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NUCLEOPHILIC CHARACTER OF CARBON FREE RADICALS. A NEW CONVENIENT,SELECTIVE CARBOXYLATION OF HETEROAROMATIC BASES.

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The reactions of nucleophilic radicals with protonated heteroaromatic bases have become in a short time one of the most important chapters of heteroaromatic chemistry.
Alkyl[1] and acyl[2] derivatives,amides[3], alcohols[4], ethers[4] and aldehydes[5] are obtained with great selectivity by direct homolytic substitution with a variety of higly versatile methods.
In this note we show that also the direct homolytic carboxylation of protonated heteroaromatic bases is another synthetically useful and theoretically interesting process.The possibility of using alkoxycarbonyl radicals ($\cdot COOR$) was suggested by the successful use of carbamoyl[3] ($\cdot CONR_2$) and acyl[2] ($\cdot COR$) radicals.
Three radical sources have been explored :

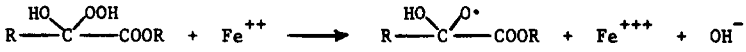
a) Hydrogen abstraction from alkyl formates :

$$R'O\cdot + HCOOR \longrightarrow R'OH + \cdot COOR$$

b) Oxidative decarboxylation of semiesters of oxalic acid by peroxydisulfate or lead tetraacetate

$$ROOC\text{-}COOH \xrightarrow{-e} ROOC\cdot + CO_2 + H^+$$

c) Redox decomposition of oxyhydroperoxides of α-ketoesters:



$$R-\overset{HO\ \ OOH}{C}-COOR + Fe^{++} \longrightarrow R-\overset{HO\ \ O\cdot}{C}-COOR + Fe^{+++} + OH^{-}$$

(I)

$$(I) \longrightarrow RCOOH + \cdot COOR$$

Even though all of the three methods lead to the introduction of the •COOR group into the protonated bases,until now the method c) has proved to be the most convenient one,owing to the very simple experimental conditions and the higher yields.

The reaction is carried out very easily,in aq. solution at room temperature, and the peroxide need not be isolated : the ketoester is simply mixed with hydrogen peroxide and the mixture is used as such in the reaction,as shown in the following example :

The oxyhydroperoxide was obtained by dropping,under stirring and cooling (-10°C),aq. H_2O_2 (34%, 0.15 mole) into ethyl pyruvate (0.225 mole). This mixture and a soln of $FeSO_4.7\ H_2O$ (0.15 mole) in water(40 ml) were then slowly and simultaneously dropped into a stirred soln of benzothiazole(0.05 mole) in water (20 ml) and conc H_2SO_4 (0.15 mole),keeping the temp. at 0-5° C.The mixture was poured into ice,basified with $NaHCO_3$ and extracted with ethyl ether.The residue after removal of the solvent and the excess pyruvate was analysed by GLPC.A yield of 82% of 2-carboxyethylbenzothiazole,based on starting benzothiazole,was obtained.The compound was identified by crystallization from ligroine (m.p. 71°C) and comparison with an authentic sample (I.R.,NMR and Mass spectra).

The Table shows the results obtained with a variety of heteroaromatic bases. In the case of acridine,in addition to the substitution product,the dihydroderivative was obtained : the same fact was observed also in the homolytic acylation of acridine[2], and the analogy suggests a similar reaction mechanism.

The formation of minor amounts of the isomer 3 together with the isomer 2 in the case of the 4-cyanopyridine would indicate that the alkoxycarbonyl radical is less nucleophilic than both the carbamoyl and the acyl radicals,which,on the contrary,attack exclusively the position 2 of the 4-cyanopyridine.The fact is interesting theoretically since it would indicate that an alkoxy group α to a carbon radical increases the nucleophilic character when the radical is of the π type,like the α-oxy and α-alkoxy radicals,in which there is a back donation of charge from the lone pair of the oxygen atom to the carbon radical[4,6]; on the contrary,when the radical is of the σ type,as the alkoxycarbonyl radical,the inductive electron withdrawing effect of the alkoxy group would prevail decreasing the nucleophilic character. Quantitative studies,based on the substituent effects,are in progress in order to elucidate this theoretical aspect.

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TABLE

Heteroaromatic Base	Base/peroxide ratio	Position of attack (%)	Conversion (%)	Yield[a] (%)
Pyridine	3 : 1[b]	2 (58);4 (34); 2,4+2,6+2,4,6 (8)	--	--
4-Cyanopyridine	3 : 1[b]	2 (68);3 (10); disubstituted (22)	--	--
Quinoline	1 : 3	2 (4.5);4 (17.5) 2,4 (78)	76	92
Acridine	1 : 2	9 (35);9-carboxyethyl-9,10-dihydro (65)	--	--
Pyrazine	1 : 2	2 (48); disubstituted (52)	90	85
Quinoxaline	1 : 2	2 (77);2,3-disubstituted (23)	91	90
Benzothiazole	1 : 3	2 (100)	96	85

a) Yield based on the converted heteroaromatic base.

b) In order to minimize polysubstitution.

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