A STUDY OF 5-NITROINDOLE ALKYLATION

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A detailed study of the 5-nitroindole alkylation, the key step in the synthesis of Zafirlukast, is presented. A broad distribution of alkyl derivatives has been found. 2,3- And 1,3-dialkylindoles can be selectively obtained in a $ZnBr_2$-catalyzed reaction. Structure of all the products was fully assigned.

Keywords: Indoles; Alkylations; Lewis acid catalysis; Electrophilic substitutions; Friedel–Crafts alkylation; Leukotriene antagonists.

Alkylation reactions are one of the important methods of synthesis of indole derivatives[1–5]. It is generally accepted that the alkyl substituent preferentially enters position 3 of indole and the N-1 position is the next active position. If the indole bears a substituent at C-3, products of C-2 substitution have also been found. In some cases, it was postulated that 2,3-disubstituted derivatives may be formed by a rearrangement of the primary formed 3,3-disubstituted 3*H*-indoles. On the other hand, in some instances it is assumed that alkylation can occur by a direct attack of the C-2 position. To avoid formation of *N*-substituted products, alkylation of *N*-indolylmagnesium halides has usually been recommended. Introduction of a strong electron-accepting nitro group to 4, 5, or 6 position of indole has not shown any influence on and change of the observed regioselectivity of the alkylation[5–12] and the corresponding 3-alkyl derivatives have been isolated. Alkylation of nitroindoles is generally catalyzed with weak Lewis acids, such as, Ag_2O (refs[5,7,8]), $ZnBr_2$ (ref.[13]), $Zn(OTf)_2$ (refs[9,10]), $Cu(OTf)_2$ (ref.[14]), and various transition metal halides[15–17]. A method of a reductive C-3 alkylation has also been developed[18,19].

Recognition of the arachidonic acid biochemical cascade[20,21] led to a formulation of new generations of cyclooxygenase and lipoxygenase inhibitors and prostaglandin and/or leukotriene antagonists as potent anti-

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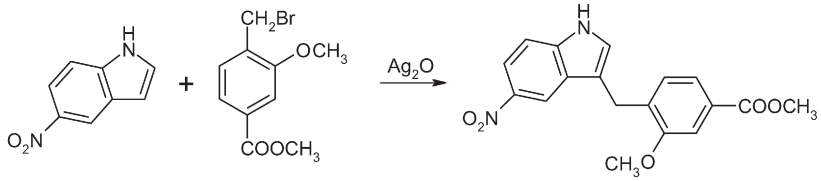
inflammatory and antiasthmatic drugs[22,23]. Synthesis of the first antiasthmatic leukotriene antagonist Zafirlukast was first described[24] in a patent, and later in paper[5]. The key step of the claimed process involves an Ag_2O-catalyzed alkylation of 5-nitroindole (**1**) with substituted benzyl bromide **2** leading to 3-substituted product **3** in 45% yield (Scheme 1).



1 **2** **3**

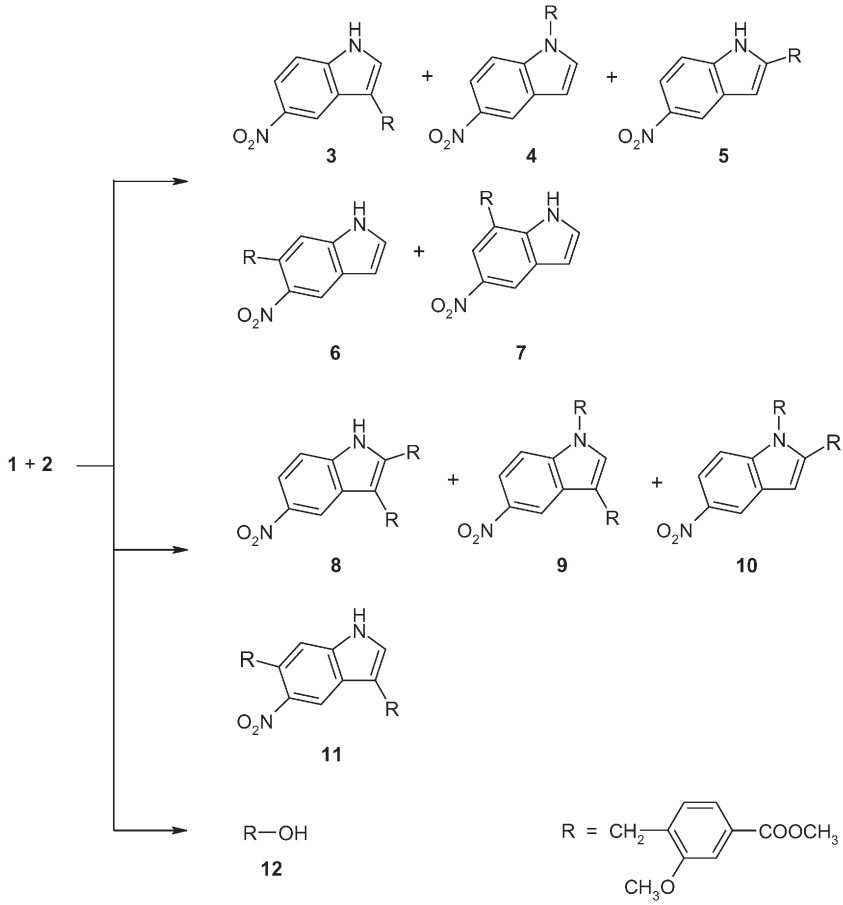
SCHEME 1

This alkylation procedure was also claimed[25,26] for preparation of other 3-alkyl-5-nitroindole derivatives, which served for preparation of analogous active lipoxygenase inhibitors. Formation and characterization of alkylation products with different regioselectivity has not been described. Thus, it was rather surprising that the inventors in description of the recently released patent[27] declare, without any additional data and evidence, that the earlier claimed[5,24] alkylation procedure suffers from serious drawbacks due to the fact that 5-nitroindole alkylation is accompanied by an undesired process of polyalkylation, isomerization and disproportionation leading – in addition to **3** – to formation of substantial amounts of 1,3- and 2,3-dialkylated products. To the best of our knowledge, formation of other than 3-alkylated nitroindoles has not been mentioned in the literature[5–12,24]. Because we were involved in the chemistry of prostaglandins and their antagonists some time ago, the published inconsistent results inspired us to perform a detailed study of this alkylation reaction and clear up these discrepancies. This note summarizes the obtained results.

RESULTS AND DISCUSSION

The starting 5-nitroindole (**1**) and methyl 4-(bromomethyl)-3-methoxybenzoate (**2**) were prepared by known procedures[28–30]. Alkylation of **1** was first catalyzed with silver oxide according to the published procedure (equimolar amounts of **1**, **2**, and catalyst, 60 °C, 20 h)[5,24]. After the standard workup of the reaction mixture, the crude product was separated by column chromatography and the minor products were isolated from the mixed fractions by preparative thin layer chromatography. The structures of all the obtained products, their distribution and isolated yields are sum-

marized in Scheme 2 and Table I (Entry 1). For the full assignment of the product structures, ^{1}H and ^{13}C NMR spectra, COSY, HMBC and HMQC experiments were utilized.



SCHEME 2

The product distribution analysis showed that the silver oxide-mediated alkylation provided a mixture of isomeric products. Besides the already known 3-benzyl derivative **3** (42% yield), alkylation proceeded also in positions 1 (*N*-alkylated product **4**, 12% yield) and 2 (compound **5**, 3% yield). Although it is well known that aromatic nitro compounds do not enter into the Friedel–Crafts alkylation reaction, surprisingly, 6- and 7-alkyl derivatives **6** and **7** were also isolated, though, in trace amounts. 2,3- And 1,3-dialkylated indoles **8** and **9** were also formed in the yield 3% and, unlike

TABLE I
Product yields[a] in the alkylation reaction of 5-nitroindole (**1**) with methyl 4-(bromomethyl)- 3-methoxybenzoate (**2**)

Entry	Catalyst	**1**[b]	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
1	Ag_2O	17	42	12	3	0.3	0.3	3	3	0.15	0.1	8
2	$[Zn(Py)_2]Cl_2$	25	37	13	5			7				5
3	ZnI_2	19	33	6	5			3				3
4	$ZnBr_2$	21	43	3	5			5				3
5	–[c]	38	41		1.5			12				

[a] Isolated; [b] recovered; [c] 5-nitroindol-1-ylmagnesium bromide.

previously[27], the 1,2-dialkyl derivative **10** was isolated in a very low yield (0.15%). The 3,6-dialkyl derivative **11** was also detected. The corresponding benzyl alcohol **12** as a result of bromide **2** substitution was isolated in 8% yield.

In a series of small-scale attempts, alkylation of **1** was further studied with various weak Lewis acids, $[Zn(Py)_2]Cl_2$ (ref.[13]), ZnI_2, $ZnBr_2$, and alkylation of the corresponding 5-nitroindolylmagnesium bromide was also investigated. From the results (Table I, Entries 2–5) it can be observed that the product distribution is quite similar to that in Ag_2O catalysis. The highest selectivity of alkylation was observed when using $ZnBr_2$ catalysis and the earlier indolylmagnesium bromide procedure.

With the aim to explain formation of particular products we investigated first the behaviour of monoalkyl derivatives **3**–**5** under the alkylation conditions. Long-term heating of compounds **3**–**5** in dioxane in the presence of an equimolar amount of Ag_2O or $ZnBr_2$ showed that no reaction took place. The starting alkyl derivatives **3**–**5** were recovered in an almost quantitative yields and not even traces of rearranged products could be detected. Thus, the observed product distribution results from the direct attack of benzyl bromide **2** in positions 1, 2, or 3 of nitroindole **1**.

Further, formation of the products of consecutive alkylation was studied by individual alkylation of alkyl derivatives **3**–**5** with an equivalent of bromide **2** and Ag_2O under the above given conditions. We found that the alkylation of 3-benzyl compound **3** afforded approximately a 1:1 mixture of 2,3-dibenzyl derivative **8** and 1,3-dibenzyl derivative **9** (Table II). Reaction of *N*-substituted compound **4** proceeded very slowly. While the 1,3-dibenzyl derivative **9** was obtained after 24 h in 20% yield, the 1,2-dibenzyl

TABLE II
Dialkylindole yields[a] in the alkylation of alkylindoles **3**–**5** with benzyl bromide **2**

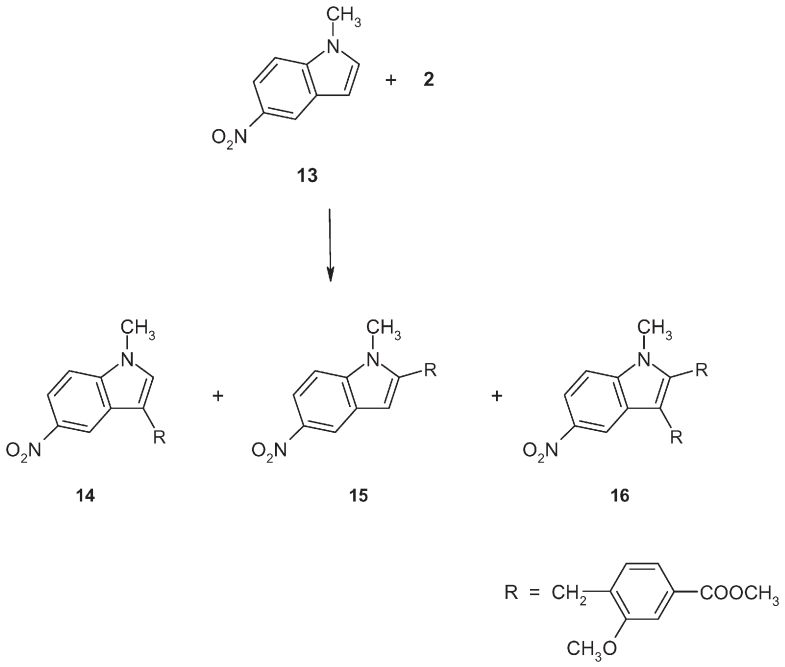
Indole	Catalyst	**8**	**9**	**10**
3	Ag_2O	41	35	
3	$ZnBr_2$	95	0	
4	Ag_2O		20	0.2
4	$ZnBr_2$		24	0.2
5	Ag_2O	37		10
5	$ZnBr_2$	50		0

[a] Isolated.

compound **10** was isolated only in a trace amount. Finally, the 2-benzyl derivative **5** afforded a mixture of **8** (37%) and **10** (10%).

Analogously to monoalkylation of **1**, alkylation of **3**–**5** in the presence of $ZnBr_2$ also proceeded with higher selectivity: alkylation of the 3-alkyl derivative **3** and alkylation of the 2-alkyl-substituted indole **5** afforded exclusively the 2,3-dibenzyl derivative **8**. Alkylation of the 1-substituted indole led again to a selective formation of the 1,3-dialkyl derivative **9**. In no case, rearrangement of the starting **3**–**5** to their isomers was detected, which excludes a possible mechanism of successive alkylation–dealkylation.

The low reactivity of 1-substituted indole derivatives in alkylation reactions was further confirmed in a study of 1-methyl-5-nitroindole (**13**) alkylation (Scheme 3). The 1-methyl derivative **13** was easily obtained by alkylation of indole **1** with methyl iodide in basic medium. Alkylation reaction with an equimolar amount of **2** under the same conditions proceeded very slowly. With Ag_2O catalysis, the 3-substituted derivative **14** was formed in low yield (27%) along with a small amount of 2-benzyl derivative **15** (1%) and 2,3-dibenzyl analogue **16** (1%) (Scheme 3). Application of



SCHEME 3

$ZnBr_2$ led to a substantial increase in 2,3-dialkylation: while the yield of **14** dropped to 8%, the yield of **16** increased to 24% and compound **15** was formed only in trace amount (0.5%). These results are strongly different from those published[31], where formation of **14** as the sole product was claimed under the same reaction conditions.

Thus, in contrast to generally accepted pattern of indole reactivity, alkylation of 5-nitroindole leads to the formation of a mixture of 3-, 1- and 2-monosubstituted products along with products of dialkylation reaction. From the experiments it can be deduced, that alkylation proceeds by a direct attack of the corresponding indole site and the reactivity of positions decreases in the order 3 > 1 >> 2.

No alkyl derivative is formed by rearrangement of the primary products **3**–**5**. The $ZnBr_2$-catalyzed alkylation of 3- or 1-substituted indoles can be utilized for a selective preparation of the corresponding 2,3- and 1,3-disubstituted indoles. In addition, reactivity of *N*-alkylindoles in alkylations is very low.

With respect to these results, it seems to be unusual that in the earlier studies[6–14] formation of other than 3-substituted derivatives has not been mentioned. One can conclude that the frequently used column chromatography for isolation of the principal product can lead to a substantial loss of chemical information concerning reactivity patterns of various organic molecules.

EXPERIMENTAL

Melting points were determined on a Leica VM TG block and are uncorrected. Elemental analyses were carried out on a Perkin–Elmer 2400. NMR spectra were recorded on a Varian Gemini 300 HC (300 MHz), deuteriochloroform was used as solvent and the signal of the solvent served as internal standard. Chemical shifts are given in ppm (δ-scale), coupling constants (*J*) in Hz. Signal multiplicities in the ^{13}C NMR were determined in the APT experiment. The 2D experiments, COSY, HMBC, HMQC were carried out using pulse sequence and program provided by the manufacturer. IR spectra were recorded on a Nicolet 740 FT-IR instrument in chloroform.

Reaction of Indole **1** with Benzyl Bromide **2**. General Procedure

Method A[5,24]. To a mixture of indole **1** (28.5 g, 176 mmol) and benzyl bromide **2** (45.4 g, 176 mmol) in dry 1,4-dioxane (180 ml), freshly prepared and vacuum dried silver oxide (40.6 g, 176 mmol) was added in one portion. The mixture was stirred at 60 °C for 20 h, the solvent was evaporated, diluted with ethyl acetate (400 ml) and filtered. The filtrate was evaporated to dryness. The crude product (66.0 g) was subjected to column chromatography (1500 g of silica gel, elution with hexane–ethyl acetate 3:1–1:1). Fractions containing pure products were collected and evaporated. The mixed fractions were collected, evaporated and

the residues were either rechromatographed or separated by preparative thin layer chromatography (20 × 20 cm plates, Merck). Distribution and yields of isolated products are summarized in Table I.

Methyl 3-methoxy-4-[(5-nitroindol-3-yl)methyl]benzoate (**3**). M.p. 161–163 °C (ref.[5] m.p. 153–155 °C). ^{1}H NMR: 8.59 d, 1 H, J = 2.2 (H-4); 8.41 bs, 1 H (H-1); 8.09 dd, 1 H, J_1 = 8.8, J_2 = 2.2 (H-6); 7.56 s, 1 H (H-3´); 7.55 d, 1 H, J = 8.0 (H-5´); 7.37 d, 1 H, J = 8.8 (H-7); 7.16 d, 1 H, J = 8.2 (H-6´); 7.11 d, 1 H, J = 2.2 (H-2); 4.15 s, 2 H (CH_2); 3.95 s, 3 H (OCH_3); 3.90 s, 3 H ($COOCH_3$). ^{13}C NMR: 166.9 (CO); 156.8 (C-2´); 141.4 (C-5); 139.1 (C-7a); 134.2 (C-1´); 129.5 (C-6´); 129.4 (C-4´); 126.8 (C-3a); 125.3 (C-2); 122.0 (C-5´); 117.6 (C-4); 117.2 (C-3); 116.6 (C-6); 111.0 (C-3´); 110.9 (C-7); 55.6 (OCH_3); 52.2 ($COOCH_3$); 25.3 (CH_2).

Methyl 3-methoxy-4-[(5-nitroindol-1-yl)methyl]benzoate (**4**). M.p. 158.5–160 °C. For $C_{18}H_{16}N_2O_5$ (340.3) calculated: 63.53% C, 4.74% H, 8.23% N; found: 63.45% C, 4.58% H, 8.18% N. IR: 1720 (CO), 1517 and 1337 (NO_2). ^{1}H NMR: 8.61 d, 1 H, J = 2.2 (H-4); 8.09 dd, 1 H, J_1 = 9.3, J_2 = 2.2 (H-6); 7.57 s, 1 H (H-3´); 7.52 d, 1 H, J = 7.7 (H-5´); 7.32 d, 1 H, J = 3.3 (H-2); 7.31 d, 1 H, J = 9.3 (H-7); 6.73 d, 1 H, J = 8.2 (H-6´); 6.72 d, 1 H, J = 3.3 (H-3); 5.38 s, 2 H (CH_2); 3.95 s, 3 H (OCH_3); 3.90 s, 3 H ($COOCH_3$). ^{13}C NMR: 166.3 (CO); 156.4 (C-2´); 141.6 (C-5); 139.0 (C-7a); 131.5 (C-6´); 131.1 (C-1´); 129.5 (C-4´); 127.6 (C-3a); 127.5 (C-2); 122.1 (C-5´); 118.2 (C-4); 117.3 (C-6); 111.1 (C-3´); 109.5 (C-7); 104.3 (C-3); 55.7 (OCH_3); 52.3 ($COOCH_3$); 45.7 (CH_2).

Methyl 3-methoxy-4-[(5-nitroindol-2-yl)methyl]benzoate (**5**). M.p. 177.5–179 °C. For $C_{18}H_{16}N_2O_5$ (340.3) calculated: 63.53% C, 4.74% H, 8.23% N; found: 63.38% C, 4.68% H, 8.12% N. IR: 3457 (NH), 1718 (CO), 1521 and 1340 (NO_2). ^{1}H NMR: 8.65 bs, 1 H (H-1); 8.46 d, 1 H, J = 2.2 (H-4); 8.02 dd, 1 H, J_1 = 8.8, J_2 = 2.2 (H-6); 7.61 d, 1 H, J = 8.2 (H-5´); 7.60 s, 1 H (H-3´); 7.25 d, 1 H, J = 9.3 (H-7); 7.25 d, 1 H, J = 8.2 (H-6´); 6.47 s, 1 H (H-3); 4.15 s, 2 H (CH_2); 4.00 s, 3 H (OCH_3); 3.91 s, 3 H ($COOCH_3$). ^{13}C NMR: 166.5 (CO); 156.6 (C-2´); 140.8 (C-2); 140.8 (C-5); 139.0 (C-7a); 131.7 (C-1´); 130.4 (C-4´); 130.2 (C-6´); 127.8 (C-3a); 122.6 (C-5´); 117.0 (C-4); 117.0 (C-6); 111.7 (C-3´); 110.3 (C-7); 102.5 (C-3); 56.1 (OCH_3); 52.3 ($COOCH_3$); 29.6 (CH_2).

Methyl 3-methoxy-4-[(5-nitroindol-6-yl)methyl]benzoate (**6**). M.p. 171–172 °C. For $C_{18}H_{16}N_2O_5$ (340.3) calculated: 63.53% C, 4.74% H, 8.23% N; found: 63.36% C, 4.49% H, 8.10% N. IR: 3473 (NH), 1717 (CO), 1523 and 1335 (NO_2). ^{1}H NMR: 8.58 bs, 1 H (H-1); 8.42 s, 1 H (H-4); 7.55 d, 1 H, J = 7.7 (H-5´); 7.53 s, 1 H (H-3´); 7.30 m, 1 H (H-2); 7.06 s, 1 H (H-7); 7.02 d, 1 H, J = 7.7 (H-6´); 6.67 m, 1 H (H-3); 4.44 s, 2 H (CH_2); 3.84 s, 3 H (OCH_3); 3.91 s, 3 H ($COOCH_3$). ^{13}C NMR: 167.1 (CO); 157.3 (C-2´); 143.6 (C-5); 137.9 (C-7a); 134.2 (C-1´); 129.8 (C-6´); 129.7 (C-4´); 129.0 (C-6); 127.0 (C-2); 125.8 (C-3a); 122.1 (C-5´); 119.1 (C-4); 113.3 (C-7); 111.1 (C-3´); 104.3 (C-3); 55.6 (OCH_3); 52.1 ($COOCH_3$); 33.7 (CH_2).

Methyl 3-methoxy-4-[(5-nitroindol-7-yl)methyl]benzoate (**7**). M.p. 174.5–175 °C. For $C_{18}H_{16}N_2O_5$ (340.3) calculated: 63.53% C, 4.74% H, 8.23% N; found: 63.29% C, 4.61% H, 8.15% N. IR: 3466 (NH), 1719 (CO), 1527 and 1340 (NO_2). ^{1}H NMR: 9.23 bs, 1 H (H-1); 8.47 d, 1 H, J = 1.7 (H-4); 8.03 d, 1 H, J = 1.7 (H-6); 7.61 d, 1 H, J = 0.8 (H-3´); 7.57 dd, 1 H, J_1 = 7.9, J_2 = 1.0 (H-5´); 7.30 dd, 1 H, J_1 = 3.0, J_1 = 2.7 (H-2); 7.24 d, 1 H, J = 7.9 (H-6´); 6.68 dd, 1 H, J_1 = 3.0, J_2 = 2.7 (H-3); 4.25 s, 2 H (CH_2); 4.04 s, 3 H (OCH_3); 3.89 s, 3 H ($COOCH_3$). ^{13}C NMR: 166.6 (CO); 156.0 (C-2´); 141.9 (C-5); 138.0 (C-7a); 132.3 (C-1´); 130.5 (C-6´); 130.2 (C-4´); 127.0 (C-2); 123.7 (C-7); 123.7 (C-3a); 123.0 (C-5´); 117.4 (C-6); 116.6 (C-4); 112.2 (C-3´); 105.4 (C-3); 56.3 (OCH_3); 52.2 ($COOCH_3$); 31.5 (CH_2).

Dimethyl 3,3´-dimethoxy-4,4´-[(5-nitroindol-2,3-diyl)dimethyl]dibenzoate (**8**). M.p. 208–209 °C. For $C_{28}H_{26}N_2O_8$ (518.5) calculated: 64.84% C, 5.05% H, 5.40% N; found: 64.58% C, 4.91% H,

5.15% N. IR: 3454 (NH), 1717 (CO), 1521 and 1338 (NO_2). ^{1}H NMR: 8.51 bs, 1 H (H-1); 8.41 d, 1 H, *J* = 1.7 (H-4); 8.02 dd, 1 H, J_1 = 8.8, J_2 = 1.7 (H-6); 7.59 d, 1 H, *J* = 1.7 (H-3´); 7.55 d, 1 H, *J* = 1.7 (H-3´); 7.54 dd, 1 H, J_1 = 7.7, J_2 = 1.7 (H-5´); 7.47 dd, 1 H, J_1 = 7.7, J_2 = 1.7 (H-5´); 7.26 d, 1 H, *J* = 8.8 (H-7); 7.04 d, 1 H, *J* = 7.7 (H-6´); 6.94 d, 1 H, *J* = 7.7 (H-6´); 4.19 s, 2 H (CH_2); 4.13 s, 2 H (CH_2); 3.97 s, 6 H (OCH_3); 3.91 s, 3 H ($COOCH_3$); 3.89 s, 3 H ($COOCH_3$). ^{13}C NMR: 167.3 (2 × CO); 157.7 (C-2´); 157.6 (C-2´); 142.3 (C-5); 139.1 (C-2); 138.2 (C-7a); 134.9 (C-1´); 132.4 (C-1´); 131.1 (C-4´); 130.9 (C-6´); 130.1 (C-4´); 129.8 (C-6´); 128.8 (C-3a); 123.3 (C-5´); 122.7 (C-5´); 118.0 (C-4); 116.8 (C-6); 112.7 (C-3); 112.4 (C-3´); 111.5 (C-3´); 111.0 (C-7); 56.7 (OCH_3); 56.2 (OCH_3); 53.0 ($COOCH_3$); 52.8 ($COOCH_3$); 28.0 (CH_2); 24.6 (CH_2).

Dimethyl 3,3´-dimethoxy-4,4´-[(5-nitroindol-1,3-diyl)dimethyl]dibenzoate (**9**). M.p. 166.5–167.7 °C. For $C_{28}H_{26}N_2O_8$ (518.5) calculated: 64.84% C, 5.05% H, 5.40% N; found: 64.66% C, 4.90% H, 5.19% N. IR: 1719 (CO), 1517 and 1337 (NO_2). ^{1}H NMR: 8.59 d, 1 H, *J* = 2.2 (H-4); 8.06 dd, 1 H, J_1 = 9.1, J_2 = 2.2 (H-6); 7.60 m, 2 H (H-3´); 7.55 m, 1 H (H-5´); 7.51 m, 1 H (H-5´); 7.26 d, 1 H, *J* = 9.1 (H-7); 7.17 d, 1 H, *J* = 8.2 (H-6´); 7.02 s, 1 H (H-2); 6.71 d, 1 H (H-6´); 5.31 s, 2 H (CH_2); 4.14 s, 2 H (CH_2); 3.94 s, 3 H (OCH_3); 3.91 s, 3 H (OCH_3); 3.90 s, 6 H ($COOCH_3$). ^{13}C NMR: 167.0 (CO); 166.5 (CO); 157.0 (C-2´); 156.6 (C-2´); 141.4 (C-5); 139.5 (C-7a); 134.2 (C-1´); 131.2 (C-1´); 129.8 (C-4´); 129.8 (C-6´); 129.6 (C-4´); 129.6 (C-6´); 127.5 (C-2); 127.3 (C-3a); 122.2 (C-5´); 122.1 (C-5); 117.5 (C-4); 116.9 (C-6); 116.7 (C-3); 111.2 (C-3´); 111.1 (C-3´); 109.5 (C-7); 55.7 (OCH_3); 55.5 (OCH_3); 52.3 ($COOCH_3$); 52.1 ($COOCH_3$); 45.5 (CH_2); 25.3 (CH_2).

Dimethyl 3,3´-dimethoxy-4,4´-[(5-nitroindol-1,2-diyl)dimethyl]dibenzoate (**10**). M.p. 189–190 °C. For $C_{28}H_{26}N_2O_8$ (518.5) calculated: 64.84% C, 5.05% H, 5.40% N; found: 64.72% C, 4.98% H, 5.26% N. IR: 1719 (CO), 1517 and 1337 (NO_2). ^{1}H NMR: 8.51 d, 1 H, *J* = 2.2 (H-4); 8.01 dd, 1 H, J_1 = 9.1, J_2 = 2.2 (H-6); 7.53 d, 1 H, *J* = 1.4 (H-3´); 7.51 dd, 1 H, *J* = 1.4 (H-5´); 7.44 d, 1 H, *J* = 1.4 (H-3´); 7.35 dd, 1 H, *J* = 1.4 (H-5´); 7.15 d, 1 H, *J* = 9.1 (H-7); 7.06 d, 1 H, *J* = 7.7 (H-6´); 6.43 s, 1 H (H-3); 6.18 d, 1 H, *J* = 7.7 (H-6´); 5.32 s, 2 H (CH_2); 4.06 s, 2 H (CH_2); 3.96 s, 3 H (OCH_3); 3.90 s, 3 H ($COOCH_3$); 3.89 s, 3 H ($COOCH_3$); 3.80 s, 3 H (OCH_3). ^{13}C NMR: 166.7 (CO); 166.5 (CO); 156.7 (C-2´); 156.0 (C-2´); 142.6 (C-5); 141.8 (C-7a); 140.2 (C-2); 130.8 (C-1´); 130.5 (C-1´); 130.1 (C-4´); 129.7 (C-4´); 127.1 (C-3a); 125.9 (C-6´); 125.8 (C-6´); 122.0 (C-5´); 121.9 (C-5´); 117.1 (C-4); 117.0 (C-6); 110.9 (C-3´); 110.5 (C-3´); 109.1 (C-7); 103.8 (C-3); 55.4 (OCH_3); 55.5 (OCH_3); 52.2 ($COOCH_3$); 52.1 ($COOCH_3$); 42.5 (CH_2); 27.1 (CH_2).

Dimethyl 3,3´-dimethoxy-4,4´-[(5-nitroindol-3,6-diyl)dimethyl]dibenzoate (**11**). M.p. 228–230 °C. For $C_{28}H_{26}N_2O_8$ (518.5) calculated: 64.84% C, 5.05% H, 5.40% N; found: 64.68% C, 4.85% H, 5.01% N. IR: 3473 (NH), 1717 (CO), 1521 and 1331 (NO_2). ^{1}H NMR: 8.40 s, 1 H (H-4); 8.08 bs, 1 H (H-1); 7.55 m, 2 H (H-5´); 7.54 s, 2 H (H-3´); 7.16 d, 1 H, *J* = 8.2 (H-6´); 7.03 s, 1 H (H-7); 7.02 d, 1 H, *J* = 8.2 (H-6´); 6.98 s, 1 H (H-2); 4.13 s, 2 H (CH_2); 4.12 s, 2 H (CH_2); 3.96 s, 3 H (OCH_3); 3.84 s, 3 H (OCH_3); 3.90 s, 6 H ($COOCH_3$). ^{13}C NMR: 166.9 (CO); 166.8 (CO); 157.1 (C-2´); 156.8 (C-2´); 143.0 (C-5); 138.3 (C-7a); 134.2 (C-1´); 134.1 (C-1´); 129.7 (C-6´); 129.6 (C-6´); 129.5 (C-4´); 129.4 (C-4´); 129.0 (C-6); 125.4 (C-3a); 124.9 (C-2); 122.0 (C-5´); 121.9 (C-5´); 117.9 (C-4); 116.7 (C-3); 113.2 (C-7); 111.0 (C-3´); 110.9 (C-3´); 55.6 (2 × OCH_3); 52.1 (2 × $COOCH_3$); 33.8 (CH_2); 25.3 (CH_2).

Methyl 4-(hydroxymethyl)-3-methoxybenzoate (**12**). M.p. 103–104 °C (ref.[32] m.p. 99–100 °C). ^{1}H NMR: 7.65 d, 1 H, *J* = 7.7 (H-6´); 7.53 s, 1 H (H-3´); 7.37 d, 1 H, *J* = 7.7 (H-5´); 4.73 d, 2 H, *J* = 4.4 (CH_2); 3.91 s, 3 H (OCH_3); 3.90 s, 3 H ($COOCH_3$).

Method B. A mixture of indole **1** (162 mg, 1 mmol), catalyst (1 mmol, see Table I) and dioxane (5 ml) was reacted and worked up as above. The products were separated by column chromatography, for distribution and yields, see Table I.

Method C. To a solution of **1** (162 mg, 1 mmol) in dry dichloromethane (15 ml), a freshly prepared solution of butylmagnesium bromide (1 mmol) in diethyl ether (10 ml) was added dropwise under stirring at room temperature and the mixture was stirred for 10 min in argon atmosphere. Benzyl bromide **2** (311 mg, 1.2 mmol) was added, and the stirring was continued at room temperature for 2 h and at 40 °C for 24 h. The mixture was diluted with dichloromethane (20 ml), washed with water (20 ml) and dried with anhydrous magnesium sulfate. After removing the solvent, the residue was chromatographed (see method *A*). Distribution and yields of the obtained products are summarized in Table I.

Alkylation of Monoalkylindoles **3**–**5**. General Procedure

A mixture of indole **3**–**5** (68.0 mg, 0.2 mmol), Ag_2O (46 mg, 0.2 mmol) or $ZnBr_2$ (45 mg, 0.2 mmol), and dry dioxane (10 ml) was heated at 60 °C for 24 h in argon atmosphere. The reaction mixture was worked up as above and the products were separated by column chromatography. The results are summarized in Table II.

1-Methyl-5-nitrondole (**13**)

To 60% sodium hydride in mineral oil (1.1 g, 27.5 mmol) in dry tetrahydrofuran (15 ml), a solution of indole **1** in tetrahydrofuran (10 ml) was added dropwise at 0 °C and the mixture was stirred for 10 min. Methyl iodide (1.7 ml, 27.5 mmol) was added and the mixture was stirred at room temperature for 1 h, decomposed with saturated ammonium chloride solution (250 ml) and washed with ethyl acetate (4 × 100 ml). The combined organic solution was washed with water (10 ml), brine (100 ml), dried with anhydrous magnesium sulfate and the solvent removed by evaporation. Crystallization from a toluene–hexane mixture afforded 3.8 g (78%) of **13**, m.p. 165–166 °C (ref.[33] m.p. 166 °C). ^{1}H NMR: 8.58 d, 1 H, J = 2.2 (H-4); 8.13 dd, 1 H, J_1 = 8.8, J_2 = 2.2 (H-6); 7.34 d, 1 H, J = 8.8 (H-7); 7.21 d, 1 H, J = 3.3 (H-2); 6.67 d, 1 H, J = 3.3 (H-3); 3.86 s, 3 H (1-CH_3).

Alkylation of 1-Methylindole **13**

A mixture of **13** (70.5 mg, 0.4 mmol), Ag_2O (93 mg, 0.4 mmol) or $ZnBr_2$ (90 mg, 0.4 mmol), and dioxane (10 ml) was stirred at 60 °C for 24 h in argon atmosphere. The mixture was diluted with ethyl acetate (100 ml), filtered and washed with water (20 ml), brine (20 ml), and dried with anhydrous magnesium sulfate. After evaporation, the residue was chromatographed (silica gel, hexane–ethyl acetate 3:1–1:1) and products **14**–**16** were isolated.

Methyl 3-methoxy-4-[(1-methyl-5-nitroindol-3-yl)methyl]benzoate (**14**). M.p. 149–150 °C (ref.[5] m.p. 143–146 °C). ^{1}H NMR: 8.57 d, 1 H, J = 2.2 (H-4); 8.11 dd, 1 H, J_1 = 8.8, J_2 = 2.2 (H-6); 7.55 d, 1 H, J = 1.6 (H-3´); 7.54 dd, 1 H, J_1 = 8.0, J_2 = 1.4 (H-5´); 7.28 d, 1 H, J = 8.8 (H-7); 7.16 d, 1 H, J = 7.7 (H-6´); 6.92 s, 1 H (H-2); 4.13 s, 2 H (CH_2); 3.96 s, 3 H (OCH_3); 3.90 s, 3 H ($COOCH_3$); 3.79 s, 3 H (1-CH_3). ^{13}C NMR: 166.8 (CO); 156.8 (C-2´); 141.0 (C-5); 139.6 (C-7a); 134.2 (C-1´); 130.0 (C-2); 129.5 (C-6´); 129.4 (C-4´); 127.0 (C-3a); 122.0 (C-5´); 117.2 (C-4); 116.7 (C-6); 116.1 (C-3); 109.0 (C-7); 111.0 (C-3´); 55.6 (OCH_3); 52.1 ($COOCH_3$); 33.2 (1-CH_3); 25.2 (CH_2).

Methyl 3-methoxy-4-[(1-methyl-5-nitroindol-2-yl)methyl]benzoate (**15**). M.p. 193–194 °C. For $C_{19}H_{18}N_2O_5$ (354.4) calculated: 64.40% C, 5.12% H, 7.91% N; found: 64.19% C, 5.22% H, 7.87% N. IR: 1718 (CO), 1517 and 1334 (NO_2). ^{1}H NMR: 8.48 d, 1 H, J = 2.1 (H-4); 8.09 dd, 1 H, J_1 = 9.1, J_2 = 2.1 (H-6); 7.57 d, 1 H, J = 7.6 (H-5′); 7.27 d, 1 H, J = 9.1 (H-7); 7.58 s, 1 H (H-3′); 6.99 d, 1 H, J = 7.6 (H-6′); 6.39 s, 1 H (H-3); 4.76 s, 2 H (CH_2); 3.93 s, 3 H (OCH_3); 3.91 s, 3 H ($COOCH_3$); 3.64 s, 3 H (1-CH_3). ^{13}C NMR: 166.8 (CO); 156.8 (C-2′); 142.0 (C-5); 141.5 (C-2); 140.4 (C-7a); 131.2 (C-1′); 130.2 (C-4′); 129.5 (C-6′); 122.2 (C-3a); 122.2 (C-5′); 117.1 (C-4); 116.7 (C-6); 111.1 (C-3′); 108.7 (C-7); 103.5 (C-3); 55.7 (OCH_3); 52.5 ($COOCH_3$); 30.1 (1-CH_3); 27.2 (CH_2).

Dimethyl 3,3′-dimethoxy-4,4′-[(1-methyl-5-nitroindol-2,3-diyl)dimethyl]dibenzoate (**16**). M.p. 201–203 °C. For $C_{29}H_{28}N_2O_8$ (532.6) calculated. 65.41% C, 5.30% H, 5.26% N; found: 65.28% C, 5.22% H, 5.10% N. IR: 1717 (CO), 1517 and 1337 (NO_2). ^{1}H NMR: 8.52 d, 1 H, J = 2.2 (H-4); 8.09 dd, 1 H, J_1 = 8.8, J_2 = 2.2 (H-6); 7.52 d, 1 H, J = 1.1 (H-3′); 7.45 d, 1 H, J = 1.1 (H-3′); 7.42 dd, 1 H, J_1 = 7.7, J_2 = 1.1 (H-5′); 7.40 dd, 1 H, J_1 = 7.7, J_2 = 1.1 (H-5′); 7.27 d, 1 H, J = 8.8 (H-7); 6.96 d, 1 H, J = 7.7 (H-6′); 6.58 d, 1 H, J = 7.7 (H-6′); 4.20 s, 2 H (CH_2); 4.14 s, 2 H (CH_2); 3.95 s, 3 H (OCH_3); 3.90 s, 3 H (OCH_3); 3.87 s, 6 H ($COOCH_3$); 3.56 s, 3 H (1-CH_3). ^{13}C NMR: 168.3 (2 × CO); 158.3 (C-2′); 158.2 (C-2′); 141.1 (C-2); 128.4 (C-3a); 142.6 (C-5); 139.5 (C-7a); 135.5 (C-1′); 132.5 (C-1′); 131.0 (C-4′); 130.5 (C-4′); 130.3 (C-6′); 129.5 (C-6′); 123.0 (C-5′); 123.2 (C-5′); 118.1 (C-4); 117.3 (C-6); 114.5 (C-3); 111.7 (C-3′); 111.7 (C-3′); 109.6 (C-7); 55.9 (OCH_3); 56.1 (OCH_3); 52.7 ($COOCH_3$); 52.5 ($COOCH_3$); 30.6 (1-CH_3); 24.9 (CH_2); 24.6 (CH_2).

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