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ELECTROPHILIC SUBSTITUTION IN INDOLES: DIRECT ATTACK AT THE 2-POSITION OF 3-ALKYLINDOLES

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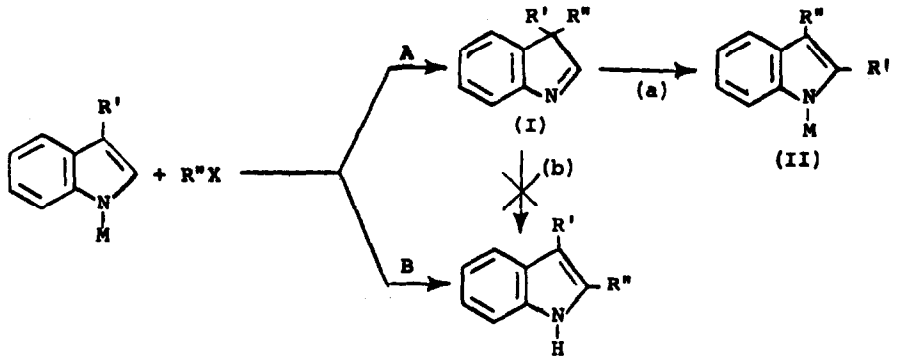
The reactivity of 3-alkylindoles towards alkylation has been extensively studied in the last few years.[1] The general conclusion was that substitution at the 2-position of 3-alkylindoles involved a primary attack at position 3- followed by rearrangement. (Scheme 1 : pathway A).[2] On the contrary, our own work, which was started some years ago,[3] is concerned with a direct attack at the 2-position of 3-alkylindoles. (Scheme 1 : pathway B). We report now the general course of the reaction.

Scheme 1



M = H; MgBr

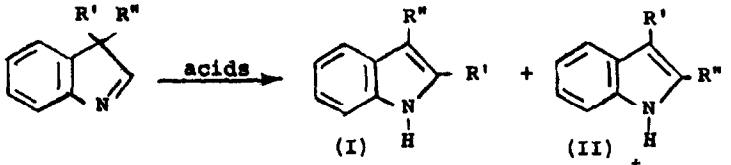
Migratory aptitude R'>R"

It is known in literature that each of the two different alkyl groups present at the 3-position of an indolenine (I) rearranges under acidic conditions with different rate. Accordingly, indolenine I leads, by rearrangement, to only one of the two isomeric alkylindoles (pathway a only).[4] Therefore, the ratio between isomer III and the total amount of isomers I and II obtained by alkylation of a 3-alkylindole can account for the relative reactivity of its 2- and 3-positions. Obviously it is necessary to operate on a 3-R',indole substrate, where R' has a migratory aptitude much higher than the R" present in the alkylating agent. However, the validity of this method has been carefully verified in order to study the alkylation of a particular series of 3-alkyl-indoles: with this aim we prepared the indolenines (I)[5] and successively studied

their rearrangement.

The results obtained, reported in Table 1, show that at the presence of either protic or Lewis acids all the indolenines examined afford prevalently one rearrangement product.[6]

Table 1



R'	R"	CF_3COOH %I	CF_3COOH %II	$CH_3COOH/Na^{\dagger}$ %I	$CH_3COOH/Na^{\dagger}$ %II	$MgBr_2$ %I	$MgBr_2$ %II
$C_6H_5CH_2$	$CH_2=CH-CH_2$ [ƒ]	100	-	-	-	~100	-
$(CH_3)_2C=CH-CH_2$	$CH_2=CH-CH_2$ [§]	100	-	-	-	100	-
$(CH_3)_2C=CH-CH_2$	$CH_3CH=CH-CH_2$ [§¶]	90	10	85	15	82	18
$C_6H_5CH(CH_3)$-	$C_6H_5-CH_2$ (+) [§¶]	80	20	-	-	90	10
$C_6H_5CH(CH_3)$-	$C_6H_5CH_2$ (-) [§]	98	2	-	-	95	5

[†] CH_3COOH 100 ml, H_2O 20 ml, CH_3COONa 8 g.

[ƒ] See reference 3.

[§] By gas-chromatographic analysis.

[¶] Two diastereomers were isolated during the preparation of this indolenine: + and - indicate their relative R_fs (hexane-ethylacetate : 85-15).

On the other side, alkylation of 3-alkylindoles and of their magnesium halides in protic buffered medium led to the results reported in Table 2.

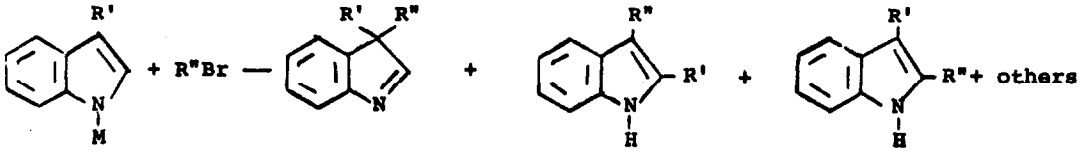
These results suggest that in general the direct attack at position 2- is competitive with the alkylation at position 3- in 3-alkylindoles. In particular, the more the reactivity of the reagent increases the more the attack at the position 2- of the substrate becomes prevalent.

Indeed, the reactivity of the reagent may be increased by modifying the nature of the alkylating agent according to the following series :

$$CH_2=CH-CH_2Br < (CH_3)CH=CH-CH_2Br < (CH_3)_2C=CH-CH_2Br$$

or in the case of indole magnesium halides by modifying the interaction between the alkylating agent and the cation ($MgBr^+$).[8] In the latter case it was possible to modify the coordinating power and consequently the catalytic activity of $MgBr^+$ by solvation effects: in the reaction of 3-benzylindole magnesium halide with allylbromide the ratio between attack 2- and 3- was 37/63 in a solvent with low basicity as Et_2O, but decreased to a value of 0/100 in THF.

Table 2



(I) (II) (III)

M	R'	R"	Solv.	I + II†	III	III/I+II
MgBr	$C_6H_5CH_2$-	CH_2=CH-CH_2-§	Et_2O	63	37	0.59
MgBr	$C_6H_5CH_2$-	CH_2=CH-CH_2-	THF	100	-	0
MgBr	$(CH_3)_2$C=CH-CH_2-	CH_2=CH-CH_2-	Et_2O	87	13	0.15
MgBr	$(CH_3)_2$C=CH-CH_2-	CH_3CH=CH-CH_2-	Et_2O	58	42	0.72
MgBr	$C_6H_5CH(CH_3)$-	$C_6H_5CH_2$-	Et_2O	78	22	0.28
H	$(CH_3)_2$=CH-CH_2-	CH_3CH=CH-CH_2-	Acetic buffer¶	49	51	1.04

†See ref.[8]; §see ref. [3]; ¶see Tab. 1.

Hence, our data enforce a complete revision of the statement reported before.[2] In fact, on the base of the generally accepted hypothesis that in any case the transition state during the alkylation of indole systems may be assimilated to the reaction intermediate (protonated indolenine as Wheland compound),[9,2] alkylation was believed to occur exclusively at position 3-.

Actually, our results support the more general hypothesis that the transition state for 3-alkylindoles may shift towards the initial state (π-complex or early transition state).[10] In this case the positional selectivity is determined by the electronic densities in the substrate, rather than by the relative stability of the Wheland intermediates.

Nevertheless, it is known that,by replacing a hydrogen atom with a CH_3 in an aromatic system,the electronic density decreases in the position α and increases in the position β to the CH_3.[11] Accordingly,we could observe a decrease of the reactivity at position 3- in alkylindoles and a relative increase of attack 2- as the reactivity of the reagent grows, as expected.[10]

Recently, pK_As of conjugated acids of heterocyclic systems, indoles included, have been accounted for the stability-indexes of the Wheland intermediates and have been connected to the relative reactivities of various substrates.[12]

Competitive alkylation experiments of skatole and indole in acetic buffer with γ,γ-dimethylallyl bromide indicate that the reactivity sequence is opposite in order to what expected on the base of the relative pK_As (pK_A indole = -3.55; pK_A 3-methylindole = -4.55;[13] K_{3-CH_3}/K_H=1.5).[14]

This result and the low sensitivity of the reaction towards substituent effects[15] in the competitive prenylation of 2-methylindole and indole itself ($K_{2\text{-}CH_3}/K_H \approx 3.2$) confirm the general lines we followed in this problem.

References and footnotes

[1] R. J. Sundberg: "The Chemistry of Indoles", Academic Press, New York, 1970 p. 19.

[2] Ibid. p. 78.

[3] A. Pochini, Ateneo Parmense, Sez. 2, 1969, 5 (3), 9.

[4] A. H. Jackson and P. Smith, Tetrahedron, 1968, 24, 2227.

[5] All structures are based on analytical, mass spectra, n.m.r., i.r., and u.v. data.

[6] In all cases isomeric 2,3-dialkylindoles have been prepared with unambiguous sintheses and compared with the products obtained by rearrangement; for alkenylindoles comparison has been made with hydrogenated derivatives.

[7] In general, indolenines (I) rather than rearrangement products (II) are obtained from 3-alkylindole magnesium halides. However, the non-rearrangement of indolenines in the reaction medium remains an unsolved problem .

[8] $MgBr^+$ acts as Friedel-Crafts catalyst located on a pole of the ion pair: B. Cardillo, G. Casnati, and A. Pochini, Chimica e Industria, 1967, 49, 6119.

[9] A. H. Jackson, B. Naidoo, and P. Smith, Tetrahedron, 1968, 24, 6119.

[10] a) R.O.C. Norman and R. Taylor: "Electrophilic Substitution in Benzenoid Compounds", Elsevier, Amsterdam, 1965, p. 282.
b) G.A.Olah, Acad. Chem. Res., 1971, 4, 240.

[11] See for example: T. D. Alger, D. M. Grant, and E. G. Paul, J. Am. Chem. Soc., 1966, 88, 5397; W. J. Hehre, L. Radom, and J. A. Pople, ibidem, 1972, 94, 1796; R. G. Parker and J. D. Roberts, ibidem, 1970, 35, 996.

[12] For benzenoid compounds see ref. 10a, p.28. For indole compounds: S. Clementi, P. Linda, and G. Marino, Chem. Comm., 1972, 427.

[13] R. L. Hinman and J. Lang, J. Am. Chem. Soc., 1964, 86, 3796.

[14] In contrast, the reactivity order is in agreement with the relative stability of the charge-transfer complexes: R. Foster and C. A. Fyfe, J. Chem. Soc.(B), 1966, 926; B. Sabourault and J. Bourdais, C. R. Acad. Sci. Ser. C., 1972, 274, 813.

[15] See for example : G. Marino in "Advances in Heterocyclic Chemistry" Vol.13, eds. A. R. Katritzky and A. J. Boulton, Academic Press, New York, 1971, p.311.