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HOMOLYTIC AMIDATION OF HETEROAROMATIC BASES: A NEW SELECTIVE PROCESS

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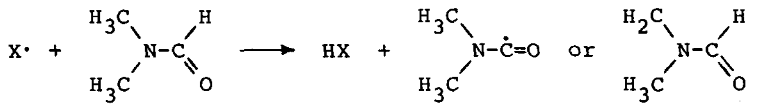
In a previous communication (1) we showed the possibility of the introduction of $CONH_2$ group directly into heteroaromatic bases through the oxidation of formamide.

We now wish to describe a new method of amidation of heteroaromatic bases by oxidation of dimethylformamide with the redox decomposition of hydrogen peroxide, t-butyl-hydroperoxide, ammonium peroxydisulphate and the thermal decomposition of ammonium peroxydisulphate, di-t-butyl-peroxide and di-benzoyl-peroxide. The $HO\cdot$, $(CH_3)_3CO\cdot$, $SO_4^{\overline{\cdot}}$, $C_6H_5COO\cdot$, $C_6H_5\cdot$ radicals can lead to hydrogen abstraction from the formyl C-H bond, forming the radical (I) similar to that obtained from formamide, or from one of the methyl groups, forming the radical (II).

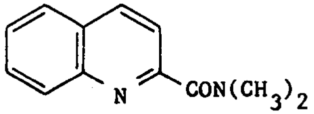


$$X\cdot + (H_3C)_2N{-}CH{=}O \longrightarrow HX + (H_3C)_2N{-}\dot{C}{=}O \text{ or } H_2\dot{C}(H_3C)N{-}CH{=}O$$

(I) (II)

We have found that both the radicals (I) and (II) selectively attack protonated heteroaromatic bases in the positions with high nucleophilic reactivity to form the corresponding substitution products and that some oxidising agents generated very selectively the radical (I) or (II), while other agents generated a mixture of both.

For example, in the case of quinoline, compounds (III)-(X) were obtained (Table 1) by reacting quinoline with dimethylformamide in the presence of various oxidants. All compounds were characterized by IR, NMR and mass spectra. Several reactions were repeated with a greater ratio quinoline/oxidant to minimize the formation of di-substitution products (Table 2). 4-Methyl-quinoline gave only (XI) and (XII) (Table 3).



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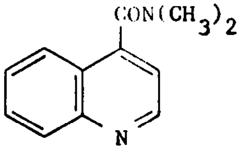

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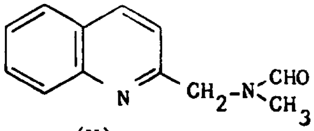

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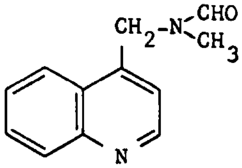

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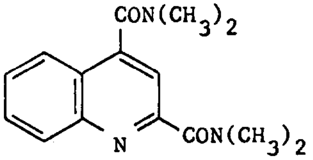

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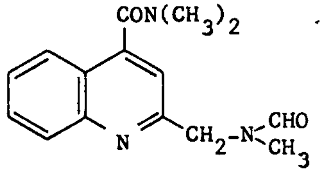

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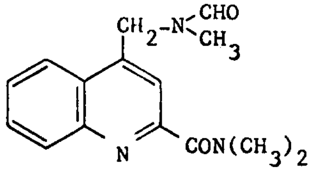

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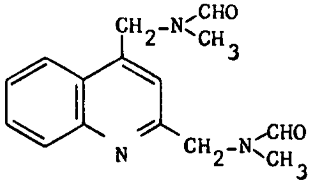


(X)

TABLE 1 - Reaction of quinoline and DMF in the presence of various oxidants[§]

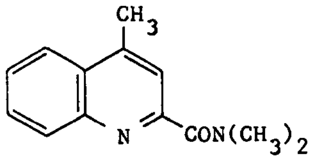
Radical source	Temp °C	III%	IV%	V %	VI %	VII %	VIII%	IX %	X %	Total yields[†]
t-Bu-OOH + Fe^{++}	10	37	4	4	4	20	5	17	9	83
$S_2O_8^{--}$ + Fe^{++}	10	1.5	0.5	23	56	--	--	--	19	45
t-Bu-OO-Bu-*t*	130	27	8	22	19	4	4	6	10	56
$S_2O_8^{--}$	90	6	4	12	68	--	--	--	10	54

§ Ratio quinoline/oxidant 1:1, except with *t*-Bu-OOH (1:3)
† Based on quinoline; yields of the converted base were quantitative

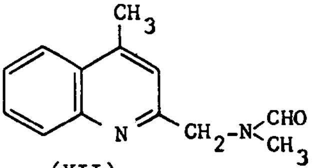
TABLE 2

Radical source	Temp °C	III %	IV %	V %	VI %	Total yields[†]
t-Bu-OOH + Fe^{++}	10	69	12	6	13	47
$S_2O_8^{--}$ + Fe^{++}	10	1.5	0.5	42	56	53
$S_2O_8^{--}$	90	7	5	21	67	54

† Based on the oxidant (ratio quinoline/oxidant 5:1)



(XI)



(XII)

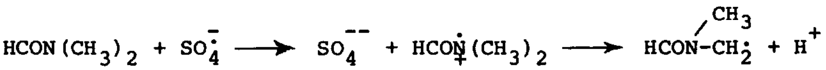
TABLE 3 - Reaction of lepidine and DMF in the presence of various oxidants[§]

Radical source	Temp °C	XI %	XII %	Total yields[†]
t-Bu-OOH + Fe^{++}	10	97	3	58
H_2O_2 + Fe^{++}	10	85	15	31
$S_2O_8^{--}$ + Fe^{++}	10	2	98	40
t-Bu-OO-Bu-*t*	130	33	67	57
$S_2O_8^{--}$	90	18	82	78
$(PhCOO)_2$	90	40	60	35

§ Ratio lepidine/oxidant 1:1, except with *t*-Bu-OOH and *t*-Bu-OO-Bu-*t* (1:3)

† Based on lepidine; yields of the converted base were quantitative

These results indicate that $SO_4^{\dot{-}}$ and not HO· is certainly the radical which takes part in the oxidation with peroxydisulphate. It is a highly selective radical, but is opposite in effect to the *t*-BuO· radical in the same experimental conditions, and generates radical (II) almost exclusively. This result, while interesting from the synthetic point of view, is not easy to explain on the basis of the energies of the involved bonds and of the polar characteristics (*t*-BuO· and $SO_4^{\dot{-}}$ are both electrophilic radicals). At the present we prefer the hypothesis that an electron transfer, rather than a hydrogen abstraction, takes place:



$$HCON(CH_3)_2 + SO_4^{\dot{-}} \longrightarrow SO_4^{--} + HCO\overset{\cdot}{\underset{+}{N}}(CH_3)_2 \longrightarrow HCO\overset{CH_3}{N}\text{-}CH_2^{\cdot} + H^+$$

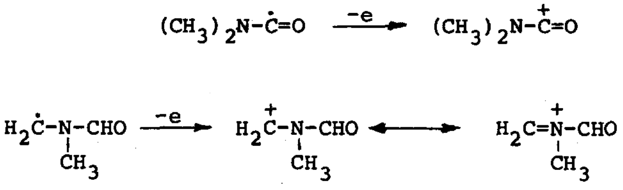
This new route for amidoalkylation is particularly interesting in synthesis for the following reasons:

a) It is applicable to a variety of heteroaromatic bases having highly nucleophilic reactive positions. Similar results have been obtained with the pyridine, pyrazine, pyrimidine and thiazole series;

b) A variety of N-alkylamides can be used; and, using peroxydisulphate, other mono- and di-N-alkylamides could be employed in this new synthetic route, for example, mono- and di-N-alkylacetamides, lactams and N-alkylureas behave similarly to dimethylformamide;

c) Complete selectivity of attack at the α and γ positions of the heterocyclic system which is related to the nucleophilic character of the radicals (I)and

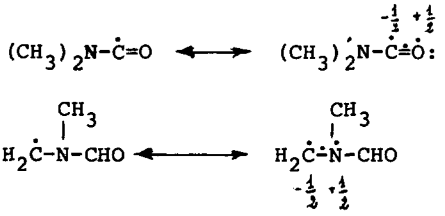
(II). We have already suggested that such a character is related to the stability of the corresponding cations (1, 2)



$$(CH_3)_2N-\dot{C}{=}O \xrightarrow{-e} (CH_3)_2N-\overset{+}{C}{=}O$$

$$H_2\dot{C}-\underset{CH_3}{N}-CHO \xrightarrow{-e} H_2\overset{+}{C}-\underset{CH_3}{N}-CHO \longleftrightarrow H_2C{=}\overset{+}{\underset{CH_3}{N}}-CHO$$

and can also be rationalized in terms of Linnett theory (3):



$$(CH_3)_2N-\dot{C}{=}O \longleftrightarrow (CH_3)_2\dot{N}-\overset{-\frac{1}{2}}{\dot{C}}\overset{\cdot}{=}\overset{+\frac{1}{2}}{\ddot{O}}:$$

$$H_2\dot{C}-\overset{CH_3}{N}-CHO \longleftrightarrow H_2\underset{-\frac{1}{2}}{\dot{C}}\overset{\cdot}{-}\underset{+\frac{1}{2}}{\overset{CH_3}{\dot{N}}}-CHO$$

Further work is in progress to determine quantitatively the polar character of the radicals (I) and (II) by measuring the relative rates in the reaction with various 4-substituted pyridines and quinolines.

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