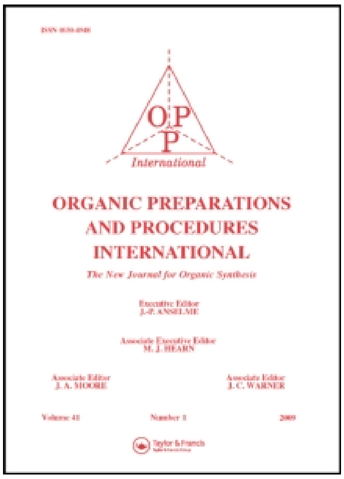

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OPPI BRIEFS

A NEW TYPE OF α-N-AMIDOALKYLATION OF HETEROAROMATIC BASES. MECHANISM OF THE OXIDATION OF THE N-ACYLAMINOETHANOLS BY PEROXYDISULFATE

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(07/27/84)

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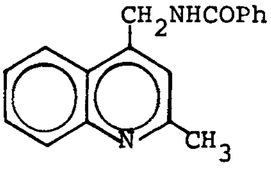
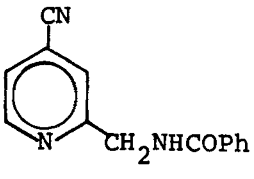
Oxidations effected by peroxydisulfate are synthetic methods of unique character and value.[1] The functionalization of heteroaromatic bases by nucleophilic carbon-centered radicals has become of increasing interest in aromatic substitution reactions.[2] In this context, the oxidation of ethanolamine derivatives with peroxydisulfate has opened further synthetic developments in homolytic aromatic substitution.

Thus when N-benzoylaminoethanol (I) was oxidized in aqueous solution by peroxydisulfate in the presence of catalytic amount of silver nitrate and of protonated heteroaromatic bases, the $\cdot CH_2NHCOPh$ group was cleanly introduced in the heteroaromatic ring. With quinaldine, the 4-substituted derivative (II) was the only reaction product formed in 80% yield (32% conversion), thus making the reaction of clear synthetic interest. With 4-cyanopyridine, the reaction was quite clean; compounds III and IV were

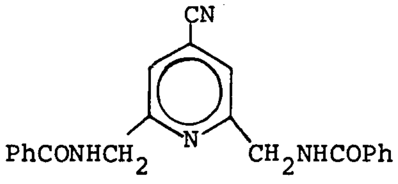


II

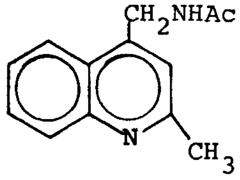


III

isolated in 86% and 14% yields, respectively, calculated on converted base.



IV

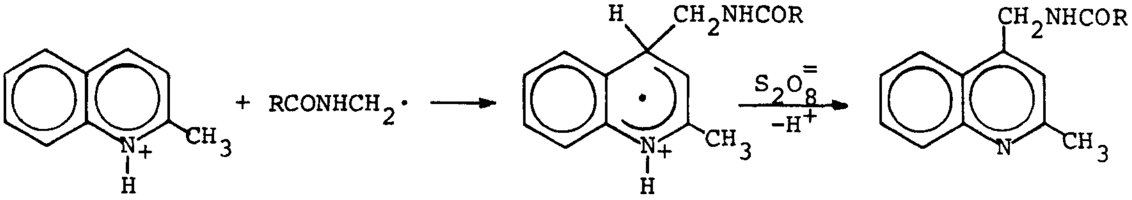


V

The reaction also occurred very easily with the corresponding N-acetylaminoethanol giving compound V as the only product with 2-methylquinoline, albeit in considerably lower conversion, under the same conditions. This suggests that acetamido derivative is a less efficient source of the α-N-alkylamido radical than the corresponding benzamide. A possible path is illustrated for quinaldine.

$$2\,Ag^{+} + S_2O_8^{=} \longrightarrow 2\,SO_4^{=} + 2\,Ag^{++}$$

$$Ag^{++} + RCONHCH_2CH_2OH \longrightarrow Ag^{+} + H^{+} + RCONHCH_2CH_2O\cdot \xrightarrow{-CH_2O} RCONHCH_2\cdot$$



The β-scission of the alkoxy radical can be related to the resonance stabilization of the α-N-amidoalkyl radical ($RCONHCH_2\cdot \longleftrightarrow RCO\overset{+}{N}HCH_2^{-}$), which reacts with electron-poor substrates such as protonated heteroaromatic bases, thus displaying nucleophilic character in agreement with the hypothesis of its resonance stabilization.[3] It is also possible to describe the transition state with significant contribution of polar form shown below:

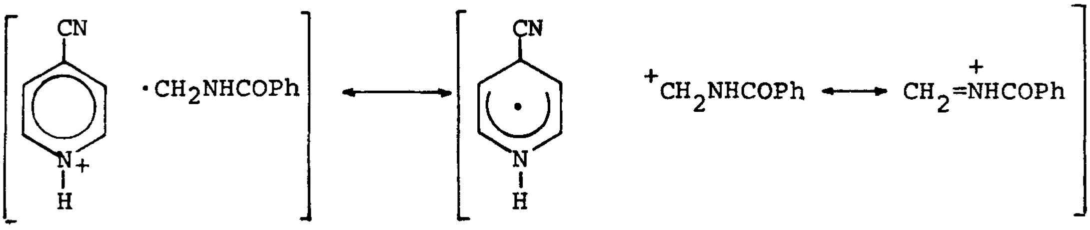


TABLE 1. Yields of Aminoalkylated Products

Heterocycle	Amide	Reaction Products	Conversion[a]	Yield[a]
2-Methylquinoline	N-benzoyl	II	32%	80%
4-Cyanopyridine	N-benzoyl	III(86%); IV(14%)	34%	99%
2-Methylquinoline	N-acetyl	V	12%	67%

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a) Conversion derived from the ratios between the recovered and the initial amount of heterocycles.

TABLE 2. Physical and Spectral Data

Products	mp.	IR	NMR	MS	Elemental Analysis	
	(°C)	(cm^{-1})	(δ)		Calcd.	Found
II	96-97	3460-3260	2.68(s,$-CH_3$,3H)	276(M^+)	C 78.25	78.42
		(N-H)	5(d,$-CH_2$,2H)	161	H 5.83	6.10
		1640(C=O)	7.3-8.1(m,ArH,10H)	(M^+-105)	N 10.13	9.90
		760-700		105		
		(C-H)				
III	92-99	3300(N-H)	4.83(d,$-CH_2$,2H)	273(M^+)	C 70.88	71.20
		2240(C-N)	7.4-8.0(m,ArH,7H)	132	H 4.74	4.48
		1630(C=O)	8.8(d,H_6,pyridine	(M^+-105)	N 17.72	17.49
		1550(N-H)	ring)	117,105,77		
IV	185	3400-3300	4.8(d,$-CH_2$,4H)	370(M^+)	C 71.35	71.33
		(N-H)	7.3-8.0(m,ArH,16H)	265	H 4.86	4.82
		2240(C-N)		(M^+-105)	N 15.40	15.20
		1640(C=O)		105,77		
		710(C-H)				
V	120	3500(N-H)	2.05(s,$-COCH_3$,3H)	214(M^+)	C 72.90	72.63
		1670(C=O)	2.7(s,CH_3,3H)	171	H 6.50	6.54
		750(C-H)	4.85(d,$-CH_2$,2H)	(M^+-43)	N 13.08	12.80
			7.3-8.1(m,ArH,5H)	157,144		

EXPERIMENTAL SECTION

Mps, determined on Kõffler apparatus, are uncorrected. IR spectra were recorded as nujol mulls on a Perkin-Elmer 177 spectrophotometer. NMR spectra were run in $CDCl_3$ (TMS as internal standard) using a Varian A 90 spectrometer. Mass spectra were obtained on a Hitachi Perkin-Elmer RMU-6D spectrometer at 70 eV. Quantitative TLC analyses were performed on a Camag TLC/HPTLC scanner using a Camag nanoapplicator.

General Procedure.- A solution of ammonium peroxydisulfate (10 mmoles) in 15 ml of water was added to a stirred solution of the heterocycle (10 mmoles), silver nitrate (1 mmole), sulphuric acid (50 mmoles) and N-acetylaminoethanol (15 mmoles) at 80° over a period of 30 min. The solution was stirred and warmed (80°) for an additional 3 hrs. After cooling in ice, the solution was basified with 3 N solution of NaOH, filtered and exaustively extracted with ethyl acetate (300 ml) in a separatory funnel; the ethyl acetate extract was dried over anhydrous sodium sulfate, the solvent evaporated and the residue chromatographed on silica gel. The unreacted bases were eluted with hexane and thus separated from the products; compounds II, III and IV were then isolated by using hexane-ethyl acetate as eluent and compound V by using ethyl acetate-methanol. All the products were recrystallized from ethyl acetate to give white crystals. The yields of III and IV were based on isolated products; for II and V, the yields were determined by instrumental thin layer chromatography.

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