The Chemistry of 2*H*-3,1-Benzoxazine-2,4(1*H*)-dione (Isatoic Anhydride). 11. Reaction of *N*-Methylisatoic Anhydride With 1-Cyanoacetylpiperidine

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The reaction of *N*-methylisatoic anhydride with 1-cyanoacetylpiperidine in the presence of sodium hydride produces a tautomeric mixture of **4a** and **4b**, with **4b** predominating. When heated in xylene, **4** is converted to the piperidine adduct **5** whereas heating in dimethylsulfoxide furnishes **3**. Spectral data for **4** and **5** are also discussed.

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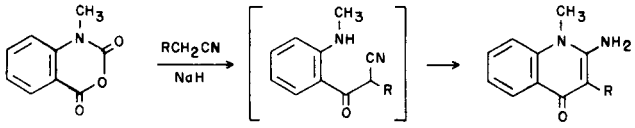
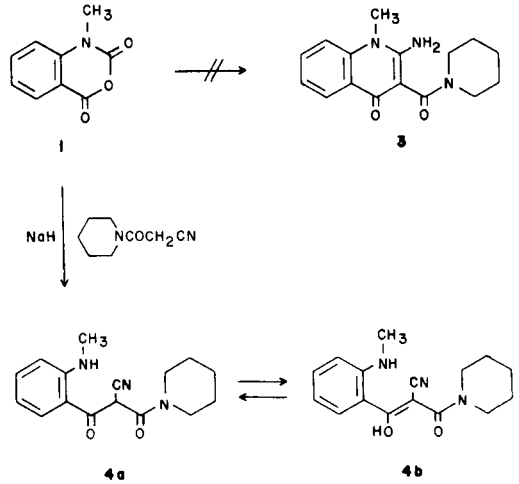
The reaction of *N*-methylisatoic anhydride (**1**) with metallated methylene compounds possessing a nitrile group as an activating substituent produces 2-amino-1-methyl-4-quinolones (**2**) by an intermediate nucleophilic attack of the unmasked *N*-methylanilino function on the nitrile [1,2].



1 2

R = CN, $PO(OC_2H_5)_2$, SO_2CH_3, $SO_2C_6H_5$

When an analogous reaction is performed using 1-cyanoacetylpiperidine, the expected aminoamide **3** is not produced, instead the acyclic intermediate **4** is isolated in 59% yield.



1 3

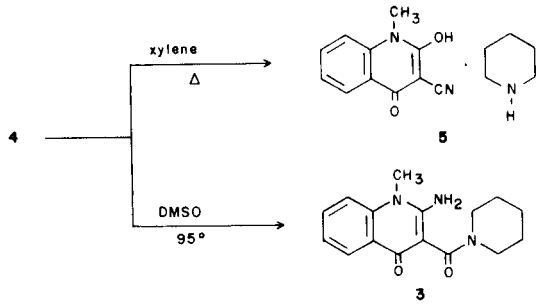
4a 4b

In solution, **4** exists as a mixture of tautomers, the equilibrium favoring **4b**. Analysis of its proton nmr spectrum shows a methyl singlet at δ 2.82 (2.7 protons) with an accompanying methyl doublet at δ 2.92 (J = 6 Hz, 0.3 protons) which correspond to a 90:10 mixture of **4b** and **4a**, respectively. The methinyl proton of **4a** is also seen as a small singlet at δ 5.42 in the appropriate proportion to the methyl signal at δ 2.92. This tautomeric ratio is confirmed by studying the carbon-13 nmr spectrum of **4** (see Figure 1). In deuteriochloroform, two sets of peaks are revealed in a 90:10 ratio. The major set is consistent with **4b** while the minor set, as determined from the proton-coupled carbon-13 spectrum, with **4a**. When the deuteriochloroform is replaced with the more polar DMSO-d_6, two sets are still observed but now in a more equal ratio, thus proving the tautomeric relationship of **4a** and **4b**.

In an attempt to induce cyclization, compound **4** was heated in refluxing xylene. After 5 hours, consumption of **4** is complete and a new more polar material (as observed by thin-layer chromatography) is formed. Its infrared spectrum still exhibits a prominent nitrile absorption at 2200 cm^{-1}, therefore ruling out cyclization with the nitrile. Its nmr spectrum shows two multiplets at δ 1.75 and 3.2 corresponding to the piperidine protons, an *N*-methyl singlet at δ 3.5 and a two proton multiplet at δ 9.2 (both protons are exchangeable). In the aromatic region, one proton is shifted downfield and is observed as a multiplet at δ 8.1. A shift such as this is somewhat reminiscent of that of the C-5 proton in a 4-quinolone system [3].

Mass spectral analysis of the product was carried out under both electron impact (EI) and chemical ionization (CI) conditions. In the EI mass spectrum, the highest mass observed is m/z 200 which may correspond to the molecular weight of the compound. However, the examination of the single ion mass chromatograms of m/z 200 and another prominent ion at m/z 85 reveals that these two ions have different rates of evaporation and thus are likely to originate from two different components of the sample. A similar phenomenon is observed under the CI mode where m/z 86 and 201, the two major ions, also exhibit different evaporation rates. The observation of m/z 201 and 86 (at one mass unit higher than their corresponding EI mass peaks) and their respective adduct ions at 41, 43 and 57 mass units higher, support the molecular weight assignments of 200 and 85 for each of the two components. The accurate mass measurements suggest their elemental compositions to be $C_{11}H_8N_2O_2$ (mw 200) and $C_5H_{11}N$ (mw 85).

Taking this data and the proton nmr data into account, the results strongly suggest the saltlike structure **5**.



Although the above evidence favors **5** as the structure, the possibility of thermal decomposition in the mass spectral probe cannot be totally ruled out. This potential problem is readily solved by carbon-13 analysis using the method of deuterium-induced isotope shifts [4]. If the piperidine is covalently attached to some portion of the molecule, doubling of the non-protonated carbons would be observed whereas the salt **5** would show doubling of the piperidine carbons. In fact the latter situation is observed which confirms the salt structure. The assignment of the 4-quinolone tautomeric configuration is based on the comparison of the carbon shifts of **5** with those of the 2-quinolone tautomer **6**. These values are in full agreement with earlier work of ours distinguishing 2- and 4-quinolone systems [5].

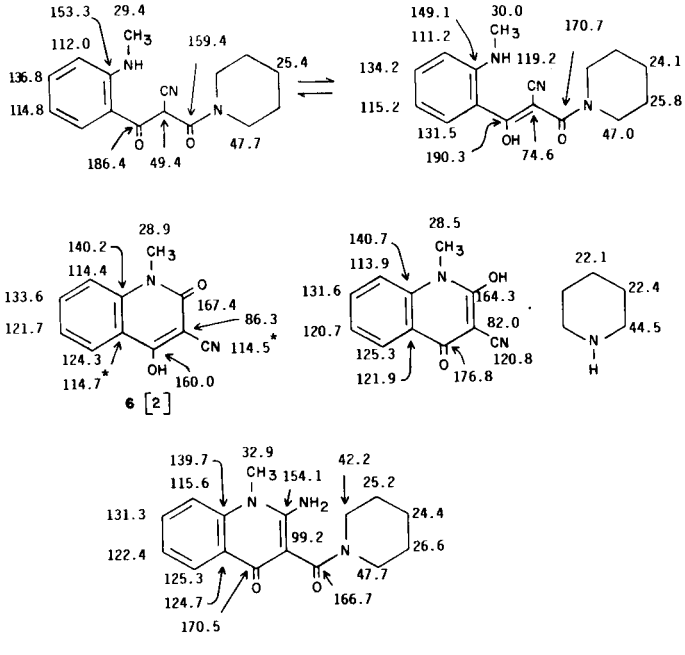


Figure 1. Carbon-13 Data

Solvents: **5** and **6**, deuteriochloroform + DMSO-d_6; **3**, DMSO-d_6; **4**, deuteriochloroform.

Compound **4** can be coaxed to cyclize with the nitrile group by using dimethylsulfoxide as the solvent. After 24 hours at 95°, compound **3** is isolated in 83% yield. All spectral data is compatible with the proposed structure. analysis of the remainder of the reaction mixture indicates that **5** is also formed but only in minor quantities.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected. The infrared spectra were recorded on Perkin-Elmer Model 257 and 457 spectrophotometers. Absorption frequencies are quoted in reciprocal centimeters. The proton nmr spectra were recorded on Varian T-60, EM-360 and Varian XL-100 spectrometers using tetramethylsilane as an internal reference. Chemical shifts are quoted in parts per million (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet).

The carbon-13 magnetic resonance spectra were obtained in the Fourier transform mode on a Varian XL-100-12 spectrometer system equipped with a Varian 620/L computer with 16K memory. The spectra were obtained at an observing frequency of 25.159 MHz. Sample concentrations were *ca.* 0.5 *M* in deuteriochloroform or DMSO-d_6 in 10 mm (od) sample tubes. General nmr spectral and instrumental parameters employed were: internal deuterium lock to the solvent, spectral width of 5120 Hz, a pulse width of 25 μs corresponding to a 43° pulse angle, and a pulse repitition time of 1.8 seconds. For all spectra, 8K time-domain points were used. All shifts reported are referenced to internal tetramethylsilane and are estimated to be accurate to ±0.05 ppm.

The EI mass spectra were obtained on a Kratos MS-30 double beam double focusing mass spectrometer at 70 eV electron energy. The accurate mass measurements were carried out in the double beam mode at 3000 resolving power. The CI spectra were obtained on a VG 7070E double focusing mass spectrometer using isobutane as the reagent gas. The isobutane pressure was adjusted so as to achieve a value of approximately 1:1 for the 57/43 intensity ratios. The ion source temperature was maintained at 150° and an electron energy of 50 eV was used. The sample was introduced by solid probe in both instruments.

Unless otherwise stated, all solutions of organic compounds were washed with saturated sodium chloride solution and dried over sodium sulfate. No attempt has been made to optimize the yields of the described reactions.

Tautomers **4**.

To a solution of 7.6 g of 1-cyanoacetylpiperidine in 75 ml of dimethylacetamide was added 2.1 g of sodium hydride (57% in mineral oil, pentane washed) in portions. After stirring at room temperature for 15 minutes, the mixture was placed in an oil bath at 120°. To this was added dropwise a solution of 8.8 g of **1** in 75 ml of dimethylacetamide (carbon dioxide evolution occurred), then the mixture was stirred at 120° for 18 hours. The solvent was removed under reduced pressure and water was added to the residue. The solution was washed once with methylene chloride, then the aqueous phase was acidified with 2*N* hydrochloric acid. The resulting yellow solid was filtered, washed with water, then dissolved in methylene chloride. After treating with decolorizing carbon, the solvent was exchanged for ethanol to give 8.3 g (59%) of **4**, mp 140-142°; ir (chloroform): 3450, 2200 cm^{-1}; nmr (deuteriochloroform): δ 7.7-7.15 (m, 2 H), 6.8-6.4 (m, 2 H), 5.42 (s, 0.1 H), 3.9-3.35 (m, 4 H), 2.92 (d, 0.3 H, J = 6 Hz), 2.82 (s, 2.7 H), 1.7 (m, 6 H), both exchangeable protons are seen as broadening of the baseline; ms: m/z 285 (M^+).

Anal. Calcd. for $C_{16}H_{19}N_3O_2$: C, 67.3; H, 6.7; N, 14.7. Found: C, 67.0; H, 6.8; N, 14.8.

1,4-Dihydro-2-hydroxy-1-methyl-4-oxo-3-quinolinecarbonitrile 1:1 Piperidine Adduct (**5**).

A suspension of 3.0 g of **4** in 100 ml of xylene was refluxed for 5 hours (the material slowly goes into solution, then a suspension occurs). After

cooling, the resulting precipitate was filtered, washed twice with benzene, once with ether, and then recrystallized from methylene chloride/ether to give 2.0 g (66%) of **5**, mp 191-193°; ir (chloroform): 2200 cm^{-1}; nmr (deuteriochloroform + DMSO-d_6): δ 9.2 (m, 2 H, exchangeable), 8.1 (m, 1 H), 7.7-6.9 (m, 3 H), 3.5 (s, 3 H), 3.2 (m, 4 H), 1.75 (m, 6 H).

Anal. Calcd. for $C_{16}H_{19}N_3O_2$: C, 67.3; H, 6.7; N, 14.7. Found: C, 67.1; H, 6.9; N, 14.7.

2-Amino-1,4-dihydro-1-methyl-4-oxoquinoline-3-piperidinocarboxamide (**3**).

A solution of 0.6 g of **4** in 3.0 ml of dimethylsulfoxide was heated at 95° for 24 hours. The solvent was removed under reduced pressure and the residue was chromatographed on a column of silica gel using 10% methanol/chloroform to elute the product, 0.5 g (83%) of **3**. An analytical sample was crystallized from ethyl acetate, mp 215-218°; ir (potassium bromide): 3380, 3145, 1670, 1600, 1520 cm^{-1}; nmr (deuteriochloroform): δ 8.18 (m, 1 H), 7.5-6.82 (m, 3 H), 6.55 (s, broad 2 H, exchangeable), 3.55 (s, 3 H), 3.38 (m, 4 H), 1.57 (m, 6 H); ms: m/z 285 (M^+).

Anal. Calcd. for $C_{16}H_{19}N_3O_2$: C, 67.3; H, 6.7; N, 14.7. Found: C, 67.6; H, 7.1; N, 14.4.

REFERENCES AND NOTES

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