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THE REACTION BETWEEN 2,3-DIALKYLINDOLES AND DICHLOROCARBENE

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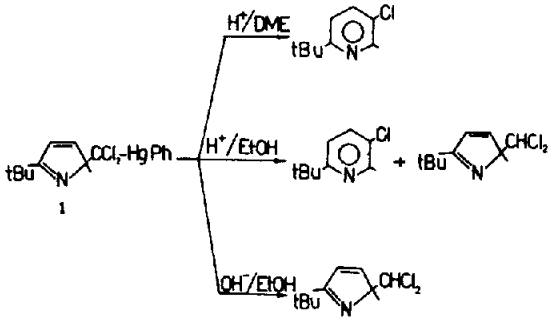
Abstract—A zwitterionic intermediate in the reaction between 2,3-dimethylindole and dichlorocarbene–PhHgI, has been detected and converted into 3-chloroquinoline **3** and 3H-indole **4**. This suggests the existence of a single intermediate for both products.

2,3-Dialkylindoles react with dichlorocarbene giving addition (2,3-dialkyl-3-dichloromethyl-3H-indoles or indolenines) and ring expansion products (2,4-dialkyl-3-chloroquinolines).[1]

This reaction is very similar to that of 2,3-dialkylpyrroles with dichlorocarbene[2] in which 3-chloropyridines and 2-dichloromethyl-2H-pyrroles are formed.

In a preceeding note[3] we have shown the easy conversion of the phenylmercury derivative **1**—isolated from the reaction mixture of 2-methyl-5-*t*-butylpyrrole and $PhHgCCl_3$/NaI system as the source of dichlorocarbene[4]—into both ring expansion and/or addition products after treatment with acids or bases in aprotic or protic solvents.



1

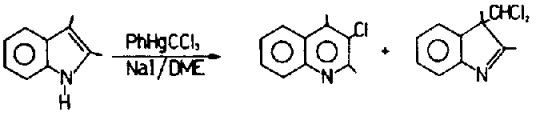
This behaviour prompted us to draw the conclusion that, in neutral or moderate alkaline conditions, a single intermediate is involved in the mechanism of the reaction between 2,5-dialkylpyrroles and dichlorocarbene.

This conclusion is in contrast with a preceeding one[5] where two different species—arising from the alternative attack of dichlorocarbene on the undissociated substrate or its conjugate base—have been described as intermediates for ring expansion and addition products respectively. The same scheme is described to operate also in the reaction of indoles with dichlorocarbene.[6]

Thus, in order to verify whether the mechanism we have proposed is also operative for indoles, we have studied the reaction between 2,3-dimethylindole **2** and dichlorocarbene generated in aprotic medium (dimethoxyethane; DME) by $PhHgCCl_3$/NaI system.[4]

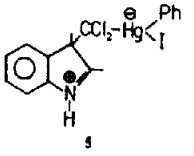
RESULTS AND DISCUSSION

2,4-dimethyl-3-chloroquinoline **3** (25.6%) and 2,3-dimethyl-3-dichloromethyl-3H-indole **4** (15.0%) were obtained, as expected, from the crude reaction mixture after the usual reaction procedure.[3] Several attempts to isolate the phenylmercury derivative, corresponding to **1**, were unsuccessful.



2 3 4

Nevertheless, once we used a shorter reaction time, after removal of the compounds **2**, **3** and **4** from the reaction mixture by an anhydrous work-up, the residual crude fraction showed the presence, in small amounts, of a mercury derivative. We assigned to this derivative the zwitterionic structure **5** on the basis of the following data.



5

In the crude, DME soluble, fraction containing **5**, compounds **2**, **3** and **4** were present in a total amount (gas-chromatographic detection) of less than 10% with reference to an added internal standard (C_{20}). After treatment with EtOH, the solution gave a crystalline precipitate of PhHgI, while the total amount of **3** and **4** increased to 40%. The use of 1% TsOH in EtOH resulted in an acceleration of the process (see experimental).

The chemical shifts of the main signals present in the NMR spectrum of the crude fraction containing **5** are reported in Table 1 where they are compared with those of 2,3-dimethyl-3-dichloromethyl-3H-indole **4** and its conjugate acid **4a**. The NMR signals of **5** are superimposable on those of the *N*-protonated 3H-indole **4a**, the only difference being the absence of the dichloromethyl proton in the spectrum of **5**. The NMR absorptions observed for **5** and **4a** are in agreement with the literature values for both methyl signals of 3-protonated 2,3-dimethylindoles.[7]

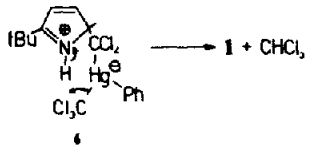
Table 1. Chemical shifts of significative NMR signals for 4 and 5

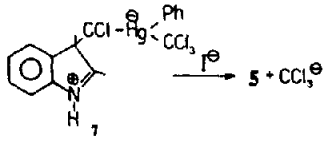
Compound	Solvent	Chemical shifts (δ)[a]		
		$CHCl_2$	C_2-CH_3	C_3-CH_3
4	DMSO-d_6	6.87	2.33	1.46
4a	DMSO-d_6/CF_3CO_2H[b]	6.75	3.35	1.70
5	DMSO-d_6	-	3.35	1.65

a) All reported signals are singlets.

b) In molar ratio 1:1

The origin of 5 and its chemical behaviour are both related to the well-known tendency of the halomercury organic derivatives to give coordination complexes with Lewis bases[8] and to undergo easily nucleophilic substitution.[9] The presence of 5, rather than the expected mercury derivative corresponding to 1, can be rationalized in terms of different routes of formation of compounds 6 and 7, likely intermediates in the formation of 1 and 5 respectively





In the first case, a concerted intramolecular elimination of $CHCl_3$ leading to 1 is probably the most favoured process because of the proximity of the two reaction centers. On the other hand, a nucleophilic substitution on mercury should lead to the conversion of 7 to 5.

The similarity between the mercurials 1 and 5 prompted us to test the ability of the latter to give both ring expansion and addition products. The attempts made to isolate compound 5 were unsuccessful as a consequence of its high sensitivity to hydrolysis. Therefore, all the experiments were carried out on the crude DME solution.

This solution, which still contained small amounts of 2, 3 and 4, besides the dipolar ion 5, was treated overnight with *p*-toluensulphonic acid and KOH in protic and aprotic solvents at different temperatures. The percentage increases of 3-chloroquinoline 3 and/or 3H-indole 4 were carefully measured *via* GC analysis with reference to the added internal standard (C_{20}). No change was observed in the amount of 2,3-dimethylindole 2. Results are reported in Table 2.

In all the reactions carried out in the aprotic medium (DME), both ring expansion and addition products are formed (see Table 2, runs 1–4), but the route to quinoline 3 becomes important only in acidic conditions (runs 3 and 4).

In the protic solvent (EtOH), both in neutral and alkaline conditions (runs 5–8), only the 3H-indole 4 is formed, while in the protic and acidic medium, the ring expansion process operates again (runs 9 and 10).

The data presented in Table 2 can be rationalized in terms of the following scheme:

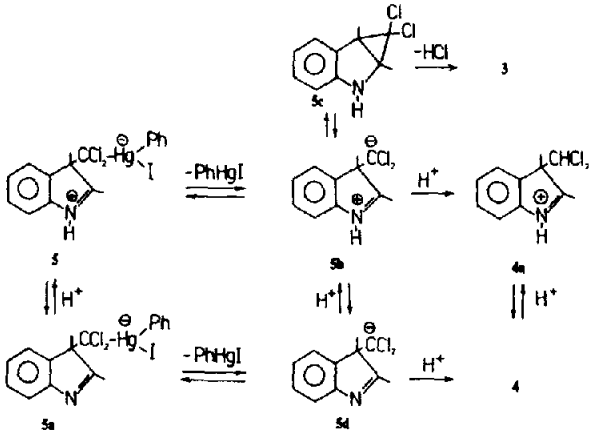


Table 2. Action of solvents, acids, bases and temperature on 5 for 18 h

Run	Solvent	Temp °C	Product GC% increments[a]		Overall GC% increment[a]
			3	4	3+4
1	DME	20	7	34	7
2	DME	60	55	188	28
3	DME/TsOH 1%	20	20	60	16
4	DME/TsOH 1%	60	145	232	29
5	EtOH	20	0	83	16
6	EtOH	60	0	100	23
7	EtOH/KOH 1%	20	0	50	14
8	EtOH/KOH 1%	60	0	95	28
9	EtOH/TsOH 1%	20	12	92	21
10	EtOH/TsOH 1%	60	62	240	28

a) Percentual increments with respect to a blank DME solution kept for 18 h at -20°C. In this solution no increase in the amounts of 3 and 4 was observed. All percentual calculations were made with respect to n-eicosane as internal standard

Mercurial **5**, in contrast to **1**, is already an *N*-protonated species and does not need any added acid to give the ring expansion product **3** through the tricyclic intermediate **5c** (runs 1 and 2), but, in this case, competitive proton transfer processes are also operating.

Species **5**, **5b** and **4a**, in fact, can act as proton donors with respect to the dichloromethyl moiety present and **5d** and **5b** itself, leading to 3H-indole **4** in the aprotic medium too. This is not unexpected because 3H-indoles are always formed along with 3-chloroquinolines in reactions of indoles with dichlorocarbene carried out in neutral conditions and aprotic solvents.[6]

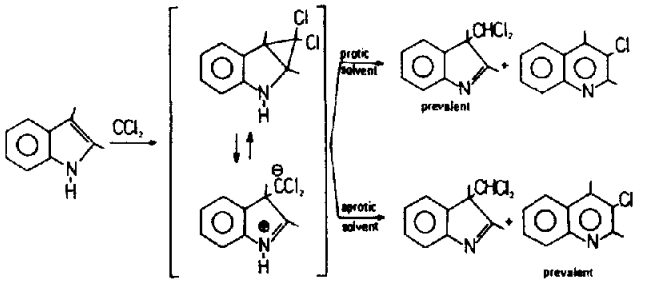
The increase of the ratio 3-chloroquinoline/3H-indole in the aprotic solvent and acidic conditions (runs 3 and 4) is consistent with our scheme. In the presence of added acid, the concentration of species **5a** and **5d** is depressed in favour of the formation of **5b**. As a consequence, one of the two routes to 3H-indole **4** is inhibited and the amount of 3-chloroquinoline **3** increases. The hypothesis that indoles, unlike pyrroles, can act as proton donors in these reactions, leading to 3H-indoles, has been already put forth.[3,10]

In the aprotic medium (neutral and/or basic conditions) both proton transfers and concentrations of the ionic species **5a**, **5b** and **5d** are increased. Thus, the only operating process gives rise to the 3H-indole **4** (runs 5–8), unless an acid is added (runs 9 and 10).

The experiments carried out at different temperatures show that the cyclic expansion route is favoured by a higher temperature, as expected for an elimination process.

The behaviour of **5** parallels that observed for 2H-pyrrole mercury derivative **1**[3] and differences are consistent both with different structure of **5**—as compared with **1**—and different behaviour of indoles[6]—as compared with pyrroles[5]—in the reaction with dichlorocarbene.

All these data are in agreement with previous observations on general reactions of dichlorocarbene on indoles.[6,11] Therefore, we feel that when this reaction is carried out in neutral (aprotic) or in moderate alkaline (protic) media a single intermediate, like **5b** in equilibrium with **5c** (both formed by electrophilic attack and/or cycloaddition of the reagent), can give rise to both ring expansion and addition products, their ratio being regulated by the medium proticity. Thus, we think that, in these conditions, the mechanism of the reaction between 2,3-dialkylindoles and dichloracarbene can be depicted as follows:



In strongly alkaline conditions,[6,12] where the concentration of the indolyl anion is high, the attack of dichlorocarbene on this conjugate base can operate alone or along with the scheme outlined above.

EXPERIMENTAL

Gas chromatographic analyses were carried out on a HP 5880 using a 2 m long column (2% Carbowax 20 M on Chromosorb P, 80–100 mesh) and N_2 as carrier gas. NMR spectra were recorded on a Perkin–Elmer R_{32} (TMS as internal standard).

Action of PhHgCCl$_3$/NaI system on 2,3-dimethylindole 2. The reaction was carried out overnight in dry DME, as described in the literature,[3] using indole 2 (0.5 g), $PhHgCCl_3$[12] (2.72 g) and dry NaI (1.03 g). Chromatographic elution (SiO_2, 1:100) with light petroleum (b.p. 40–70°)–AcOEt (9:1) led to unreacted substrate (0.31 g), 2,4-dimethyl-3-chloroquinoline 3 (0.17 g, 25.6%) and 2,3-dimethyl-3-dichloromethyl-3H-indole 4 (0.12 g, 15.0%). Both products 3 and 4 were identified by comparison with authentic samples. All chromatographic fractions were treated with 1% EtOH/KOH solution under reflux for 3 h and analyzed by GC looking for 3H-indole 4, in order to provide evidence for the presence of a 3H-indole-like mercury derivative, but all the experiments were unsuccessful.

Detection and identification of 5. Substrate 2 (1.00 g) was treated for 3 h with the appropriate amount of $PhHgCCl_3$/NaI. After a quick filtration and solvent removal at room temperature under anhydrous conditions, the crude solid residue (7.75 g) was triturated five times with 50 ml portions of dry Et_2O. The etheral phases were collected and evaporated to give compounds 2, 3 and 4 (1.55 g). Dry DME (8 ml) was added to the crude solid residue (6.20 g), the soluble fraction was collected (residue 5.65 g) and showed the presence of the dipolar ion 5 as indicated by the following experiments. *n*-Eicosane as a standard (1.05 mg) was added to 0.5 ml of the above solution and GC analysis showed the presence of 2, 3 and 4 in 9.0%, 2.0% and 7.5% respectively with reference to the standard. Then EtOH (0.5 ml) was added and the resulting solution refluxed for 3 h. During this time crystals precipitated (50 mg) and were identified as Phenylmercury iodide by TLC (hexane–AcOEt 9:1) and m.p. comparison with an authentic sample.[4] A new analysis gave compounds 2, 3 and 4 in 9.0%, 2.0% and 40.5% respectively with reference to the standard. Similar results were obtained at room temperature after 1 h using 1% EtOH/TsOH solution. The residual DME solution was evaporated *in vacuo* and the NMR spectrum was recorded in DMSO-d_6 (see Table 1).

Action of solvents, acids, bases and temperature on 5 (*see Table* 2). 5.40 mg of *n*-eicosane were added to a DME solution of 5 (8 ml), obtained as described above. 0.1 ml portions of this solution were put into test tubes and the appropriate reagent was added (0.1 ml). The tubes were sealed and kept for 18 h at the indicated temperature. The vials were then opened and the solutions directly analyzed without any prior work-up.

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