Access to Ring Labelled Pyridines from Ethyl 2-Oxo-3-Piperidinecarboxylate. Syntheses of 3-Carboxy-2-Pyridone-3-^{14}C, Nicotinic-2,7-$^{14}C_2$ Acid and 2-Deuterionicotinic Acid

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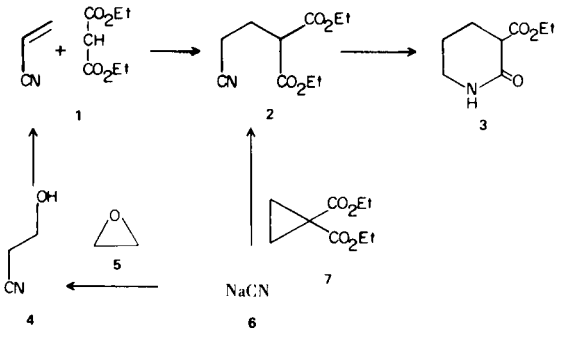
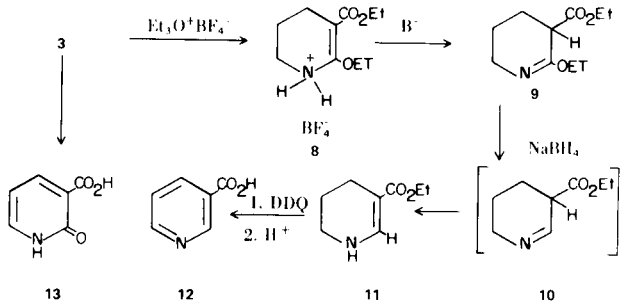
Reported syntheses for various carbon-14 ring labelled nicotinic acids utilized the components of the Skraup or Friedlander quinoline syntheses for insertion of the label (1). Thus a suitably labelled aniline and/or a suitably labelled three-carbon moiety are combined to produce a quinoline which on selenium oxidation provides the nicotinic acid. We wish to report an alternate approach which offers considerable opportunity to prepare substituted pyridine derivatives as well as flexibility for high activity ring labelling.

Ethyl 2-Oxo-3-piperidinecarboxylate (**3**) (2) is prepared by reductive cyclization of ethyl 2-carbethoxy-4-cyanobutanoate (**2**), a reaction that we found could be carried out conveniently at atmospheric pressure and is, therefore, amenable to a radiochemical synthesis.



The nitrile (2) is prepared by Michael addition of ethyl malonate (3) to acrylonitrile which in turn has been prepared carbon-14 labelled by dehydration of β-cyanoethanol (**4**) obtained by reaction of ethylene oxide (**5**) and sodium cyanide (**6**) (4). Alternatively, we found that **2** may be prepared directly in 50-60% yield from the reaction of sodium cyanide and ethyl 1,1-cyclopropanedicarboxylate (**7**) (5).

Conversion of **3** to nicotinic acid (**12**) is effected by a partial Borch amide reduction (6) yielding ethyl 1,4,5,6-tetrahydronicotinate (**11**) (7) which is easily aromatized with DDQ. Direct aromatization of **3** with DDQ yields 3-carboxy-2-pyridone after hydrolysis. The use of **3** prepared from ethyl malonate-2-^{14}C led to **13** labelled at C-3



and nicotinic-2,7-$^{14}C_2$ acid was prepared from **3** derived from ethyl malonate-1,3-$^{14}C_2$.

Since the reaction of **3** with the Meerwein reagent (8) followed by an excess of borohydride yielded only the partial reduction product **11** (61% after chromatography), we examined this sequence in some detail. The intermediate fluoroborate salt (**8**) was shown by 100 MHz nmr to exist solely as the enol ether. In an effort to isolate the corresponding eneamine, **8** was treated with cold bicarbonate solution. This led to a mixture containing mainly starting material (**3**) but from which about 5% of the imino ether (**9**) was isolated. Since borohydride is the base used in this sequence, it adds hydride to **9** as it is formed followed by elimination of ethoxide as described (6). However, the resulting imine (**10**) rapidly tautomerizes to the eneamine (**11**) which is resistant to borohydride under these conditions and is the only product isolated. Carrying out this sequence with an excess of sodium borodeuteride (90% D) under equilibrating conditions gave only the monodeuteriated analog of **11** which was aromatized to 2-deuterionicotinic acid (85% D).

EXPERIMENTAL

Melting and boiling points are uncorrected. All solvents were distilled prior to use. Radiochemical purity was determined on thin layer chromatograms with a Packard Model 7201 Radiochromatogram Scanner System and was at least 99% in all instances.

Ethyl 2-carbethoxy-4-cyanobutanoate (**2**).

This compound was routinely prepared from ethyl malonate

and acrylonitrile as described (3). Alternatively, **2** was prepared by heating at 150° for 10 minutes, a mixture of 49 mg. (1 mmole) of sodium cyanide and 373 mg. (2 mmoles) of ethyl 1,1-cyclopropanedicarboxylate (5) in 0.5 ml. of HMPA. After cooling, the mixture was treated with 50 ml. of water and extracted with three 10 ml. portions of benzene which were combined, dried (magnesium sulfate), concentrated *in vacuo* and the residue distilled yielding 117 mg. (0.54 mmoles, 54% based in cyanide) of product, b.p. 115-125° (0.1 mm).

Ethyl 2-Oxo-3-piperidine Carboxylate (**3**).

A mixture of 213 mg. (1 mmole) of ethyl 2-carbethoxy-4-cyanobutanoate, 50 ml. of triethylamine, 0.1 ml. of Raney nickel suspension and 2 ml. of absolute ethanol was hydrogenated at 65° and 1 atmosphere for 7 hours when uptake ceased at 94% of theory. After filtration, the solution was concentrated *in vacuo* and the residue dissolved in a warm mixture of 1 ml. of hexane and 0.4 ml. of benzene from which the product crystallized. After washing the crystals with the above solvent, they were dried to a constant weight of 98 mg. (0.57 mmole, 57%), m.p. 78-79°, (lit. (2), m.p. 78-79°).

3-Carbethoxy-2-ethoxy-1,4,5,6-tetrahydropyridinium Tetrafluoroborate (**8**).

A mixture of triethyloxonium fluoroborate (8) 1.004 g. (5.28 mmoles) and 833 mg. (4.87 mmoles) (**3**) dissolved in 5 ml. of methylene chloride was magnetically stirred at room temperature for 16 hours. The mixture was then concentrated *in vacuo* to a residue of 1.48 g. of crude product which was not further purified. The 100 MHz nmr spectrum of this material in deuteriochloroform, while contaminated with the excess of Meerwein reagent, exhibited the two methyl groups as triplets, 1.30 and 1.38 ppm; the C-5 protons at 1.95 ppm; the C-4 protons at 2.2 ppm; the C-6 protons at 3.65 ppm; the ester and vinyl ether methylene protons as characteristic quartets at 4.08 and 4.28 ppm respectively; and 2 N-H protons as a singlet at 10.06 ppm.

3-Carbethoxy-2-ethoxy-3,4,5,6-tetrahydropyridine (**9**).

The tetrafluoroborate salt (**8**), prepared from 1.71 g. (10 mmoles of **3**, after drying was partitioned between 10 ml. of ether and a cold mixture of 10 ml. of 1*N* sodium bicarbonate solution and 5 ml. of 2*N* sodium carbonate solution. After separation, the aqueous phase was extracted with five 10 ml. portions of ether. The combined ether extracts were concentrated *in vacuo* to a residue of 481 mg. which by tlc (silica gel, chloroform:ethyl acetate; 3:1) consisted mainly of **3**, R_f 0.09 and a material at R_f 0.32. This mixture was chromatographed on a column of silica gel (E. Merck, No. 7734), 100 g., packed in chloroform:ethyl acetate; 3:1, and eluted with this solvent mixture. Those fractions containing the higher R_f material were pooled and concentrated *in vacuo* to a residue of 130 mg. (0.65 mmole). The mass spectrum (70 eV) of this compound showed a molecular ion at M/e 199 and a fragmentation pattern compatible with either the enol ether or the imino ether. The ir spectrum (3% in chloroform) showed no N-H absorption and the ester at 1740 cm^{-1} and the imine at 1690 cm^{-1}. The 100 MHz nmr spectrum (deuteriochloroform) showed the C-3 proton as a triplet at 3.2 ppm separated now from the C-6 protons which appeared as a triplet at 3.54 ppm. The methyl and methylene protons appeared at their characteristic resonances and no N-H proton was detectable.

Ethyl 1,4,5,6-Tetrahydronicotinate (**11**).

The dry tetrafluoroborate salt (**8**) prepared on a 4.87 mmole scale was dissolved in 10 ml. of absolute ethanol and then treated with 461 mg. (12.2 mmoles) of sodium borohydride portionwise over a 15 minute period at 0°. Gas evolution was vigorous but diminished rapidly. The mixture was stirred at room temperature for 22 hours, then diluted with 50 ml. of water and extracted with four 25 ml. portions of ether which were combined, extracted with brine, dried (magnesium sulfate), filtered and concentrated *in vacuo*. The residual oil (686 mg.) was chromatographed on 68.6 g. of silica gel (E. Merck No. 7734), packed in chloroform with chloroform:ethyl acetate; 3:1. After a 50 ml. forerun, 10 ml fractions were taken and those containing product were pooled and concentrated *in vacuo* to a residue of 461 mg. The 60 MHz nmr spectrum (deuteriochloroform) integrated for 13 protons and showed one N-H at 4.7 ppm (broad) and the C-2 proton as a doublet (J=6 cps) at 7.45 ppm; uv max (ethanol): 286 nm. (ε 34,780).

Anal. Calcd. for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 61.97; H, 8.41; N, 8.78.

Nicotinic Acid (**12**)

A solution of 288 mg. (1.85 mmoles) of **11** in 25 ml. of ether was added to a stirred solution of 884 mg. (3.9 mmoles) of DDQ in 200 ml. of ether. After 15 minutes, the suspension was filtered, washed with ether and the filtrate extracted with five 25 ml. portions of 6*N* hydrochloric acid. The combined extracts were washed with ether, allowed to stand at room temperature for 16 hours, refluxed for 30 minutes, then concentrated *in vacuo* to a solid residue which was dissolved in 5 ml. of 1*N* sodium carbonate solution and extracted with ether. The aqueous was acidified with hydrochloric acid and continuously extracted with ether for 1 hour. The *p*H of the aqueous solution was then adjusted to 3.00 and again extracted continuously with ether for 36 hours resulting in 121 mg. of extract which was sublimed at 120° (5 μ) yielding 108 mg. (0.88 mmole, 48%) of nicotinic acid, m.p. 233-234.5° and identical by tlc with an authentic sample.

2-Deuterionicotinic Acid.

The tetrafluoroborate salt (**8**) prepared from 5.5 mmoles of **3** and 6.1 mmole of triethyloxonium fluoroborate was dissolved in 10 ml. of absolute ethanol. To the solution, at ice bath temperature, was added 0.6 g. of sodium borodeuteride (> 90% D) portionwise. The resulting mixture was allowed to stand at room temperature for two days then diluted with 100 ml. of water and extracted with five 15 ml. portions of ether. These were combined, dried (magnesium sulfate), filtered and concentrated *in vacuo* to a residue of 809 mg. The 60 MHz nmr spectrum (deuteriochloroform) was identical to that of **11** with the exception of an 85% reduction in the C-2 proton (doublet) at 7.45 ppm and the detection of an impurity due to excess of Meerwein reagent. Of the 809 mg. obtained, 686 mg. was treated with DDQ and after the described workup, 171 mg. of sublimed product, m.p. 232.5-234° was obtained. Mass spectral analysis of this material showed 14.2% D_0 and 85.8% D_1. By nmr (DMSO), the singlet at 8.93 ppm assigned to the C-2 proton of nicotinic acid was shown to be reduced by over 80%.

Nicotinic-2,7-$^{14}C_2$ Acid.

Ethyl 1,4,5,6-tetrahydronicotinate-2,7-$^{14}C_2$, on a 1 mmole, scale (171 mg.) was converted to nicotinic acid by the procedures described above in 23% overall yield (28.8 mg., 0.23 mmole). the addition of small quantities of nonradioactive carrier during this conversion diluted the specific activity of the final product to 1,415 dpm/mg. (78.35 nCi/mmole).

3-Carboxy-2-pyridone (**13**).

Ethyl 2-oxo-3-piperidine carboxylate 121 mg. (0.708 mmoles

prepared as described above) and 338 mg. (1.49 mmoles) of DDQ were dissolved in 10.5 ml. of benzene and stirred magnetically for 16 hours at room temperature. The resulting mixture was dissolved in 70 ml. of ethyl acetate and then extracted with five 3 ml. portions of 6*N* hydrochloric acid. After washing with 2 ml. of ethyl acetate, the combined acid extracts were distilled to 105° then refluxed for 30 minutes to effect hydrolysis, cooled to 40° and concentrated *in vacuo* to a crystalline residue of 67 mg. which was sublimed at 155° (3 μ). The sublimate, 35 mg. (36%), m.p. 252-253°, was homogeneous by tlc (cellulose; methanol elution, Rf 0.25) and compared exactly to an authentic sample.

3-Carboxy-2-pyridone-3-^{14}C.

On the above scale, **3** derived from ethyl malonate-2-^{14}C provided 3-carboxy-2-pyridone-3-^{14}C when treated as described above. Overall radio chemical yield of 12% was obtained on product of specific activity of 74.1 μCi/mg. (10.3 mCi/mmole).

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