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FIRST REACTIONS OF VINYLINDOLES WITH DIETHYL MESOXALATE, NITROSOBENZENE, AND CHLOROSULFONYL ISOCYANATE: NEW FUNCTIONALIZED AND [b]ANNELLATED INDOLES

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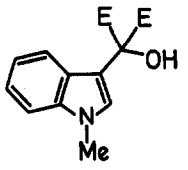
Abstract: Diethyl mesoxalate reacts with 2- and 3-vinylindoles via electrophilic substitution to give new, functionalized and annellated indoles in high regioselectivities. Regio-controlled dimerization processes occur in the reactions of the vinylindoles **5a** and **8a**. Nitrosobenzene reacts with 2- and 3-vinylindoles in a multi-stage sequence including regiospecific tandem hetero-Diels-Alder reactions to give the new, 2,3-difunctionalized indoles **11** and **12** which are conformationally stabilized by proton chelation. The heterocumulene chlorosulfonyl isocyanate reacts as a simple electrophile (like diethyl mesoxalate) with 2-vinylindole **5b** to give the indole-3-carboxamide **14**. In addition, analogous reactions of N-methylindole were also studied and, in most cases, gave comparable reactivity patterns.

2- and 3-vinylindoles undergo various cycloaddition processes such as, e.g., Diels-Alder reactions. In such reactions, the vinylindoles may react both as heterocyclic dienes[1,2] and as dienophiles[2]; they have been used by others[1-3] and by us[1,2] in syntheses of alkaloids and other heterocyclic compounds of the [b]annellated indole series, respectively. The first stage of these reactions is the formation of new C-C bonds by $[4_\pi + 2_\pi]$cycloadditions. In nature also, 2-vinylindoles in particular play an important role as biogenetic precursors of aspidosperma and iboga alkaloids[3]. But the reactivity and scope of the synthetic potential of Diels-Alder reactions of 2- and 3-vinylindoles with heterodienophiles have been documented in only a few studies[4]. In continuation of our related work, we now report some new, unexpected results from the reactions of 2- and 3-vinylindoles **5** and **8** with diethyl mesoxalate (DEMOX)[5-8], nitrosobenzene[9-11], and chlorosulfonyl isocyanate[12,13] as electrophilic heterodienophiles.

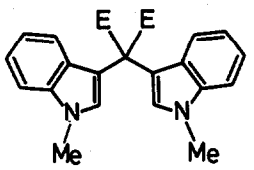
The formation of new pyrano[b]indoles was the expected result of the Diels-Alder reactions of vinylindoles with DEMOX. However, we have found that this dienophile reacts with the tested indole derivatives **3**, **5**, and **8**, as well

as N-methylindole for comparison, as a simple carbonyl electrophile. In all cases, MNDO calculations[14] predict both a charge- and an FMO-controlled[15] orientation of the reactants. Thus, N-methylindole reacts smoothly and regiospecifically with DEMOX to give the new 3-indolyl hydroxymalonate **1**. In the presence of $EtAlCl_2$ as Lewis acid catalyst, electrophilic reaction with DEMOX yields solely the 3,3'-bisindolyl derivative **2**. Similarly, DEMOX reacts with the 2,2'-bisindolyl **3**, formally containing a 2-vinylindole unit, to give the new, pharmacologically interesting indolocyclopentano[b]indole **4**[16]. The 2-

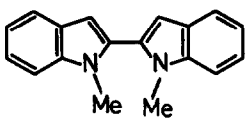


1 (95%)

E = CO_2Et



2 (38%)



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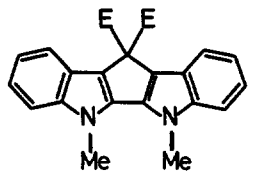
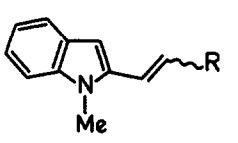
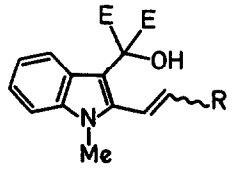


4 (20%)

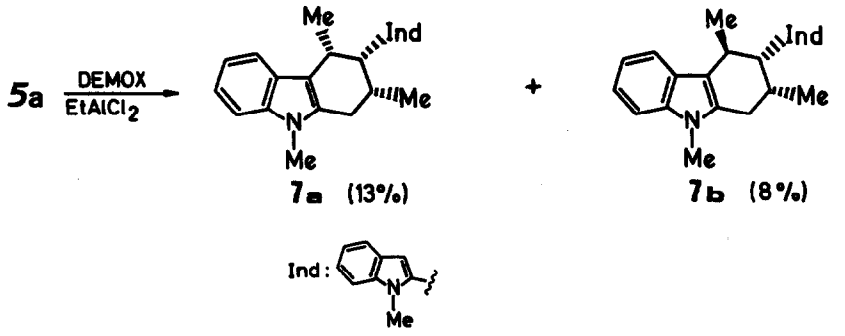
vinylindoles **5a,b** are regiospecifically functionalized at the 3-position by DEMOX to give **6a,b**. Introduction of a nitro group into the 2-vinylindole moiety markedly lessens the nucleophilicity and thus no product was detected in the reaction of **5c** with DEMOX whereas the reaction of **5d** produced the expected indole derivative **6d** (detected by ^{1}H-NMR) which, however, decomposed during further purification (e.g by MPLC). The presence of a Lewis catalyst favors the dimerization of certain 2-vinylindoles. As exemplarily shown by the reaction of **5a** (E/Z-mixture) with DEMOX, dimerization is faster than electrophilic substitution at the indole 3-position. The dimerization, the sole process, yields only two epimers **7a,b** as a result of high regiocontrol in the





5	R	E/Z
a	Me	8:1
(E)-b	COOMe	—
(E)-c	NO_2	—
(E/Z)-d	OMe	10:1

6	R	E/Z	Yield [%]
a	Me	20:1	46
(E)-b	COOMe	—	65
c	NO_2	no product formed	
d	OMe	unstable derivative	



transition states. The relative configuration and conformation (half chair of the cyclohexene ring) were clarified for compound **7a** using several 400 MHz ^{1}H- and 110.6 MHz ^{13}C-NMR methods (NOE, selective decoupling, APT techniques, $^{1}H,^{13}C$-COSY, see also Fig. 1)[17].

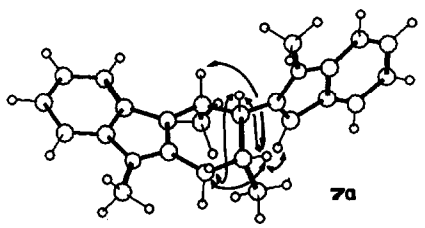
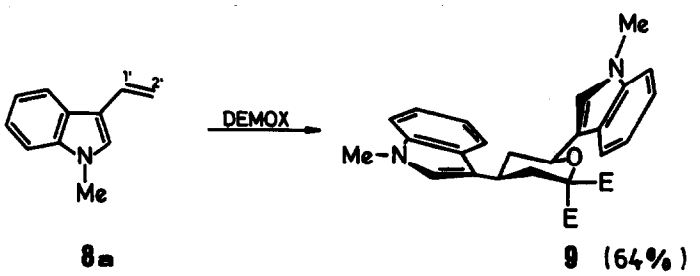
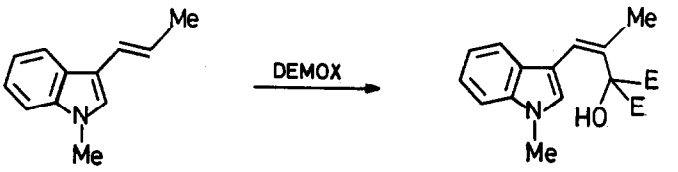


Fig. 1. Energy minimized molecular structure of **7a** with demonstration of the diagnostically relevant $^{1}H,^{1}H$-NOE's.

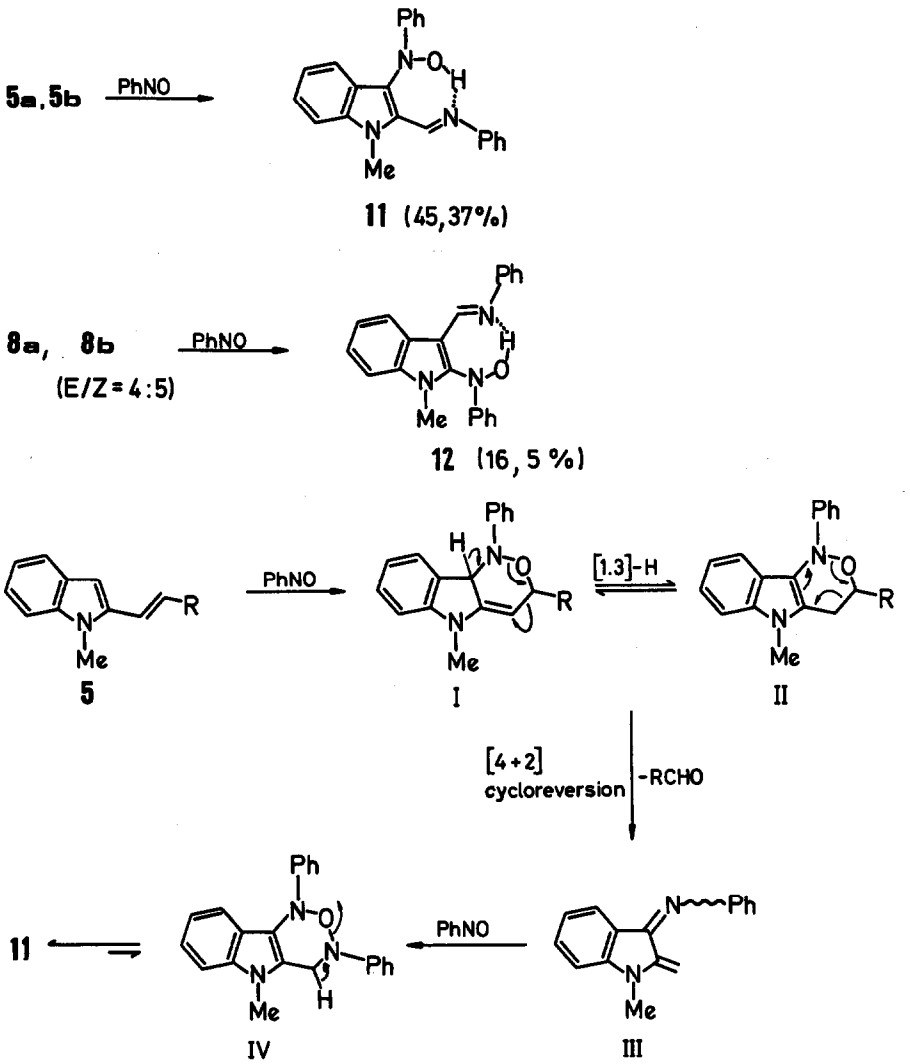
In the 3-vinylindole series, the reactive 1-methyl-3-vinylindole (**8a**) reacts with DEMOX highly regio- and stereoselectively (no other isomer detected by HPLC) even in the absence of Lewis acid catalysts to give the new bisindolyl-substituted tetrahydropyran derivative **9**. In this tandem process, the first step is an electrophilic addition of DEMOX at the vinyl 2'-position. The resultant betaine intermediate reacts regiospecifically with a further molecule of **8a** to give an intermediate which then undergoes stereospecific ring closure (see above for NMR methods used). When a methyl group is introduced at the 2'-position of the vinyl group, the DEMOX-induced "dimerization" reaction is blocked sterically. Thus, 3-propenylindole (**8b**) reacts with DEMOX via a simple, regiospecific electrophilic substitution at the vinyl function to form **10** solely.





8b **10** (48 %)

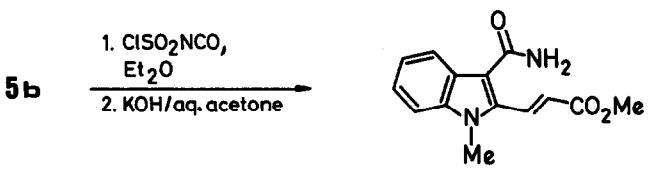
Reactions of 2- and 3-vinylindoles with nitrosobenzene also yield novel, unexpected 2,3-disubstituted indole derivatives with 2 nitrogen functions on the side-chain. Thus, the exemplarily tested 2-vinylindoles **5a, b** each reacted to give the same product **11** while the regioisomeric 3-vinylindoles **8a, b** also reacted with nitrosobenzene under mild conditions to give the regioisomeric indole derivative **12**. The E-isomers of both products were formed stereospeci-



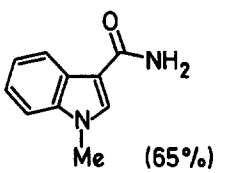
Scheme 1

fically (no other isomers detected) and the conformations stabilized by formation of a seven-membered proton chelate (IR, ^{1}H-NMR). These products are the result of a multi-step sequence including two regiospecific, FMO-controlled[15] Diels-Alder steps (Scheme 1: reaction of **5** with PhNO). Further decisive factors are the labilities of the N-O bonds in the intermediate oxazines **I** and **II** and the oxadiazine **IV** which are cleaved during the process leading to the only isolable product **11**. N-Methylindole does not react with PhNO to furnish characterizable products.

The synthetic potential of chlorosulfonyl isocyanate as a dienophile is low. From several attempts we only obtained definable results with the sufficiently stable 2-vinylindole **5b**. Also in this case, the dienophile reacts like DEMOX as a simple electrophile and alkaline work-up yields the novel indole-3-carboxamide **13** regiospecifically. In a similar charge-controlled process, N-methylindole reacts with chlorosulfonyl isocyanate to give the carboxamide **14**[18].



13 (45%)



(65%)

14

The present results demonstrate for the first time that, in contrast to the reactions of vinylindoles with CC-dienophiles, the heterodienophiles used react in most cases as simple electrophiles. Nitrosobenzene, which functions as a normal dienophile, is an exception.

EXPERIMENTAL SECTION

Melting points were determined on a Büchi SMP-20 apparatus and are uncorrected. Mass spectra were recorded on a Varian MAT CH 7 spectrometer at an ionization voltage of 70 eV, ^{1}H- and ^{13}C-NMR spectra (400 and 100.6 MHz) were obtained on a Bruker WM 400 spectrometer [δ (ppm) scale, TMS as internal standard]. The CHN analyses were performed with a Carlo-Erba Strumentazione 1164 apparatus. For flash chromatography, Merck silica gel 60 (grain size: 0.040 - 0.063 mm) was used. The MPLC separations were carried out using a Büchi 681/683 apparatus on LiChroprep® Si 60 (grain size: 25 - 40 µm). All reactions must be performed in highly pure, anhydrous solvents under an inert gas atmosphere.

Diethyl α-Hydroxy-α-(1-methylindol-3-yl)-malonate (1).

1-Methylindole (262 mg, 2 mmol) and diethyl mesoxalate (385 mg, 2.2 mmol) were dissolved in toluene (30 ml) and heated under reflux at 100 °C for 3 h. Toluene was then removed with warming on a rotary evaporator. The residue was recrystallized from dichloromethane and petroleum ether (40 - 60 °C) to give colorless, needle-shaped crystals. Yield: 580 mg (95%); m.p. 78 °C (CH_2Cl_2/petroleum ether 40 - 60 °C). Anal. calcd. for $C_{16}H_{19}NO_5$ (305.33): C 62.94, H 6.27, N 4.29; found: C 62.80, H 6.04, N 4.30. MS (m/e): 305 ($M^{+\bullet}$, 12%), 159 (100%). ^{1}H-NMR (400 MHz, $CDCl_3$): 1.15 (t, ^3J = 7.0 Hz, 6H, 2 $COOCH_2\underline{CH_3}$), 3.63 (s, 3H, NCH_3), 4.18 (m, 4H, 2 $COO\underline{CH_2}CH_3$), 4.21 (s, 1H, OH), 6.97 (t, ^3J = 8.0 Hz, 1H, indole C6-H), 7.08 (dd, ^3J = 7.9 Hz and 8.0 Hz, 1H, indole C5-H), 7.16 (d, ^3J = 8.2 Hz, 1H, indole C7-H), 7.23 (s, 1H, indole C2-H), 7.57 (d, ^3J = 7.9 Hz, 1H, indole C4-H).

Diethyl α,α-Bis(1-methylindol-3-yl)-malonate (2).

To a solution of diethyl mesoxalate (570 mg, 3.3 mmol) in dichloromethane (30 ml) was slowly added dropwise from a syringe $EtAlCl_2$ (1.8 ml of a 25% solution in toluene, 3.3 mmol) and the mixture was stirred at room temperature for 20 min. Then 1-methylindole (393 mg, 3.3 mmol) in dichloromethane (20 ml) was added and stirring at room temperature was continued for 5 h. The solvents were then removed on a rotary evaporator, the residue was separated by "flash" chromatography [petroleum ether (40 - 60 °C)/ethyl acetate, 9/1], and recrystallized from petroleum ether to furnish colorless crystals. Yield: 263 mg (38%); m.p. 172 °C. Anal. calcd. for $C_{25}H_{26}N_2O_4$ (418.49): C 71.75, H 6.26, N 6.69; found: C 71.60, H 6.37, N 6.54. MS (m/e): 418 ($M^{+\bullet}$, 21%), 345 (100%). ^{1}H-NMR (400 MHz, CD_2Cl_2): 1.22 (t, ^3J = 7.2 Hz, 6H, 2 $COOCH_2\underline{CH_3}$), 3.75 (s, 6H, 2 NCH_3), 4.23 (q, ^3J = 7.2 Hz, 4H, 2 $COO\underline{CH_2}CH_3$), 6.96 (t, ^3J = 7.9 Hz and 8.0 Hz, 2H, 2 indole C6-H), 7.17 (t, ^3J = 8.0 Hz, 2H, 2 indole C5-H), 7.26 (s, 2H, 2 indole C2-H), 7.32 (d, ^3J = 8.2 Hz, 2H, 2 indole C7-H), 7.37 (d, ^3J = 8.2 Hz, 2H, 2 indole C4-H). ^{13}C-NMR (100.6 MHz, CD_2Cl_2): 14.12 (2 $COOCH_2\underline{CH_3}$), 33.16 (2 NCH_3), 60.01 (1 C_α of the diethyl malonate moiety), 62.02 (2 $\underline{CH_2}CH_3$), 109.62 (2 indole C7), 111.76 (2 indole C3), 119.23 (2 indole C4), 121.73 (2 indole C5 and 2 indole C6), 127.20 (2 indole C3a), 130.03 (2 indole C2), 137.61 (2 indole C7a), 170.39 (2 C=O).

N,N'-Dimethyl-2,2'-biindolyl (3).

To a solution of 1-methylindole (8 g, 61 mmol) in diethyl ether (100 ml) was slowly added dropwise from a syringe n-butyllithium (46 ml of a 1.6 molar solution in hexane, 68 mmol) and the mixture was heated under reflux for 3 h. The mixture was then allowed to cool to room temperature, treated portionwise with anhydrous $CuCl_2$ (4.15 g, 30 mmol), and again heated under reflux for 1 h. The mixture was then poured into ice/water, the aqueous phase was extracted three times with diethyl ether (30 ml each), and the organic phase was filtered. The filtrate was dried with Na_2SO_4, evaporated, and the residue was recrystallized from dichloromethane and diethyl ether to furnish yellow crystals. Yield: 2 g (25%); m.p. 170 °C (CH_2Cl_2/diethyl ether). Anal. calcd. for $C_{18}H_{16}N_2$ (260.34): C 83.04, H 6.19, N 10.76; found: C

82.86, H 6.13, N 10.58. MS (m/e): 260 ($M^{+\bullet}$, 36%), 131 (100%). ^{1}H-NMR (400 MHz, CD_2Cl_2): 3.72 (s, 6H, 2 NCH_3), 6.68 (s, 2H, 2 indole C3-H), 7.18 (t, ^3J = 7.9 Hz, 2H, 2 indole C6-H), 7.30 (t, ^3J = 8.1 Hz, 2H, 2 indole C5-H), 7.43 (d, ^3J = 8.2 Hz, 2H, 2 indole C7-H), 7.68 (d, ^3J = 7.9 Hz, 2H, 2 indole C4-H). ^{13}C-NMR (100.6 MHz, CD_2Cl_2): 31.20 (2 NCH_3), 104.60 (2 indole C3), 110.80 (2 indole C7), 120.27 (2 indole C4), 120.98 (2 indole C5 or indole C6), 122.51 (2 indole C6 or indole C5), 128.13 (2 indole C3a), 132.05 (2 indole C2), 138.45 (2 indole C7a).

Diethyl 5,6-Dimethyl-5H,6H-cyclopentano[1,2-b:4,3-b']diindole-11,11-dicarboxylate (4).

Aluminum trichloride (270 mg, 2 mmol) and diethyl mesoxalate (348 mg, 2 mmol) were suspended in toluene (25 ml) and stirred at room temperature for about 20 min. N',N'-dimethyl-2,2'-biindolyl (3; 400 mg, 1.54 mmol) dissolved in dichloromethane (20 ml) was added and the mixture heated at 100 °C for 4 h. For the work-up, the reaction mixture was poured into water (50 ml), the organic phase was separated, and extracted twice with dichloromethane (30 ml each). The combined organic phases were dried with Na_2SO_4, evaporated, and the oily residue was crystallized from dichloromethane and diethyl ether to furnish yellow crystals. Yield: 150 mg (20%), m.p. 286 °C (CH_2Cl_2/diethyl ether). Anal. calcd. for $C_{25}H_{24}N_2O_4$ (416.48): C 72.10, H 5.81, N 6.73; found: C 72.12, H 5.52, N 6.34. MS (m/e): 416 ($M^{+\bullet}$, 80%), 343 (100%). ^{1}H-NMR (400 MHz, CD_2Cl_2): 1.30 (t, ^3J = 7.0 Hz, 6H, 2 $COOCH_2CH_3$), 4.06 (s, 6H, 2 NCH_3), 4.25 (q, ^3J = 7.0 Hz, 4H, 2 $COOCH_2CH_3$), 7.20 (m, 4H, C2-H, C3-H, C8-H, C9-H), 7.38 (m, 2H, C4-H, C7-H), 7.74 (m, 2H, C1-H, C10-H). ^{13}C-NMR (100.6 MHz, CD_2Cl_2): 14.39 (2 $COOCH_2CH_3$), 33.42 (2 NCH_3), 60.21 (C11), 62.49 (2 $COOCH_2CH_3$), 110.60 (C4 and C7), 119.58 (C1 and C10), 121.11 (C2 and C9), 121.59 (C3 and C8), 122.29 (C10b and C11a), 124.85 (C10a and C11b), 138.97 (C5a and C5b), 141.31 (C4a and C6a), 169.08 (2 C=O).

Diethyl α-Hydroxy-α-[1-methyl-2-(1-propenyl)-indol-3-yl]malonate (6a).

1-Methyl-2-(1-propenyl)-indole (5a, E/Z = 8:1; 685 mg, 4 mmol) was treated at room temperature with diethyl mesoxalate (1.39 g, 8 mmol) in toluene (30 ml) and the mixture was stirred for 2 h. The white crystals formed were separated, washed with dichloromethane, and dried to furnish the product as a 20:1 E/Z mixture; yield: 640 mg (46%), m.p. 105 °C (CH_2Cl_2). Anal. calcd. for $C_{19}H_{23}NO_5$ (345.40): C 66.07, H 6.71, N 4.06; found C 65.84, H 6.62, N 4.14. MS (m/e): 345 ($M^{+\bullet}$, 12%), 198 (100%). ^{1}H-NMR (400 MHz, $CDCl_3$): 1.24 (t, ^3J = 7.1 Hz, 6H, 2 $COOCH_2CH_3$, E), 1.30 (t, ^3J = 7.1 Hz, 6H, 2 $COOCH_2CH_3$, Z), 1.60 (dd, ^3J = 6.7 Hz, ^4J = 1.6 Hz, 3H, R-CH=CH-CH_3, Z), 1.90 (dd, ^3J = 6.6 Hz, ^4J = 1.6 Hz, 3H, R-CH=CH-CH_3, E), 3.56 (s, 3H, NCH_3, Z), 3.62 (s, 3H, NCH_3, E), 4.20 (mc, ^3J = 7.1 Hz, 4H, $COOCH_2CH_3$, E and Z), 4.33 (s, 1H, OH), 4.53 (mc, ^3J not resolved, 4H, $COOCH_2CH_3$, E and Z), 6.05 (dq, ^3J = 15.9 Hz and 6.6 Hz, 1H, R-CH=CH-CH_3, E), 6.07 (mc, ^3J not resolved, 1H, R-CH=CH-CH_3, Z), 6.31 (dd, ^3J and ^4J not resolved, 1H, R-CH=$CHCH_3$, Z), 6.36 (dd, ^3J = 15.9 Hz, ^4J = 1.6 Hz, 1H, R-CH=$CHCH_3$, E), 7.04 (t, ^3J = 7.9 Hz, 1H, indole C6-H, E), 7.15 (t, ^3J = 7.4 Hz and 7.9 Hz, 1H, indole C5-H, E), 7.24 (d, ^3J = 7.0 Hz, 1H, indole C7-H, E), 7.39

(d, ^3J = 8.0 Hz, 1H, indole C4-H, E). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 13.89 (2 $COOCH_2\underline{C}H_3$), 18.77 (R-CH=CH-$\underline{C}H_3$), 30.29 (NCH_3), 62.78 (2 $COO\underline{C}H_2CH_3$), 78.19 (Cα of the diethyl hydroxymalonate moiety), 108.18 (indole C3), 109.29 (indole C7), 119.50 (R-CH=$\underline{C}$H-CH_3), 119.81 (indole C4), 119.88 (indole C5), 121.70 (indole C6), 125.83 (indole C3a), 136.35 (R-$\underline{C}$H=CH-CH_3), 136.58 (indole C2), 137.55 (indole C7), 170.33 (2 C=O).

Diethyl (E)-α-Hydroxy-α-[1-methyl-2-(2-methoxycarbonylvinyl)-indol-3-yl]-malonate (6b).

To a solution of methyl (E)-3-(1-methylindol-2-yl)-acrylate (**5b**; 430 mg, 2 mmol) in toluene (10 ml) at room temperature was added dropwise diethyl mesoxalate (383 mg, 2.2 mmol) and the mixture was heated at 85 °C for 3 days. Toluene was then removed on a rotary evaporator, the residue was treated with water (30 ml), extracted three times with dichloromethane, and dried with $CaCl_2$. The solvent was evaporated, the residue was separated by "flash" chromatography [petroleum ether (40 - 60 °C)/ethyl acetate, 6/4], and recrystallized from petroleum ether to furnish colorless crystals. Yield: 506 mg (65%), m.p. 113 °C [petroleum ether (40 - 60 °C)]. Anal. calcd. for $C_{20}H_{23}NO_7$ (389.40): C 61.69, H 5.95, N 3.60; found C 61.89, H 5.59, N 3.32. MS (m/e): 389 ($M^{+\bullet}$, 11%), 242 (100%). ^{1}H-NMR (400 MHz, $CDCl_3$): 1.23 (t, ^3J = 7.1 Hz, 6H, 2 $COOCH_2\underline{C}H_3$), 3.75 (s, 3H, NCH_3), 3.79 (s, 3H, OCH_3), 4.26 (mc, ^3J = 7.1 Hz, 4H, 2 $COO\underline{C}H_2CH_3$), 4.43 (s, 1H, OH), 6.25 (d, ^3J = 16.2 Hz, 1H, R-CH=$\underline{C}$H-$COOCH_3$, E), 7.08 (t, ^3J = 7.5 Hz, 1H, indole C6-H), 7.24 (t, ^3J = 8.2 Hz, 1H, indole C5-H), 7.30 (d, ^3J = 8.2 Hz, 1H, indole C7-H), 7.54 (d, ^3J = 8.2 Hz, 1H, indole C4-H), 7.93 (d, ^3J = 16.2 Hz, R-$\underline{C}$H=CH-$COOCH_3$). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 13.80 (2 $CH_2\underline{C}H_3$), 31.44 (NCH_3), 51.80 (OCH_3), 63.09 (2 $COO\underline{C}H_2CH_3$), 78.43 (Cα of the diethyl hydroxymalonate moiety), 109.73 (indole C7), 112.33 (indole C3), 120.48 and 120.50 (indole C7 and CH=$\underline{C}$H-$COOCH_3$), 123.50 and 123.54 (indole C5 and indole C6), 125.84 (indole C3a), 133.55 (indole C2), 133.93 ($\underline{C}$H=CH-$COOCH_3$), 138.28 (indole C7a), 166.54 ($\underline{C}OOCH_3$), 170.26 (2 $\underline{C}OOCH_2CH_3$).

3α-(1-Methylindol-2-yl)-2α,4α,9-trimethyl-1,2,3,4-tetrahydro-9H-carbazole (7a) and Enantiomer.

A solution of diethyl mesoxalate (578 mg, 3.3 mmol) in dichloromethane (30 ml) was treated dropwise with $EtAlCl_2$ (1.8 ml of a 25% solution in toluene, 3.3 mmol) and the mixture was stirred at room temperature for 20 min. A solution of **5a** (343 mg, 2 mmol) in dichloromethane (30 ml) was added and, after 2 h, the reaction mixture was poured into ice/water. The organic phase was separated, the aqueous phase was extracted with dichloromethane, and the combined organic phases were dried with Na_2SO_4. The solvents were evaporated, the residue was separated first by "flash" chromatography and then by MPLC [petroleum ether (40 - 60 °C)/ethyl acetate, 8/2] to furnish **7a** and **7b** as colorless crystals.

7a: Yield: 86 mg (13%), m.p. 192 °C [CH_2Cl_2/petroleum ether (40 - 60 °C)]. Anal. calcd. for $C_{24}H_{26}N_2$ (342.49): C 84.17, H 7.65, N 8.18; found: C 84.11, H 7.55, N 8.10. MS (m/e): 342 ($M^{+\bullet}$, 6%), 171 (100%). ^{1}H-NMR (400 MHz, $CDCl_3$): 0.90 (d, ^3J =

6.5 Hz, 3H, C2-CH_3), 1.34 (d, ^3J = 6.7 Hz, 3H, C4-CH_3), 2.33 (mc, ^3J not resolved, 1H, C2-H), 2.55 (ddd, ^2J = 16.2 Hz, $^3J_{1H\alpha-2H\beta}$ = 7.3 Hz, $^4J_{1H\alpha-3H\beta}$ = 2.4 Hz, 1H, C1-Hα), 2.62 (dd, $^3J_{2H\beta-3H\beta}$ = 10.7 Hz, $^3J_{3H\beta-4H\beta}$ = 7.3 Hz, 1H, C3-H), 2.96 (dd, ^2J = 16.2 Hz, $^3J_{1H\beta-2H\beta}$ = 4.9 Hz, 1H, C1-Hβ), 3.42 (mc, ^3J not resolved, $^3J_{3H\beta-4H\beta}$ = 7.3 Hz, 1H, C4-H), 3.67 (s, 3H, NCH_3), 3.77 (s, 3H, NCH_3), 6.36 (s, 1H, indole C3'-H), 7.09 (mc, 2H, C7-H, indole C6'-H), 7.20 (mc, 2H, C6-H, indole C5'-H), 7.33 (2d, ^3J = 8.1 Hz and 8.2 Hz, 2H, C8-H, indole C7'-H), 7.61 (2d, ^3J = 7.7 Hz and 7.9 Hz, 2H, C5-H, indole C4'-H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 20.00 (C2-CH_3), 20.47 (C4-CH_3), 29.08 and 30.03 (2 NCH_3), 31.49 (C1), 36.01 (C2), 37.03 (C3), 48.02 (C4), 108.72 (indole C3'), 109.04 (indole C7'), 113.30 (C4a), 118.76, 119.36, 119.51, 119.86, 120.34, 120.55, 126.41 (indole C2'), 128.39 (C9a), 134.68 (C4b), 137.04, 137.68, 145.01.

3α-(1-Methylindol-2-yl)-2α,4β,9-trimethyl-1,2,3,4-tetrahydro-9H-carbazole (**7b**) and Enantiomer.

Yield: 53 mg (8%), m.p. 146 °C [CH_2Cl_2/petroleum ether (40 - 60 °C)]. Anal. calcd. for $C_{24}H_{26}N_2$ (342.49): C 84.17, H 7.65, N 8.18; found: C 84.09, H 7.58, N 8.12. MS (m/e): 342 ($M^{+\bullet}$, 16%), 171 (100%). ^{1}H-NMR (400 MHz, $CDCl_3$): 0.99 (d, ^3J = 6.8 Hz, 3H, C2-CH_3), 1.50 (d, ^3J = 6.8 Hz, 3H, C4-CH_3), 2.49 (mc, ^3J not resolved, 1H, C2-H), 2.58 (dd, ^2J = 15.8 Hz, $^3J_{1H\alpha-2H\beta}$ = 6.4 Hz, 1H, C1-Hα), 2.93 (dd, ^2J = 15.8 Hz, $^3J_{1H\beta-2H\beta}$ = 4.5 Hz, 1H, C1-Hβ), 3.10 (dd, $^3J_{2H\beta-3H\beta}$ = 3.2 Hz and 6.0 Hz, 1H, C3-H), 3.46 (mc, ^3J = 6.3 Hz, 1H, C4-H), 3.67 (s, 3H, NCH_3), 3.77 (s, 3H, NCH_3), 6.15 (s, 1H, indole C3'-H), 7.04 - 7.23 (m, 4H, C6-H, C7-H, indole C5'-H, indole C6'-H), 7.30 - 7.34 (m, 2H, C8-H, indole C7'-H), 7.48 (d, ^3J = 7.8 Hz, 1H, C5-H or indole C4'-H) 7.61 (2d, ^3J = 7.8 Hz, 1H, indole C4'-H or C5-H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 16.63 (C2-CH_3), 21.53 (C4-CH_3), 28.44 (C1), 29.10 (NCH_3), 29.71 (C2), 30.09 (NCH_3), 31.55 (C3), 44.14 (C4), 99.24 (indole C3'), 108.72 (C8 or indole C7'), 108.87 (indole C7' or C8), 112.76 (C4a), 118.62, 118.85, 119.23, 119.88, 120.47, 120.49, 126.73 (indole C2'), 128.03 (C9a), 134.22 (C4b), 137.48, 137.60, 142.19.

2,2-Diethoxycarbonyl-4β,6β-bis(1-methylindol-3-yl)-2,3,5,6-tetrahydro-4H-pyran (**9**) and Enantiomer.

1-Methyl-3-vinylindole (**8a**; 472 mg, 3 mmol) and diethyl mesoxalate (870 mg, 5 mmol) were dissolved in toluene (20 ml) and the mixture stirred at room temperature for 30 min. The formed precipitate was then separated and dried in vacuum to furnish the product as colorless crystals. Yield: 470 mg (64%), m.p. 192 °C. Anal. calcd. for $C_{29}H_{32}N_2O_5$ (488.58): C 71.29, H 6.60, N 5.73; found: C 71.05, H 6.39, N 5.62. MS (m/e): 488 ($M^{+\bullet}$, 27%), 158 (100%). ^{1}H-NMR (400 MHz, $CDCl_3$): 1.23 (t, J = 7.1 Hz, 3H, $COOCH_2CH_3$), 1.41 (t, J = 7.1 Hz, 3H, $COOCH_2CH_3$), 2.01 (t, ^2J = 13.0 Hz, ^3J = 13.0 Hz, 1H C3-H(ax)), 2.19 (dd, ^2J = 13.0 Hz, ^3J = 12.2 Hz, 1H, C5-H(ax)), 2.38 (ddd, ^2J = 13.0 Hz, ^3J = 11.8 Hz, $^3J_{C5-H(eq),C6-H(ax)}$ = 1.7 Hz, 1H, C5-H(eq)), 2.96 (ddd, ^2J = 13.0 Hz, $^3J_{C3-H(eq),C4-H(ax)}$ = 3.4 Hz, $^4J_{C3-H(eq),C5-H(eq)}$ = 1.7 Hz, 1H, C3-H(eq)), 3.47 (m, $^3J_{C3-H(eq),C4-H(ax)}$ = 3.4 Hz, ^3J = 12.4 Hz, 1H, C4-H(ax)), 3.73 (s, 6H, 2 NCH_3), 4.20 (q, ^3J = 7.1 Hz, 2H, $COOCH_2CH_3$), 4.44 (m, 2H, $COOCH_2CH_3$), 5.18

(dd, $^3J_{C6\text{-}H(ax),C5\text{-}H(ax)}$ = 11.5 Hz, $^3J_{C6\text{-}H(ax),C5\text{-}H(eq)}$ = 1.8 Hz, 1H, C6-H(ax)), 6.86 (s, 1H, indole C2'-H or indole C2"-H), 7.11 (s, 1H, indole C2"-H or indole C2'-H), 7.10 - 7.31 (m, 6H, indole C5'-H, C5"-H, C6'-H, C6"-H, C7'-H, C7"-H), 7.74 (d, ^3J = 7.9 Hz, 1H, indole C4'-H or indole C4"-H), 7.91 (d, ^3J = 7.9 Hz, 1H, indole C4"-H or indole C'4-H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 13.95 and 14.28 (2 $COOCH_2\underline{C}H_3$), 30.00 (C4), 32.60 and 32.64 (2 NCH_3), 37.11 (C3), 37.50 (C5), 61.86 and 61.89 (2 $COO\underline{C}H_2CH_3$), 71.35 (C6), 82.92 (C2), 109.11 and 109.37 (indole C7' and indole C7"), 115.59 and 118.54 (indole C3' and indole C3"), 118.87, 119.20, 120.26, 121.75, 121.80, 124.54, 126.26, 126.84, 137.26, 169.17 and 169.87 (2 C=O).

Diethyl (Z)-α-Hydroxy-α-[(1-methylindol-3-yl)-propen-2-yl]-malonate (10).

1-Methyl-3-(1-propenyl)-indole (**8b**, E/Z = 4/5; 514 mg, 5 mmol), diethyl mesoxalate (871 mg, 5 mmol), and toluene (30 ml) were heated at 100 °C for 2 h. Toluene was then removed in a rotary evaporator, the residue was separated by "flash" chromatography, and the combined and evaporated fractions were recrystallized from dichloromethane and diethyl ether to furnish colorless crystals. Yield: 498 mg (48%), m.p. 87 °C (CH_2Cl_2/diethyl ether). Anal. calcd. for $C_{19}H_{23}NO_5$ (345.40): C 66.07, H 6.71, N 4.06; found: C 65.93, H 6.91, N 4.01. MS (m/e): 345 ($M^{+\bullet}$, 18%), 199 /100%). ^{1}H-NMR (400 MHz, $CDCl_3$): 1.33 (t, ^3J = 7.1 Hz, 6H, 2 $COOCH_2\underline{C}H_3$), 2.04 (s, 3H, C2'-CH_3), 3.79 (s, 3H, NCH_3), 4.16 (s, 1H, OH), 4.34 (m, 4H, 2 $COO\underline{C}H_2CH_3$), 7.00 (s, 1H, C1'-H), 7.14 (t, ^3J = 7.8 Hz, 1H, indole C6-H), 7.16 (s, 1H, indole C2-H), 7.24 (t, ^3J = 7.8 Hz, 1H, indole C5-H), 7.29 (d, ^3J = 8.1 Hz, indole C7-H), 7.66 (d, ^3J = 7.9 Hz, 1H, indole C4-H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 14.00 (2 $COOCH_2\underline{C}H_3$), 16.81 (C2'-$\underline{C}H_3$), 32.89 (NCH_3), 62.55 (2 $COO\underline{C}H_2CH_3$), 82.74 (C_α of the diethyl hydroxymalonate moiety), 109.10 (C7), 111.73 (C3), 118.99 (indole C4), 119.06 and 119.54 (indole C5 and indole C6), 122.13 (C1'), 127.87 (C2), 128.12 and 128.20 (C3a and C2'), 136.27 (C7a), 170.24 (2 C=O).

(E)-3-[(N-Hydroxy-N-phenyl)-amino]-2-[N-(phenylimino)]-indole (11).

1-Methyl-2-(1-propenyl)-indole (**5a**; 514 mg, 3 mmol) was dissolved in dichloromethane (30 ml) at -75 °C, a solution of nitrosobenzene (428 mg, 4 mmol) in dichloromethane (20 ml) was added, and the mixture was stirred at -75 °C for 30 min and at room temperature for 5 h. Dichloromethane was then removed on a rotary evaporator under mild conditions and the residue was recrystallized from diethyl ether to furnish red crystals. Yield: 461 mg (45%),m.p. 191 °C (diethyl ether): Anal. calcd. for $C_{22}H_{19}N_3O$ (341.41): C 77.40, H 5.61, N 12.31; found: C 77.20, H 5.74, N 12.05. MS (m/e): 341 ($M^{+\bullet}$, 64%), 324 ($M^{+\bullet}$ - OH, 100%). ^{1}H-NMR (400 MHz, DMSO-d_6): 3.72 (s, 3H, NCH_3), 6.74 (mc, ^3J = 7.5 Hz and 7.9 Hz, 3H, phenyl C3,5-H and indole C5-H or indole C6-H), 6.99 (t, ^3J = 7.4, Hz 1H, indole C6-H or indole C5-H), 7.13 (dt, ^3J = 8.0 Hz, 2H, phenyl C3,5-H), 7.24 (d, ^3J = 8.2 Hz, 1H, indole C4-H), 7.32 (t, ^3J = 7.9 Hz, 1H, phenyl C4-H), 7.54 (mc, 4H, phenyl C2,6-H, phenyl C4-H, indole C7-H), 7.98 (dd, ^3J = 7.9 Hz, 2H, phenyl C2,6-H), 8.31 (s, 1H, OH), 8.78 (s, 1H, -C<u>H</u>=NPh). ^{13}C-NMR (100.6 MHz, DMSO-d_6): 30.50 (NCH_3), 110.43 (indole C7), 114.45, 118.56, 119.90 (indole C3), 120.83 (indole C4a), 121.13, 121.47, 124.74, 125.58 (indole C2),

128.64, 128.91, 128.95, 129.72, 139.29 (indole C7a), 144.75 (phenyl C1), 146.88 (phenyl C1). Compound **5b** reacts in the same manner to produce **11** in 37% yield.

(E)-2-[(N-Hydroxy-N-phenyl)-amino]-3-[N-(phenylimino)]-indole(12).

1-Methyl-3-(1-propenyl)-indole (**8b**; 428 mg, 2.5 mmol) was treated at room temperature with a solution of nitrosobenzene (428 mg, 4 mmol) in dioxane (30 ml) and the mixture was stirred for 10 h. The yellow crystals formed were separated by filtration and dried. Yield: 137 mg (16%), m.p. 234 °C. Anal. calcd. for $C_{22}H_{19}N_3O$ (341.41): C 77.40, H 5.61, N 12.31; found: C 77.51, H 5.81, N 12.02. MS (m/e): 341 ($M^{+\bullet}$, 100%), 324 ($M^{+\bullet}$ - OH, 73%). ^{1}H-NMR (400 MHz, $CDCl_3$): 3.44 (s, 3H, NCH_3), 6.88 (d, ^3J = 7.6 Hz, 2H, phenyl C3,5-H), 6.93 (t, ^3J = 7.4 Hz, 1H, indole C5-H or indole C6-H), 7.21 (mc, 5H, aromatic H), 7.38 (mc, 4H, aromatic H), 7.75 (2d, ^3J = 8.0 Hz, 2H, phenyl C2,6-H), 8.13 (s, 1H, CH=N-Ph), 10.56 (s, 1H, N-OH). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 31.47 (NCH_3), 95.07, 109.37, 116.23, 117.60, 121.40, 121.50, 121.53, 121.77, 126.86, 128.89, 129.04, 129.30, 131.73, 136.67, 143.56, 145.12, 147.43. Compound **8a** reacts in the same manner to produce **12** in 5% yield.

(E)-[1-Methyl-2-(2-methoxycarbonylvinyl)]-indole-3-carboxamide (13).

A solution of methyl (E)-3-(1-methylindol-2-yl)-acrylate (**5b**; 430 mg, 2 mmol) in diethyl ether (30 ml) was cooled in an ice bath and treated with chlorosulfonyl isocyanate (283 mg, 2 mmol). The mixture was stirred with cooling in an ice bath for 20 min and at room temperature for 30 min. The precipitate that formed was separated by filtration and dissolved in acetone/water (15 ml, 4/1). The pH of this solution was then adjusted to 8 by addition of 10% KOH solution. After 5 min, the solution was diluted with water (30 ml), extracted three times with ethyl acetate (30 ml each), and the combined extracts were dried with Na_2SO_4. The organic phase was finally evaporated to furnish light brown crystals. Yield: 232 mg (45%), m.p. 227 °C (ethyl acetate). Anal. calcd. for $C_{14}H_{14}N_2O_3$ (258.29): C 65.11, H 5.46, N 10.85; found: C 64.92, H 5.32, N 10.25. MS (m/e): 258 ($M^{+\bullet}$, 11%), 199 (100%). ^{1}H-NMR (400 MHz, DMSO-d_6): 3.75 (s, 3H, NCH_3), 3.88 (s, 3H, OCH_3), 6.61 (d, ^3J = 16.5 Hz, 1H, R-CH=CH-$COOCH_3$, E), 7.17 (t, ^3J = 7.2 Hz and 7.9 Hz, 1H, indole C6-H), 7.30 (t, ^3J = 7.2 Hz and 8.0 Hz, 1H, indole C5-H), 7.44 - 7.53 (br. d, 2H, NH_2), 7.58 (d, ^3J = 8.4 Hz, 1H, indole C7-H), 7.77 (d, ^3J = 8.0 Hz, 1H, indole C4-H), 8.12 (d, ^3J = 16.5 Hz, R-CH=CH-$COOCH_3$, E). ^{13}C-NMR (100.6 MHz, DMSO-d_6): 31.48 (NCH_3), 51.52 (OCH_3), 110.47 (C7), 114.70 (C3), 120.67 (CH=CH-$COOCH_3$), 120.90 and 123.90 (C4, C5, and C6), 124.94 (C3a), 132.71 (CH=CH-$COOCH_3$), 134.07 (C2), 137.87 (C7a), 166.14 and 166.40 (2 C=O).

(1-Methylindol-3-yl)-carboxamide (14).

The preparation was carried out as described above for **13** using 1-methylindole (262 mg, 2 mmol) and chlorosulfonyl isocyanate (283 mg, 2 mmol). The residue obtained was recrystallized from ethyl acetate to furnish colorless crystals which acquired a violet color on exposure to air. Yield: 227 mg (65%), m.p. 176 °C. Anal. calcd. for $C_{10}H_{10}N_2O$ (174.20): C 68.95, H 5.79, N 16.08; found: C 68.70, H 5.66, N 15.99. MS (m/e): 174 ($M^{+\bullet}$, 8%), 151 (100%). ^{1}H-NMR (400 MHz, DMSO-d_6): 3.79 (s, 3H, NCH_3),

6.80 (br. d, 2H, NH_2), 7.12 (t, ^3J = 7.8 Hz, 1H, indole C6-H), 7.18 (t, ^3J = 8.2 Hz, 1H, indole C5-H), 7.45 (d, ^3J = 8.2 Hz, 1H, indole C7-H), 7.97 (s, 1H, indole C2-H), 8.14 (d, ^3J = 7.9 Hz, 1H, indole C4-H). ^{13}C-NMR (100.6 MHz, DMSO-d_6): 32.77 (NCH_3), 109.50 (C3), 109.97 (C7), 120.40 (C4), 121.07 and 121.70 (C5 and C6), 126.45 (C3a), 132.22 (C2), 136.69 (C7a), 165.99 (C=O).

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