STUDIES ON THE REACTIVITY OF ISOQUINOLINE AND RELATED COMPOUNDS. III. ADDITION REACTION OF ACETIC ANHYDRIDE WITH ISOQUINOLINE AND PHTHALAZINE.

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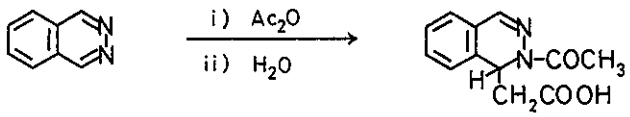
Addition of acetic anhydride to phthalazine and isoquinoline was investigated. The structures of the products were assigned 2-acetyl-1,2-dihydrophthalazine-1-acetic acid and 2-acetyl-1,2-dihydroisoquinoline-1-acetic acid, respectively. In the case of quinoline and quinoxaline this reaction did not occur.

In our preceding paper[1], we have reported the addition of diketene to isoquinoline in acidic media yielding 1-acetonyl-2-acetyl-1,2-dihydroisoquinoline. During the course of this investigation, it was found that acetic anhydride reacted with the carbon-nitrogen double bond of phthalazine to give an addition product. This observation stimulated us to investigate the reaction of aromatic heterocycles with acetic anhydride.

When phthalazine (I) was added to acetic anhydride at room temperature, a colorless crystalline solid was precipitated.

This mixture was heated at 115-120° (bath temp.) for 5 hr. After heating for a few minutes, the crystals disappeared and the solution turned brown. After removal of excess acetic anhydride by distillation in vacuo, the residue was extracted with dil. sodium hydroxide, followed by neutralization with conc. hydrochloric acid to give colorless prisms of II, mp 196-198°, $C_{12}H_{12}O_3N_2$, in a 45% yield.



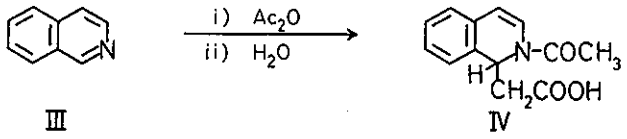
I II

The IR spectrum of II (KBr) exhibits the characteristic bands of carboxylic acid (1725 and 2500-3000 cm^{-1}) together with a band at 1640 cm^{-1} assigned to the amide carbonyl group. The NMR spectrum of II (CF_3COOH) shows an ABX multiplet due to the $-\overset{1}{C}H-CH_2-$ group (2H, m, 2.7-3.2 ppm and 1H, m, 6.4-6.7 ppm) in addition to a siglet of the acetyl methyl group (3H, s, 2.60 ppm).

From these spectral data II could be assigned the 2-acetyl-1,2-dihydrophthalazine-1-acetic acid structure.

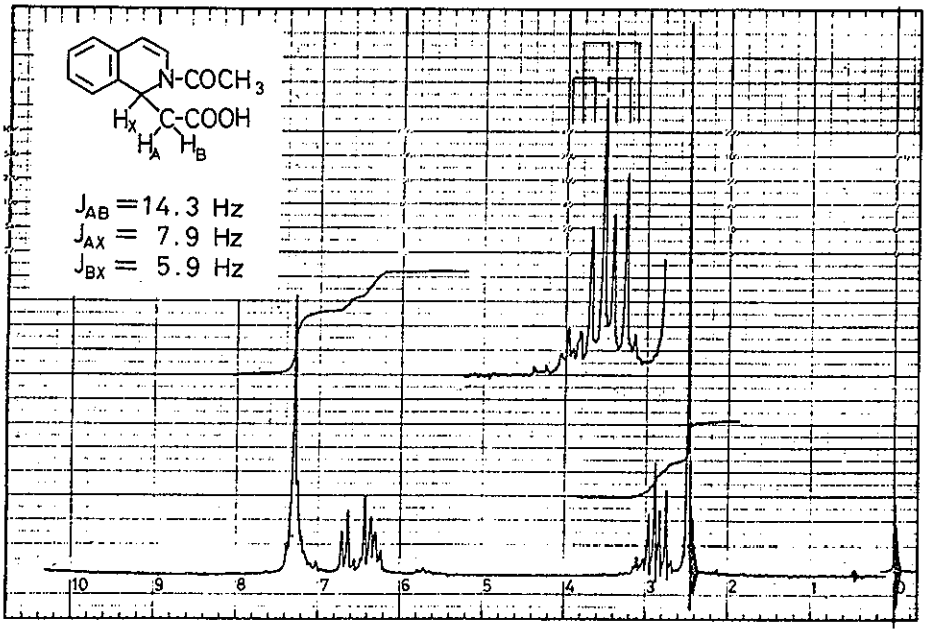
In order to extend and generalize this addition reaction, we investigated the behavior of such aromatic heterocycles as isoquinoline, quinoline, and quinoxaline in acetic anhydride. Thus, isoquinoline (III) was heated in acetic anhydride at 150-160°(bath temp.) for 40 hr. The reaction mixture was treated in the same manner as described for II, and the crystals separated were purified by recrystallization from acetone to give colorless prisms, mp 161-162°, $C_{13}H_{13}O_3N$ (IV), in a 40% yield. The

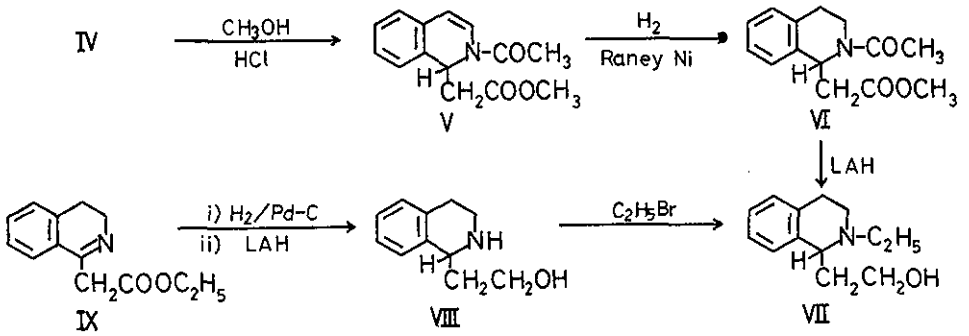
elemental analysis showed IV being a 1:1 adduct of III and acetic anhydride.



III IV

The NMR spectrum of IV (CF_3COOH) is shown in the following chart. The structure of IV was confirmed by chemical methods as follows:





Compound IV was soluble in dil. sodium bicarbonate and recovered unchanged from the solution by adding conc. hydrochloric acid. This indicated IV having a carboxyl group. Furthermore, on treatment with methanol in the presence of hydrochloric acid, IV was transformed into its methyl ester (V), bp 145-150° (2mmHg) in a 81% yield. Catalytic hydrogenation of V in methanol in the presence of Raney nickel afforded its dihydro compound (VI), $C_{14}H_{17}O_3N$, mp 91-93°, which was then treated with LAH in ether to give the corresponding aminoalcohol (VII), $C_{13}H_{19}ON$, bp 115-118° (2mmHg), in a 65% yield. The picrate of VII, mp 122-123°, yellow needles (EtOH), was obtained in the usual way.

According to the method reported by Van Binst *et al.*[2], 1-(2-hydroxyethyl)-1,2,3,4-tetrahydroisoquinoline (VIII) was prepared by the reaction of phenethyl chloride with ethyl cyanoacetate *via* ethyl 3,4-dihydroisoquinoline-1-acetate (IX)[3]. Ethylation of VIII with ethyl bromide afforded 1-(2-hydroxyethyl)-2-ethyl-1,2,3,4-tetrahydroisoquinoline whose IR spectrum (neat) was identical with that of VII. The picrate of VII was also identical with that of the authentic sample.

As described above, it was concluded that phthalazine (I)

and isoquinoline (III) reacted with acetic anhydride in the presence of no catalyst to give the addition products (II, IV). In contrast, the reaction of quinoline and quinoxaline under the identical conditions resulted in the recovery of the starting materials.

The study of the cyclization of IV and V under basic conditions is in progress.

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