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Reaction of Aromatic N-Oxides with Indoles in the Presence of an Acylating Agent

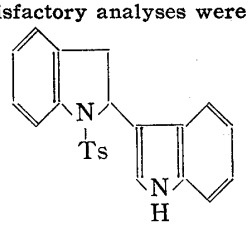
The recent report by Colonna and Bruni[1] on the reaction of indoles with activated aromatic N-oxides prompts us to communicate our results from a similar study. As an extention of researches on the reaction of aromatic N-oxides with enamines,[2] we applied indoles to quinoline and pyridine N-oxides in the presence of an acylating agent, and obtained the results shown in Table I under refluxing conditions, while no reaction was observed at room temperatures. Some representative reactions are shown in Chart 1.

Table I. Reaction of Indoles with Aromatic N-Oxides in the Presence of an Acylating Agent

Indole	Aromatic N-oxide	Acylating agent	Solvent	Reflux period (hr.)	Product[a] Yield (%)
Indole	Quinoline	BzCl	$CHCl_3$	2	Ia (67)
		TsCl	〃	2	Ia (57), Ⅲ[b]
		Ac_2O	—	10	Ib (10)
1-Methylindole	〃	BzCl	$CHCl_3$	7	Ic (56), Ⅱa (10)
		TsCl	〃	7	Ic (12), Ⅳ[c] (55)
	4-Chloroquinoline	BzCl	〃	3	Id (54)
	2-Chloroquinoline	〃	〃	10	Ⅱb (65), Ⅴ (16)
2-Phenylindole	Quinoline	〃	〃	5	Ie (40)
Indole	Ethyl nicotinate	〃	〃	2.5	Ⅵ (30)
		TsCl	〃	5	Ⅵ (5), Ⅲ[b] (17)

a) Satisfactory analyses were obtained for all the products.

b) Ⅲ: The structure of Ⅲ was confirmed by comparison with specimen prepared from diindole and tosyl chloride.[3]



c) Ⅳ: carbostyril.

3-(2-Quinolyl)indole (Ia), m.p. 190～191°, IR ν_{max}^{Nujol} cm^{-1} : 3300 (NH), 1603 (indole C=C), UV λ_{max}^{EtOH} mμ (log ε) : 215 (4.71), 267 (4.32), 302 (4.11), 355 (4.19), was proved to be identical with a specimen prepared from 1-indolylmagnesium bromide and 2-chloroquinoline in a very poor yield.[4] 1-Acetyl-3-(2-quinolyl)-indole (Ib), m.p. 194～194.5°, IR ν_{max}^{Nujol} cm^{-1} : 1703 ($NCOCH_3$), 1605 (indole C=C), might be formed by acetylation of Ia in view of the reaction condition employed.

1-Methyl-3-(2-quinolyl) indole (Ic), m.p. 182～183°, IR ν_{max}^{Nujol} cm^{-1} : 1588 (indole C=C), UV λ_{max}^{EtOH} mμ (log ε) : 215 (4.74), 267 (4.31), 310 (4.11), 355 (4.21), showing the ultraviolet

1) M. Colonna, P. Bruni : Boll. Sci. Fac. Chim. Ind. Bologna, **23** (4), 401 (1965); C. A., **64**, 17536 (1966).
2) M.Hamana, H. Noda : This Bulletin, **13**, 912 (1965), **14**, 762 (1966).
3) G. F. Smith : Chem. Ind., **1954**, 1451; H. F. Hodoson, G. F. Smith : J. Chem. Soc., **1957**, 3544.
4) G. M. Reinecke, H. Johnson, J. F. Sebastian : Tetrahedron Letters, **1963**, 1183; J. C. Powers : J. Org. Chem., **30**, 2534 (1965).
5) D. A. Shirley, P. A. Roussel : J. Am. Chem. Soc., **75**, 375 (1951). They did not elucidate but only deduced the structure of Ⅵ; as shown above, we confirmed its structure by the Fischer's synthesis.

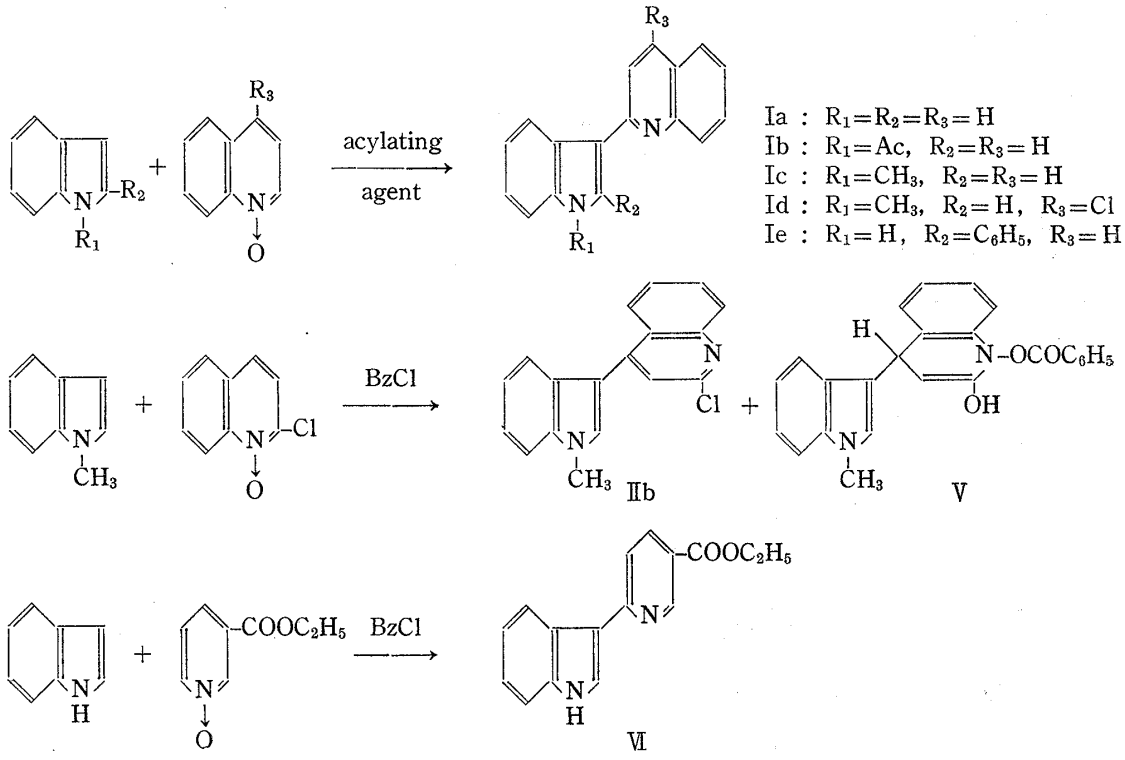


Chart 1.

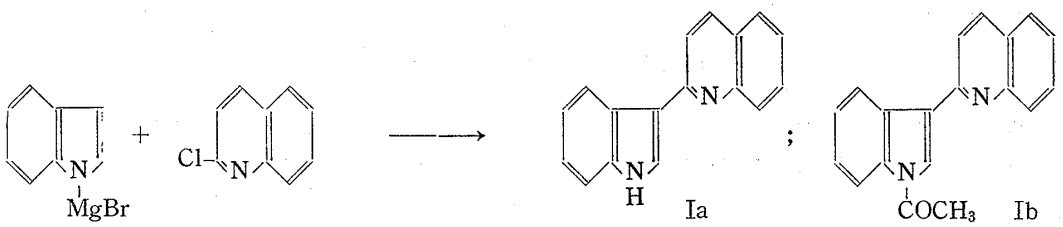


Chart 2.

spectrum closely similar to that of Ia, was shown to be obviously different from 1-methyl-2-(2-quinolyl)indole (Ⅶ) obtained from another routes.[5] 1-Methyl-3-(4-chloro-2-quinolyl)-indole (Id), m.p. 157.8~158°, resulted from a similar reaction of 1-methylindole with 4-chloroquinoline 1-oxide, was converted into Ic by catalytic reduction over palladium-charcoal. These facts are in agreement with the structures assigned to Ic and Id.

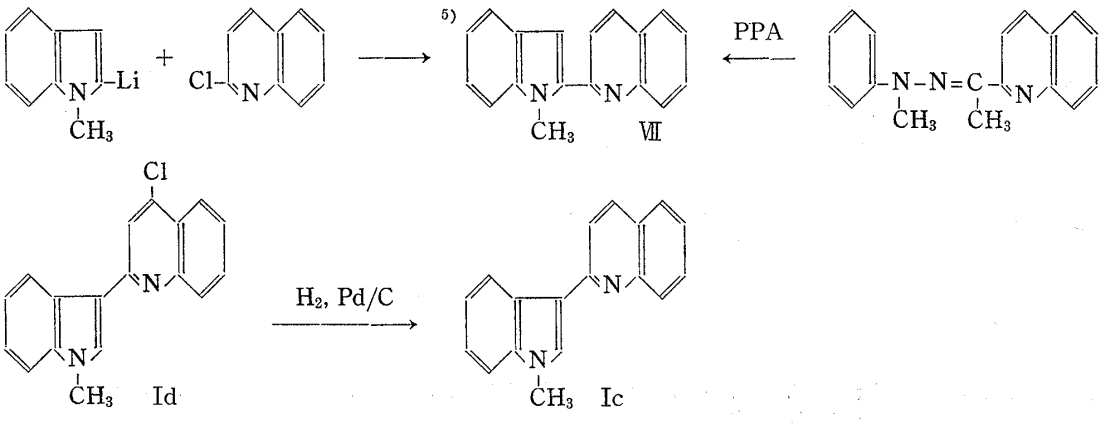


Chart 3.

2-Phenyl-3-(2-quinolyl)indole (Ie), m.p. 273~274°, IR ν_{max}^{Nujol} cm^{-1} : 3125 (NH), 1600 (indole C=C), was identified by direct comparison with an authentic specimen prepared by the Fischer's method.

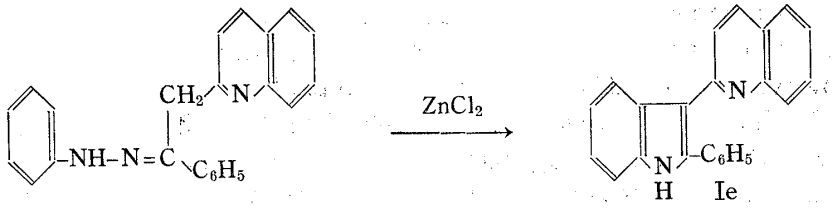


Chart 4.

1-Methyl-3-(4-quinolyl)indole (IIa), m.p, 146~147°, IR ν_{max}^{Nujol} cm^{-1} : 1610, 1583, an isomer of Ic, was also obtained by catalytic reduction of IIb, m.p, 140~140.5°, IR ν_{max}^{Nujol} cm^{-1} : 1610, 1580, the main product of the reaction between 1-methylindole and 2-chloroquinoline 1-oxide. As 2-chloroquinoline 1-oxide reacts with enamines or their analogues to afford 2-chloro-4-substituted quinolines,[6] *e.g.* 2-(2-chloro-4-quinolyl)cyclohexanone from cyclohexanone enamine, IIa and IIb are most probably assumed to be 3-(4-quinolyl)-indole derivatives.

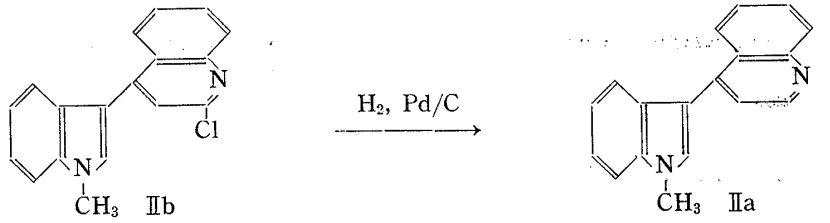


Chart 5.

Of more interest is the formation of 1-benzoyloxy-2-hydroxy-4-(1-methyl-3-indolyl)-1,4-dihydroquinoline (V), m.p. 293~293.5°, IR ν_{max}^{Nujol} cm^{-1} : 3200, 3100, 3150, 1723, 1690, besides IIb from the same reaction. The structure of V was deduced from its elemental analysis, infrared spectrum and the following sequence of reactions. Treatment of V with 10% ethanolic potassium hydroxide resulted in elimination of benzoic acid to give VIII, which was converted by refluxing with phosphoryl chloride into IIb; conversely, IIb was transformed into VIII with hot concentrated hydrochloric acid. The formation of V might be rationalized by hydrolysis of the corresponding 2-chloroquinoline derivative (IX), which could be formed as an intermediate of the reaction.

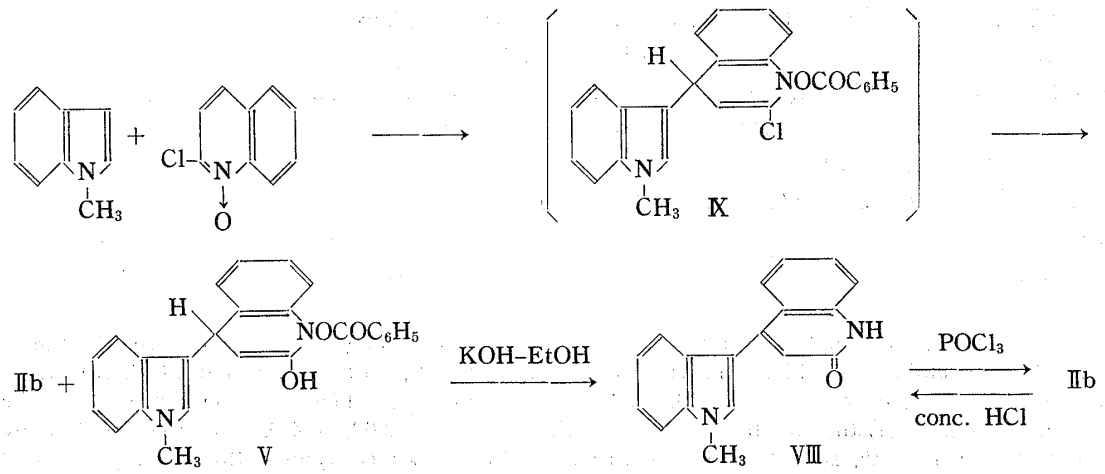


Chart 6.

Skatol did not react with quinoline 1-oxide under comparable conditions as noticed by Colonna and Bruni.[1]

6) M. Hamana, H. Noda : This Bulletin, in press.

Attempted reactions between acyl-adduct of pyridine 1-oxide or 1-methoxypyridinium iodide and indoles under various conditions failed and the starting materials were recovered. However, application of ethyl nicotinate 1-oxide to quinoline 1-oxide resulted in formation of ethyl 2-(3-indolyl)pyridine-5-carboxylate (Ⅵ), m.p. 169~170°, IR ν_{max}^{Nujol} cm^{-1} : 3250 (NH), 1690 (ester C=O), 1600 (indole C=C). The structure of Ⅵ was deduced from its conversion with potassium permanganate to pyridine-2,5-dicarboxylic acid, followed by transformation into the diethylester.

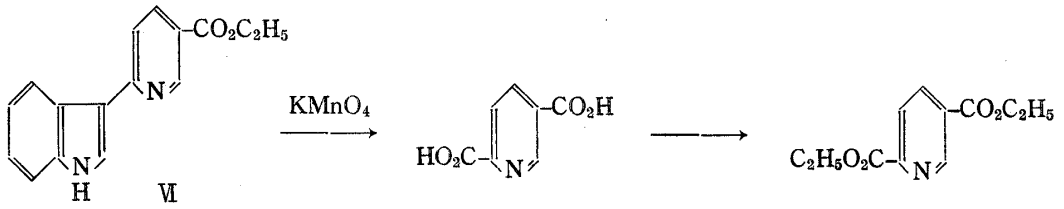


Chart 7.

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1,3-Dipolar Cycloaddition of 5-Nitro-2-furonitrile Oxide

As a part of a continuing study[1] of 5-nitrofuran antimicrobials, an interest in the 1,3-dipolar cycloaddition of 5-nitro-2-furonitrile oxide (Ⅰ) has led to the synthesis of (5-nitro-2-furyl)isoxazole derivatives, which possess excellent antimicrobial activities. We now report examples of this reaction with various olefinic dipolarophiles involving a series of enamines*1 (Ⅲ) of aldehydes and ketones, although the reaction of enamines as the dipolarophile had been reported[2] recently using other dipolar species.

5-Nitro-2-furonitrile oxide (Ⅰ) was generated by the addition of triethylamine to 5-nitro-2-furhydroxamoyl chloride[3] (Ⅱ) and isolated as an unstable liquid (IR ν^{liq} cm^{-1} : 2240). The cycloaddition, however, was conveniently effected by mixing equimolar amounts of Ⅰ, the enamine (Ⅲ) and triethylamine at room temperature to form easily amino-3-(5-nitro-2-furyl)-4,5-dihydroisoxazole (Ⅳ) as the exclusive product in a good yield. Structual assignment of the products was made on the basis of a study of

*1 The enamines employed in this experiment were prepared according to the procedure of Mannich (for the aldehyde enamines; C. Mannich, H. Davidsen : Ber., **69**, 2106 (1963)) and Stork (for the ketone enamines; G. Stork, *et al.* : J. Am. Chem. Soc., **85**, 207 (1963)). The following are new enamines; 1-piperidino-1-(4-pyridyl)ethylene (b.p_3 107~110°, IR ν^{liq} cm^{-1} : 1600, 1545), 1-morpholino-1-(3-pyridyl)-ethylene (b.p_6 131~134°, IR ν^{liq} cm^{-1} : 1605) and 1-piperidino-1-(2-pyridyl)ethylene (b.p_3 117~120°, IR ν^{liq} cm^{-1} : 1585, 1563).

1) Part Ⅵ : Yakugaku Zasshi, **86**, 1014 (1966); The present paper constitutes Part Ⅶ of the series entitled "Studies on Nitrofuran Derivatives."
2) *a*) M. E. Munk, Y. KiKim : J. Am. Chem. Soc., **86**, 2213 (1964). *b*) M. E. Kuehne, S. J. Weaver, P. Franz : J. Org. Chem., **29**, 1582 (1964).
3) R. Lenaers, F. Eloy : Helv. Chim. Acta, **46**, 1067 (1963).