A NOVEL REACTION OF DICHLOROCARBENE WITH 2-CHLOROSUBSTITUTED NITROGEN HETEROAROMATIC BASES UNDER PHASE TRANSFER CONDITIONS

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Abstract - Some 2-chlorosubstituted heteroaromatic bases, under phase-transfer catalysis conditions, suffer the attack of dichlorocarbene and the substitution of the chlorine giving rise to the corresponding N-dichloromethyl-2-oxo-derivatives.

Dichlorocarbene, generated under classical conditions, reacts[1] with several five-membered heterocyclic substrates leading to ring expansion products, sometimes together with addition compounds. Recently[2], in the case of benzimidazole, further types of compounds have been isolated. Furthermore[3], among the six-membered aromatic nitrogen bases, phenolic quinolines and pyridines are formylated, 2- and 4-methylpyridines give phenylisocyanides, pyridine N-oxide is deoxygenated while uracil derivatives and carbostyril give mainly ring expansion products[4]. Also when generated under two-phase conditions[5] $:CCl_2$ attacks various heteroaromatics: in the case of indoles, pyrroles and pyrazoles both ring expansion and addition products are formed[6]. No report however appeared on reaction of $:CCl_2$, under two-phase conditions, with benzothiazole and six-membered nitrogen heteroaromatics nor, on the other hand, the 3-chloro quinolines, 3-chloropyridines and 4-chloropyridazines (the ring expansion products from, respectively, indoles, pyrroles and pyrazoles) undergo further reaction with $:CCl_2$ under both classical[1] and two-phase conditions[6].

Now we report briefly on the reaction of $:CCl_2$, obtained under the Makosza conditions[7], upon 2-chlorosubstituted quinoline, pyridine and benzothiazole. Typically, the mixture of the base in $CHCl_3$, 50% aq. NaOH and a catalytic amount of triethylbenzylammonium chloride (TEBA) was vigorously stirred at 50-60°C for 4-6 hrs. Disregarding the brown insoluble deposits always present under these conditions[8], the usual work up led to the N-dichloromethyl-3-oxo-derivative of the base. With quinoline, 4-cyanopyridine, 4-chloropyridine hydrochloride, 2-methylthiobenzothiazole and 2-chloro-6-methoxypyridine only the starting bases were recovered unchanged. In the case of 2-chloro-6-methylpyridine, 2-bromopyridine, 4-chloro-2-methylquinoline and 2-cyanopyridine labile products were formed which could not be identified. From the 2-chlorobenzothiazole the product was obtained even in the absence of the catalyst, although in lower yield (8.5%). Tributylamine[9,10] and solid NaOH[11] were also tried as catalyst, but the yields fall to a few per cent. Notwithstanding the synthetic limitations, the reaction is interesting for its

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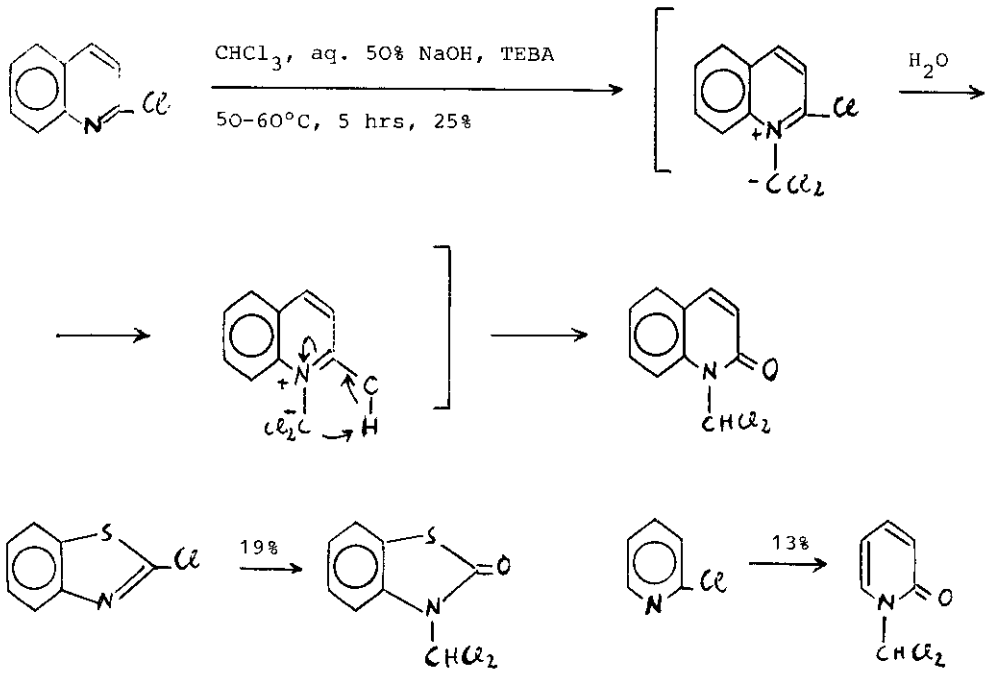
mechanistic implications. A suggestion for a possible pathway could tentatively be the following:



The first interaction of $:CCl_2$, generated at the interface[12], should be the formation of a quinolinium ylid (for pyridinium ylid see[13]). Now water alone, always at the interface, is sufficient to displace the strongly activated chlorine. Subsequently (or simultaneously) proton migration, through a five-membered transition state, and bond rearrangements as indicated lead to the final product. The survival of the $CHCl_2$ group, under these conditions, is unprecedented when bonded to nitrogen[14], but precedented when bonded to carbon[6]. Some final points: the 2-chloroquinoline is partially recovered, while the other bases disappear completely and minor amounts of unidentified compounds are present in addition to the product. The facts indicate that other reaction paths, concurrent with and/or successive to that suggested, must not be excluded.

As example for the procedure, 2-chloroquinoline (1.63 g; 10 mmol) in $CHCl_3$ (20 ml), TEBA (0.2 g; 0.9 mmol) and NaOH (8 g) in H_2O (8 ml) were vigorously stirred at 50-60°C for 5 hrs. The mixture became dark brown with insoluble deposits on the walls. After filtration, and phase separation, the aq. layer was extracted twice with $CHCl_3$, the chloroform layers combined, washed twice with water, dried over anhydrous Na_2SO_4 and evaporated under vacuum. The crude residue was separated through a silica gel column (hexane: ethyl acetate = 9:1, V/V) collecting 2-chloroquinoline (620 mg, 38%) and then a white solid (570 mg, 25% calcd. on the starting base) m.p. 138-140°C, identified as 1-dichloromethyl-2(1H)-quinolinone. IR: 1670

cm^{-1} (CO). MS: 227 (2 Cl, M^+), 192 (1 Cl, M-Cl), 164 (1 Cl, 192-CO), 140 (192 → 164), 128, 83 (2 Cl, $CHCl_2$). ^1H NMR (δ, $CDCl_3$): 6.55 (1 H, d, H_3, J = 10 Hz), 7.30-7.80 (4 H, m, aromatics), 8.35 (1 H, d, H_8, J_{7-8} = 9 Hz), 9.05 (1 H, s, $CHCl_2$). ^{13}C NMR (δ, $CDCl_3$): 72.2 (s, $CHCl_2$), 160.0 (s, CO), 135.6 (s, 8a), 121.9 (s, 4a), 141.5 - 130.2 - 129.4 - 123.8 - 119.9 - 118.3 (6 CH). In a similar manner from 2-chlorobenzothiazole the 3-dichloromethyl-2(3 H) benzothiazolone was obtained: white solid, m.p.: 96-99°C; yield: 19% calcd. on the starting base. IR:1665 cm^{-1} (CO). MS: 233 (2 Cl, M^+), 198 (1 Cl, M-Cl), 170 (1 Cl, 198-CO), 150 (M-$CHCl_2$), 146 (198 → 170), 135, 83 (2 Cl, $CHCl_2$). ^1H NMR (δ, $CDCl_3$): 7.15-7.55 (3 H, m, aromatics), 7.90 (1 H, dd, H_4), 8.11 (1 H, s, $CHCl_2$). The 2-chloropyridine gave the 1-dichloromethyl-2(1 H)-pyridinone: yellowish liquid; yield: 13% calcd. on the starting base. IR: 1670 cm^{-1} (CO). MS: 170 (2 Cl, M^+), 142 (1 Cl, M-Cl), 114 (1 Cl, 142-CO), 106, 78. ^1H NMR (δ, $CDCl_3$): 6.35 (1 H, t, H_5, J = 7.5 Hz), 6.50 (1 H, d, H_3, J = 9 Hz), 7.35 (1 H, ddd, H_4, J_{4-6} = 2 Hz), 7.80 (1 H, dd, H_6), 8.41 (1 H, s, $CHCl_2$).

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