# AROMATIZATION REACTIONS OF SOME N-ACYL-1,2-DIHYDROQUINOLINES AND ISOQUINOLINES*

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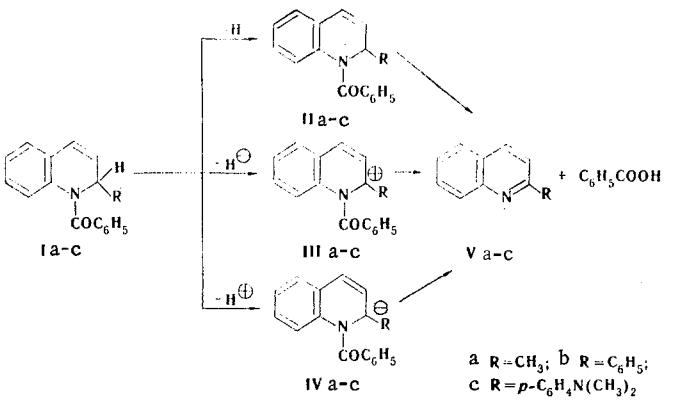
The proton and hydride lability of the α-hydrogen atom in various α-substituted N-acyl-1,2-dihydroquinolines and N-acyl-1,2-dihydroisoquinolines was investigated. It was shown that splitting out of both a hydride ion and an α-substituent as carbanions is possible in the presence of strong electron-acceptor substituents in the α position under the influence of electrophilic agents. A new transhetarylation reaction consisting in the migration of the heterocyclic residue from one compound with a labile hydrogen atom to another was found.

A surprising diversity of transformations of Reissert compounds (I, R = CN) has been observed in recent years and makes it possible to use them in organic synthesis [2-4]. The most interesting peculiarity of such compounds is the appreciable proton activity of the α-hydrogen atom, which is due, in all likelihood, to the strong electron-acceptor effect of the neighboring CN group. In addition, various 1,2-dihydroquinolines and other partially hydrogenated heterocycles, for which 6πp-paired electrons are released by the

group, readily split out a hydride ion to form a heteroaromatic system [5, 6]. Some 1,4-dihydropyridines are capable of splitting out hydrogen not only as a hydride ion [7] but also as a hydrogen atom [8,9].

In this connection, it was natural to assume that, by changing the electronic nature of the substituent in the α position of I, both heterolytic (III and IV) and homolytic splitting out of the geminal hydrogen atom might be possible:




In fact, when there is an electron-donor substituent (Ic) in the α position, a hydride ion splits out under the influence of diverse electrophilic agents, and aromatic system Vc is formed. In this case, Ic proved to be a more active hydride-ion donor than the corresponding 2-benzoyl-1-(p-dimethylaminophenyl)-1,2-dihydroisoquinoline (VI) (Table 1).

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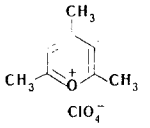
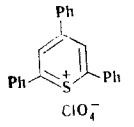
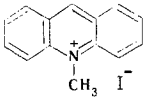
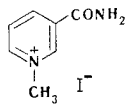
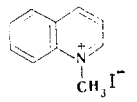
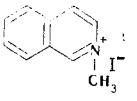
TABLE 1

| Hydride-ion acceptors | Ic, in acetonitrile | VI | |
|---|---|---|---|
| | | in acetonitrile | in dimethylformamide |
| $(C_6H_5)_3C^+ ClO_4^-$ | +* | + | + |
|  | + | –† | + |
|  | + | – | + |
|  | + | + | + |
|  | + | + | + |
|  | + | – | + |
|  | + | – | + |

*The plus sign indicates that Vc and its isoquinoline analog are formed.

† The minus sign indicates that no hydride shift occurs.

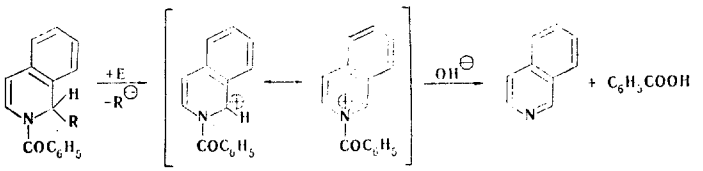
Heteroaromatic cations with different electrophilicities and trityl perchlorate were used as hydride-ion acceptors.

On the other hand, the proton activity of Ia-c proved to be extremely insignificant. We could not carry out even one of the reactions characteristic for Reissert compounds with them, although the presence of coloration during the action of phenyllithium or sodium hydride is evidence that the Reissert anion is nevertheless formed, even though in only very small amounts. The final products of the side reactions in all cases were Vc, which are obtained as a result of splitting out of an acyl residue from the intermediately formed anions (IV). The proton activity of I increased regularly as the electron-donor properties of the $\alpha$-substituents decreased, which made it possible to carry out the direct alkylation of quinoline and isoquinoline by the action of excess Grignard reagents on their N-acyl salts.

Compounds I are formed when Grignard reagents are added carefully to a mixture of the quinolines and an acyl halide. When the reagents are mixed in the reverse order, in which case the reaction proceeds in excess organomagnesium compound, further transformations of I occur to form (with the loss of a proton and an acyl residue) $\alpha$-substituted quinolines (V). The acyl residue was converted to the corresponding tertiary alcohol. Thus 1-benzoyl-2-methyl-1,2-dihydroquinoline (Va) was obtained in the reaction of quinoline, benzoyl chloride, and methylmagnesium iodide. This compound was converted to quinaldine as a result of alkaline hydrolysis, which confirms its structure.

When the order of mixing the reagents was reversed, quinoline, quinaldine, and dimethylphenylcarbinol were found in the reaction mixture according to gas-liquid chromatography. Similarly, Ib was obtained in the reaction of N-benzoylquinolinium chloride with phenylmagnesium bromide, while Vb was further obtained under the influence of excess Grignard reagent.

Unexpectedly, I with electron-acceptor substituents in the $\alpha$ position were converted to aromatic systems under the influence of electrophilic agents, not always as a consequence of splitting out of a hydride ion but as a result of loss of carbanions, especially in those cases where the detached carbanions were stabilized by neighboring carbonyl groups:

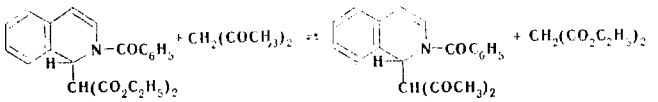


VII a-c VIII

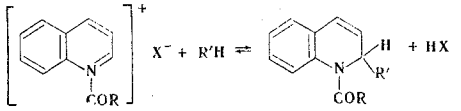
a R = $-CH(CO_2C_2H_5)_2$; b R = $-CH(COCH_3)_2$; c R = $-CH(CN)CO_2C_2H_5$;

E = $(C_6H_5)_3C^+ClO_4^-$; $Br_2$; $ZnCl_2$; HCl; $PCl_5$; $H_2SO_4$

These reactions with their surprisingly facile cleavage of the carbon-carbon bond in N-acyl derivatives of 1,2-dihydroquinoline and isoquinoline with electron-acceptor substituents in the side chain made it possible to expect that a heterocyclic residue in such compounds may migrate to other compounds with a labile hydrogen atom, similar to what occurs in analogous derivatives of cycloheptatriene [10]. In fact, rapid transhetarylation occurs when VIIa-c are heated with excess acetylacetone, acetoacetic ester, or cyanoacetic ester:



Thus the electrophilic N-acylquinolinium and N-acylisoquinolinium cations readily hetarylate various nucleophilic organic compounds and are thereby converted to partially hydrogenated derivatives (I) [11]. However, the tendency to form an energetically favorable aromatic system in such compounds determines the extremely facile heterolytic cleavage of not only the carbon-hydrogen bond but also of the carbon–carbon bond. In this connection, both hetarylation [11] and aromatization reactions to form aromatic N-acylcyclic ammonium cations and, subsequently, free bases proceed quite readily and, in a number of cases, are apparently reversible, like the recently found transformations in the tropylium system – substituted cycloheptatriene [10].



The possibility of selective reduction of the olefinic double bond in Ia-c was also investigated in addition to the aromatization reactions. For this purpose, the various methods of hydrogenation of 1,2-dihydroquinolines described in the literature [4, 12, 13] were tested. Catalytic hydrogenation with palladium on carbon in ethyl acetate solution proved to be the best method for Ia-c.

## EXPERIMENTAL

Hydride Exchange of 1-Benzoyl-2-(p-dimethylaminophenyl)-1,2-dihydroquinoline (Ic) with Triphenylmethyl Perchlorate. A solution of 1.0 g (2.8 mmole) of Ic and 0.98 g (2.8 mmole) of triphenylmethyl perchlorate in 10 ml of dry acetonitrile was held at 100° for 7 h. The reaction mass was then extracted with ether. The ether was removed by distillation, and the residue was washed with methanol to give white crystals of triphenylethane with mp 91-92° [14]. 2-(p-Dimethylaminophenyl)quinoline (Vc) with mp 172-174° [15] precipitated from the methanol solution on cooling; $R_f$ 0.56 [the chromatography was carried out in a loose, thin layer of activity II aluminum oxide with elution with benzene–hexane–chloroform (6:1:30) and development with iodine]. The precipitate that formed by the addition of ether to the methanol solution was decomposed with ammonium hydroxide, and the mixture was extracted with ether. The picrate of Vc with mp 206-208° [15] was obtained from the extracts.

Hydride exchange of Ic and VI with heteroaromatic cations with different electrophilicities was carried out similarly (Table 1).

As described above, the reaction of 2-benzoyl-1-di(ethoxycarbonyl)methyl-1,2-dihydroisoquinoline (VIIa) with triphenylmethyl perchlorate in acetonitrile gave 2-benzoylisoquinolinium perchlorate (VIII), the decomposition of which with ammonia gave isoquinoline, the picrate of which had mp 226-229°. This picrate did not depress the melting point of the picrate of an authentic sample of isoquinoline.

Reaction of 1-Acylquinolinium Salts with Grignard Reagents (Typical Method). A mixture of 12.9 g (0.1 mole) of dry quinoline and 14.0 g (0.1 mole) of benzoyl chloride was held at 100° for 1.5 h. A total of 100 ml (0.1 mole) of Grignard reagent in absolute ether was added with vigorous stirring in the course of 1 h to the cooled (to 0°) mixture. The mixture was then refluxed for 3 h, cooled, and decomposed with 50 ml of water and 150 ml of saturated ammonium chloride solution. The ether layer was separated, and the aqueous layer was extracted several times with ether. The combined ether extracts were dried with potassium carbonate, and the solvent was evaporated to give Ia-c.

1-Benzoyl-2-methyl-1,2-dihydroquinoline (Ia). This compound [8.2 g (33%)] had mp 119-120° (from acetone), $R_f$ 0.50, and $\lambda_{max}$ 270 nm [log ε 4.60 (in ethanol)], IR spectrum: 1650 $cm^{-1}$ (CO). The PMR spectrum of a trifluoroacetic acid solution contains a doublet of the $CH_3$ group with δ 1.14 ppm and J = 6.03 Hz due to the spin–spin coupling of the protons of the $CH_3$ group with the geminal proton in the α position, a quartet of the geminal proton with δ 4.62 ppm and J = 6.02 Hz, and a multiplet of aromatic protons at 6.4-8.8 ppm. The PMR spectra were recorded with a JNMS-60 spectrometer at 60 MHz, and the chemical shifts were determined relative to hexamethyldisiloxane as the external standard. Found: C 82.2; H 6.2; N 5.8%. $C_{17}H_{15}NO$. Calculated: C 81.9; H 6.1; N 5.6%. Quinaldine (established by means of gas-liquid chromatography *) was formed when the compound obtained was refluxed in alcoholic potassium hydroxide for 5 h.

1-Benzoyl-2-phenyl-1,2-dihydroquinoline (Ib). This compound [6.6 g (21%)] had mp 114-115° (from petroleum ether). Found: C 85.2; H 5.7; N 4.6%. $C_{22}H_{17}NO$. Calculated: C 84.9; H 5.5; N 4.5%. Alkaline hydrolysis gave Vb with mp 86-87°. The picrate had mp 191-192° [14]. Quinaldine and Vb were obtained in one step when these reactions were carried out in excess Grignard reagent.

Catalytic Hydrogenation of 1-Acyl-2-aryl-1,2-dihydroquinoline (Ia-c) (Typical Method). A 250-ml two-necked flask was charged with 5 mmole of Ia-c, 50 ml of ethyl acetate, and 0.1 g of palladium on carbon. The hydrogenation vessel was flushed two to three times with dry, purified nitrogen to remove air, and the vessel was then filled with hydrogen. The hydrogenation was carried out at room temperature and was complete when hydrogen absorption ceased. The catalyzate was filtered through a dense filter and washed several times with ethyl acetate. The solvent was removed by vacuum distillation, and crystals of 1-benzoyl-2-aryl-1,2,3,4-tetrahydroquinoline precipitated from the saturated solution. The catalyzer can be used repeatedly. The same method was used to obtain the compounds below.

1-Benzoyl-2-(p-dimethylaminophenyl)-1,2,3,4-tetrahydroquinoline (Ic). This compound was obtained in 84% yield as pale-yellow needles with mp 165-166° (from ethyl acetate) and $R_f$ 0.43 (mp 168-169° [16]).

1-Benzoyl-2-(p-diethylaminophenyl)-1,2,3,4-tetrahydroquinoline. This compound was obtained in 64% yield as colorless crystals with mp 105-106° (from ethyl acetate) and $R_f$ 0.40. Found: C 81.4; H 7.4; N 7.4%. $C_{26}H_{28}N_2O$. Calculated: C 81.2; H 7.3; N 7.3%.

1-Benzoyl-2-(1-methyl-2,3-dihydro-5-indolyl)-1,2,3,4-tetrahydroquinoline. This compound was obtained in 62% yield as yellow crystals with mp 157-158° (from ethyl acetate) and $R_f$ 0.49. Found: C 81.8; H 6.6; N 7.6%. $C_{25}H_{24}N_2O$. Calculated: C 81.5; H 6.6; N 7.7%.

Reaction of VIIa-c with Sulfuric Acid (Typical Method). A mixture of 1 g (2.5 mmole) of VIIa [11] and 2 ml of concentrated sulfuric acid was held at room temperature for 30 min, made alkaline, and extracted with chloroform. The picrate of isoquinoline was obtained as yellow crystals with mp 227-229° (from ethanol) from the chloroform extract. Found: N 15.9%. $C_9H_7N \cdot C_6H_3N_3O_7$. Calculated: N 15.6%.

Reaction of 1-Di(ethoxycarbonyl)methyl-2-benzoyl-1,2-dihydroisoquinoline (VIIa) with Bromine. A solution of 2.4 g (30 mmole) of bromine in 10 ml of dry chloroform was added dropwise to a solution of 1 g (3 mmole) of VIIa in 10 ml of dry chloroform, and the resulting precipitate of a molecular compound of isoquinoline with bromine was removed by filtration to give 32% of a product with mp 239-241° (from ethanol). Found: C 37.1; H 2.4; Br 55.3; N 4.7%. $C_9H_7N \cdot Br_2$. Calculated: C 37.4; H 2.4; Br 55.3; N 4.8%. The

*Gas-liquid chromatography was carried out with a UKh-1 chromatograph (column length 6 m, diameter 4 mm). The stationary phase was 0.4% ethylene oxide–tetrahydrofuran copolymer on NaCl, and the gas carrier was helium.

picrate of isoquinoline with mp 228-229° (from ethanol) was obtained from the ethanol solution of the molecular compound of isoquinoline by the addition of picric acid.

The remaining experiments relative to the cleavage of VII by reaction with various electrophilic reagents were carried out similarly.

Transhetarylation (Typical Method). A mixture of 1 g (2.5 mmole) of VIIa in 2.5 g (25 mmole) of acetylacetone was held at 100° for 8 h, after which the excess acetylacetone and resulting malonic ester were removed by vacuum distillation. The residue was washed with hot petroleum ether and recrystallized from methanol to give 0.5 g (60%) of a product with mp 90-92° and $R_f$ 0.35. This product did not depress the melting point of an authentic sample of 1-diacetylmethyl-2-benzoyl-1,2-dihydroisoquinoline [11]. Unchanged VIIa with mp 85-86° and $R_f$ 0.32 precipitated from the cooled petroleum ether.

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