil. HCl, and extracted with EtOAc. Both the ethereal and the EtOAc extracts were dried and separately evaporated to small bulk.

With indole - 3 - acetic acid (**7**). From the EtOAc extracts, by preparative TLC (EtOAc:*i*-PrOH:conc. NH_3, 10:10:4) compound **14** was obtained (yield 42.5%) which was crystallized from hexane:EtOAc (m.p. 80–81°): ν_{max} 3300 (NH), 3100 (OH), 1660 (C=O) cm^{-1}; λ_{max} 227 (4.52), 284 (3.87), 291 (3.82); δ 1.7 (6H, s), 3.35 (2H, d, J = 7 Hz), 3.6 (2H, s), 5.25 (1H, broad t, J = 7 Hz), 6.8–7.8 (4H, m, aromatic H), 7.95 (1H, broad NH), 8.5 (1H, s, OH); *m/e* 243 (M^+), 198, 184, 130; (Found: C, 73.95; H, 6.94; N, 5.68. $C_{15}H_{17}O_2N$ requires: C, 74.05; H, 7.04; N, 5.76%).

From the ethereal extracts, by preparative TLC (hexane:EtOAc, 6:4) compound **15** (yield 37%) and compound **16** (yield 16.6%) were obtained, together with 7.5% of unreacted starting material. Compound **15**: ν_{max} 3340 (NH), 1750 (C=O), 1190 (COOR) cm^{-1}; λ_{max} 319 (4.30), 242 (3.25), 293 (3.13); δ 1.55 (3H, s), 1.72 (3H, s), 2.42 (2H, d, J = 7.5 Hz), 2.88 (2H, s), 5.1 (1H, broad t, J = 7.5 Hz), 5.65 (1H, s), 6.0 (1H, s, NH), 6.5–7.3 (4H, m, aromatic H); *m/e* 243 (M^+), 198, 184, 168, 156, 143, 130, 115; (Found: C, 73.83; H, 6.90; N, 5.55. $C_{15}H_{17}O_2N$ requires: C, 74.05; H, 7.04; N, 5.76%). Compound **16**: ν_{max} 1770 (C=O), 1150 (COOR) cm^{-1}; λ_{max} 248 (3.98), 298, (3.49); δ 1.55 (3H, s), 1.72 (9H, s), 2.42 (4H, m), 2.88 (2H, s), 3.95 (2H, d, J = 7 Hz), 5.0–5.5 (2H, m), 5.6 (1H, s), 6.4–7.4 (4H, m, aromatic H); *m/e* 311 (M^+), 266, 243, 198, 184, 182, 168, 130; (Found: C, 77.05; H, 7.95; N, 4.40. $C_{20}H_{25}O_2N$ requires: C, 77.14; H, 8.10; N, 4.49%).

With indole - 3 - acetic acid methyl ester (**8**). From the ethereal extracts, by preparative TLC (hexane:EtOAc, 6:4) compound **17** was obtained. The yield (64%) was determined by GLC at 200° using n-butyl phtalate as internal standard: ν_{max} 3350 (NH), 1710 (C=O) cm^{-1}; λ_{max} 227 (4.53), 284 (3.88), 291 (3.83); δ 1.8 (6H, s), 3.5 (2H, d, J = 7.5 Hz), 3.7 (3H, s), 3.76 (2H, s), 5.35 (1H, broad t, J = 7.5 Hz), 6.9–7.7 (4H, m, aromatic H), 7.9 (1H, broad s, NH); *m/e* 257 (M^+), 198, 184, 149, 130; (Found: C, 74.50; H, 7.22; N, 5.40. $C_{16}H_{19}O_2N$ requires: C, 74.68; H, 7.44; N, 5.44%).

With indole - 3 - propionic acid (**9**). From the ethereal extracts by preparative TLC (EtOAc:i-PrOH:conc. NH_3, 10:10:4) compound **18**, m.p. 82–83° (white needles from hexane/EtOAc), was obtained; the yield (63%) and unreacted acid (14.8%) were determined by GLC at 200° using n-butyl phtalate as internal standard: ν_{max} 3400 (NH), 1710 (C=O) cm^{-1}; λ_{max} 230 (4.15), 284 (3.23), 291 (3.16); δ 1.75 (3H, s), 1.85 (3H, s), 2.35–3.30 (4H, m), 3.45 (2H, d, J = 7.5 Hz), 5.3 (1H, t, J = 7.5 Hz), 6.6–7.75 (4H, m, aromatic H), 8.0 (1H, s, NH), 9.7 (1H, s, OH); *m/e* 257 (M^+), 198, 184, 156, 143, 130; (Found: C, 74.60; H, 7.25; N, 5.35. $C_{16}H_{19}O_2N$ requires: C, 74.68; H, 7.44; N, 5.44%).

With indole - 3 - propionic acid methyl ester (**10**). From the ethereal extracts, by preparative TLC (hexane:EtOAc, 6:4), compound **19** as colourless oil was obtained. The yield (64%) was determined by GLC at 200° using n-butyl phtalate as internal standard:† ν_{max} 3400 (NH), 1730 (C=O) cm^{-1}; λ_{max} 221 (4.25), 285 (3.40), 291 (3.26); δ 1.7 (6H, s), 2.4–2.9 (2H, m), 2.9–3.3 (2H, m), 3.45 (2H, d, J = 7.5 Hz), 3.62 (3H, s), 5.3 (1H, t, J = 7.5 Hz), 6.9–7.7 (4H, m, aromatic H), 7.82 (1H, broad s, NH); *m/e* 271 (M^+), 198, 184, 130; (Found: C, 75.10; H, 7.60; N, 5.20. $C_{17}H_{21}O_2N$ requires: C, 75.24; H, 7.80; N, 5.16%).

With tryptamine (**11**). From the ethereal extracts by preparative TLC ($CHCl_3$:EtOH, 2:1) compound **20** was obtained as a colourless oil. The yield (72%) was determined by GLC analysis of the ethereal extracts acetylated with Ac_2O at 230° using bis - (2 - hydroxy - 3,4 - dimethyl) diphenyl methane as internal standard. Compound **20**: ν_{max} 3300 (NH); λ_{max} 207 (4.02), 243 sh (3.49), 282 (3.34); δ 1.5 (3H, s), 1.62 (3H, s), 2.42 (2H, d, J = 7 Hz), 1.8–3.3 (4H, m), 3.6 (2H, s, NH), 4.8 (1H, s), 5.08 (1H, t, J = 7 Hz), 6.3–7.3 (4H, m, aromatic H); *m/e* 228 (M^+), 198, 171, 159, 130; (Found: C, 78.70; H, 8.80; N, 12.33. $C_{15}H_{20}N_2$ requires: C, 78.90; H, 8.83; N, 12.27%).

†Compound **19** was obtained with a yield of 90% by using a ratio **10**/**2** 1:10.

Diacetyl derivative (**20'**). ν_{max} 1670 (C=O) cm^{-1}; λ_{max} 245 (4.02), 275 (3.28), 283 (3.22); δ 1.55 (3H, s), 1.7 (3H, s), 2.05 (3H, s), 2.4 (2H, d), 2.6 (3H, s), 2–4.0 (4H, m), 5.0 (1H, t, J = 7.5 Hz), 5.9 (1H, s), 7–8.3 (4H, m, aromatic H); *m/e* 312 (M^+), 270, 201, 159, 130; (Found: C, 72.93; H, 7.71; N, 8.70. $C_{19}H_{24}O_2N_2$ requires: C, 73.05; H, 7.74; N, 8.97%).

With N-acetyltryptamine (**12**). From the ethereal extracts by preparative TLC ($CHCl_3$:EtOAc, 8:2) compounds **21** m.p. 94–95° (65%) and **22** (15%) were obtained. Compound **21**: ν_{max} 3300 (NH), 1670 (C=O) cm^{-1}; λ_{max} 242 (3.92), 296 (3.43); δ 1.52 (3H, s), 1.72 (3H, s), 1.98 (3H, s), 1.9–2.6 (2H, m), 2.9–3.7 (2H, m), 5.2 (1H, t, J = 7 Hz), 5.23 (1H, s), 5.28 (1H, broad s, NH), 6.3–7.3 (4H, m, aromatic H); *m/e* 270 (M^+), 201, 159, 130; (Found: C, 75.20; H, 8.13; N, 10.05. $C_{17}H_{22}ON_2$ requires: C, 75.52; H, 8.20; N, 10.36%). Compound **22**: ν_{max} 3300 (NH), 1650 (C=O) cm^{-1}; λ_{max} 230 (4.48), 287 (3.85), 295 (3.84); δ 1.5–1.8 (12H, 4s), 1.86 (3H, s), 2.92 (2H, t, J = 6 Hz), 3.45 (2H, t, J = 6 Hz), 3.48 (2H, d, J = 6.5 Hz), 3.90 (2H, d, J = 6.5 Hz), 5.0–5.2 (2H, m), 6.3–7.4 (4H, m, aromatic H); (Found: C, 77.95; H, 8.75; N, 8.25. $C_{22}H_{30}ON_2$ requires: C, 78.06; H, 8.93; N, 8.27%).

With cyclo - L - alanyl - L - tryptophyl (**13**). From the EtOAc extracts by preparative TLC (diisopropyl ether: $CHCl_3$:AcOH, 6:3:1) two diastereoisomeric compounds were obtained (15%) together with 80% of unreacted starting material. Compound **23**: δ 1.38 (3H, d, J = 7 Hz), 1.55 (3H, s), 1.64 (3H, s), 2.4 (2H, d, J = 7 Hz), 2.44 (2H, d, J = 8 Hz), 4.01 (1H, q, J = 7 Hz), 4.24 (1H, t, J = 8 Hz), 5.05 (1H, t, J = 7 Hz), 5.24 (1H, s), 5.76 (1H, s), 6.44–7.28 (4H, m, aromatic H); *m/e* 325 (M^+), 256, 202, 157, 149, 130. Compound **23'**: δ 1.40 (3H, d, J = 6.6 Hz), 1.46 (3H, s), 1.64 (3H, s), 2.34 (2H, d, J = 7.6 Hz), 2.24 (1H, dd, J_{gem} = 14 Hz, J_{vic} = 12 Hz), 2.59 (1H, dd, J_{gem} = 14 Hz, J_{vic} = 6 Hz), 3.97 (1H, m), 4.16 (1H, q, J = 6.6 Hz), 5.02 (1H, broad s, NH), 5.06 (1H, t, J = 7.6 Hz), 5.25 (1H, s), 5.84 (1H, broad s, NH), 6.4–7.6 (4H, m, aromatic H); *m/e* 325 (M^+), 256, 167, 157, 149, 130.

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