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Notes

Reaction of Electrogenerated Dichlorocarbene with Methylindoles

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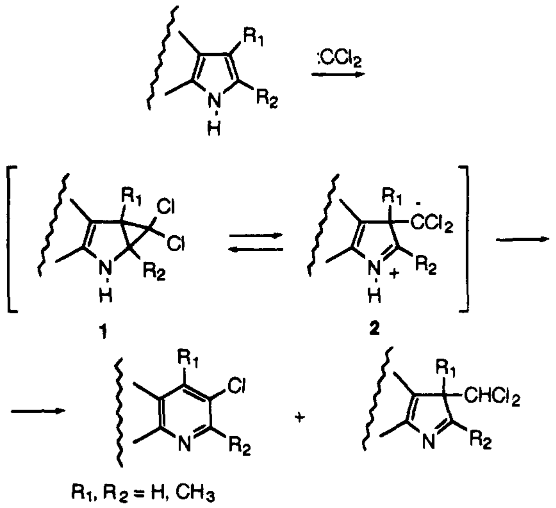
Under Reimer–Tiemann reaction conditions,[1] pyrroles and indoles undergo an initial cycloaddition of dihalocarbene, usually formed by treatment of the appropriate haloform with an alkali metal hydroxide solution, to the electron rich double bond of the heteroaromatic ring, which results in ring expansion.[2] This reaction, which has been called the "abnormal" Reimer–Tiemann reaction,[2b,c] ("normal" refers to the formylation of phenols and naphthols), has stimulated intriguing discussions of its mechanistic aspects.[3] It is generally accepted that the initially-formed dihalocyclopropane adduct undergoes loss of HCl or HBr with concomitant electrocyclic ring opening.[4] The reaction, however, is complicated by the formation of addition products, *i.e.* aldehydes or dihalomethyl derivatives. Several of the reported studies of the reaction mechanism support the hypothesis of a common intermediate which leads to both types of products.[3i–n] According to these papers, the intermediate exists in two isomeric forms, one neutral (**1**, Scheme 1) and one zwitterionic (**2**, Scheme 1), which transform independently to the ring expansion product and the dihalomethyl derivative, respectively, depending upon the proton-donating ability of the reaction medium. These conclusions, however, disagree with those of other authors[3c] who refer to two different intermediates, arising by the attack of dihalocarbene on the undissociated substrate or on its conjugated base, the latter arising from the action of the base that is necessarily present in the reaction medium. The fate of these intermediates is, again, to become the ring enlargement and the addition products, respectively. It should be noted that, as a ring expansion method, this reaction is of little use due to the low percentage of transformation. Reasonable yields can be obtained under phase-transfer conditions.[5]

Scheme 1



Halogen-containing carbenes can be prepared under a number of experimental conditions,[6] some of which rely on the electrochemical generation of carbene precursors.[7] The electrochemical method does not require the presence of a base in the reaction system; reduction of the C–X (X = halogen) bond of the precursor occurs at the cathode, thus initiating the carbene generation process.

Since no studies of the electrochemically induced "normal" and "abnormal" Reimer–Tiemann reaction had been published, and with the hope that higher yields and better chemoselectivity might be achieved, an investigation of the ring enlargement reaction of methyl-substituted indoles was undertaken. These compounds were chosen because of their higher reactivity and stability with respect to pyrroles or other heterocyclic compounds.[3] Also, their reactivity with :CCl_2 under "classical" conditions was already known.[3c,d] All reaction products have been identified by comparison of their spectroscopic properties with those of authentic samples or literature data.

In a first set of experiments, dichlorocarbene was generated by reduction of CCl_4, followed by fragmentation of the carbanion CCl_3^-. The presence of $CHCl_3$ as solvent should not interfere with the carbene generation process even if, at constant current, it is not possible to exclude the concomitant reduction of $CHCl_3$.[7] Under these conditions, 2,3-dimethylindole (**3**) furnished 3-chloro-2,4-dimethylquinoline (**4**) and 3-(dichloromethyl)-2,3-dimethyl-3*H*-indole (**5**) (Scheme 2; Table 1, entry 1). Seventeen percent the starting material was recovered unchanged. It should be noted that, when the reaction is carried out in *N,N*-dimethylformamide or acetonitrile, the substrate

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[1] (a) Kirmse, W. *Carbene Chemistry*, 2nd ed.; Academic Press: New York, 1971; p 396 and ff. (b) Winberg, H.; Meijer, E. W. *Org. React.* (*N.Y.*) **1982**, *28*, 1. (c) Winberg, H. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds., 1990; Vol. 2, p 769.

[2] G. Ciamician, *Ber. Dtsch. Chem. Ges.* **1904**, *37*, 4201.

[3] (a) Nagazaki, M. *J. Chem. Soc. Jpn.* **1955**, *76*, 1169. (b) Robinson, B. *Chem. Ind.* (*London*) **1962**, 1291. (c) Rees, C. W.; Smithen, C. E. *J. Chem. Soc.*, **1964**, 928. (d) Rees, C. W.; Smithen, C. E. *J. Chem. Soc.* **1964**, 938. (e) Nicoletti, R.; Forcellese, M. L. *Gazz. Chim. Ital.* **1965**, *95*, 83. (f) Nicoletti, R.; Forcellese, M. L.; Germani, C. *Gazz. Chim. Ital.* **1967**, *97*, 685. (g) Jones, R. L.; Rees, C. W. *J. Chem. Soc.* **1969**, 2255. (h) Gambacorta, A.; Nicoletti, R.; Forcellese, M. L. *Tetrahedron* **1971**, *27*, 985. (i) Gambacorta, A.; Nicoletti, R. *Tetrahedron Lett.* **1978**, 2439. (l) Gambacorta, A.; Nicoletti, R.; Cerrini, S.; Fedeli, W.; Gavuzzo, G. *Tetrahedron* **1980**, *36*, 1367. (m) Botta, M.; De Angelis, F.; Gambacorta, A. *Tetrahedron* **1982**, *38*, 2315. (n) Botta, M.; De Angelis, F.; Gambacorta, A. *Gazz. Chim. Ital.* **1983**, *113*, 129.

[4] Winberg, H. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds., 1990; Vol. 4, p 1021.

[5] De Angelis, F.; Gambacorta, A.; Nicoletti, R. *Synthesis* **1976**, 798.

[6] (a) Reference 2a, *loc. cit.* p 9 and ff. (b) Kostikov, R. R.; Molchanov, A. P.; Khlebnikov, A. F. *Russ. Chem. Rev.* **1989**, *58*, 654.

[7] Petrosyan, V. E.; Nijazymbetov, M. N. *Russ. Chem. Rev.* **1989**, *58*, 644.

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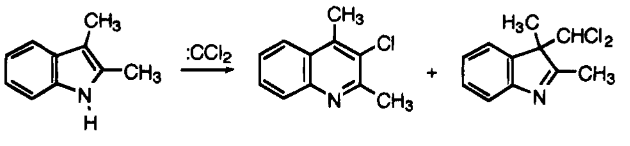
Scheme 2



3 **4** **5**

is consumed, but no products are detectable in the reaction mixture.

$CHCl_3$ itself can be a convenient electrochemical source of dichlorocarbene.[7] When $CHCl_3$ is reduced at a Pb cathode, it undergoes a decomposition cascade according to Scheme 3. Indeed, the electrolysis of $CHCl_3$ in the presence of 2,3-dimethylindole afforded the expected products in fairly high yields (Table 1, entry 2).

Preparation of the intermediate carbene by the action of an electrogenerated base[8] on $CHCl_3$ was also successful. Tetraethyl ethylenetetracarboxylate was used as a probase (*i.e.*, strong base precursor).[8,9] Its reduction first gives the anion, which is then able to deprotonate $CHCl_3$. Finally, $:CCl_2$ can be captured by 2,3-dimethylindole to give the known products (Table 1, entry 3). 3-Methylindole (entry 4) and indole itself (entry 5) undergo the same reaction. Yields are not particularly high due to the lower reactivity of these substrates, relative to that of **3**.[10]

Finally, the reaction of 1,2,3-trimethylindole (**6**) with dichlorocarbene, generated by direct reduction of $CHCl_3$, was also investigated (entry 6). Despite the successful conversion of the substrate into the ring expansion and substitution products, isolation of these products proved to be difficult, due to their known instability under Reimer–Tiemann conditions and rapid autoxidation during workup and chromatographic separation (Scheme 4).[3b,d]

Compounds **8–10** were identified by their spectroscopic properties (some spectral data are also reported in the literature[3d]). Compound **7** was at no time present in detectable amounts, as it is rapidly converted into the quinolone **9**.

The results, which have been summarized in Table 1, show that in only two cases were the overall yields of products and recovered starting materials greater than 50%. It should be considered that tars are often produced in this reaction. It is worth noting that the reaction of 2,3-dimethylindole, reported herein, using $CHCl_3$ as the dichlorocarbene source, represents the highest conversion of any indole derivative under Reimer–Tiemann conditions, even upon comparison with phase-transfer catalytic conditions.

Mechanistic Implications. The base strength[3c] and the proton-donating ability of the reaction medium[11] have been reported to be important factors in controlling the relative ratio of ring-expanded and five-membered ring products in the modified Reimer–Tiemann reaction of heterocyclic systems.[12] The absence of base in the procedure described in this paper is therefore significant, and the proton-donating ability of the medium remains the only controlling factor.

In order to acquire data on this particular point, some experiments using CCl_4 as a depolarizer, *i.e.* the carbene precursor, have been performed. CH_2Cl_2 and $CHCl_3$ were the reaction media in which $:CCl_2$ was generated. Under these conditions, where $:CCl_2$ reacts with the undissociated substrate, it is possible to assume that only $CHCl_3$, if present, is able to transfer a proton to the zwitterionic intermediate **2** (Scheme 1). $CHCl_3$ is assumed to be a better acid than CH_2Cl_2.[13] The results obtained using different proportions of $CHCl_3$ and CH_2Cl_2 as the solvents are summarized in Table 2 (one run for each entry). When CH_2Cl_2 was used as solvent (entry 1), 3-chloro-2,4-dimethylquinoline (**4**) was essentially the only product formed, this product being the only possible outcome of the reaction intermediate **1** (Scheme 1). Conversely, $CHCl_3$ (entry 5) is able to transfer a proton to the zwitterionic form of the intermediate (**2**, Scheme 1), thus giving rise also to the addition product **5**. Intermediate values of the relative amounts of the products are observed as a direct function of different proportions of the two solvents (entries 2 to 4).[14]

The obvious conclusion of these experiments is that the reaction mechanism and product formation are determined by the acidity of the solvent. These findings support the hypothesis of a single reaction intermediate that can be viewed as two interconverting forms: a dichlorocyclopropane adduct and an open ring indolyldichloromethyl anion.

Experimental Section

Reagents. The following commercial products were used as received: tetraethyl ethylenetetracarboxylate (Fluka), indole (Fluka), 3-methylindole (Merck), 2,3-dimethylindole (Aldrich), styrene (Aldrich), iodomethane (Aldrich). Standard procedures for solvent (Aldrich), purification, and dehydration were followed. Bu_4NBr (Aldrich) was used after vacuum drying (2 mmHg) at 40 °C for 30 h.

Instrumentation. Constant current electrolyses and coulometry were carried out by means of an AMEL 552 potentiostat equipped with an AMEL 721 integrator. The cathode was a Pb foil (area 10 cm^2), the counter electrode was a cylindrical platinum gauze. The electrolysis cell was a divided one working at a controlled temperature: 5.0 °C. GLC analyses were performed using a Hewlett-Packard Model 5890 gas chromatograph equipped with a flame ionization detector, a linear temperature programmer, and a Hewlett-Packard Model 3390A electronic integrator. The column used was a SP 2250 (30 m, 0.32 mm i.d. glass column). GC-MS measurements were carried out on a SE54 capillary column using a Fisons 8000 gas-chromatograph coupled with a Fisons MD 800 mass selective detector. ^1H and ^{13}C NMR spectra were recorded using an AC 200 Bruker spectrometer and $CDCl_3$ as internal standard. IR spectra were recorded by means of a Perkin Elmer 298 spectrophotometer.

General Procedure for Preparative Electrolysis. An amount of 1.05 mol (with respect to the substrate) of depolarizer was reduced at the cathode at $I = 4$ mA cm^{-2} (the voltage was not monitored) in 40 mL of solvent in the presence of 0.1 M Bu_4-

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[8] Baizer, M. M. *Organic Electrochemistry*; Lund, H., Baizer, M. M., Eds.; M. Dekker: New York, 1990; pp 1265–82 and refs therein.

[9] De Angelis, F.; Feroci, M.; Inesi, A. *Bull. Soc. Chim. Fr.* **1993**, *130*, 712.

[10] To our knowledge this is the first example of a conversion of indole itself into 3-chloroquinoline.

[11] Forcellese, M. L.; Gambacorta, A.; Nicoletti, R. *Atti Acc. Naz. Lincei* **1972**, *53*, 569.

[12] Jones, R. A. *Comprehensive Heterocyclic Chemistry*; Potts, K. T., Ed., Pergamon Press: New York, 1984, Vol. 4, p 257.

[13] Catalan, J.; Cuoto, A.; Gomez, J.; Saiz, J. L.; Laynez, J. *J. Chem. Soc. Perkin Trans. 2* **1992**, *7*, 1181.

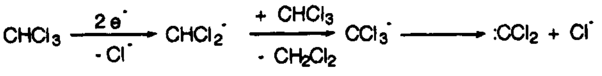
[14] An alternative mechanism would be the fast, reversible addition of the carbene to form the zwitterion: only in the presence of a good proton donor is the intermediate converted to the addition product. Conversely, the cyclopropane adduct, which leads to ring expansion, is formed slowly but irreversibly. The authors wish to thank one of the referees who drew this possibility to their attention.

Table 1. Reaction of Methylindoles with Electrogenerated Dichlorocarbene in $CHCl_3$

					products (yields, %)	
entry	electroactive species	F/mol[a]	indole	unreacted substrate	3*H*-indole	quinoline
1	CCl_4	2.08	2,3-dimethyl	17	13	16
2	$CHCl_3$	2.22	2,3-dimethyl	19	32	46
3	TEETC[b]	2.00	2,3-dimethyl	70	11	15
4	$CHCl_3$	1.77	3-methyl	21	2	16
5	$CHCl_3$	2.00	indole	26	–	5
6	$CHCl_3$	2.00	1,2,3-trimethyl	25	14[c]	5[c]

[a] Faraday per mole of the indole. [b] Tetraethyl ethylenetetracarboxylate. [c] These yields refer to the oxidation products of 3*H*-indole and quinoline.

Scheme 3



Scheme 4

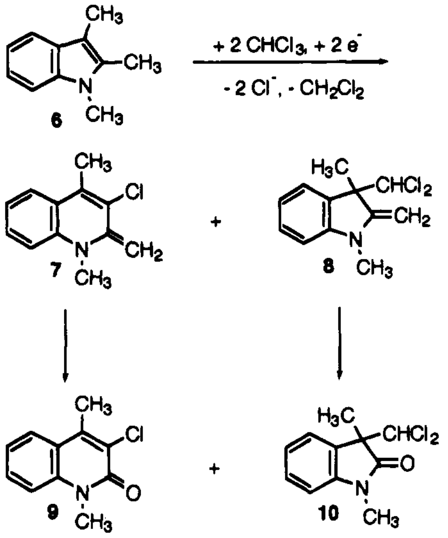


Table 2. Reaction of 2,3-Dimethylindole with Electrogenerated Dichlorocarbene (from CCl_4): Solvent Effect

entry	solvent: $CHCl_3/CH_2Cl_2$	unreacted substrate (%)	4: current yield (%)	5: current yield (%)	4/5: ratio of yields
1	0:100	51	39	<1	>39
2	25:75	66	21	8	2.6
3	50:50	85	35	18	1.9
4	75:25	68	15	10	1.5
5	100:0	67	13	9	1.4

NBr as the supporting electrolyte;[15] styrene was used as bromine scavenger at the anode, which was separated from the cathode by a classical glass frit septum. Air was excluded from the catholite by bubbling N_2 (purity grade: 99.998%) during the entire experiment. During the electrolysis, renewal of the septum became a necessity when current intensity lowered almost to zero due to the precipitation onto the septum of polymeric material.[16] After electrolysis the cathodic solution was taken up, washed with water, and then dried ($CaCl_2$). The solvent was evaporated and the products were separated by column chromatography on silica gel 60, using n-hexane/ethyl acetate (9:1) as the eluent. The structure of the products was confirmed by comparison of their spectral data with those reported in the literature.[3c,d] Only spectral data which augment previously published data are presented.

N-Methylation of 2,3-Dimethylindole. A mixture of 2,3-dimethylindole (1.00 g, 6.89 mmol), Bu_4NBr (0.10 g, 0.31 mmol), and CH_3I (1.37 g, 9.63 mmol) in 10 mL of toluene was added to 10 mL of 50% aqueous KOH. The mixture was stirred vigorously at room temperature for 20 h. The organic layer was washed with water and NaCl (saturated solution) and then dried (Na_2SO_4). The solvent was removed and the product was purified by column chromatography on silica gel 60, using n-hexane/ethyl acetate (9:1) as the eluent. An amount of 0.52 g of 1,2,3-trimethylindole (**6**) was isolated: ^{1}H NMR δ ($CDCl_3$) 2.31 (s, 3H), 2.38 (s, 3H), 3.66 (s, 3H), 7.09−7.29 (m, 3H), 7.52−7.56 (m, 1H); ^{13}C NMR δ ($CDCl_3$) 8.7, 9.4, 10.0, 106.2, 108.3, 117.8, 118.5, 120.4, 128.4, 132.5, 136.5; MS *m/z* (relative intensity) 159 (M^+, 51%), 158 (100%), 144 (24%), 143 (37%).

3-(Dichloromethyl)-1,3-dimethyl-2-methylene-3*H*-indole (8): ^{1}H NMR, δ ($CDCl_3$) 7.47−7.24 (m, 2H), 6.86−6.78 (m, 1H), 6.60−6.57 (m, 1H), 5.69 (s, 1H), 4.06 (s, 2H), 3.05 (s, 3H), 1.59 (s, 3H); ^{13}C NMR, δ ($CDCl_3$) 147.8, 129.7, 126.7, 124.2, 105.2, 79.1, 77.1, 55.1, 28.7, 25.2; MS *m/z* (relative intensity) 243 ($M^+ + 2$, 5%), 241 (M^+, 9%), 158 (100%).

3-Chloro-1,4-dimethyl-2-quinolone (9): ^{1}H NMR, δ ($CDCl_3$) 7.75−7.71 (m, 1H), 7.63−7.50 (m, 1H), 7.38−7.24 (m, 2H), 3.77 (s, 3H), 2.63 (s, 3H); ^{13}C NMR, δ ($CDCl_3$) 142.4, 138.1, 130.4, 125.4, 120.7, 114.5, 77.1, 30.7, 16.3; MS *m/z* (relative intensity) 209 ($M^+ + 2$, 32%), 207 (M^+, 100%), 179 (36%).

3-(Dichloromethyl)-1,3-dimethyl-2-oxoindole (10): ^{1}H NMR, δ ($CDCl_3$) 7.62−6.86 (m, 4H), 6.03 (s, 1H), 3.22 (s, 3H), 1.55 (s, 3H); ^{13}C NMR, δ ($CDCl_3$) 175.8, 144.1, 129.2, 126.0, 124.7, 122.8, 108.2, 76.3, 55.7, 26.3, 21.9. MS *m/z* (relative intensity): 245 ($M^+ + 2$, 11%), 243 (M^+, 18%), 160 (100%).

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Supplementary Material Available: Copies of cyclic voltammograms of CCl_4, $CHCl_3$ and CH_2Cl_2. Copies of ^{1}H and ^{13}C NMR spectra of **6** and **8−10** (14 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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[15] We chose Bu_4NBr as the supporting electrolyte since it is reported that other ammonium salts can lead to a passivation of the electrode: Fritz, H. P.; Kornrumpf, W. *J. Electroanal. Chem., Interfacial Electrochem.* **1979**, *100*, 217.

[16] Fritz, H. P.; Kornrumpf, W. *Liebigs Ann. Chem.* **1978**, 1416.