Preparation, X-ray Crystal Structure and ^{13}C- and ^{1}H-NMR Study of 1-Methyl-2-(*N*-methyl-*N*-phenylglycyl)-3-(*N*-methylanilino)indole

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Reaction of *N*-methylaniline with 40% glyoxal yields 1-methyl-2-(*N*-methyl-*N*-phenylglycyl)-3-(*N*-methylanilino)indole (**1a**) as the main product together with 1-methyl-3-(*N*-methylanilino)indole (**1b**). The reaction appears to be general for aromatic secondary amines since *N*-ethylaniline and *N*-phenylbenzylamine yield the corresponding indoles. The structure of **1a** has been verified by single crystal X-ray diffraction. Compound **1a** ($C_{25}H_{25}N_3O$) crystallized in the triclinic space group $P\bar{1}$ with cell dimensions a = 10.085(3) Å, b = 10.371(3) Å, c = 11.908(5) Å, α = 74.2(3)°, β = 74.7(3)° and γ = 60.7(2)° with Z = 2. The complete ^{1}H and ^{13}C nmr assignment of indoles **1a** and **1b** was achieved from two-dimensional HETCOR and COSY spectra with the aid of homonuclear and heteronuclear double resonance experiments.

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Introduction.

The pharmacological interest of indoles lead us to reinvestigate [1-3] the reaction of several secondary anilines, which include *N*-methylaniline, *N*-ethylaniline and *N*-phenylbenzylamine, with 40% aqueous glyoxal as a route to 3-*N*-substituted indoles.

Results and Discussion.

Reaction of *N*-methylaniline with 40% aqueous glyoxal in ethanol at 70° during 16 hours yields 1-methyl-2-(*N*-methyl-*N*-phenylglycyl)-3-(*N*-methylanilino)indole (**1a**) as the main product, as established by single crystal X-ray diffraction studies (Figure 1). The known 1-methyl-3-(*N*-methylanilino)indole (**1b**) is also obtained in agreement with previous reports [1-3]. Similarly, reactions of *N*-ethylaniline and of *N*-phenylbenzylamine yield indoles **1c** and **1d**, respectively.

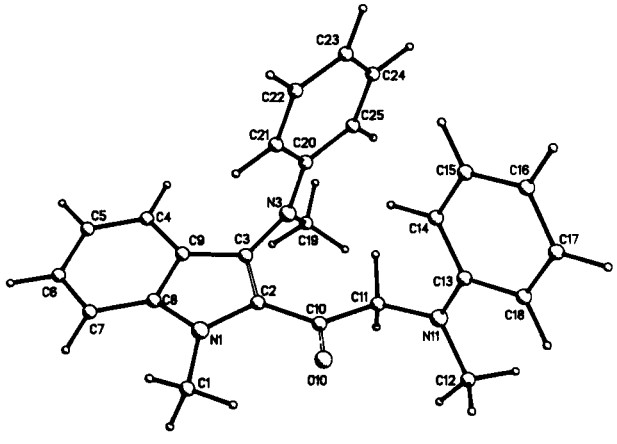


Figure 1. Molecular perspective view of **1a**. The atom labelling is different from the chemical nomenclature of **1a**.

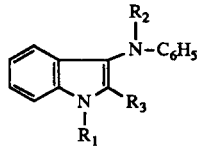
Table 1

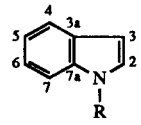
Carbon-13 NMR Data of Indole Derivatives (in ppm at 75.43 MHz)

	1a	**1b**	**1c**	**1d**	**2a** [a]	**2b**
Indole-*N*-phenyl						
C-2	130.0	124.3	123.9	124.7	126.7	128.2
C-3	130.8	124.4	122.4	123.8	100.8	101.6
C-3a	122.8	124.2	125.3	124.7	128.6	128.7
C-4	121.0	119.0	119.3	119.4	120.7	120.9
C-5	120.7	118.9	119.0	119.4	119.0	119.5
C-6	126.0	121.8	121.8	122.2	121.1	121.6
C-7	110.6	109.3	109.4	110.0	109.1	109.6
C-7a	138.8	135.7	135.1	135.6	135.6	136.3
C-1'	149.1	150.0	149.2	149.4		
C-2',6'	111.7	113.3	113.0	113.8		
C-3',5'	129.0	128.6	128.9	128.4		
C-4'	116.5	116.8	116.3	117.2		
R_1						
CH_3	32.4	32.4	15.5		14.8	
CH_2			40.9	50.0	40.3	50.0
C *ipso*				137.3		137.5
C *ortho*				126.7		126.7
C *meta*				128.8		128.6
C *para*				127.6		127.5
R_2						
CH_3	40.8	40.1	13.1			
CH_2			46.8	57.2		
C *ipso*				139.6		
C *ortho*				126.7		
C *meta*				128.8		
C *para*				126.7		
R_3						
CO	191.6					
CH_2	60.1					
NMe	39.6					
C-1"	148.8					
C-2",6"	113.1					
C-3",5"	129.3					
C-4"	118.1					

[a] At 22.49 MHz.

The unequivocal ^1H and ^{13}C nmr assignments for indoles **1a** and **1b** were achieved by 2D carbon-proton correlated experiments with the aid of $^1H[^1H]$ and $^{13}C[^1H]$ decoupling experiments, and also by comparison with model compounds [4-8]. The ^{13}C chemical shift assignments for





1a $R_1 = R_2 = CH_3$, $R_3 = COCH_2N(CH_3)C_6H_5$
1b $R_1 = R_2 = CH_3$, $R_3 = H$
1c $R_1 = R_2 = C_2H_5$, $R_3 = H$
1d $R_1 = R_2 = CH_2C_6H_5$, $R_3 = H$

2a $R = C_2H_5$
2b $R = CH_2C_6H_5$

1a to **1d** are listed in Table 1 together with those of 1-ethyl- **2a** and 1-benzylindole **2b**, which were used as models. In general the ^{13}C nmr spectral assignments for C-2, C-7 and the 1-methyl groups are trivial based on characteristic chemical shifts and evaluation of the $^1J(CH)$ splittings, and the fact that the ^{13}C nmr signals for C-7 can be recognized readily [4-6] allows ascription of the corresponding proton from the ^{13}C-^1H heterocorrelated spectra.

Complete ^1H and ^{13}C assignment of **1a** was achieved using a combination of homonuclear (COSY) and heteronuclear (HETCOR) chemical shift correlation techniques. The results of these experiments are shown in Figures 2 and 3. Selective proton decoupling experiments of the *N*-methyl and of the methylene groups were also carried out to support the assignments of the quaternary carbons 2, 3, 3a, 7a, 1′ and 1″. The chemical shifts for carbons 2, 3, 3a and 6 are similar to those of indoles having a carbonyl group as the substituent at the C-2 position [8]. Futhermore, the *N*-methyl signals *alpha* to the CH_2 groups show a long range coupling constant of 4 Hz and the chemical shift of the 1-Me group stays invariable on going from 1-methylindole (32.40 ppm) [7] to compounds **1a** (32.40 ppm) and **1b** (32.36 ppm). The $^1J(CH)$ values for C-2 in compounds **1b-1d**, **2a** and **2b** deviate substantially from those of the benzene range, their values being here in the order of 180 Hz. Assignment of the ^{13}C nmr signals for the ethyl group in **1c** and the benzyl group in **1d**, was done using 1-ethyl- **2a** and 1-benzylindole **2b** as the model compounds.

The complete proton and carbon assignment for the benzene ring of compound **1b** was accomplished by homonuclear spin decoupling of H-4 which allows identification

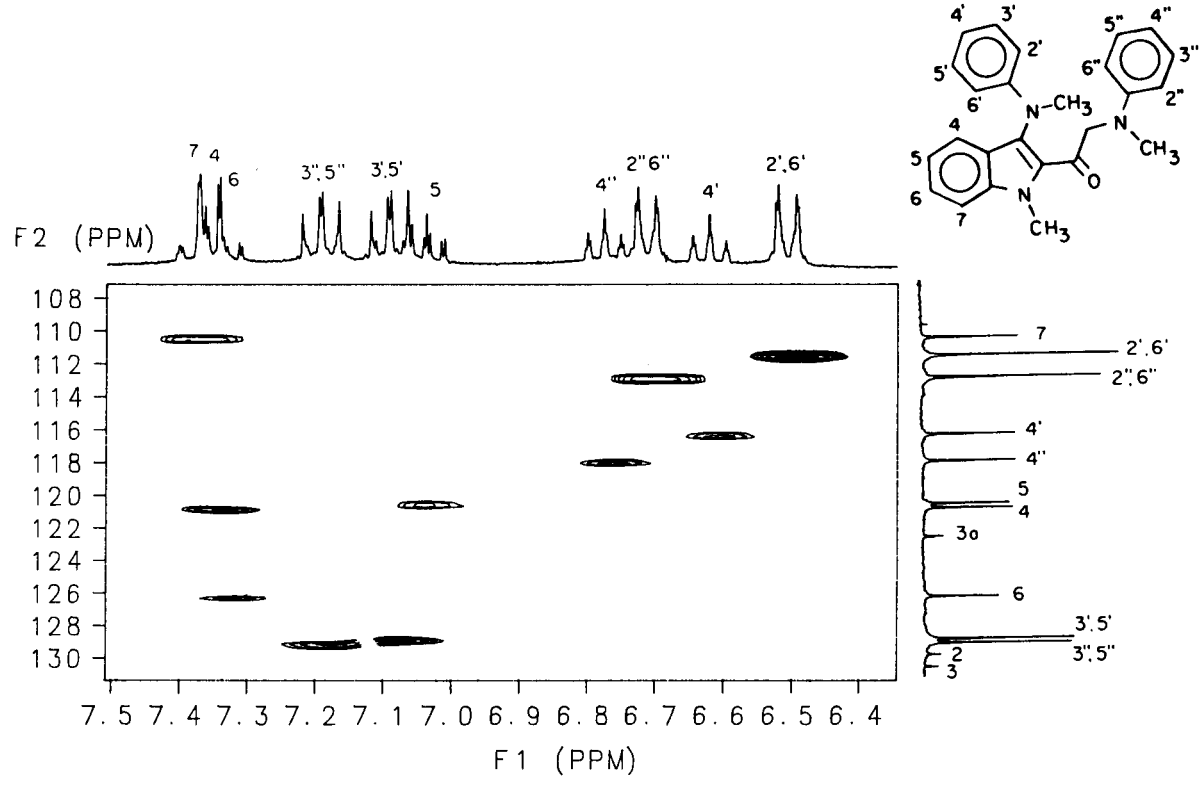


Figure 2. Two-dimensional ^{13}C-^1H HETCOR diagram of **1a**.

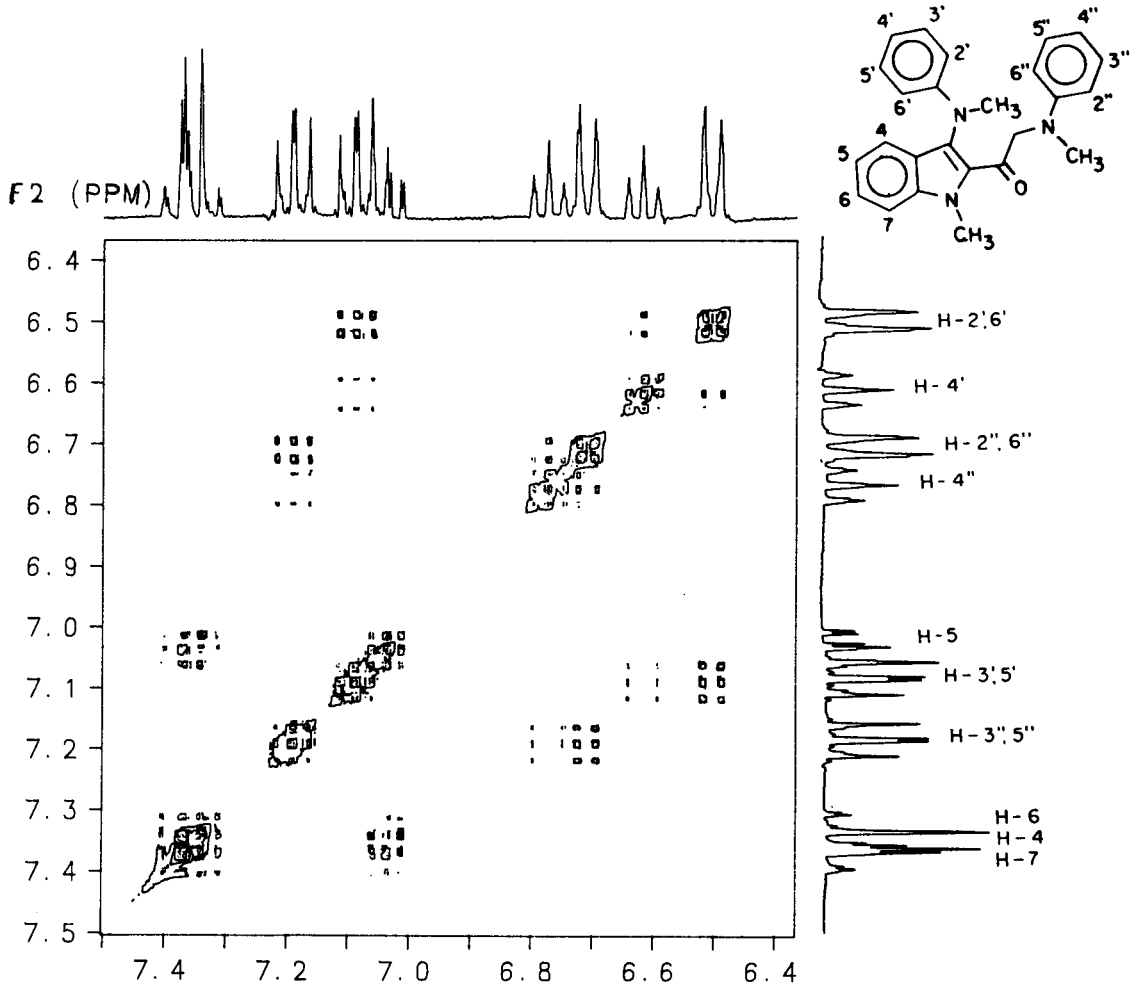


Figure 3. Two-dimensional ^{1}H COSY diagram of **1a**.

Table 2

Crystal Data, Collection and Refinement Parameters for 1-Methyl-2-(*N*-methyl-*N*-phenylglycyl)-3-(*N*-methylanilino)indole (**1a**)

A. Crystal parameters	
chemical formula	$C_{25}H_{25}N_3O$
molecular weight	383.497
crystal system	Triclinic
space group	P1
crystal size, mm	0.85 x 0.60 x 0.20
crystal color	yellow
cell constants	
a, Å	10.085 (3)
b, Å	10.371 (3)
c, Å	11.908 (5)
α, deg	74.2 (3)
β, deg	74.7 (3)
γ, deg	60.7 (2)
cell volume, Å^3	1032.4 (6)
ρ (calc), g/cm^3	1.23
Z	2
F(000), e$^-$	408
B. Data collection parameters	
μ (CuKα, 1.5418Å), cm^{-1}	6.08
scan width, below $K_{α1}$, above $K_{α2}$, deg	0.9 - 1.0
2θ limits, deg	3 - 110
scan speed (variable), deg min^{-1}	4.0 - 29.3
exposure time, h	41.82
reflections collected	2782
unique reflections, I ≥ 3 σ (I)	2603
C. Structure refinement	
reflections for final refinement	2563
parameters refined	270
R (F), %	5.66
R (W), %	8.72
goodness of fit for the last cycle	1.209
final G	0.01100
residual electron density (e$^-$/Å^3)	+0.34; -0.20

Table 3

Atom Coordinates (x10^4) for 1-Methyl-2-(*N*-methyl-*N*-phenylglycyl)-3-(*N*-methylanilino)indole (**1a**)

Atom	x	y	z
C(1)	4290(3)	1049(2)	6607(2)
N(1)	5236(2)	1684(2)	5716(1)
C(2)	4886(2)	2607(2)	4638(1)
C(3)	6086(2)	2977(2)	4116(1)
N(3)	6279(2)	3784(2)	2955(1)
C(4)	8619(2)	2253(2)	4841(2)
C(5)	9413(3)	1473(2)	5767(2)
C(6)	8805(3)	685(3)	6773(2)
C(7)	7442(2)	678(2)	6845(2)
C(8)	6627(2)	1493(2)	5892(1)
C(9)	7187(2)	2289(2)	4890(2)
C(10)	3474(2)	3004(2)	4187(2)
O(10)	2720(2)	2307(2)	4607(1)
C(11)	2961(2)	4349(2)	3200(2)
N(11)	1706(2)	4519(2)	2686(1)
C(12)	133(3)	5435(3)	3199(2)
C(13)	2022(2)	3624(2)	1870(1)
C(14)	3521(2)	2739(2)	1372(2)
C(15)	3808(3)	1944(2)	509(2)
C(16)	2628(3)	1955(3)	125(2)
C(17)	1121(3)	2802(3)	628(2)
C(18)	816(2)	3635(3)	1497(2)
C(19)	5962(3)	5343(2)	2837(2)
C(20)	6872(2)	3045(2)	1987(1)
C(21)	7462(2)	1485(2)	2152(2)
C(22)	8001(2)	749(2)	1198(2)
C(23)	7971(3)	1549(3)	53(2)
C(24)	7406(3)	3084(3)	-118(2)
C(25)	6864(2)	3842(2)	827(2)

of H-5 and H-6, followed by correlation with the ^{13}C signals in the two-dimensional contour plots. Selective proton decoupling experiments of the N-Me groups provided further evidence for the assignments of the quaternary carbons 3, 3a and 7a. The *N*-methyl signals for **1b** are easily distinguished by evaluation of J(CH) coupling constants since the 1-Me shows a $^3J(CH) = 2$ Hz with H-2.

The study of the reaction of glyoxal with the above aromatic amines allows to conclude that the transformation appears to be a general one, and might provide an alternative simple route to 3-*N*-substituted indoles.

The conditions used for X-ray data collection and the results of the structural refinement of **1a** are summarized in Table 2. The non-hydrogen atoms were refined anisotropically and hydrogen atoms, ideally fixed (CH, 1.09 Å), were refined isotropically. Table 3 lists the atom coordinates for the non-hydrogen atoms and Table 4 provides the relevant bond distances and bond angles. It can further be seen that bond lenghts and bond angles can be considered as normal.

Table 4

Selected Bond Lengths (Å) and Bond Angles (deg.) for 1-Methyl-2-(*N*-methyl-*N*-phenylglycyl)-3-(*N*-methylanilino)indole (**1a**)

C(1)-N(1)	1.472(3)	N(1)-C(2)	1.389(2)
N(1)-C(8)	1.383(3)	C(2)-C(3)	1.387(3)
C(2)-C(10)	1.482(3)	C(3)-N(3)	1.427(2)
C(3)-C(9)	1.414(3)	N(3)-C(19)	1.459(3)
N(3)-C(20)	1.394(2)	C(4)-C(5)	1.363(3)
C(4)-C(9)	1.412(3)	C(5)-C(6)	1.431(3)
C(6)-C(7)	1.358(4)	C(7)-C(8)	1.404(3)
C(8)-C(9)	1.410(2)	C(10)-O(10)	1.221(3)
C(10)-C(11)	1.522(2)	C(11)-N(11)	1.464(3)
N(11)-C(12)	1.457(2)	N(11)-C(13)	1.394(3)
C(1)-N(1)-C(2)	127.9(2)	C(1)-N(1)-C(8)	122.7(1)
C(2)-N(1)-C(8)	109.3(2)	N(1)-C(2)-C(3)	107.8(2)
N(1)-C(2)-C(10)	122.2(2)	C(3)-C(2)-C(10)	129.9(1)
C(2)-C(3)-N(3)	126.8(2)	C(2)-C(3)-C(9)	108.2(1)
N(2)-C(3)-C(9)	124.7(2)	C(3)-N(3)-C(19)	118.0(2)
C(3)-N(3)-C(20)	119.8(1)	C(19)-N(3)-C(20)	122.0(1)
C(5)-C(4)-C(9)	119.5(2)	C(4)-C(5)-C(6)	120.1(2)
C(5)-C(6)-C(7)	122.0(2)	C(6)-C(7)-C(8)	117.4(2)
N(1)-C(8)-C(7)	130.4(2)	N(1)-C(8)-C(9)	107.6(1)
C(7)-C(8)-C(9)	122.0(2)	C(3)-C(9)-C(4)	134.1(2)
C(3)-C(9)-C(8)	107.1(2)	C(4)-C(9)-C(8)	118.8(2)
C(2)-C(10)-O(10)	121.6(2)	C(2)-C(10)-C(11)	117.6(2)
O(10)-C(10)-C(11)	120.7(2)	C(10)-C(11)-N(11)	113.8(2)
C(11)-N(11)-C(12)	118.0(2)	C(11)-N(11)-C(13)	119.7(1)
C(12)-N(11)-C(13)	121.5(2)	N(11)-C(13)-C(14)	122.2(2)
N(11)-C(13)-C(18)	119.9(2)	N(3)-C(20)-C(21)	120.5(1)
N(3)-C(20)-C(25)	121.2(2)		

EXPERIMENTAL

The ^1H and ^{13}C nmr spectra were recorded on a Varian EM-390, Varian XL300GS and Jeol FX90Q spectrometers in deuteriochloroform solution containing internal TMS. The HETCOR standard pulse sequence was used, which incorporates quadrature detection in both domains. The spectral windows of HETCOR experiments were adjusted in order to perform separate measurements for the aromatic and aliphatic regions. The X-ray study was performed on a Nicolet R3m four circle diffractometer. Mass spectra were obtained with a Hewlett-Packard 5985-A spectrometer and infrared spectra with a Nicolet MX-1 FT spectrophotometer. Elemental analyses of compounds **1a** and **1d** were peformed by Butterworth Laboratories Ltd., Middlesex, U. K. and that of compound **1c** by Division de Estudios de Posgrado, Facultad de Químca, UNAM, México.

1-Methyl-2-(*N*-methyl-*N*-phenylglycyl)-3-(*N*-methylanilino)indole (**1a**).

Glyoxal (6.7 ml, 46 mmoles, 40% aqueous) was added to 5 g (46 mmoles) of *N*-methylaniline in 80 ml of ethanol. The reaction mixture was stirred for a period of 16 hours followed by removal of the solvent. The residue was chromatographed on silica gel 60, using hexane to afford 3.8 g (10 mmoles, 63%) of yellow crystals, mp 144-145°; ir (potassium bromide): ν max 1665, 1611, 1600, 1500, 1410, 1369, 1343, 1249, 747 and 691 cm^{-1}; ms: (ei) m/z (%) 383 (M^+, 37), 384 ($M^+ + 1$, 10), 264 (10), 263 (42), 248 (15), 120 (100) and 77 (18); ^1H nmr (deuteriochloroform): 300 MHz, δ 2.98 (3H, s, CH_2N-CH_3), 3.45 (3H, s, N-CH_3), 3.98 (3H, s, 1-CH_3), 4.63

(2H, s, CH_2), 6.50 (2H, dd, J = 8 and 1, H-2' and H-6'), 6.62 (1H, tt, J = 7 and 1 Hz, H-4'), 6.71 (2H, dd, J = 8 and 1 Hz, H-2'' and H-6''), 6.77 (1H, tt, J = 7 and 1 Hz, H-4''), 7.03 (1H, d of dd, J = 8, 7 and 1, H-5), 7.09 (2H, dd, J = 7 and 8 Hz, H-3' and H-5'), 7.19 (2H, dd, J = 8 and 7 Hz, H-3'' and H-5''), 7.34 (1H, m, H-6), 7.32 (1H, m, H-4) and 7.38 (1H, m, H-7).

Anal. Calcd. for $C_{25}H_{25}N_3O$: C, 78.30; H, 6.56; N, 11.03. Found: C, 78.46; H, 6.56; N, 11.03.

1-Methyl-3-(*N*-methylanilino)indole (**1b**).

The title compound was also obtained from the reaction of *N*-methylaniline with glyoxal, yellow crystals, 0.70 g, (2.9 mmoles, 12%) mp 64-66°; ir (potassium bromide): ν max 1596, 1573, 1499, 1491, 1476, 1384, 1333, 1122, 750 and 697 cm^{-1}; ms: (ei) m/z (%) 236 (M^+, 100), 237 ($M^+ + 1$, 15.5), 222 (15), 221 (46), 206 (10), 205 (10) and 77 (10); ^1H nmr (deuteriochloroform): 300 MHz, δ 3.27 (3H, s, N-CH_3), 3.52 (3H, s, 1-CH_3), 6.66 (1H, tt, J = 7 and 1 Hz, H-4'), 6.73 (2H, dt, J = 8 and 1 Hz, H-2' and H-6'), 6.79 (1H, s, H-2), 6.96 (1H, d of dd, J = 8, 7 and 1 Hz, H-5), 7.09 (2H, dd, J = 8 and 7 Hz, H-3' and H-5'), 7.19 (1H, d of dd, J = 8, 7 and 1 Hz, H-6), 7.21 (1H, dt, J = 8 and 1 Hz, H-7) and 7.29 (1H, dt, J = 7 and 1, H-4).

The elemental analysis is published elsewhere [1].

1-Ethyl-3-(*N*-ethylanilino)indole (**1c**).

Compound **1c** was prepared from 5 g (41 mmoles) of *N*-ethylaniline with 5.9 ml (40 mmoles) of glyoxal (40% aqueous) using the procedure described for the preparation of **1a**. The product (3.4 g, 12 mmoles, 62%) is a viscous oil; ir (carbon tetrachloride): ν max 2974, 1597, 1498, 1392, 1345, 1266, 740 and 692 cm^{-1}; ms: (ei) m/z (%) 264 (M^+, 100), 265 ($M^+ + 1$, 20), 249 (51), 235 (68) and 77 (27); ^1H nmr (deuteriochloroform): 90 MHz, δ 1.25 (3H, t, J = 7 Hz, CH_3), 1.47 (3H, t, J = 7 Hz, 1-CH_2CH_3) 3.75 (2H, q, J = 7 Hz, CH_2), 4.15 (2H, q, J = 7 Hz, 1-CH_2), 7.10 (1H, s, H-2) and 6.50-7.30 (10 H, m, Ph).

Anal. Calcd. for $C_{18}H_{20}N_2$: C, 81.77; H, 7.62; N, 10.59. Found: C, 81.97; H, 7.65; N, 10.69.

1-Benzyl-3-(*N*-phenylbenzylamino)indole (**1d**).

Compound **1d** was prepared from 5 g (27 mmoles) of *N*-phenylbenzylamine with 3.9 ml (27 mmoles) of glyoxal (40% aqueous) using the procedure described for the preparation of **1a**. The product (2.9 g, 7.5 mmoles, 54%) shows mp 108-110°; ir (potassium bromide): ν max 1600, 1499, 1463, 1453, 1391, 749, 744, 740, 731 and 694 cm^{-1}; ms: (ei) m/z (%) 388 (M^+, 12.6), 389 ($M^+ + 1$, 4), 297 (16) and 91 (100); ^1H nmr (deuteriochloroform): 90 MHz, δ 4.95 (2H, s, 1-CH_2), 5.25 (2H, s, CH_2) and 6.70-7.50 (20 H, m, Ph).

Anal. Calcd. for $C_{28}H_{24}N_2$: C, 86.56; H, 6.22; N, 7.34. Found: C, 86.30; H, 6.35; N, 7.34.

Acknowledgments.

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