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1-AROYLMETHYLISOQUINOLINES

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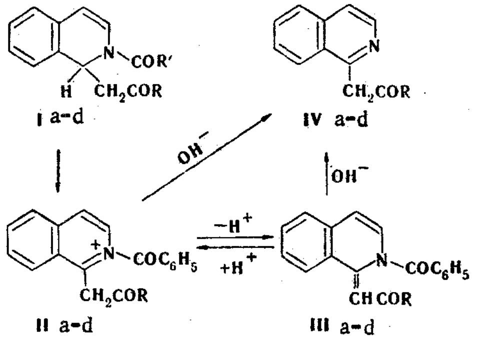
The reaction of 1-aroylmethyl-2-benzoyl-1,2-dihydroisoquinolines with the hydride-ion acceptor 2,2,6,6-tetramethyl-1-oxidopiperidinium perchlorate gives stable N-acyl salts, which are converted to either 1-aroylmethylisoquinolines or anhydro bases when they are treated with some bases.

Compounds with a keto group in the side chain are almost unknown in the isoquinoline series. Only recently Jamanaka and co-workers [3-5], during a study of the intermediates that are formed in the synthesis of the so-called "Wollenberg compounds" (see, e.g., [1, 2]), established that isoquinoline reacts with diketene and a carboxylic acid to give 1-acetonyl-2-acyl-1,2-dihydroisoquinoline (I, R = CH_3). Similarly, the corresponding 1-substituted 2-acetyldihydroisoquinolines (I, R' = CH_3) were isolated in 12 to 40% yields when isoquinoline was heated in acetic anhydride with sufficiently strong C—H acids (acetone, acetophenone, and malonic and acetoacetic esters) [5, 6]; however, the aromatization of the substances obtained was fraught with considerable difficulties. The synthesis of 1-benzoylmethylisoquinoline by reaction of 1-chloroisoquinoline with acetophenone in the presence of sodium hydride was described somewhat earlier, but this substance has not been investigated in greater detail [7].

It was found that salt IIa, which is sufficiently stable during storage, readily splits out a proton from the side chain to give anhydronium base IIIa when it is treated with nucleophiles, even with a weak nucleophile such as aniline. Treatment of IIIa with perchloric acid regenerates salt IIa.



I R′=C_6H_5; II—IV a R=C_6H_5; b R=2-thienyl; c R=3-indolyl; d R=4-pyridyl

In analogy with the properties of N-acylpyridinium salts [8], one might have expected acylation of the amine by salt II; however, even when we used a strong nucleophile such as methylamine, we observed only deprotonation to anhydronium base IIIa, the stability of which

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is determined substantially by conjugation of the carbon—carbon multiple bonds with the carbonyl group. Under severe conditions we assumed the possibility of opening of the pyridine ring under the influence of the nucleophile with subsequent elimination of the acyl group and recyclization to naphthalene derivatives as described for quaternary 2-acetonylpyridinium [9] and 1-methylisoquinolinium [10] salts. However, only elimination of the benzoyl group to give ketone IVa occurs in the case of prolonged refluxing of salt IIa with aqueous alcoholic alkali. The same ketone was obtained by alkaline hydrolysis of anhydronium base IIIa.

Since anhydronium base IIIa may display the properties of a dipolar ion, one should have assumed migration of the benzoyl group to the strongly nucleophilic carbon atom or even acylotropic tautomerism with migration of the acyl group to the oxygen atom [11], however; IIIa was found to be stable under the conditions that we used.

Replacement of the phenyl residue in the I molecule by the less effective electron-acceptor thienyl grouping led to a decrease in the stability of salt IIb, which is readily hydrolyzed in alkaline media to give ketone IVb, whereas aniline is acylated by salt IIb under anhydrous conditions to give the same ketone. The corresponding salt IIc, which contains an indole residue in the side chain, is even less stable. It is evidently formed from dihydroisoquinoline ketone Ic, but we were unable to isolate it preparatively, and anhydronium base IIIc was obtained in the aromatization process. The isolation as a side product of a stable piperidineoxyl radical, which is formed by transfer of a hydride ion from the dihydroheterocycle molecule to the oxammonium salt, is a fact that confirms the intermediate formation of salt IIc in the reaction of the dihydroisoquinoline ketone with a hydride-ion acceptor, viz., 2,2,6,6-tetramethyl-1-oxidopiperidinium perchlorate (V).

Replacement of the phenyl group in I by an electron-acceptor pyridine grouping was fraught with difficulty, since we were unable to carry out aromatization of dihydro ketone Id under the standard conditions (by the action of perchlorate V in anhydrous acetonitrile [12]). Under the influence of triphenylmethyl perchlorate, exchange by bases takes place, and the perchlorate of ketone Id, which subsequently undergoes aromatization with, however, splitting out of an acylmethyl group rather than a hydride ion, is obtained.

EXPERIMENTAL

The IR spectra were recorded with a UR-20 spectrometer. The UV spectra (of solutions in acetonitrile) were obtained with a Specord UV-vis spectrophotometer. Chromatography was carried out in a thin layer of aluminum oxide (activity II on the Brockmann scale) with elution with a chloroform—benzene—hexane system (30:6:1) and development with iodine vapors and in UV light.

1-(3-Indolylcarbonylmethyl)-2-benzoyl-1,2-dihydroisoquinoline (Ic). A 3.5-g (25 mmole) sample of benzoyl chloride was added dropwise with stirring to a solution of 6.5 g (50 mmole) of isoquinoline and 4 g (25 mmole) of 3-acetylindole in 30 ml of dry benzene, and the mixture was refluxed for 15 h. It was then treated with 10% ammonium hydroxide, and the precipitate was separated, washed with methanol, and recrystallized from 1-butanol to give 4.1 g (42%) of a product with mp 229-230°C and R_f 0.35. IR spectrum: 1660 and 1680 (C=O), 1615 (C=C), and 3490 cm^{-1} (NH). Found: C 80.0, H 4.9, N 7.1%. $C_{26}H_{20}N_2O_2$. Calculated: C 79.6; H 5.1; N 7.1%.

1-Isonicotinoylmethyl-2-benzoyl-1,2-dihydroisoquinoline (Id). This compound, with mp 172-174°C (from 1-butanol) and R_f 0.40, was similarly obtained in 47% yield. IR spectrum: 1650 and 1680 (C=O) and 1610 cm^{-1} (C=C). Found: C 78.1; H 5.1; N 7.9%. $C_{23}H_{18}N_2O_2$. Calculated: C 80.0; H 5.1; N 7.9%.

1-Benzoylmethyl-2-benzoylisoquinolinium Perchlorate (IIa). A 0.70-g (2 mmole) sample of Ia was added in the course of 10 min at 25°C to a solution of 0.77 g (3 mmole) of perchlorate V in 10 ml of dry acetonitrile, and the mixture was allowed to stand for 1-1.5 h. It was then treated with 100 ml of dry ether, and the yellow precipitate of salt IIa was separated and recrystallized from dry acetonitrile to give 0.51 g (54%) of a product with mp 175-177°C. Found: C 62.6; H 6.4; N 3.2%. $C_{24}H_{27}N_2O_2 \cdot HClO_4$. Calculated C 62.6; H 6.1; N 3.0%.

1-Benzoylmethylene-2-benzoyl-1,2-dihydroisoquinoline (IIIa). A) A suspension of 0.45 g (10 mmole) of salt IIa in 15 ml of 10% ammonium hydroxide was stirred at room temperature for 15-20 min, after which the precipitate was separated and recrystallized from methanol to give 0.31 g (89%) of a product with mp 188-189°C. UV spectrum, λ_{max} (log ε): 226 (4.53) and 261 nm (4.23). Found: C 82.4; H 5.0; N 3.9%. $C_{24}H_{17}NO_2$. Calculated: C 82.1; H 4.8; N 4.0%.

B) A mixture of 0.45 g (10 mmole) of perchlorate IIa with 0.15 g (16 mmole) of aniline in 10 ml of dry acetonitrile was refluxed for 2 h, after which 100 ml of water was added, and the resulting yellow precipitate was separated and recrystallized from methanol to give 0.28 g (80%) of a product with mp 188-189°C. No melting-point depression was observed for a mixture of this product with a sample obtained by method A. Neutralization of the filtrate gave 0.6 g (67%) of aniline (identified through the picrate).

1-Benzoylmethylisoquinoline (IVa). A) A suspension of 0.90 g (20 mmole) of perchlorate IIa in 10% aqueous NaOH solution was refluxed for 2.5-3 h, after which it was extracted with ether. The ether extracts were combined, the ether was removed by distillation, and the residue was recrystallized from hexane to give 0.43 g (88%) of a product with mp 84-85°C (mp 85-86°C [7]) and R_f 0.40. UV spectrum, λ_{max} (log ε): 222 (4.41), 245 (4.05), and 294 nm (3.90). Found: C 82.4; H 5.2; N 5.7%. $C_{17}H_{13}NO$. Calculated: C 82.6; H 5.3; N 5.7%.

B) A suspension of 0.70 g (20 mmole) of IIIa in 10% aqueous alcoholic NaOH solution was refluxed for 2.5-3 h, after which it was worked up as described above to give 0.40 g (81%) of a product with mp 84-86°C (from hexane). No melting-point depression was observed for a mixture of this product with a sample obtained by method A.

1-(2-Thenoylmethyl)isoquinoline (IVb). This compound, with mp 145-147°C (from acetonitrile) and R_f 0.30, was similarly obtained in 98% yield. UV spectrum, λ_{max} (log ε): 223 (4.27) and 294 nm (3.89). Found: C 72.2; H 4.4; N 5.6%. $C_{15}H_{11}NOS$. Calculated: C 72.0; H 4.4; N 5.5%.

1-(3-Indolylcarbonylmethylene)-2-benzoyl-1,2-dihydroisoquinoline (IIIc). A mixture of 0.39 g (1 mmole) of Ic and 0.38 g (1.5 mmole) of perchlorate V in 10 ml of dry acetonitrile was maintained at room temperature for 24 h, after which the precipitate was separated and recrystallized from acetonitrile to give 0.20 g (51%) of a product with mp 237-239°C. UV spectrum, λ_{max} (log ε): 227 (4.49) and 264 nm (4.06). Found: C 80.1; H 4.3; N 7.5%. $C_{26}H_{18}N_2O_2$. Calculated: C 80.0; H 4.6; N 7.2%. Workup of the filtrate yielded 2,2,6,6-tetramethylpiperidine 1-oxide, which was identified by comparison with an authentic sample.

Reaction of Dihydroisoquinoline Id with Triphenylmethyl Perchlorate. A 0.35-g (1 mmole) sample of dihydroisoquinoline Id was added in portions in the course of 10 min at 25°C to a solution of 0.68 g (2 mmole) of triphenylmethyl perchlorate in 10 ml of dry acetonitrile, and the mixture was allowed to stand for 10 h. It was then treated with 100 ml of dry ether, and the precipitate was removed by filtration and recrystallized from acetonitrile to give 0.26 g (79%) of 2-benzoylisoquinolinium perchlorate with mp 174-175°C. No melting-point depression was observed for a mixture of this product with a geniune sample. Workup of the filtrate after separation of the salt yielded 0.22 g (81%) of triphenylcarbinol [mp 161-162°C (from methanol)] and 0.13 g (60%) of 4-acetylpyridine perchlorate [mp 130-131°C (from ethanol—ether, 1:1)]; no melting-point depressions were observed for mixtures of these product with genuine samples.

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^{13}C NMR SPECTRA OF S-METHYLQUINOLINES

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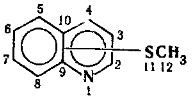
The ^{13}C chemical shifts and the increments ($\Delta\delta$) of the SCH_3 group in the NMR spectra of S-methylquinolines were measured. It is shown that the chemical shifts of S-methylquinolines correlate satisfactorily with the total charges on the carbon atoms calculated within the CNDO/2 approximation. The coupling of the SCH_3 group with the quinoline ring was examined on the basis of the $\Delta\delta$ values.

In the present research we examined the ^{13}C NMR spectra of quinoline (1), 2-methylthio- (2), 3-methylthio- (3), 4-methylthio- (4), 5-methylthio- (5), 6-methylthio- (6), 7-methylthio- (7), and 8-methylthioquinoline (8) in order to ascertain the electronic structures of these compounds, the nature of the coupling of the SCH_3 group with the quinoline ring, and the effect of this group on the chemical shifts of the ring carbon atoms.



(1-8)

The literature contains very little information regarding the ^{13}C chemical shifts of quinoline derivatives, viz., communications dealing with the spectra of quinoline [1-7], 5-aminoquinoline [3], methylquinolines [5, 8, 9], 8-hydroxyquinoline [10], and 6-methoxyquinoline [8]. The effect of the SCH_3 group on the ^{13}C chemical shifts of aromatic compounds has been studied for thioanisole [11, 12] and S-methyl derivatives of purine [13]. The literature data show that the $\Delta\delta_R$ ^{13}C substituent increments measured in the spectra of monosubstituted benzenes can be applied to polycyclic aromatic derivatives with a great deal of caution [3, 4, 14].

The ^{13}C NMR spectra with decoupling of the protons and without it (with the Overhauser nuclear effect) and the spectra with extraresonance suppression of the $^{13}C-^{1}H$ spin–spin coupling (SSC) were obtained for 1-8 (Fig. 1). The parameters of the signals in the ^{13}C NMR spectra of 1-8, for the assignment of which we used the increments of the SCH_3 group in thioanisole and the $^{13}C-^{1}H$ spin–spin coupling constants (SSCC), are presented in Tables 1-3.

In the literature the ^{13}C chemical shifts are often correlated with the chemical shifts calculated within the CNDO/2 approximation [1, 15, 16]. Good correlation is observed for this approach only for the carbon atoms of the aromatic ring that are bonded to hydrogen atoms. The chemical shifts are much too high for the nodal and α-carbon atoms [1]. In this connection, the discussion of the ^{13}C chemical shifts and their changes of the spectra in 2-8 (relative to 1) was carried out on the basis of the total charges q calculated within the CNDO/2 approximation.

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