Novel Heterocycles. 4. Synthesis of the Pyrido[2,3-*c*]-1,2-thiazine Ring System

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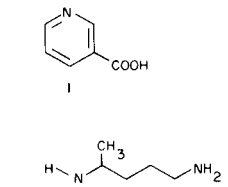
Received May 29, 1979

The reaction of 2-chloronicotinonitrile with *N*-methylmethanesulfonamide and subsequent treatment with base furnished the novel pyrido[2,3-*c*]-1,2-thiazine ring system **7**. Spectrally, it was determined that the predominant tautomer in solution was the 4-amino form **7a**. Acidic hydrolysis of **7** furnished the 4-oxo tautomer **8b**, compound **8b** was alkylated on oxygen with 1-bromopentane in the presence of sodium hydride. Reaction of **8b** with isocyanates occurs at the 3 position to produce carboxanilides **10**. Spectral characteristics of these compounds are also discussed.

J. Heterocyclic Chem., **16**, 1361 (1979).

In a continuing search for compounds exhibiting pharmacological activity, the pyridine nucleus is considered our logical starting point. The pyridine ring is incorporated in a wide variety of chemicals possessing biological activity. Simple compounds such as Niacin (nicotinic acid) (**1**), a vitamin of the B group (1) or Isoniazid (**2**), a potent tuberculostatic agent (2) examplifies such activity. Fused pyridines such as Pamaquine (**3**) (3) or Nalidixic acid (**4**) (4) exhibit antimalarial activity or antibacterial activity, respectively.



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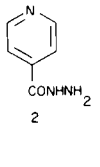

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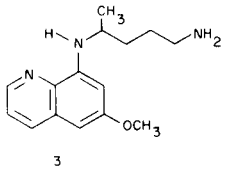

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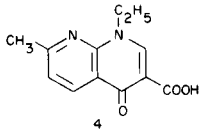

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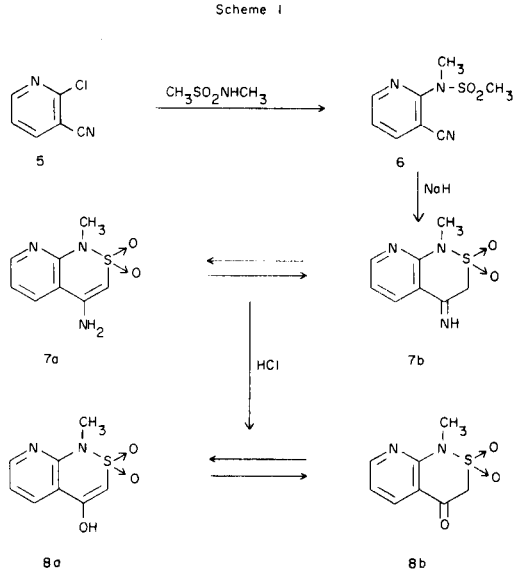
The annelation of a pyridine ring can be accomplished if the substrate contains the appropriate functionalities capable of reaction. A molecule lending itself to such an operation is 2-chloronicotinonitrile (**5**). The readily displaceable chlorine atom in the 2-position and its proximity to the reactive 3-cyano substituent make it an ideal compound for the construction of polycyclic heterocycles.

In a previous report (5) the use of *N*-methylmethanesulfonamide in the preparation of novelly fused indoles was described. The employment of this synthon in a reaction with 2-chloronicotinonitrile would allow entrance into previously unreported pyrido[2,3-*c*]-1,2-thiazine ring system. Thus, when **5** was allowed to react with *N*-methylmethanesulfonamide in the presence of sodium hydride, a mixture of **6** and **7** (the majority being **6**) was isolated in 98% yield (Scheme 1). The mixture may be separated into its pure components *via* fractional crystallization or by column chromatography; however, it can be converted directly to pure **7** by treatment with sodium hydride in tetrahydrofuran.

Scheme I



5 6 7a 7b 8a 8b

It appears that **7** is capable of existing in both the 4-amino tautomer **7a** and 4-imino form **7b**. The infrared spectrum of **7** in the solid phase (potassium bromide) exhibits the typical dual amino absorptions at 3450 and 3380 cm^{-1}. These are also accompanied by an imino (=NH) absorption at 3280 cm^{-1} and a C=N stretching vibration at 1650 cm^{-1} indicating that possibly both tautomers are present. However, in the nmr spectrum of **7** (deuteriochloroform) one observes a broad singlet at δ 5.95, integrating for three protons, which consists of the proton at position 3 and two protons which appear to be that of an amino functionality. The methylene protons in position 3 of **7b** would not be expected to fall this far downfield. If the spectrum is run in DMSO-d_6, the signal for the two amino protons in shifted downfield to δ 6.7

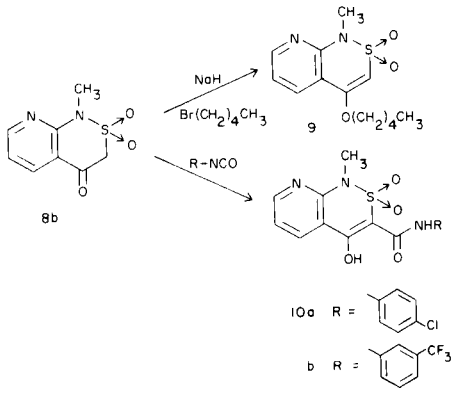
0022-152X/79/071361-03$02.25

while the proton at position 3 remains at δ 5.95. Thus, in solution, the predominant tautomer is that of **7a**.

Acidic hydrolysis of **7** furnished **8** in 88% yield. Compound **8** also possesses the capability of existing in two tautomeric forms **8a** or **8b**. It was found that in solution the predominating form is that of the oxo tautomer **8b** based on the following observations; the infrared spectrum exhibits a strong carbonyl stretching frequency at 1700 cm^{-1}. The nmr spectrum lacks the corresponding enolic and olefinic signals which would be characteristic for that of tautomer **8a**. However, a sharp singlet, which integrates for two protons, appears at δ 4.35 which indicates the presence of **8b**.

Alkylation of **8** can be acheived (Scheme 2) by the generation of its anion with sodium hydride followed by reaction with an alkylhalide (*e.g.* 1-bromopentane). Under these conditions, alkylation occurs on oxygen and the 4-pentoxy analog **9** was isolated. The *O*-alkylalted structure was assigned after examination of the ir and nmr spectra. In the infrared spectrum, the ketonic carbonyl formerly at 1700 cm^{-1} has disappeared. The nmr spectrum clearly shows a triplet at δ 4.0 which corresponds to the methylene protons adjacent to the oxygen. This is also accompanied by a sharp singlet at δ 6.1 which is assigned to the olefinic proton at the 3-position. The appearance of this proton at δ 6.1 also assists in the confirmation of the structure of tautomer **7a**.

Scheme 2



Treatment of **8b** with isocyanates in the presence of triethylamine afforded carboxanilides **10a** and **10b** in good yields. It appears that these compounds exist predominantly in the enolized form as deduced from the nmr spectrum of **10b**. A sharp singlet is observed at δ 14.5 which is typical for that of an enolic proton. In addition, comparison of this proton to one with approximately the same environment, *e.g.* 1,2-dihydro-4-hydroxy-1-(2-propynyl)-2-oxo-3-quinolinecarboxylic acid ethyl ester or t-butyl ester (6), where the enolic signals appear at δ 14.4 and δ 14.6, respectively, shows that these values are in close accord.

EXPERIMENTAL

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

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

Reaction of 2-Chloronicotinonitrile with *N*-Methylmethanesulfonamide.

To a solution of 26.0 g. of *N*-methylmethanesulfonamide in 700 ml. of dimethylacetamide, was added 9.7 g. of sodium hydride (57% in mineral oil, pentane washed) in portions. After stirring at room temperature for three hours, a solution of 28.0 g. of **5** (7) in 120 ml. of dimethylacetamide was added dropwise over a period of 2.5 hours, then the mixture was stirred at room temperature for 18 hours. The solvent was removed under reduced pressure and water was added to the residue. The mixture was extracted into ethyl acetate and the organic phase was treated with decolorizing charcoal and dried over sodium sulfate. Removal of the solvent under reduced pressure furnished 29.0 g. of a mixture of **6** and **7** (98% yield). Crystallization from ethanol resulted in the isolation of pure **6**, m.p. 93-96°; ir (chloroform): 2240, 1350, 1150 cm^{-1}; nmr (deuteriochloroform): δ 8.7 (m, 1), 8.1 (m, 1), 7.4 (m, 1), 3.4 (s, 3), 3.2 (s, 3).

Anal. Calcd. for $C_8H_9N_3O_2S$: C, 45.5; H, 4.3; N, 19.9; S, 15.2. Found: C, 45.5; H, 4.3; N, 20.0; S, 15.3.

4-Amino-1-methylpyrido[2,3-*c*]-1,2-thiazine 2,2-Dioxide (**7a**).

To a suspension of the mixture of **6** and **7** in 250 ml. of tetrahydrofuran (cooled in an ice bath) was added 7.0 g. of sodium hydride (57% in mineral oil, pentane washed) in portions. The mixture was allowed to warm to room temperature then was heated at 60° for 3.5 hours. The mixture was poured into cold water and extracted into ethyl acetate. The organic phase was dried over sodium sulfate and the solvent removed under reduced pressure to give 12.0 g. of **7a** (60%). An analytical sample was recrystallized from chloroform, m.p. 190-193°; ir (potassium bromide): 3450, 3380, 3280, 1650, 1605, 1325, 1120 cm^{-1}; nmr (DMSO-d_6): δ 8.6 (m, 1), 8.3 (m, 1), 7.3 (m, 1), 6.7 (s, 2), 5.95 (s, 1), 3.4 (s, 3).

Anal. Calcd. for $C_8H_9N_3O_2S$: C, 45.5; H, 4.3; N, 19.9; S, 15.2. Found: C, 45.4; H, 4.2; N, 19.9; S, 15.2.

1-Methyl-1*H*-pyrido[2,3-*c*]-1,2-thiazin-4(3*H*)one 2,2-Dioxide (**8b**).

To a warm solution of 1.6 g. of **7** in 50 ml. of ethanol was added 40 ml. of 2*N* hydrochloric acid and the resulting mixture was heated on a steam bath for 45 minutes. The reaction mixture was cooled in a refrigerator and the resulting precipitate was filtered, washed twice with water and dried to yield 1.4 g. of **8b** (88%), m.p. 95-98°; ir (chloroform): 1700, 1590, 1355, 1155, cm^{-1}; nmr (deuteriochloroform): δ 8.6 (m, 1), 8.3 (m, 1), 7.1 (m, 1), 4.35 (s, 2), 3.5 (s, 3).

Anal. Calcd. for $C_8H_8N_2O_3S$: C, 45.3; H, 3.8; N, 13.2; S, 15.1. Found: C, 45.2; H, 4.2; N, 13.1; S, 15.1.

1-Methyl-4-(*n*-pentoxy)pyrido[2,3-*c*]-1,2-thiazine 2,2-Dioxide (**9**).

To a solution of 6.0 g. of **8** in 60 ml. of dimethylacetamide was added 1.2 g. of sodium hydride (57% in mineral oil, pentane washed) in portions. After stirring at room temperature for 30 minutes, 4.5 g. of 1-bromopentane was added and the mixture was stirred at room temperature for 48 hours. The resulting solution was poured into cold water and extracted into ethyl acetate. Removal of the solvent under reduced pressure furnished an oil which was subsequently dissolved in ether. Cooling in an acetone/dry ice bath caused crystallization to occur and furnished 3.7 g. of **9** (45%), m.p. 72-74°; ir (chloroform): 1615, 1315, 1130 cm^{-1}; nmr (deuteriochloroform): δ 8.6 (m, 1), 8.15 (m, 1), 7.1 (m, 1), 6.1 (s, 1), 4.0 (t, 2), 3.6 (s, 3), 2.1-0.7 (m, 9).

Anal. Calcd. for $C_{13}H_{16}N_2O_3S$: C, 55.3; H, 6.4; N, 9.9; S, 11.4. Found: C, 55.0; H, 6.5; N, 10.0; S, 11.6.

4'-Chloro-4-hydroxy-1-methylpyrido[2,3-*c*]-1,2-thiazine-3-carboxanilide 2,2-Dioxide (**10a**).

A mixture of 4.3 g. of **8**, 3.4 g. of 4-chlorophenylisocyanate, and 3.0 g. of triethylamine in 100 ml. of tetrahydrofuran was refluxed for 4 hours. The reaction was allowed to cool to room temperature then was poured into 300 ml. of cold 2*N* hydrochloric acid. The resulting precipitate was filtered, dissolved in methylene chloride, and dried over sodium sulfate. Upon exchanging the solvent for ethanol the product crystallized to yield 6.0 g. of **10a** (80%), m.p. 221-224°; ir (chloroform): 3340, 1600, 1330, 1150 cm^{-1}.

Anal. Calcd. for $C_{15}H_{12}ClN_3O_4S$: C, 49.2; H, 3.3; N, 11.5; Cl, 9.7; S, 8.8. Found: C, 49.3; H, 3.5; N, 11.5; Cl, 9.6; S, 9.0.

4-Hydroxy-1-methyl-3'-trifluoromethylpyrido[2,3-*c*]-1,2-thiazine-3-carboxanilide 2,2-dioxide (**10b**).

The reaction, employing 3-trifluoromethylphenylisocyanate, was performed similar to the one described for the preparation of **10a** and the product, **10b**, was isolated in 69% yield, m.p. 118-120°; ir (chloroform): 3330, 1600, 1335, 1135 cm^{-1}; nmr (deuteriochloroform): δ 14.5 (s, 1), 9.6 (s, broad, 1), 8.7-8.3 (m, 2), 8.0-7.1 (m, 5), 3.65 (s, 3).

Anal. Calcd. for $C_{16}H_{12}F_3N_3O_4S$: C, 48.1; H, 3.0; N, 10.5; S, 8.0. Found: C, 48.1; H, 3.1; N, 10.3; S, 8.2.

Acknowledgement.

The authors wish to thank Dr. Sandoz Barcza and his associates for ir and nmr spectra and Mr. William Bonkoski and associates for performing the microanalyses.

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