SOME REACTIONS OF 1-HYDROXY-2-PHENYLINDOLE

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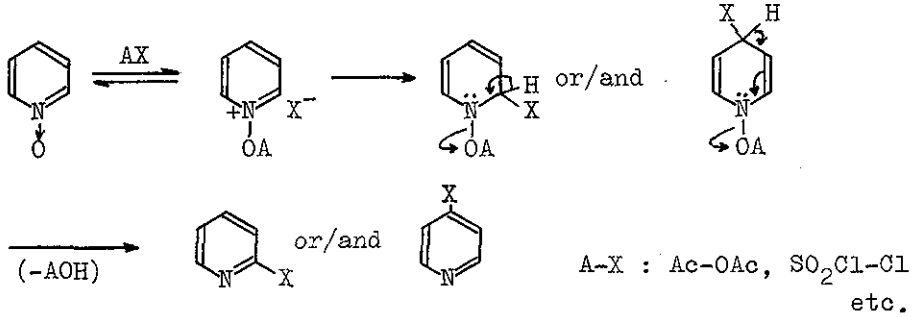
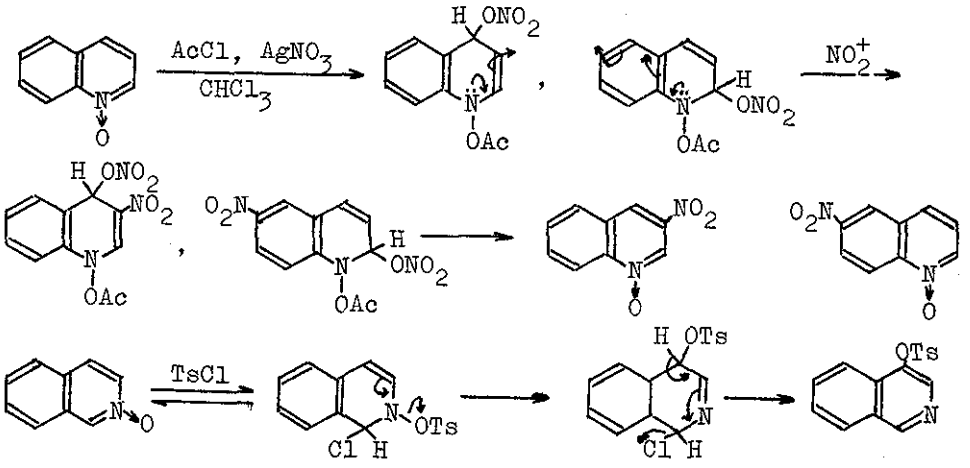
The reaction of aromatic N-oxide in the presence of an acylating agent is now established to proceed through a 1,2- or a 1,4-dihydro intermediate, that is, a dienehydroxylamine or an enehydroxylamine system[1]. In most cases, the consecutive elimination of an acid component occurs, producing α- or/and γ-substituted product.

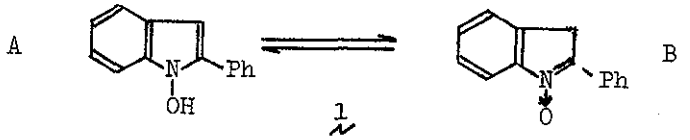


However in some cases, the dihydro intermediate is able to undergo electrophilic or nucleophilic reaction and gives the respective β-substituted product either with retention or with simultaneous deoxygenation of the N-oxide function, as exemplified below[2,3].



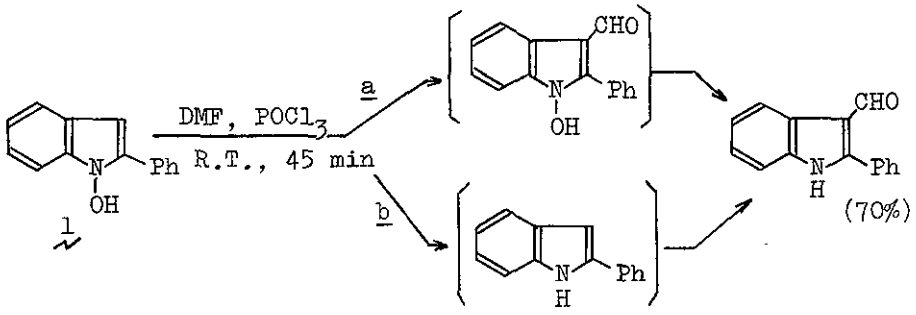
These results apparently suggest the possibility that the enehydroxylamine system might behave as both nucleophilic and electrophilic species. In order to explore this aspect, 1-hydroxy-2-phenylindole[4] (1) was chosen as enehydroxylamine system and its reactions with some electrophiles and nucleophiles were examined.

The nitrone form (B) is also possible besides the enehydroxylamine form (A) for 1, and the preliminary examinations by means of NMR spectroscopy indicate that 1 exists exclusively as A in DMF and the A/B ratio is around 40/60 in deuteriochloroform.



At first, the reaction of 1 with electrophiles was tried.

While the Vilsmeier-Haak reaction gave 2-phenyl-3-formylindole[5] in a good yield of 70%, it is not yet clear whether the reaction follows course a or b because the details of dehydroxygenation of N-hydroxy group remains ambiguous.



On the other hand, enamine-like polarization of 1 was shown to operate apparently in the reaction with quinoline N-oxide (2) in the presence of benzoyl chloride. When 2 equivalents of benzoyl chloride was added to an ice-cooled solution of 1 and 2 in chloroform and the reactants were refluxed for 4 hr, 1-benzoyloxy-2-phenyl-3-(2-quinolyl)indole (4; 27%) and 1-hydroxy-2-phenyl-3-(2-quinolyl)indole (5; 2.4%) were obtained in addition to 1-benzoyloxy-2-phenylindole (3; 45.2%) and 2-phenylisatogen (6; 1%). From the reaction using 1 equivalent benzoyl chloride, 5 (8%) and 4 (trace) were isolated, and treatment of 3 with 2 and benzoyl chloride (1 equiv.) in boiling chloroform for 10 hr afforded 4 as the sole product in 31% yield. From these results, the formation of 5 and 4 should be explained in the paths shown in Chart 1, although the possibility can not be excluded that the work-up has caused the hydrolysis of a part of 4 to 5.

Subsequently, some nucleophilic reactions of 1 were examined.

Sundberg[6] has previously described that treatment of 1 with tosyl chloride and pyridine at low temperatures in dichloromethane affords 2-phenyl-3-tosyloxyindole (7), 2-phenylindole (8) and 2,2'-diphenyl-3,3'-bisindole (9). The formation of 7 can be ra-

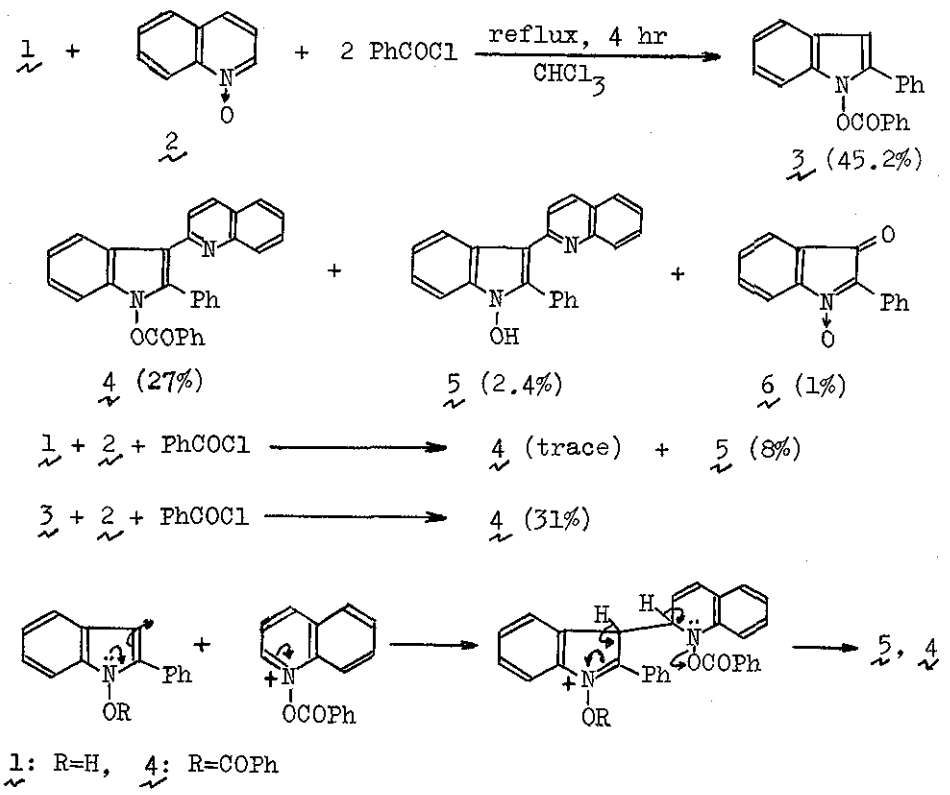
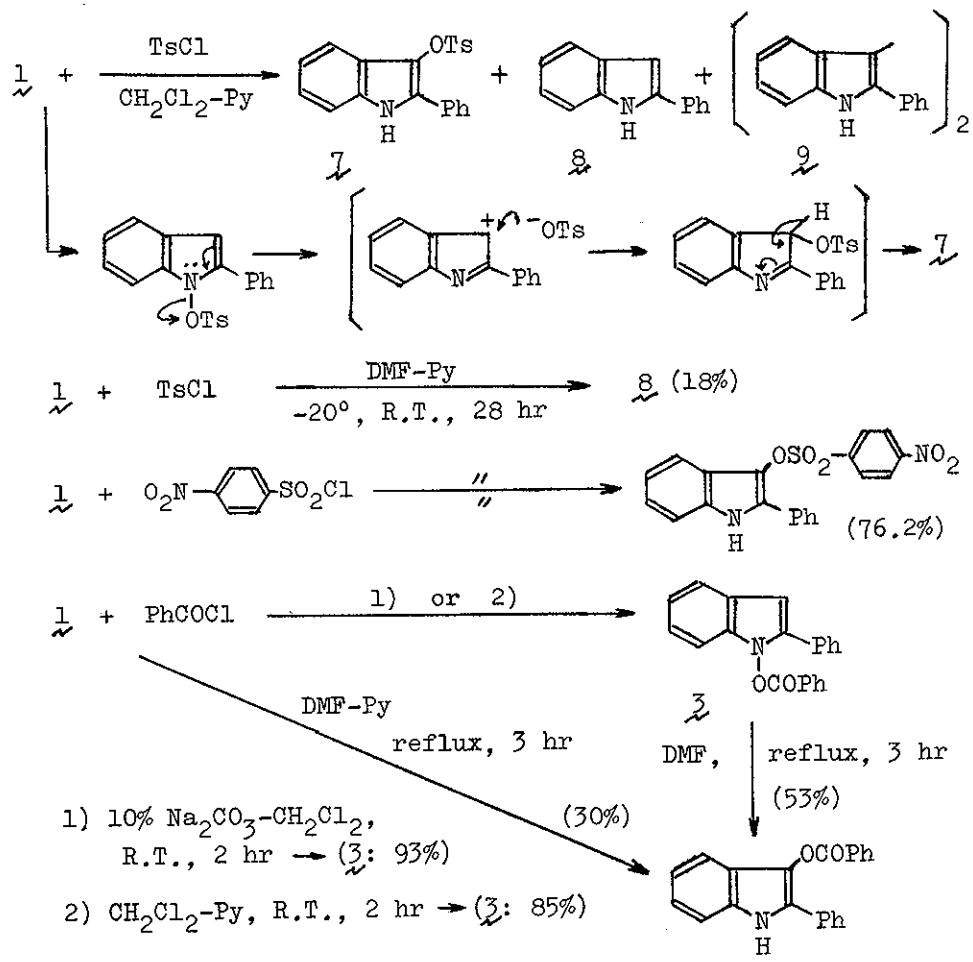


Chart 1

tionalized by the course illustrated in Chart 2. The crucial steps are the extrusion of tosyl anion from the initially formed 1-tosyloxy-2-phenylindole and consecutive nucleophilic attack of the tosyl anion thus formed at the electron-deficient β-position of the indole nucleus.

We carried out reactions using other acylating agents and found that the scope of this type of the apparent rearrangement of acyloxy group is fairly wide. The suitable reaction conditions are various depending upon the nature of acylating agent. Some representative examples are formulated in Chart 2.



Py=pyridine

Chart 2

Further, the reaction of 1 with nucleophilic species in the presence of an acylating agent was examined with an aim to introduce the nucleophilic species instead of acyloxy group into the β-position of the indole nucleus.

All attempted reactions of 1 with potassium cyanide and acylating agent failed: no 2-phenyl-3-cyanoindole was detected and N-acyloxy, 3-acyloxy derivatives or the bisindole 9 were formed in some cases.

In contrast with the inertness of cyanide anion, morpholine enamine of cyclohexanone was found to be fairly reactive as nucleophile in the presence of tosyl chloride.

1-Morpholinocyclohexene was added at ca. -20° to a solution of 1 and tosyl chloride in DMF-pyridine, and the reactants were kept at the same temperature for 4 hr and then at room temperatures for 1 day. Chromatographic separation on silica gel afforded 2-phenyl-3-(2-oxocyclohexyl)indole (10) and 6 in 23.2 and 7% yields, respectively; whereas the reaction using only pyridine as medium under the similar conditions gave also 10 in 14% yield, product 10 was not obtained at all from the reaction in dichloromethane-pyridine. The formation of 10 can be explained by the course shown in Chart 3.

Finally, some typical active methylene compounds were applied to 1 in the presence of an acylating agent.

No reaction was observed on treatment of 1 with ethyl acetoacetate and acetic anhydride in DMF at room temperature or under the refluxing condition. The reaction of 1-benzoyloxy-2-phenylindole 3 with the acetoacetate in refluxing DMF-pyridine also gave

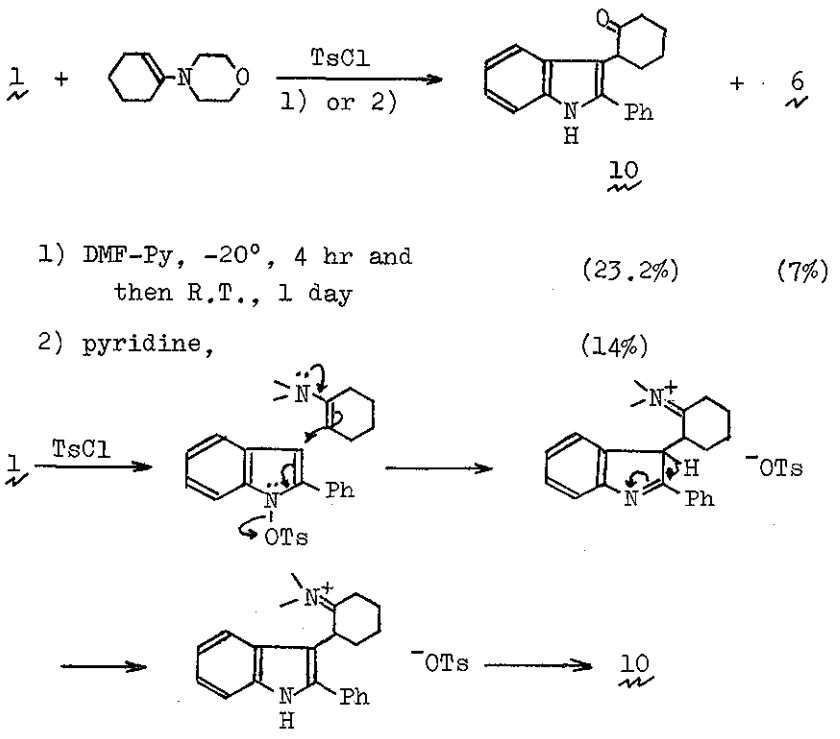


Chart 3

no expected product. However, when a solution of 1, tosyl chloride and the acetoacetate in DMF-pyridine was stirred at ca. -20° for 4 hr, ethyl α-[3-(2-phenyl)indolyl]acetoacetate (11) and 2-phenyl-4H-3.1-benzoxazone (12) were obtained in 41 and 16% yields, respectively. Product 12 is assumed to form from 2-phenylisatogen 6[7].

The reaction of 1 with ethyl cyanoacetate also proceeds under the same conditions, giving ethyl α-[3-(2-phenyl)indolyl]cyanoacetate (13) in a good yield of 61% accompanied with a trace of 12.

These results are shown in Chart 4.

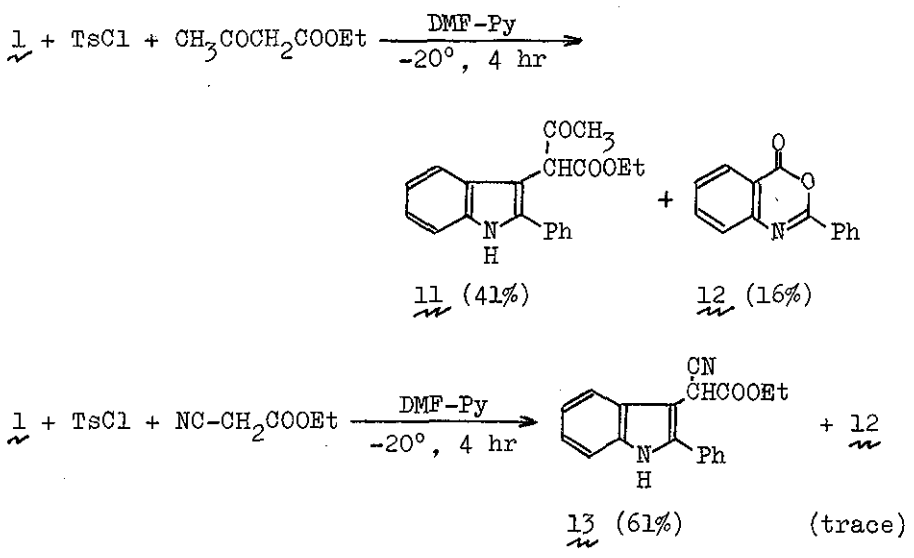
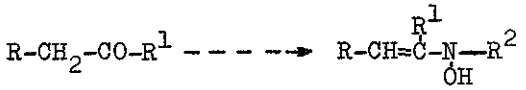


Chart 4

Diethyl malonate apparently does react with 1 under the same conditions, but the product could not be purified because of its instability. Active methylene compounds of somewhat lower acidity, such as acetophenone, benzyl cyanide and acetone, cannot enter into reaction.

As a consequence of the experiments described above it is now disclosed that 1 can react not only with electrophiles by means of its enamine-like polarization but also with nucleophiles accompanied by cleavage of 1-acyloxy group from the initially formed acylated 1 in the presence of an acylating agent. The former reactivity is similar to that of indole itself, but apparently less active as compared with indole. Of much more interest is the second type of reaction; this suggests a possibility that nucleo-

philic reaction at the α-position of carbonyl group might occur if the general procedure could be established to convert carbonyl compound into enehydroxylamine system. Such a study is now in progress in our laboratory.



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