REACTION PATHS AND NEW MECHANISTIC ASPECTS OF THE PROTON-CATALYZED REACTION OF 3-ALKYLINDOLES WITH ARYLALDEHYDES

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Abstract ——— The mechanism of the proton-catalyzed reaction of 3-alkylindoles with arylaldehydes is elucidated by the isolation of stable intermediates and products, and by the selective control of their transformations in the course of reaction. The aldehyde electrophile attacks at N1, C2 and C3 on the indole enamine structure with the temperature, the reaction time and the proton concentration controlling the relative quantities and distribution of products. It was established indirectly that an ipso-attack by intermediary cations with iminium and indolenine structure takes place at the 3- position of 3-alkylated indoles. This was made possible by the isolation of hitherto unknown tetrahydropyrrolodiindoles 14, 17. These compounds should be formed from intermediary indolylmethyl-indoleninium ions 13, 11, which are trapped by stereoelectronic controlled intramolecular cyclization.

INTRODUCTION

Electrophilic substitutions of 3-substituted indoles, as far as mechanism and synthesis are concerned, are widely held to be of great interest. They play an important role particularly in the synthesis of natural and physiologically active compounds[1,2]. Thus, 3-alkyl-substituted indoles normally react with numerous electrophiles after a preliminary ipso-attack at the indole 3-position (*greatest π-density on the C-skeleton, greatest* HOMO-coefficient)[2] via an intermediary indoleninium ion which subsequently undergoes a Wagner-Meerwein rearrangement forming a 2,3-disubstituted indole. This mechanism is widely documented in the experimental literature[3-13].

Here we are concerned with proton-catalyzed reactions of indoles with *arylaldehydes. Our report,* with experimental confirmation, for the first time establishes the reaction paths of this carbonyl electrophile in reaction with 3-alkylindoles in hydrochloric alcohols (e.g. methanol, 2-propanol)[14]. Not enough is in fact known[6,15] about the mechanistic details of the orientation of initial attack of this electrophile on 3-substituted indoles. To the best of our knowledge there is as yet no detailed and systematical elucidation of the whole course of reaction via solvolytic trapping and experimental isolation of sufficiently stable intermediates in the reaction sequence "3-alkyl-

indole / arylaldehyde". In principle two mechanistic pathways can be discussed: ipso-attack of the aldehyde at the indole 3-position with subsequent 3 ---->2 shift in the intermediaryly formed indoleninium ion [3-13] or a direct N 1- and C 2-attack. All that has been reported experimentally so far is a discussion of reversible N- and irreversible intermolecular C 2-attack on the indole nucleus based on the reactions of 3-propylindole with few aromatic aldehydes [16]. In these reactions 3-nitrobenzaldehyde yields in ethanol/sulfuric acid N-(α-ethoxy-3-nitrobenzyl)-3-propylindole and phthalaldehyde acid autocatalytically a halbaminal lactone [16,17]. In the reaction between 3-methylindole (1a) with formaldehyde [18] a mechanistically interesting substance was isolated. It was discussed as a probable intermediate with the structure 3-methyl-2-(3-methyl-3H-indole-3-yl)methyl-1H-indole. However, no mechanistic details and connections were discussed so far.

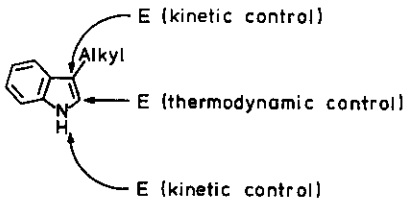
RESULTS AND DISCUSSION

3-Alkyl-substituted indoles 1 react with several arylaldehydes 2 in the molar proportion 2:1, leading to good to moderate yields of crystallizable 2,2'-bisindolylarylmethanes 20 [19] (scheme 1). The reaction is relatively smooth and takes place in hydrochloric alcohol (circa 2.5 N-HCl) at room temperature, provided that no great steric demands be placed on the reactants. Compounds 20 are thermodynamically the most stable products. However, these methanes frequently contain 1-3% impurities in the form of regioisomers. In order to elucidate the mechanism of this general reaction we chose as a suitable model system the reaction of 3-methylindole 1a ($R=CH_3$) with 4-nitrobenzaldehyde 2a (R' = 4-nitrophenyl). The first reaction described by us [19] (method I, experimental), which leads by a fast movement of the equilibrium to 20 is less suitable for a mechanism elucidation via product identification. The tlc-analysis for this reaction gave maximal multiplicity of products even before the addition of the full amount of acid (circa 2.5 N-HCl). To clarify the course of reaction, reproducible results must be obtained. It is therefore necessary to add the acid rapidly to the alcoholic solution of the reactants while accepting that there will be a solvatation-induced rise in temperature.

By varying the temperature, the reaction time, the acid concentration and the solvent, and by keeping the reaction under careful control, we succeeded in clarifying the whole course of the reaction in this complex system (scheme 1). Our purpose was also an attempt to gain experimental access specifically to trace products, potential key components of the reaction mechanism.

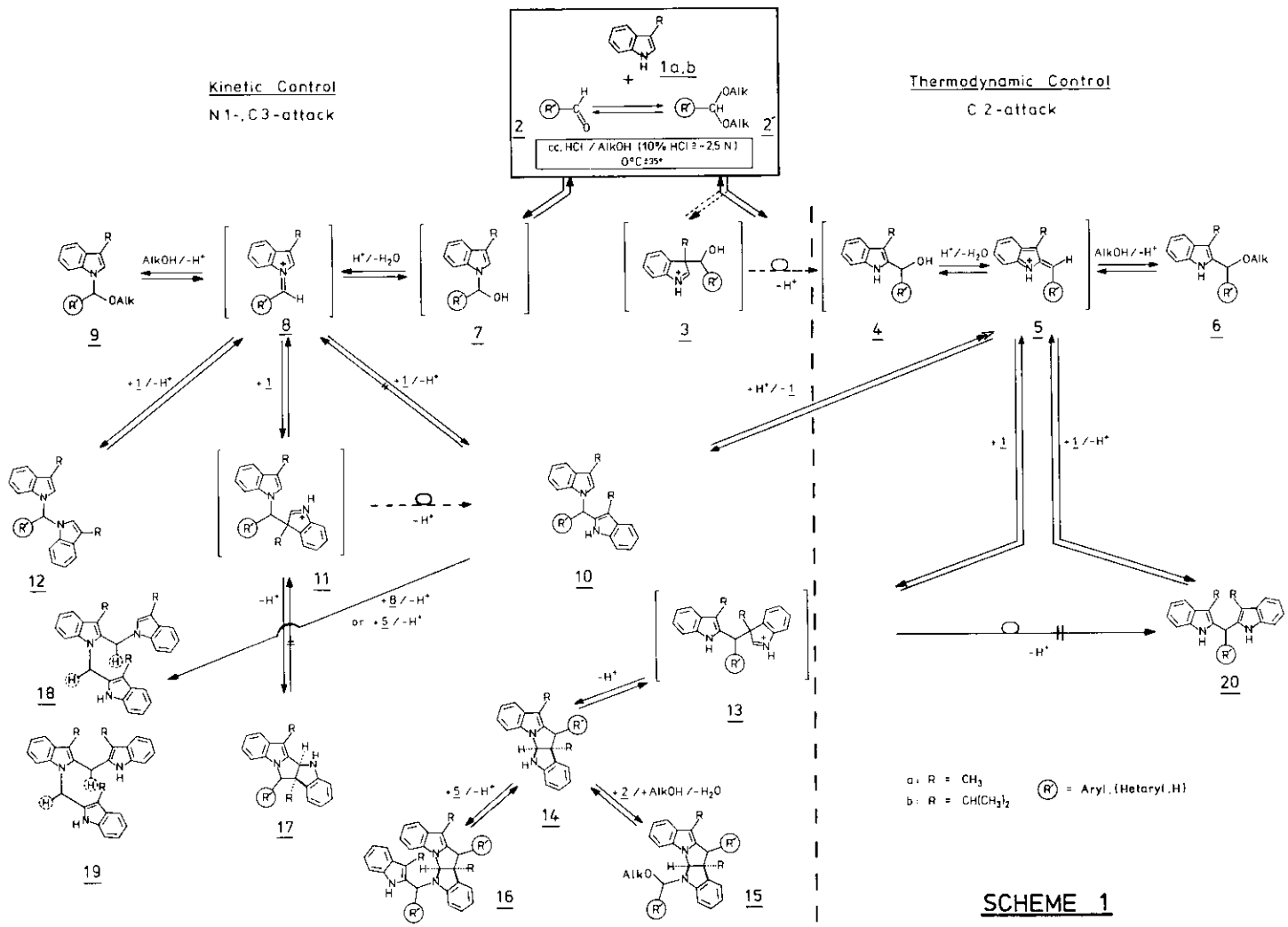
Our experiments established that the products isolated by us as part of our mechanism clarification are not artifacts resulting from contact with a base during quenching of the reaction. Our research has furthermore shown that the results here presented are also valid in principle when 3-isopropylindole 1b and other arylaldehydes (e.g. 4-dimethylaminobenzaldehyde) are employed.

The 3-substituted indole 1a is attacked by the electrophile at the N1, C2 and C3 positions. The multiplicity of linkage of the reactants reveals an almost complete mutual combination of the individual indole enamine positions. The reaction can in principle be divided into the kinetically controlled reaction paths (N1- and C3-attack), and the thermodynamically controlled reaction path (C2 direct attack).



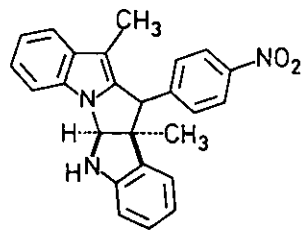
Our experiment with 1a reacting with 4-nitrobenzaldehyde is a prime example of how, at very low temperatures, and where the temperature does not rise above $-5^{o}C$ when the acid is added (method IV, experimental), a N1- and C3-attack prevails over a C2-attack. A gradual diminution of the acid concentration favours the N-attack on the indole. At $0^{o}C$, and where the temperature does not rise above $+27^{o}C$, when the acid is added (method III, experimental), the clearly direct C2-attack[15,16] becomes competitive as a result of this thermodynamic product control. The analysis of the product transformation during the course of reaction demonstrates that the whole reaction system can be expressed as a mobile equilibrium with a "steady state" character. The selective mechanistic steps derived from product identification and from controlling the product transformation can be described as follows.

A charge-controlled attack[2] by the electrophile on the indole enamine structure leads first by way of the non-isolable intermediates 7 and 8 to the hemiaminal ether 9, which can be regarded as the solvolytic product of the reactive iminium ion 8. This initial N-attack conforms to the mechanism principle discussed in the literature[15,16]. In the strongly acidic medium, 9 is produced to the extent of as much as 11% with reference to the amount of 2 employed (method II, experimental). This substance may occur either as a result of the reaction of the aldehydium ion (O-protonated aldehyde) at N1 of the indole 1a via the steps 7 and 8, or else directly in a reaction with the 4-nitrophenylalkoxy-carbenium ion. A control experiment to that without 1a shows that 4-nitrobenzaldehyde in methanol, under the given conditions, occurs to the extent of circa 50% as dimethylacetal. At lower temperatures and very short reaction times we found that when 1a reacts in hydrochloric ethanol with the dimethylacetal of the 4-nitrobenzaldehyde then no indolyl-arylmethoxymethane 6 and practically no regioisomer 9 can be formed. As a result it is clear that the dimethylacetal in the function of the arylalkoxycarbenium ion does not here perform a crucial role as an alkoxy-alkylating reagent.

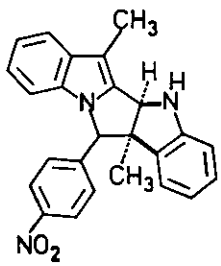

Kinetic Control
N 1-, C 3-attack
Thermodynamic Control
C 2-attack
1a,b
2
2'
cc. HCl / AlkOH (10% HCl ≙ ~2.5 N)
0°C ± 3°
AlkOH / -H+
H+ / -H2O
-H+
+1 / -H+
+1
+H+ / -1
+8 / -H+
or +5 / -H+
+5 / -H+
+2 / +AlkOH / -H2O
9
8
7
3
4
5
6
12
11
10
18
17
13
19
14
16
15
20
a: R = CH3
b: R = CH(CH3)2
(R') = Aryl, (Hetaryl, H)

SCHEME 1

From the identification of products it can furthermore be seen that the reactive iminium ion 8, which is present in the equilibrium mixture, further reacts with the indole 1a still present in the medium. This subsequent reaction follows three separate paths; firstly to the 1,1'-bisindolylarylmethane 12, secondly to the 1,2'-bisindolylarylmethane 10, and thirdly to the tetrahydropyrrolodiindole 17 (pure epimer). The fact that this sequence leads to the hitherto unknown tetrahydropyrrolodiindole 17 is indirect evidence of an initial ipso-attack by 8 on 1a. The compound



14



17

17 represents an irreversibly formed cyclization product of the indoleninium ion 11 which cannot be detected in any way. It proved possible to elucidate the constitution and stereochemistry of 17 in the first place by means of 400 - MHz - ^{1}H- and ^{13}C-nmr-spectroscopy. The stereochemistry of 17 (cis-linkage of the angular centers) results from the stereoelectronic situation in the cation 11. In principle a subsequent reaction of 10 with the arylaldehyde forming 18 and 19 (4-nitrophenyl derivatives) can take place. In the reaction with the sterically less demanding and more reactive formaldehyde, which follows the same reaction sequence, we succeeded in isolating sufficient quantities of the derivatives 18 and 19 as secondary products of the methane 10 (R' = H) for the purposes of structural identification. The comparison of the spectroscopic data of 17 with those of the indolenine described in the literature[18] (structural type of the conjugated base of 13) suggests that the constitution described refers rather to a tetrahydropyrrolodiindole (14 or 17; R' = H in scheme 1).

Among the products of the reaction of 1a with 2 those with exclusively C-C linkage are the isolable indolylarylalkoxymethanes 6 and the end product of the sequence, the relatively stable 2,2'-bisindolylarylmethanes 20. The solvolytic product 6 can in principle arise in three ways. First it is conceivable that an initial ipso-attack of the aldehyde at the indole 3-position takes place, forming 3, which then undergoes Wagner-Meerwein rearrangement to 4[2,6,7], which then leads via cation 5^{+} to 6. We regard this path as unlikely for it would certainly be difficult for a Wagner-Meerwein rearrangement to take place because of the very good leaving group in 3 in the presence of the protic and highly cation stabilizing solvent. Compound 3

$^{+}$ The first reference in the literature to the isolation of 5 (R = CH_3, R' = 4-dimethylaminophenyl) was as a perchlorate in a reaction of 1a and 4-dimethylaminobenzaldehyde[20].

was detected neither as a conjugated base nor indirectly as 3-(alkoxybenzyl)-indolenine. Clearly, the equilibrium concentration of 3, if it is formed at all, is too small. We assume that 6 is produced by a direct attack of the aldehyde on the indole 2-position (thermodynamic control) [15,16] and by solvolysis from 10. Studies of the solvolytic transformation of 10 show that the equilibrium of cleavage is far on the side of 5 so long as the reaction partner 10 remains in solution. We conclude then that this is established as one path to 6 in the whole reaction system.

The 2H-indoleninium ion 5, present in the equilibrium, reacts analogously to the regioisomeric cation 8 via C3-attack on 1a by way of the non-isolable indoleninium ion 13 to form the isolated tetrahydropyrrolodiindole 14 (2 epimeres A, B). This compound too, constitutionally isomeric to 17, should represent a trapped product, formed under stereoelectronic control, of the reactive indoleninium ion 13. A reaction whose mechanism is related, that of 3,3-dimethylindolenine with 1a to 2-(3-methylindole-1-yl)-3,3-dimethylindoline, also in a proton acidic medium, has been described in the literature[21]. The analysis of the constitution and stereochemistry (cis-annelation) of 14 required a great deal of spectroscopic investigation, particularly as it was necessary to establish beyond all doubt that it was 14 and not some conceivable dimeric/trimeric indolenines[10,22] and other isomeres. One compound with tetrahydropyrrolodiindole structure[23,24], related to 14, provided information that was useful for the elucidation of the constitution, as did a 2-(1-indolyl)-indoline mentioned in the literature[25]. In the case of an epimer of 14 we obtained suitable crystals, an X-ray analysis of which enabled us to establish the structure conclusively[26]. The N-acetylation of the epimeres of 14 provided further arguments in confirmation of the structure. As a result of the nucleophilic reactivity of the indoline-N in 14 subsequent reactions can occur, proof of which was provided when 15 (2 diastereomeres) and 16 (1 diastereomer) were isolated ; 16 also plays a role in the cleavage reaction of 14.

The experimental results show that in this reaction system, although a Wagner-Meerwein rearrangement of the intermediate 13 to 20 is conceivable,it is most unlikely. Thus, cleavage reaction of an epimer of 14, both under mild conditions (method V, experimental) and under more forced conditions (e.g. 1-2.5 N hydrochloric acid; acetic acid/100°C) always leads to 1a and 5, or 6 in the presence of alcohol. It is possible to demonstrate the epimerization of a pure epimer of 14 experimentally under conditions when proton-catalyzed solvolysis of 14 provides sufficient amounts of 6 via 5 (scheme 1). The epimer of 14 newly formed in this way occurs in considerably larger amounts than 20 (formed from 1a and 5 in a slow reaction, which is moreover suppressed at temperatures below 0°C). A control experiment to this (reacting 1a with 6, method III, experimental , circa 90% conversion within 15 min) shows that tetrahydropyrrolodiindole epimeres 14 prevail over 2,2'-bisindolylarylmethane 20 in a minimal ratio of 2 : 1. But when the N-methy-

lated derivative of 6[19] is employed in this reaction instead of 6 then a potentially formed N-monomethyl derivative of 13 does not accumulate as might be expected, since final cyclization to the tetrahydropyrrolodiindole skeleton is inhibited. In fact, in this case there is no evidence of ipso-attack at all. From all these results it follows: 1. The observed preponderance of ipso-attack under kinetic control of reaction is decisively determined by the high cyclization tendency of indoleninium ion 13. 2. Predominant reaction principle of the indoleninium ion 13 is not a Wagner-Meerwein rearrangement, but cyclization to 14 or alternatively solvolytic cleavage to 1a and 5, or as the case may be, to 6. 3. Our results are a prime example of how unambiguous experimental proof of ipso-attack by an electrophile on 3-substituted indoles does not necessarily imply also evidence in favour of indirect 2-substitution by way of intramolecular 3 $\longrightarrow$ 2 shift.

Based on our detailed experimental results we think that the Wagner-Meerwein rearrangement during the course of the electrophilic substitution on 3-substituted indoles does not always follow. Particularly when the intermediary formed indoleninium ion has a good leaving group (Aryl-$CHOH^+$, Aryl-$CHOAlk^+$) [27] the heterolytic process of this cation (for instance 3 or its alkoxy derivative) should be favoured compared with a 3 $\longrightarrow$ 2 shift, which in general conforms to the usual behaviour of the cation 13.

EXPERIMENTAL

Methods

0.02 mole 1a / 0.01 mole 4-nitrobenzaldehyde / 150 ml MeOH / 56 ml conc. HCl

I conc. HCl (of r.t.) was added dropwise to the solution of the reactants at r.t. during 20 - 25 min. Reaction time: 12 h at r.t. under nitrogen atmosphere.

II conc. HCl (of r.t.) was added rapidly to the solution of the reactants at 0°C. Reaction time: 12.5 min, intense cooling by ice.

III conc. HCl (of 0°C) was added rapidly to the solution of the reactants at 0°C. Reaction time: 30 min, intense cooling by ice.

IV conc. HCl (of -35°C) was added rapidly to the solution of the reactants at -35°C. Reaction time: 4 h at -35°C.

V Cleavage of 14 (0.95 mmole 14, 450 ml MeOH, 169 ml 1N methanolic HCl): 1N methanolic HCl (of 0°C) was added rapidly to the solution of 14 at 0°C. Reaction time: 4 h at 0°C. Cleavage of 10 can be achieved analogously.

VI Intermolecular rearrangement 10 $\longrightarrow$ 20 (1 mmole 10, 200 ml MeOH, 75 ml conc. HCl): conc. HCl (of r.t.) was added as slowly as possible so that reactant 10 remains in solution. Reaction time: complete conversion within 6 - 7 h at r.t.

Reactions I - VI were quenched by addition of aqueous NH_3 at 0°C (IV: -35°C), pH was adjusted to 8 - 9.

Method	Compound*	Procedure of Isolation	Yield(%)
I	20**	The crude product was washed with water, ice-cold MeOH. Direct crystallization from (aqueous) EtOH[19]. Purity 97-98%, by-product 10 can be separated by chromatography (SiO_2, toluene).	77 (aq.EtOH)
II		The crude material was extracted with ether, the extracts washed with water and dried. Solvent and traces of water were carefully removed. To facilitate chromatographic separation the residue was taken up in very little dry toluene, the precipitate obtained (20) was recrystallized once.	
	20**		10.9
		The collected mother liquors, concentrated under reduced pressure carefully if necessary, were chromatographed on silica gel column(s): (step of purification / eluant)	
	9	1. toluene 2. toluene / light petroleum 7 + 3	8.1 (EtOH)
	10	1. toluene 2. toluene / light petroleum 7 + 3	2.1 (EtOH)
	12	1. toluene 2. light petroleum ⟶ light petroleum / toluene 1 + 1	0.1 (EtOH)
	14 A+B	1. toluene 2. $CHCl_3$	26.8
	14A	3./4. light petroleum / diisopropyl ether 1 + 1 7.4% (EtOH)	
	14B	3./4. light petroleum / diisopropyl ether 1 + 1 11.3% (EtOH)	
III		The crude material was extracted with CH_2Cl_2, the extracts washed with water and dried. After removal of solvent the residue was chromatographed on silica gel column / tlc plates repeatedly, suffering heavy loss of yield: (step of purification / eluant)	
	15A	1. toluene 2. toluene (tlc) 3. $CHCl_3$ / light petrol 6 + 2 4. CH_2Cl_2 / light petrol 6 + 2	0.01 - 0.02
	16A	1. toluene 2. toluene (tlc) 3. $CHCl_3$ / light petrol 6 + 2 4. CH_2Cl_2 / light petrol 6 + 2	0.01 - 0.02

Method	Compound*	Procedure of Isolation	Yield (%)
III		The crude material was extracted with ether, the extracts washed with water and dried well. After evaporation the residue was chromatographed on silica gel column(s): (step of purification / eluant)	
	15B	1. light petroleum / ether / toluene 30 + 22 + 3 2. toluene	0.4 (MeOH)
III		The crude material was worked up as above (III, 15B). The residue after evaporation was chromatographed on silica gel column(s): (step of purification / eluant)	
	17	1. light petroleum / EtOAc 9 + 1 2. toluene 3. light petroleum / diisopropyl ether 6 + 4	2.4 (hexane)
V		The reaction mixture was diluted with water (1:3) and extracted with ether / light petroleum. The organic layers were washed with water, dried, and evaporated. The residue was chromatographed on silica gel column and tlc-plates affording 98 mg of 1a (= 78.7%) and 222 mg of pure 6 (various attempts to induce crystallization of semi-solid 6 failed however):(eluant)	
	6	1./2. light petroleum / ether 8 + 2	78.9
VI		The precipitate was washed with water and dried in vacuo. Direct crystallization from little absolute EtOH gave pure 20.	
	20**		62 (EtOH)

*Satisfactory elemental analyses were obtained (trace compounds 15A / 16A were identified by mass spectrometric and spectroscopic methods).

**Needles of 20 tend to retain various solvents (especially traces of water): elemental analysis, mp (decomp. temp. was found to be variable within a range of 231 - 260°C / 250 - 251°C [28]), rel. intensities of M^+ and main ms fragments can be influenced heavily.

Light petroleum had bp 30 - 50°C.

Cpd.	$M^{\oplus}$ 70 eV (% rel.)	IR ν cm^{-1}	^{1}H-NMR δ = ppm	^{13}C-NMR δ = ppm 100 MHz
6	296 (100)	3465(m, NH) 2835(w), 1355(s) 1190/1110(w) 1090(m) [CCl_4]	2.33 (s, 3H, indole-Me), 3.37 (s, 3H, -OMe), 5.62 (s, 1H, HC-O) aromatic H: 6.95 - 7.7 (m, 6H), 7.95 (br.s, 1NH, exch. NaOD), 8.09 (2H, AA' 4-nitrophenyl, J = 9Hz) [60 MHz, $CDCl_3$]	sp^3 : 8.6 (indole-Me), 57.0 (-OMe), 76.2(HC-O) sp^2 (d): 111.0, 118.9, 119.5, 122.7, 123.7, 127.25 sp^2 (s): 110.8, 128.75, 131.6, 135.9, 147.45, 147.8 [$CDCl_3$]
9	296 (8)	2835(w), 1515(s) 1350/1325(s) 1190/1180(m) 1095/795(s) 750/720(s)[KBr]	2.31 (d, $J_{Me,C2-H}$= 1.1Hz, 3H, indole-Me), 3.35 (s, 3H, -OMe), 6.41 (s, 1H, HC-O) Aryl-H: 6.90 (qu, 2 lines resolved, $J_{C2-H,Me}$= 1Hz, 1H, C2-H), 7.05 - 7.8 (m, 6H), 8.16 (2H, AA' 4-nitrophenyl, J = 9Hz) [60 MHz, $CDCl_3$]	sp^3 : 9.6 (indole-Me), 56.1 (-OMe), 86.4 (HC-O) sp^2 (d): 110.0, 119.4, 119.9, 122.3, 123.2, 123.5, 127.1 sp^2 (s): 113.1, 129.7, 136.4, 145.8, 148.0[$CDCl_3$]
10	395 (7)	3405(s,NH) 1605/1595(w) 1515/1460/1350(s) 1225/850(m) 745/735(s)[KBr]	2.19 (s, 3H, indole-Me), 2.28 (d, $J_{Me,C2-H}$= 1Hz, 3H, indole-Me), 6.68 (qu, 3 lines resolved, $J_{C2-H,Me}$= 1Hz, 1H, C2-H), 7.0 - 7.40 (m, 8Ar-H + CH), 7.45 - 7.85 (m, 2Ar-H/1NH, exch. NaOD), 8.08 (2H, AA' 4-nitrophenyl, J = 9Hz) [60 MHz, $CDCl_3$]	sp^3 : 8.6 (indole-Me), 9.7 (indole-Me, 2-unsubst.ring), 55.9(CH) sp^2 (d): 109.5, 111.15, 119.1, 119.5, 119.8, 119.95, 122.3, 122.9, 123.65, 124.25, 128.4 sp^2 (s): 111.3, 112.2, 128.9, 129.5, 129.7, 135.6, 136.4, 146.1, 147.8 [$CDCl_3$]
12	395 (7)	1610/1600(m) 1520/1460/1450/ 1350/1340(s) 1180/1015/830(m) 743/740(s)[KBr]	2.26 (d, $J_{Me,C2-H}$= 1.1Hz, 6H, Me), 7.92 (s, 1H, CH) Aryl-H: 6.53 (qu, 2 lines resolved, $J_{C2-H,Me}$= 1.1Hz, 2H, C2-H), 7.16 - 7.24 (m, 8H), 7.58 - 7.64 (m, 2H), 8.215 (2H, AA' 4-nitrophenyl, J = 9.2Hz) [400 MHz, $CDCl_3$]	sp^3 9.7 (indole-Me), 67.9 (CH) sp^2 (d): 109.2, 119.6, 120.3, 122.5, 122.7, 124.2, 128.5 sp^2 (s): 113.1, 129.6, 136.4, 144.1, 148.5 [$CDCl_3$]

Cpd.	$M^{\oplus}$ 70 eV (% rel.)	IR ν cm^{-1}	^{1}H-NMR δ = ppm	^{13}C-NMR δ = ppm 100 MHz
14A	395 (25)	3410(m,NH) 1605/1595(m) 1515/1350(s) 1242/1060/855(m) 745/740(s) [KBr]	1.06 (s, 3H, indoline-Me), 1.89 (d, ^{5}J = 0.5Hz, 3H, indole-Me), 4.80 (s, 1H, CH, ^{5}J = 0.5Hz is not resolved), 4.90 (d, $J_{NH,CH}$= 2Hz, 1NH), 5.83 (d, $J_{CH,NH}$= 2Hz, HN-CH-N) Aryl-H: 6.60, 6.86, 7.08, 7.14, 7.19 - 7.31, (m, 4H), 7.41, 7.51, 8.17 (2H, AA' 4-nitrophenyl, J = 9Hz) [400 MHz, $CDCl_3$]	sp^3 : 8.4 (indole-Me), 22.7 (indoline-Me), 52.8 (CH), 63.3 (-C-), 80.3 (HN-CH-N) sp^2 (d): 109.2, 110.6, 119.3, 119.5, 120.1, 121.25, 122.5, 123.7, 128.8, 129.7 sp^2 (s): 103.0, 131.5, 133.9, 135.2, 140.45, 147.2, 147.4 (147.2 or 147.4 = 2C) [$CDCl_3$]
			0.95 (s, 3H, indoline-Me), 1.85 (s, 3H, indole-Me), 4.96 (s, 1H, CH, sharpening on irradiation of indole-Me), 5.93 (d, $J_{CH,NH}$= 1.6Hz, 1H, HN-CH-N, on addition of D_2O : s), 7.34 (d, $J_{NH,CH}$= 1.6Hz, 1NH, exch. D_2O) Aryl-H: 6.57, 6.72, 7.00, 7.03, 7.14, 7.32 - 7.52 (br. hump BB' 4-nitrophenyl), 7.40, 7.48, 7.71, 8.21 (2H, AA' 4-nitrophenyl, J = 9Hz) [400 MHz, DMSO-d_6, additional proton decoupling experiments]	sp^3 : 8.2 (indole-Me), 22.5 (indoline-Me), 50.9 (CH), 62.5 (-C-), 79.41/79.48 (HN-CH-N) sp^2 (d): 109.2, 110.8, 118.4, 118.5, 118.95, 120.5, 123.1, 123.6, 128.5, 130.1 sp^2 (s): 100.8, 131.2, 133.1, 135.6, 141.6, 146.6, 147.53/147.59, 148.65 [DMSO-d_6]
14B	395 (26)	1315(m,NH) 1345(s),1315(m) 1230/1215(w) 1050(w) [CCl_4] KBr-spectra depend on type of crystals	1.74 (s, 3H, indoline-Me),1.84 (d, ^{5}J = 0.9Hz, 3H, indole-Me), 4.64 (s, 1H, broadened by ^{5}J = 0.9Hz, CH), 4.90 (br. d, $J_{NH,CH}\cong$ 2.9Hz, 1NH), 5.88 (d, $J_{CH,NH}$= 2.9Hz, HN-CH-N) Aryl-H: 5.90, 6.36, 6.51, 6.89, 7.14, 7.18 (br. BB' 4-nitrophenyl, J = 9Hz), 7.23, 7.42, 7.51, 8.01 (2H, AA' 4-nitrophenyl, J = 9Hz) [400 MHz, $CDCl_3$]	sp^3 : 8.45 (indole-Me), 27.45(indoline-Me), 54.8 (CH), 64.7 (-C-), 80.7 (HN-CH-N) sp^2 (d): 109.3, 110.1, 119.1 (2C), 119.55, 121.2, 123.0, 125.0, 128.5, 130.2 sp^2 (s): 102.5, 130.0, 131.5, 133.9, 140.0, 147.0, 148.3 (147.0 or 148.3 = 2C) [$CDCl_3$]

Cpd.	$M^{\oplus}$ 70 eV (% rel.)	IR ν cm^{-1}	^{1}H-NMR δ = ppm	^{13}C-NMR δ = ppm 100 MHz
14B (cont.)		modification mp 182-183.5° C 3430 (s, 1NH) 1515/1345 (s) 745(s),712(m)[KBr] modification mp 194° C 3430/3405(m,NH) 1515/1510/1345(s) 745/740(s) 715(m)[KBr]	1.68 (s, 3H, indoline-Me), 1.80 (s, broadened by $^5J_{Me,CH}$, 3H, indole-Me), 4.86 (br. s, 1H, CH; 2 populations, broadened by $^5J_{Me,CH}$), 5.915/5.919 (1H, s/d, $J_{CH,NH}$= 3Hz, cis/trans HN-CH-N; 1 s on exchange H/D; 2 s on irrad. of NH), 7.25 (d, $J_{NH,CH}$= 3Hz, 1NH, exch. D_2O) Aryl-H: 5.867/5.887 (1H), 6.230/6.237 (1H), 6.47, 6.82, 7.05, 7.14, 7.30 (2H, br. BB' 4-nitrophenyl), 7.44, 7.648/7.650 (1H), 8.07 (2H, AA' 4-nitrophenyl, J = 9Hz) [400 MHz, DMSO-d_6, decoupling experiments, all solvent effects disappeared on addition of D_2O]	sp^3 : 8.5 (indole-Me), 27.2 (indoline-Me), 53.4 (CH), 64.0 (-C-), 80.35/80.40 (HN-CH-N) sp^2 (d): 108.92/108.97, 110.5, 117.29/117.34, 118.4, 119.0, 120.5, 122.9, 124.8, 128.1, 130.5 sp^2 (s): 100.8, 130.24/130.29, 131.45, 133.3, 140.4, 146.45, 147.7, 149.31/149.37 [DMSO-d_6]
15A	560 (15)	2830(w),1605(m) 1515/1510(s) 1345(s) 1105/1075(m) 855(m) 740(s)[KBr]	1.10 (s, 3H, indoline-Me), 1.86 (d, $^5J_{Me,CH}$= 1.0Hz, 3H, indole-Me), 3.42 (s, 3H, -OMe), 4.82 (poorly resolved q, $^5J_{CH,Me}$= 1Hz, 1H, CH), 6.07 (s, 1H, N-CH-N), 6.09 (s, 1H, N-CH-O) Aryl-H: 6.76, 6.86 - 6.925 (m, 3H), 6.96, 7.06, 7.18, 7.28, 7.37 + 7.45 (2 + 2H, 2 BB' 4-nitrophenyl, J ≅ 8.5 + 8.8 Hz), 7.81 + 8.23 (2 + 2H, 2 AA' 4-nitrophenyl, J = 8.8Hz)[400 MHz, CD_2Cl_2]	
15B	560 (13)	2830(w) 1605/1595(m) 1515/1345(s) 1105/1085(m) 855/835(m) 745(s)[KBr]	1.64 (s, 3H indoline-Me), 1.88 (d, $^5J_{Me,CH}$= 1Hz, 3H, indole-Me), 3.59 (s, 3H, -OMe), 4.56 (s, broadened by $^5J_{CH,Me}$, 1H, CH), 5.77 (s, 1H, N-CH-N), 6.12 (s, 1H, N-CH-O) Aryl-H: 6.095, 6.385, 6.44, 6.87, 7.12 - 7.21 (m, 4H), 7.51, 7.59 (2H, BB' 4-nitrophenyl, J = 9Hz), 7.68, 7.98 + 8.17 (2 + 2H, 2 AA' 4-nitrophenyl, J = 8.8Hz)[400 MHz, CD_2Cl_2]	sp^3 : 8.4 (indole-Me), 28.1 (indoline-Me), 54.6 (CH), 56.2 (-OMe), 63.9 (-C-), 85.55 (N-CH-N), 90.95 (N-CH-O) sp^2 (d): 110.6, 110.8, 118.9, 119.9, 120.0, 121.5, 123.1, 123.7, 125.0, 127.7, 128.6, 130.0 sp^2 (s): 103.6, 131.4, 132.3, 134.2, 140.45, 145.4, 146.9, 147.1, 147.3, 148.0 [$CDCl_3$]

Cpd.	$M^{\oplus}$ 70 eV (% rel.)	IR ν cm^{-1}	^{1}H-NMR δ = ppm	^{13}C-NMR δ = ppm 100 MHz
16A	659 (0,3)	3440(w,NH) 2925/1605(m) 1520/1510(s) 1455(m),1350(s) 855(w) 740(s)[KBr]	0.87 (s, 3H, indoline-Me); 1.98 (d, $^5J_{Me,CH}$= 1.1Hz, 3H, indole-Me), 2.41 (s, 3H, indole-Me), 4.89 (s, broadened by $^5J_{CH,Me}$, 1H, CH), 5.96 (s, 1H, N-CH-N), 6.42 (s, 1H, N-CH-phenyl-NO_2) Aryl-H: 6.035, 6.90, 6.98, 7.05 - 7.43 (2 m, 11H, with 2 br. BB' 4-nitrophenyl circa 7.15 + 7.35), 7.57, 7.645, 7.89 (br. s, 1H, indole-NH), 8.10 + 8.22 (2 + 2H, 2 AA' 4-nitrophenyl, J = 9Hz) [400 MHz, CD_2Cl_2]	
17	395 (100)	3365(m,NH) 1605(m) 1520/1485(s) 1455(m) 1345/745(s) 705/700(m)[KBr]	1.81 (s, 3H, indoline-Me), 2.44 (s, 3H, indole-Me , sharpening on irradiation of signal 5.06), 4.33 (br. s, 1NH, exch. NaOD), 5.06 (s, 1H, HN-CH, sharpening on exch. of NH), 5.36 (s, 1H, CH) Aryl-H: 6.26, 6.38, 6.48, 6.62, 6.87, 6.95 - 7.2 (br. hump BB' 4-nitrophenyl), 6.98, 7.08, 7.57, 7.94 (2H, br. AA' 4-nitrophenyl) [400 MHz, $CDCl_3$] Solvent effects in DMSO-d_6 are analogous to those of compound 14B.	sp^3 : 8.9 (indole-Me), 27.25 (indoline-Me), 65.2 (-C-), 66.5 (HN-CH), 71.6 (CH) sp^2 (d): 110.0, 110.3, 118.7, 119.3, 119.6, 121.6, 123.1, 124.7, 128.4, 128.8 sp^2 (s): 103.6, 129.9, 132.3, 133.7, 141.8, 145.9, 147.55, 150.2 [$CDCl_3$]
20**	395 (68)	3445/3390(s,NH) 1605/1595(m) 1510/1455/1347/ 1335/740(s) 715(m)[KBr] 3445(m, NH) [CCl_4]	2.17 (s, 6H, indole-Me), 6.06 (s, 1H, CH), 7.0 - 7.8 (m, 10Ar-H + 2 NH near 7.65), 8.13 (2H, AA' 4-nitrophenyl, J = 9Hz) [60 MHz, $CDCl_3$]	sp^3 : 8.6 (indole-Me), 40.8 (CH) sp^2 (d): 111.0, 118.7, 119.8, 122.2, 124.1, 129.3 sp^2 (s): 109.5, 129.3, 131.6, 135.5, 147.05, 147.7 [25,2 MHz, $CDCl_3$]

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