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STUDIES ON THE REACTIVITY OF ISOQUINOLINE AND RELATED COMPOUNDS. IV.[1] ADDITION REACTION OF ACTIVE METHYLENE COMPOUNDS WITH ISOQUINOLINE

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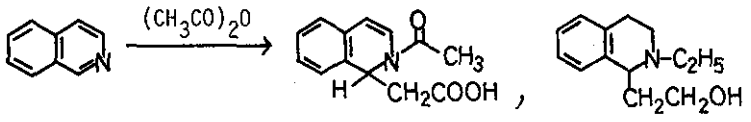
In connection with addition reaction of acetic anhydride to the isoquinoline nucleus, reaction of active methylene compounds with isoquinoline (I) in acetic anhydride was investigated. Thus, the N-acetyl-1,2-dihydroisoquinoline derivatives such as 1-acetonyl- (IV), 1-phenacyl-2-acetyl-1,2-dihydroisoquinoline (X), diethyl 2-acetyl-1,2-dihydro-1-isoquinolylmalonate (XII), and α-(2-acetyl-1,2-dihydro-1-isoquinolyl)phenylacetic acid (XIII) were obtained.

In the preceding paper,[1] we have reported that 2-acetyl-1,2-dihydroisoquinoline-1-acetic acid (II) was obtained when isoquinoline (I) was heated in acetic anhydride without adding any other reagent. The structure of the product was assigned II by converting this to 1-(2-hydroxyethyl)-2-ethyl-1,2,3,4-tetrahydroisoquinoline (III).



I II III

Chart 1

The mechanism of this reaction was assumed to be in analogy with that of the Perkin reaction.[2] It is, therefore, conceivable that a different carbanion in the solution may attack isoquinoline competitively with the carbanion from acetic anhydride. This communication deals with the reaction of I with some methyl ketones or active methylene compounds in acetic anhydride.

Treatment of I with two molar equivalent of acetone in acetic anhydride at 100° for 80 hr gave 1-acetonyl-2-acetyl-1,2-dihydroisoquinoline (IV) in 12% yield, along with II in 24.5% yield. We have already obtained IV[3] through the reaction of I with diketene in acetic acid, however, the structural elucidation of IV by chemical method has not yet performed. Thus, IV was converted via its ethylene ketal (V) to the corresponding tetrahydro compound (VI), bp 155-162° (2 mmHg). The IR spectrum (neat) of VI shows absorption band at 1640 and 1710 cm^{-1} assignable to a tertiary amide group and a methyl ketone, respectively. On the other hand, catalytic hydrogenation of II over Raney nickel afforded 2-acetyl-1,2,3,4-tetrahydroisoquinoline-1-acetic acid (VII), mp 165-166°. Ethyl chloroformate was added to the toluene solution of VII in the presence of an equimolecular amount of triethylamine to prepare the mixed anhydride (VIII), then the

reaction mixture was treated with di-tert-butyl ethoxymagnesium-malonate to afford malonic acid derivatives (IX). The resulting product (IX) was heated with *p*-toluenesulfonic acid in acetic acid containing a small amount of acetic anhydride to give

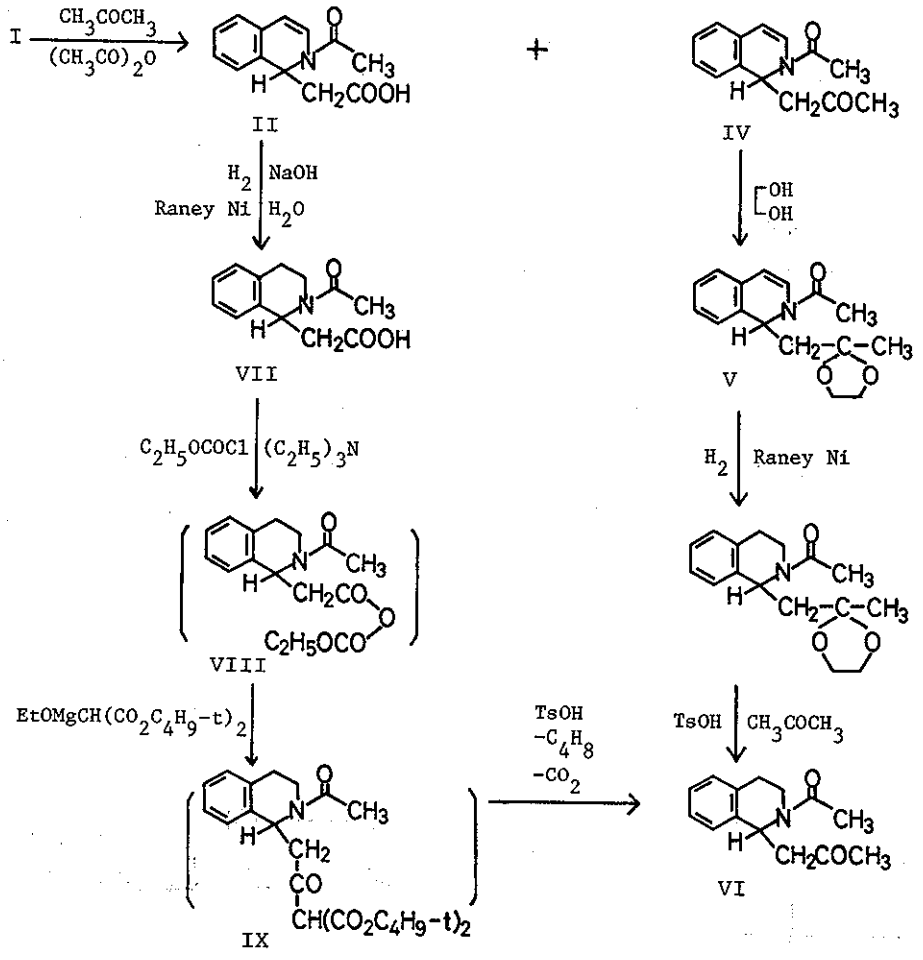
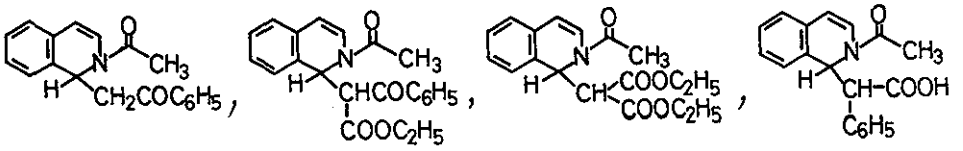


Chart 2

1-acetonyl-2-acetyl-1,2,3,4-tetrahydroisoquinoline, bp 155-160° (2 mmHg). This compound proved to be identical with VI as judged by IR (neat) and NMR ($CDCl_3$) spectral criteria.

In order to examine the scope of this reaction, acetophenone was heated with I at 80° for 93 hr to give pale yellow needles (X) of mp 107-109°, $C_{19}H_{17}O_2N$, in 12% yield, together with colorless prisms (II) (14%) of mp 165-166°. In the IR spectrum ($CHCl_3$) of X absorption bands were observed at 1680 cm^{-1} and 1695 cm^{-1} (shoulder), which are assignable to an amide and a benzoyl carbonyl groups, respectively. As shown in Fig. 1, the NMR spectrum ($CDCl_3$) of X reveals a similar pattern over the range of 2.0-7.0



X XI XII XIII and XIV

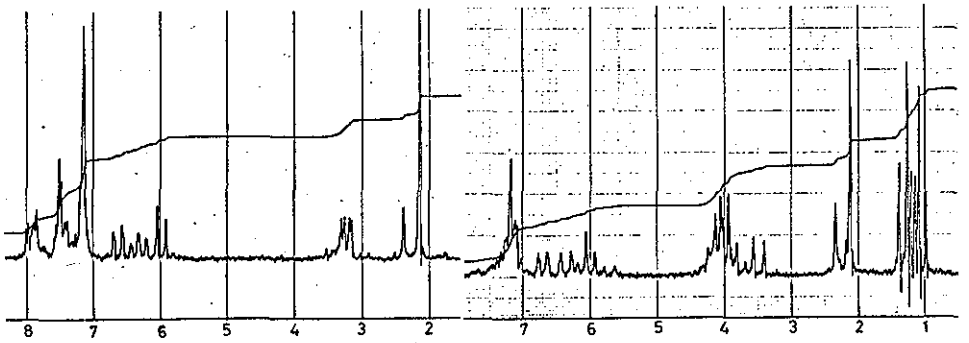


Fig.1. NMR Spectrum($CDCl_3$) of X Fig.2. NMR Spectrum(CCl_4) of XII

ppm to that of II[1] and IV;[3] that is, an ABX multiplet due to a $-\overset{1}{C}H-CH_2-$ moiety (2H, m, 2.8-3.6 ppm and 1H, m, 6.1-6.5 ppm; J_{AB}=13.9 Hz, J_{AX}=7.5 Hz and J_{BX}=6.0 Hz) is observed in addition to a singlet of the acetyl methyl group (3H, s, 2.15 ppm). On the basis of these spectral data, the structure of this compound was proposed as 1-phenacyl-2-acetyl-1,2-dihydroisoquinoline (X).

When I was treated with ethyl benzoylacetate instead of acetophenone in acetic anhydride at 100° for 65 hr, X (14%) and II (5%) were obtained. Although there was observed no evidence for an intermediate, X might be formed from ethyl α-(2-acetyl-1,2-dihydro-1-isoquinolyl)benzoylacetate (XI).

In contrast to the case of ethyl benzoylacetate, reaction of diethyl malonate with I gives rise to diethyl 2-acetyl-1,2-dihydro-1-isoquinolylmalonate (XII), bp 160-170° (2 mmHg), in 40% yield. Elemental analysis ($C_{18}H_{21}O_5N$), IR spectrum (1680 and 1730 cm^{-1}) and NMR spectrum (shown in Fig. 2) of XII are in accord with the proposed structure.

Two forms [XIII, mp 186-187° (decomp.), 32% and XIV, mp 169-170° (decomp.), 10.5%] of α-(2-acetyl-1,2-dihydro-1-isoquinolyl)phenylacetic acid were obtained through the reaction of I with free phenylacetic acid in acetic anhydride in the presence of triethylamine. On the contrary, the reaction of I with methyl phenylacetate under identical conditions failed to give the corresponding products. Elemental analysis of XIII and XIV established their empirical formulae as $C_{19}H_{17}O_3N$.

Treatment of XIII and XIV with diazomethane afforded the methyl esters, XV (mp 144-145°) and XVI (mp 112-113°), respectively.

The NMR spectrum ($CDCl_3$) of XV shows signals due to a -CH=CH-N- moiety [1H, d, 6.11 ppm and 1H, d, 6.50 ppm, (J=7.5 Hz)] and due to a -N-CH-CH- moiety [1H, d, 3.92 ppm and 1H, d, 6.54 ppm, (J=10.2 Hz)]. The NMR spectrum ($CDCl_3$) of XVI [1H, d, 5.97 ppm and 1H, d, 6.60 ppm (J=7.5 Hz), -CH=CH-N-; 1H, d, 3.92 ppm and 1H, d, 6.32 ppm (J=9.4 Hz), -N-CH-CH-] is roughly the same as that of XV. Furthermore, several weak signals owing to the existence of their rotamers were observed in the NMR spectra of XV and XVI as well as in the cases of X (Fig. 1) and XII (Fig.2).

These data suggests compound XIII and XIV to be the diastereomers of α-(2-acetyl-1,2-dihydro-1-isoquinolyl)phenylacetic acid. Further investigation on the configurations of XIII and XIV is now under progress.

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