THE REACTION OF QUINOLINE N-OXIDE WITH N,N-DIETHYLTHIOCARBAMOYL CHLORIDE

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Quinoline N-oxide (I) reacted with N,N-diethylthiocarbamoyl chloride (II) at room temperature to give S-2-quinolyl N,N-diethylthiocarbamate (III) and O-3-quinolyl N,N-diethylthiocarbamate (IV). From reactions in the presence of a base, S-3- (VII) and S-8-quinolyl N,N-diethylthiocarbamates (VIII) were formed besides III and IV. The possibility of a new mechanism for the formation of III was suggested.

Bauer and his co-workers have extensively studied the reaction of alkyl- and acyl-adducts of aromatic N-oxides with alkanethiols and thiophenols which causes the introduction of sulfur-substituents into heteroaromatic rings[1]. We now wish to report the reaction of quinoline N-oxide (I) with N,N-diethylthiocarbamoyl chloride (II) which also produces quinoline derivatives bearing sulfur-substituents.

A chloroform solution of I and II (1.2 equiv) was stirred at

room temperature for 24 h. On treatment of the reaction mixture with sodium hydrogen carbonate solution, S-2-quinolyl N,N-diethylthiocarbamate (III) (a light yellow oil, picrate : mp 122°) and O-3-quinolyl N,N-diethylthiocarbamate (IV) as colorless prisms, mp 70-72° (picrate : mp 188-189°), were obtained in 70 and 4% yields, respectively. On the other hand, if the reactants were heated with 10% hydrochloric acid, IV and 2-quinolinethiol[2] (V) (75-90% yield) instead of III were produced. Under reflux in chloroform, V and 2,2-diquinolyl sulfide[3] (VI) were formed besides III and IV.

In exploring the essential features and mechanism of the reaction, various conditions were investigated. At first, the reaction was examined in the presence of triethylamine in order to avoid the effect of the hydrogen chloride generated during the reaction. When 1 equivalent of the amine was used, amounts of III and IV decreased and S-3- (VII) (a light yellow oil, picrate : mp 193°) and S-8-quinolyl N,N-diethylthiocarbamates (VIII) as colorless prisms, mp 76° (picrate : mp 144-146°) were produced in low yields ; the use of an excess of triethylamine afforded VIII as the sole product.

Subsequently, reactions in the presence of sodium carbonate, potassium cyanide and 1-morpholinocyclohexene were examined. The effects of all of these additives were found to be practically the same as those of triethylamine ; the formation of 2-hydroxy-, 2-cyano- or 2-(2-oxocyclohexyl)quinoline was not detected. These results are very noteworthy considering that reactions of I with acylating agents in the presence of these

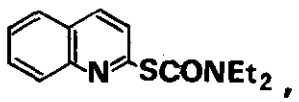
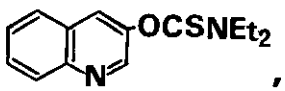
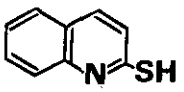
nucleophiles readily afford the corresponding 2-substituted quinolines.

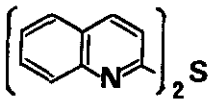
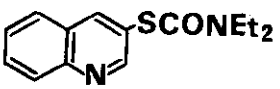
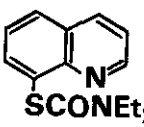
Table I summarizes the results thus obtained. The structures of these products were confirmed by direct comparison with the corresponding authentic samples prepared unequivocally by other routes.

Table I

Temp.	Time (hr)	Additives	Products (%) III	IV	V	VI	VII	VIII
R.T.	24	---	70	4	--	--	--	--
R.T.	1.5	---	--	4	80	--	--	-- a)
reflux	6	---	44	small	15	5	--	--
R.T.	24	NEt_3 (1 eq)	33	trace	--	--	4	12
R.T.	24	NEt_3 (excess)	--	--	--	--	--	27
R.T.	48	Na_2CO_3 aq	28	trace	--	--	4	16
R.T.	24	KCN aq	56	trace	--	--	small	small
R.T.	24	1-morpholino-cyclohexene	55	2.8	--	--	4	7

a) The reaction mixture was first treated with hot 10% HCl.

III  , IV  , V 

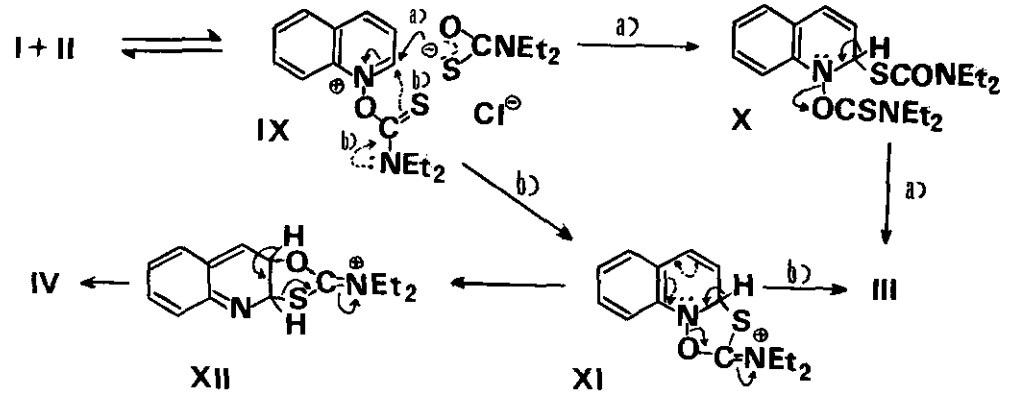
VI  , VII  , VIII 

Although the details of the reaction mechanism have not been established and the role of base is not yet clear, we would like

to mention here the possibility of a new mechanism for the formation of III.

According to one of the most generally recognized mechanism for nucleophilic reactions of acyl-adducts of aromatic N-oxides, the formation of III follows path a which involves nucleophilic attack of the thiocarbamate anion at the electron-deficient 2-position of the thiocarbamoyl-adduct of I (IX) and elimination of the thiocarbamic acid from the dihydroquinoline intermediate (X). The thiocarbamate anion acting as a nucleophile at the former step may originate from the latter one. However, this has not been clearly verified because of difficulties in the application of a suitable source of thiocarbamate anion.

Path b proceeding via the cyclic intermediate XI is conceivable as an alternative. Although there is no example of such a cyclic course in reactions of aromatic N-oxides with acylating agents, this path can not be excluded in this case, because it seems very likely that the strong electron-releasing effect of the diethylamino group and the high nucleophilicity of the sulfur atom would concertedly act as the driving force for the formation of XI from IX. Moreover, the observations obtained from reactions in the presence of sodium carbonate, potassium cyanide and especially 1-morpholinocyclohexene appear to provide supporting evidence for this pathway. In light of the intermediacy of XI, the formation of IV, and not of VII, may be rationalized through a second cyclic intermediate XII.



Further studies are in progress to explore the plausibility of path b and to elucidate the mechanism of formation of other products.

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