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Studies on Tertiary Amine Oxides. LXXI.[1] Some Electrophilic Reactions of 1-Hydroxy-2-phenylindole[2]

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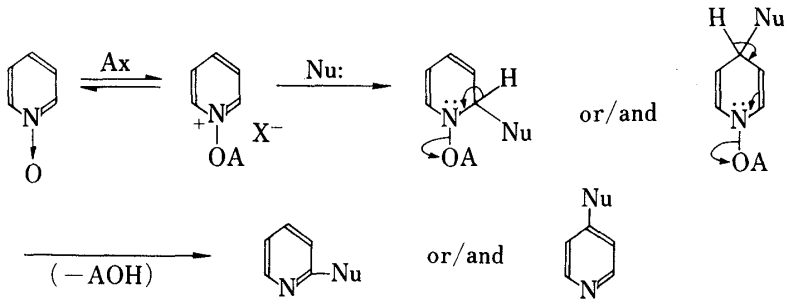
Treatment of 1-hydroxy-2-phenylindole (**1**) with phosphoryl chloride–DMF gave 2-phenylindole-3-carboxaldehyde (**2**) in 70% yield.

The reaction of **1** with quinoline 1-oxide (**3**) and benzoyl chloride in boiling chloroform produced 1-benzoyloxy-2-phenyl-3-(2-quinolyl)indole (**5**) and 1-hydroxy-2-phenyl-3-(2-quinolyl)indole (**6**). In the reaction using tosyl chloride instead of benzoyl chloride, **6** or 2-phenyl-3-(2-quinolyl)indole (**8**) was formed. These results demonstrate that the enehydroxylamine systems in **1** and 1-benzoyloxy-2-phenylindole (**4**) can behave as nucleophilic species as a result of enamine-like polarization.

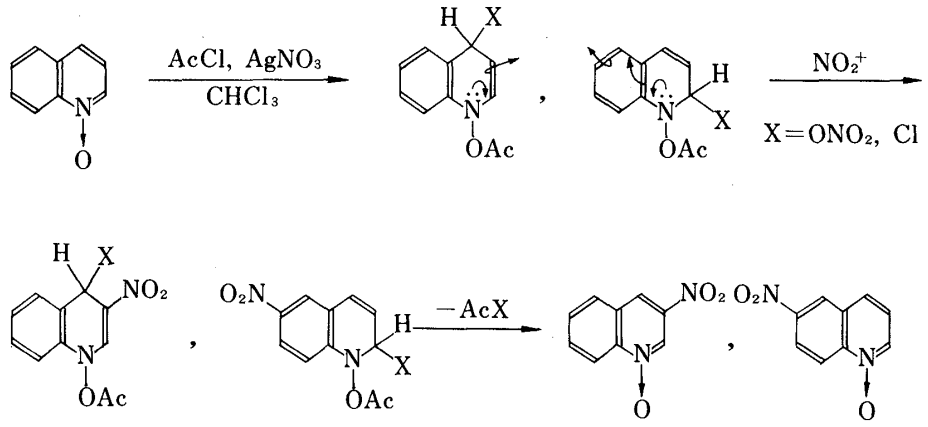
Keywords——enehydroxylamine; nitrone; 1-hydroxy-2-phenylindole; Vilsmeier–Haack reaction; 2-phenylindole-3-carboxaldehyde; quinoline 1-oxide; 1-benzoyloxy-2-phenylindole; 1-hydroxy-2-phenyl-3-(2-quinolyl)indole; 1-benzoyloxy-2-phenyl-3-(2-quinolyl)indole

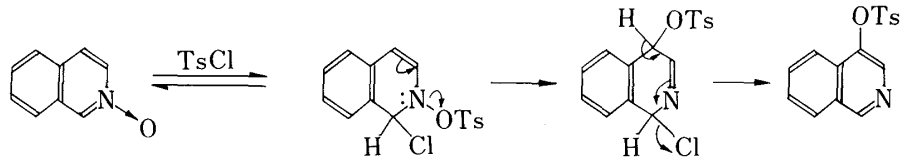
Nucleophilic reactions of aromatic N-oxides in the presence of an acylating agent are now known to proceed through the 1,2- or 1,4-dihydro intermediate, that is, a dienehydroxylamine or an enehydroxylamine system.[3] In most cases, the consecutive liberation of an acid component occurs, producing an α- or/and γ-substituted product.



AX=Ac-OAc, PhCO-Cl, Ts-Cl *etc.*
Nu: =Cl^-, Br^-, amide ion, carbanion,enamine, *etc.*

However, in some cases, the β-position of the dihydro intermediate can be attacked by electrophiles[3,4] as well as nucleophiles,[3,5] to give the β-substituted product either with retention of the N-oxide function or with deoxygenation, as exemplified below.

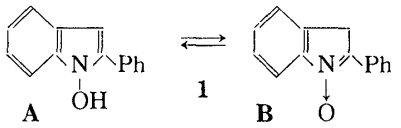




These results suggest that an enehydroxylamine system might exhibit both nucleophilic and electrophilic properties. In order to explore this concept in connection with the chemistry of aromatic N-oxides, 1-hydroxy-2-phenylindole[6] and ethyl 1-hydroxyindole-2-carboxylate[7] were chosen as enehydroxylamine systems, and their reactions with electrophiles and nucleophiles were investigated, mainly in the presence of an acylating agent. This paper describes electrophilic reactions of 1-hydroxy-2-phenylindole with phosphoryl chloride and N,N-dimethylformamide (DMF) and with quinoline 1-oxide.

As regards the structure of 1-hydroxy-2-phenylindole (**1**), the nitrone from (**B**) is possible besides the enehydroxylamine from (**A**). The **A**/**B** ratios of **1** in several solvents were roughly estimated from the integrated areas of the C_3-methine signal of form **A** and the C_3-methylene signal of form **B** in the nuclear magnetic resonance (NMR) spectra[8,9] (Table I).

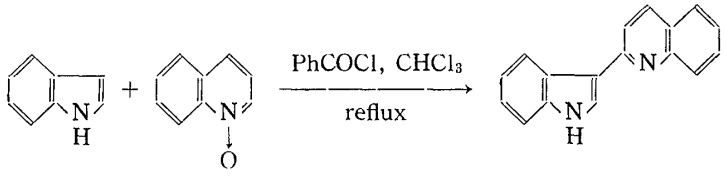
Table I. The A/B Ratios of 1-Hydroxy-2-phenylindole (**1**) estimated by NMR Spectroscopy



Solvent	δ		Ratio	
	β-H	β-H_2	**A**	**B**
CD_3OD	—	3.30	0	100
$CDCl_3$[10]	6.30	3.86	40	60
DMF	6.63	—	100	0
DMF–CF_3COOH (4 : 1)	6.60	—	100	0
DMF–CF_3COOH (1 : 1)	—	3.00	0	100

Colonna and his co-workers have described some electrophilic reactions of **1**,[10] but no report on the Vilsmeier–Haack reaction of **1** was found. When **1** was added to a DMF solution to equimolar phosphoryl chloride and the mixture was stirred at room temperature for 45 min, 2-phenylindole-3-carboxaldehyde (**2**) was obtained as colorless needles of mp 245—248 °C in 70% yield. Its structure was unambiguously established by direct comparison with an authentic sample prepared by the same reaction of 2-phenylindole.[11] Acheson *et al.* have recently reported that the Vilsmeier–Haack reaction of 1-methoxy- or 1-acetoxy-indole gives 1-methoxyindole-3-carboxaldehyde or 2-chloroindole- and 1-hydroxyindole-3-carboxaldehyde, respectively[9,12] However, no 1-hydroxy-2-phenylindole-3-carboxaldehyde was detected in the above reaction in spite of careful examination. It is not yet clear whether the reaction follows path (a) or (b) shown in Chart 1; the details of the mechanism remain to be elucidated, particularly with respect of the dehydroxylation step.

It has been shown that indoles react with aromatic N-oxides in the presence of an acylating agent to give 3-substituted indoles[13,14]; a typical example is as follows.



In order to explore this type of reaction of **1**, quinoline 1-oxide (**3**) was treated with **1** in the presence of benzoyl chloride. Two equivalents of benzoyl chloride were added to an ice-cooled solution of **1** and **3** (1 eq) in chloroform, and the mixture was refluxed for 4 h. The reaction mixture was treated with a saturated solution of sodium bicarbonate and concentrated under reduced pressure. Chromatographic separation of the residue on silica gel furnished four products (**4**, **5**, **6** and **7**.)

The infrared (IR) spectrum of **4** lacked an absorption due to NH group but exhibited a characteristic carbonyl band at 1765 cm^{-1}, and its NMR spectrum showed a one-proton singlet due to the C_3-methine proton of indole ring at δ 6.66. Thus, **4** was assigned as 1-benzoyloxy-2-phenylindole, and its identity was confirmed by comparison with an authentic sample obtained by the known method[15]; the yield was 45.2%.

Product **5** formed colorless needles of mp 158—160 °C with the empirical formula $C_{30}H_{20}N_2O_2$. Its IR spectrum exhibited a carbonyl band at 1770 cm^{-1} but no absorption due to NH group, like that of **4**. However, the NMR spectrum showed signals only in the aromatic region, no signal due to the C_3-methine proton being noticed. From these observations, **5** was assigned as 1-benzoyloxy-2-phenyl-3-(2-quinolyl)indole; the yield was 27.0%. In order to confirm this structure assignment, **4** was treated with **3** and 1 equivalent of benzoyl chloride in boiling chloroform, and **5** was successfully obtained in 31.1% yield.

Product **6** formed pale yellow needles of mp 231—234 °C. Its empirical formula, $C_{23}H_{16}N_2O$, as well as a broad band in the IR at 2560—2650 cm^{-1} (indicative of an OH group), suggests that **6** is 1-hydroxy-2-phenyl-3-(2-quinolyl)indole. In fact, when the 1-benzoyloxy

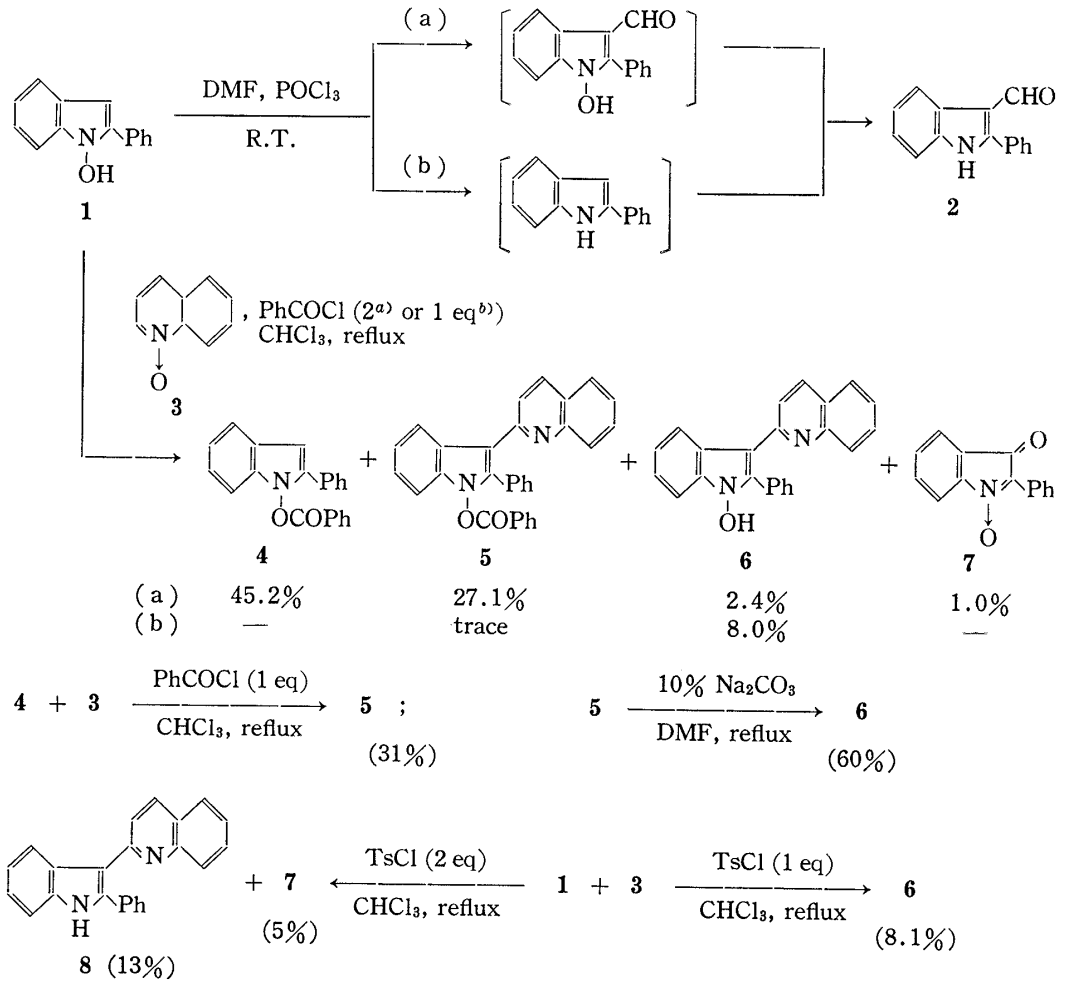


Chart 1

derivative **5** was refluxed with 10% sodium carbonate in DMF for 5 h, the 1-benzoyloxy group underwent hydrolysis to afford **6** in 60.0% yield.

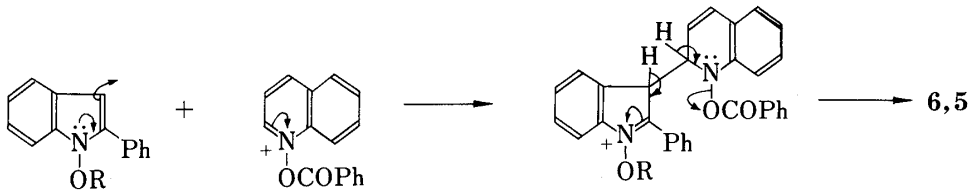
Product **7** was proved to be 2-phenylisatogen by direct comparision with an authentic sample prepared by oxidation of **1** with isoamyl nitrite.[16]

When **1** was treated with **3** in the presence of 1 equivalent of benzoyl chloride under reflux in chloroform, 1-hydroxy-3-(2-quinolyl)indole **6** was isolated in low yield (8.0%) along with a trace of the 1-benzoyloxy derivative **5**.

Subsequently, reactions using tosyl chloride as an acylating agent were examined. Treatment of **1** with **3** and 2 equivalents of tosyl chloride in boiling chloroform for 3 h resulted in the formation of the dehydroxylated 2-phenyl-3-(2-quinolyl)indole (**8**)[14] and 2-phenylisatogen **7** in 13.0 and 5.0% yields, respectively. Product **8** was identical with an authentic sample reported previously.[14] On the other hand, a similar reaction using 1 equivalent of tosyl chloride gave not **8** but the 1-hydroxy derivative **6** in 8.1% yield.

The above-mentioned reactions are formulated in Chart 1.

The formation of **5** and **6** from the reaction of **1** with **3** in the presence of benzoyl chloride can be well rationalized by the same course as in the reaction of indole,[14] as shown in Chart 2, although the possibility cannot be excluded that some portion of **6** arises from hydrolysis of **5** during the work-up. The dehydroxylated product **8** formed from the reaction using 2 equivalents of tosyl chloride seems to stem from **6**, but the details of the dehydroxylation step are again not clear. Although the yields of products in these reactions were not always good because of concomitant resinification, and the reactivity of **1** toward electrophiles is apparently lower than that of 2-phenylindole, it is very significant that not only **1** but also 1-benzoyloxy-2-phenylindole **4** can react with quinoline 1-oxide in the presence of benzoyl chloride or tosyl chloride.



1 : R=H, **4** : R=COPh

Chart 2

Experimental[17]

Reaction of 1-Hydroxy-2-phenylindole (1) with $POCl_3$-DMF——1-Hydroxy-2-phenylindole **1** (2 g) was added to a solution of $POCl_3$ (1 ml) in DMF (10 ml), previously prepared under ice-cooling and stirring. The mixture was stirred at room temperature for 45 min, and 10% NaOH (10 ml) was added. After 10 min, the whole was poured into a large amount of H_2O (*ca.* 50 ml). The resulting precipitate was collected and recrystallized from MeOH to give 1.47 g (70%) of 2-phenylindole-3-carboxaldehyde (**2**),[11] colorless needles, mp 245—248°C.

Reaction of 1 with Quinoline 1-Oxide (3) in the Presence of PhCOCl——1) PhCOCl (1.7 g) was added dropwise to a solution of **1** (1.4 g) and **3** (0.85 g) in $CHCl_3$ (20 ml), and the whole was refluxed for 4 h. The reactants were stirred for 1 h with saturated $NaHCO_3$ solution (10 ml), then concentrated under reduced pressure, and the residue was chromatographed on silica gel. The fraction eluted with *n*-C_6H_{14}–benzene (1: 1) was recrystallized from *n*-C_6H_{14}–benzene to give 0.95 g (45.2%) of 1-benzoyloxy-2-phenylindole (**4**), colorless needles, mp 89—91°C.[15] Elution with benzene gave two fractions. The first was recrystallized from *n*-C_6H_{14}–benzene to give 0.8 g (27.1%) of 1-benzoyloxy-2-phenyl-3-(2-quinolyl)indole (**5**), colorless needles, mp 158—160°C. *Anal.* Calcd for $C_{30}H_{20}N_2O_2$: C, 81.80; H, 4.58; N, 6.36. Found: C, 81.94; H, 4.66; N, 6.34. IR ν_{max}^{Nujol} cm^{-1}: 1770 (C=O). NMR ($CDCl_3$) δ: 7.1—8.5 (20H, m, Ar–H). The second fraction was recrystallized from *n*-C_6H_{14}–CH_2Cl_2 to give 0.015 g (1.0%) of 2-phenylisatogen (**7**), orange-red scales, mp 185—187°C. IR ν_{max}^{Nujol} cm^{-1}: 1721, 1707 (C=O), 1185 (N–O). It was proved to be identical with an authentic sample prepared from **1** and iso-$C_5H_{11}ONO$.[16] The fraction eluted with CH_2Cl_2 was recrystallized from CH_2Cl_2 to give 0.05 g (2.4%) of 1-hydroxy-2-phenyl-3-(2-quinolyl)indole (**6**), pale yellow needles, mp 231—

233°C. *Anal.* Calcd for $C_{23}H_{16}ON_2$: C, 82.12; H, 4.72; N, 8.33. Found: C, 81.71; H, 4.82; N, 8.22. IR ν_{max}^{Nujol} cm^{-1}: 2500—2650 (OH). NMR ($CDCl_3$) δ: 6.4—8.6 (16H, m).

2) Similar reaction of **1** (1 g) with **3** (0.85 g) and PhCOCl (0.7 g) in $CHCl_3$ (20 ml) yielded 0.13 g (8.0%) of **6** and a trace of **5**.

Reaction of 4 with 3 in the Presence of PhCOCl——A solution of **4** (1.5 g), **3** (0.85 g) and PhCOCl (0.81 g) in $CHCl_3$ (20 ml) was refluxed for 10 h. The reaction mixture was processed as in the foregoing experiment to give 0.65 g (31.0%) of **5**, colorless needles, mp 158—160°C (n-C_6H_{14}–benzene).

Hydrolysis of 5 to 6——A solution of **5** (0.2 g) and 10% Na_2CO_3 (6 ml) in DMF (10 ml) was heated on a water bath for 5 h, and poured into a large amount of H_2O (*ca.* 30 ml). The resulting precipitate was collected and recrystallized from CH_2Cl_2 to give 0.09 g (62.6%) of **6**, pale yellow needles, mp 231—233°C.

Reaction of 1 with 3 in the Presence of TsCl——1) TsCl (2.3 g) was added dropwise to a solution of **1** (1.4 g) and **3** (0.85 g) in $CHCl_3$ (30 ml), and the whole was refluxed for 4 h. The reactants were stirred for 1 h with saturated $NaHCO_3$ solution (10 ml), and then concentrated under reduced pressure. The residue was chromatographed on silica gel with n-C_6H_{14}–benzene and CH_2Cl_2 to give 0.27 g (13.0%) of 2-phenyl-3-(2-quinolyl)indole (**8**),[14] pale yellow leaflets, mp 190—191°C, and 0.08 g (5.0%) of **7**.

2) Similar reaction of **1** (1 g) with **3** (1.6 g) and TsCl (0.8 g) in $CHCl_3$ (30 ml) gave 0.13 g (8.1%) of **6**, pale yellow needles, mp 231—233°C (CH_2Cl_2).

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