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REACTIONS OF AROMATIC N-OXIDES WITH O-BENZOYL AROMATIC ALDEHYDE CYANOHYDRINS IN ACETIC ANHYDRIDE[1]

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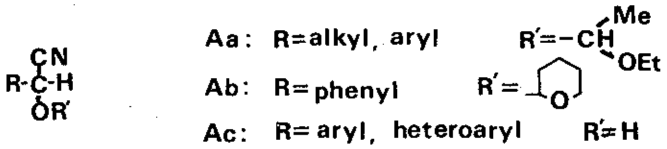
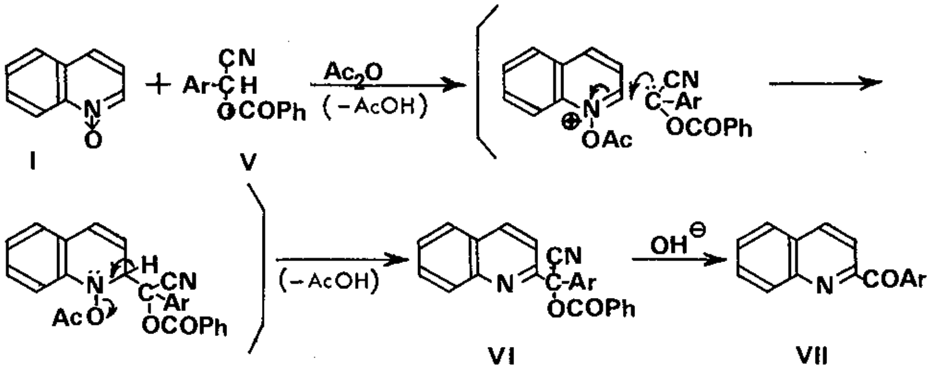
Quinoline N-oxide (I) readily reacts in hot acetic anhydride with some O-benzoyl aromatic aldehyde cyanohydrins (Va-d) to produce O-benzoylcyanohydrins (VIa-d) of 2-quinolyl aryl ketones which are easily convertible to the corresponding ketones (VIIa-d) by alkaline hydrolysis. Similar reactions occur also with N-oxides of isoquinoline, pyridine and phenanthridine (II, III and IV). The derivatives of benzaldehyde and *p*-chlorobenzaldehyde resist the reaction.

Recently Stork and Maldonado[2] have reported a new synthetic method of ketones which involves alkylation of carbanions of vinyl ether adducts (Aa) of aldehyde cyanohydrins followed by hydrolysis of the alkylated products. There are also described similar reaction starting from O-tetrahydropyran-2-yl benzaldehyde cyanohydrin (Ab)[3] and the Michael addition of aromatic aldehyde cyanohydrins (Ac)[4] to various electrophilic olefins.



The reaction of acyl-adducts of aromatic N-oxides with various nucleophilic carbon compounds has been extensively studied in our laboratory[5]. We now wish to report a new expansion of this type of reaction using O-benzoyl aromatic aldehyde cyanohydrins[6] as nucleophilic carbon compounds.

Quinoline N-oxide (I) readily reacted with O-benzoyl p-nitrobenzaldehyde cyanohydrin (Va) when heated in acetic anhydride (5 equiv.) on a water-bath, giving O-benzoylcyanohydrin of 2-quinolyl p-nitrophenyl ketone (VIa), yellow pillars, mp 200-201°, in a good yield of 75.7% after 5 h's reaction. Apparently the reaction followed the course shown below, and acetic anhydride was found to be most effective as an acylating agent in the same way as the reaction with active methylene compounds[7], benzoyl chloride or tosyl chloride being not effective. While VIa was considerably stable to hot acid, hydrolysis to the ketone (VIIa) was effected in 76.5% yield by heating with 10% sodium hydroxide in methanol.



Similar reactions with O-benzoylcyanohydrins of o-nitro- (Vb), p-carboxy-benzaldehyde (Vc) and 2-pyridinecarboxaldehyde (Vd) afforded the corresponding O-benzoylcyanohydrins (VIb-d) of 2-quinolyl aryl ketones (VIIb-d), however attempted reactions with the derivatives of benzaldehyde, p-chlorobenzaldehyde and aliphatic aldehyde failed. These results demonstrate that the acidity of the cyanohydrin derivative should be considerably high for the initiation of the reaction. It was further found that the reaction using p-nitrobenzaldehyde cyanohydrin (Va') instead of Va gave O-acetylcyanohydrin of VIIa (VIa') in a comparable yield (68.6%). The corresponding 2-quinolyl ketones (VIIb-d and VIIa) were easily obtained in the same manner from VIb-d and VIa'.

Quite similar results were obtained from reactions of isoquinoline N-oxide (II) with Va-d. Although pyridine N-oxide (III) of benzenoid structure is sometimes less reactive toward nucleophilic reaction as compared with naphthoidal benzopyridine N-oxide, III did react with Va and Vb though in somewhat lower yields. In view of its high reactivity, it was expected that phenanthridine N-oxide (IV) would react with O-benzoyl benzaldehyde cyanohydrin, however this was not achieved and only phenanthridone was formed almost quantitatively. The reaction with Va proceeded normally to give the cyanohydrin derivative (XII). These results are summarized in Table.

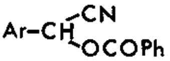
It is very significant that acylation of heteroaromatic rings was realized by the above-mentioned reaction series involving nucleophilic substitution of aromatic N-oxide. Further work on extending the reaction to more weakly acidic aldehyde cyanohydrins is in progress. At the same time, development of nucleophilic reaction of aldehyde cyanohydrin is another project worthy of pursuing, which is also under way in our laboratory.

Table Yields and Melting Points of the Products

N-oxide	cyanohydrin derivative of ketone			ketone		
		yield (%),	(mp °C)		yield (%),	(mp °C)
I	VIa	75.5,	(200-201)	VIIa	76.5,	(177-178)
I	VIb	11.4,	(172-173)	VIIb	94.5,	(125-126)
I	VIc	44.0,	(201-202)	VIIc	81.0,	(237-238)
I	VId	74.0,	(182-183)	VIId	54.0	a)
I	VIa'	68.6,	(169-170)	VIIa	68.9	
II	VIIIa	56.2,	(258-259)	IXa	68.5,	(258-259)
II	VIIIb	10.0,	(232-233)	IXb	82.0,	(171-172)
II	VIIIc	39.4,	(121-122)	IXc	56.0,	(231-232)
II	VIIId	48.0,	(144-146)	IXd	40.0,	b)
III	Xa	21.0,	(185-186)	XIa[8]	53.0,	(97-98)
III	Xd	24.5,	(181-182)	XId[9]	72.4,	c)
IV	XII	57.0,	(266-267)	XIII	97.0,	(218-219)

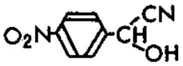
a) bp 202-207°/0.35 mm. b) bp 185-195°/0.28 mm.
c) bp 142-156°/0.3 mm.

V

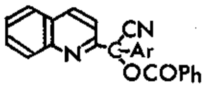


$\mathrm{Ar{-}CH(CN)OCOPh}$

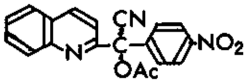
Va'



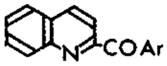
VIa d



VIa'

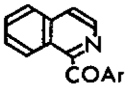


VIIa d

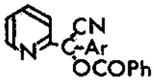


VIIIa d

IXa d



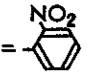
Xa,d



XIa,d

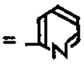
a: Ar=

b: Ar=

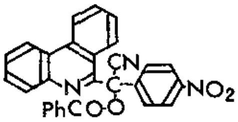


c: Ar=

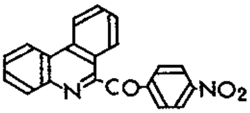
d: Ar=



XII



XIII



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