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DEUTERODECARBOXYLATION

A CONVENIENT METHOD FOR THE PREPARATION OF LABELED PYRIDINES

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Abstract—Deuterodecarboxylation, the replacement of a COOD group by a D atom, proceeds with high specificity in good yields for a series of pyridine-2-carboxylic acids. Isomeric pyridine-carboxylic acids require higher temperatures to achieve decarboxylation and give multiply deuterated products. Positions adjacent to the ring N are especially favored in the H—D exchange reactions. The role of ylid intermediates is discussed. It is suggested that the decarboxylation method of labeling may be applicable to a wide variety of heterocyclic systems. A statistical method is given for calculating a mass distribution from NMR data for a sample of partially deuterated pyridines.

INTRODUCTION

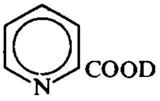
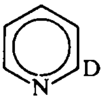
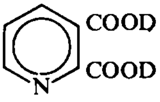
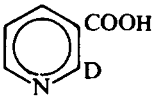
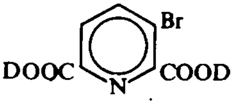
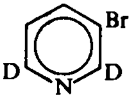
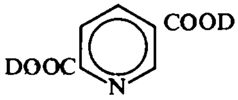
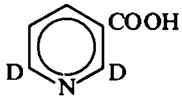
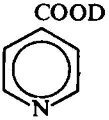
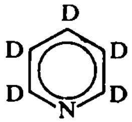
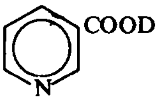
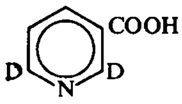
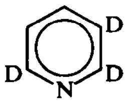
METHODS are available for the preparation of hydrogen labeled pyridines by non-selective and position specific reactions. Non-selective synthetic methods for labeling all annular positions include the use of transition metal catalysts with D_2O[1] and base catalyzed exchange in hydroxylic solvents.[2] Methods for selectively labeling one or more annular positions are more numerous. Pyridine-2,6-d_2 is conveniently prepared by an exchange reaction in neutral D_2O.[2] Monodeuterated pyridines have been prepared almost exclusively from halopyridines by the action of D_2SO_4 and zinc dust,[3] by successive treatment with n-butyl lithium and D_2O[4] and by concentrated DI[5]. An example of base catalyzed exchange to specifically label the 4-position is found with 3-chloropyridine.[5]

In spite of abundant information concerning the ease of decarboxylation of the readily available pyridinecarboxylic acids, deuterodecarboxylation appears to have been overlooked as a means of introducing deuterium into selected ring positions. There is one recorded example in which three monodeuterated pyridine-3-carboxylic acids were prepared by the deuterodecarboxylation of pyridinedicarboxylic acids.[6] The reaction was assumed to be specific, although no proof was offered to support this assumption. We have studied the decarboxylation of pyridinecarboxylic acids in order to ascertain the specificity of the labeling.

RESULTS

There are two steps in the deuterodecarboxylation sequence. Conversion of COOH to COOD is achieved by dissolving or suspending the acid in D_2O. Extended reflux is necessary for reaction in suspensions. Decarboxylation is effected by heating the dry acid directly, or in a high boiling solvent. The 2-carboxylic acids react at 200–250°, while the 3- and 4-carboxylic acids decompose more slowly, even at tem-

TABLE 1. DEUTERATED PYRIDINES PREPARED BY THE DECARBOXYLATION OF PYRIDINE–CARBOXYLIC ACIDS-O-*d*.

Starting material	Product(s)	Temp. range, °C	%D/position[a]
 I		170–180	75–87%[b]
 II		200–220	78–87%[b]
 III		188	78% 2-*d* 78% 6-*d*
 IV		250–270	13–19% 2-*d*[b] 77–84% 6-*d*[b]
 V		300–320	27% 2,6-*d*[c,d] 11% 3,5-*d*[c,d] 15% 4-*d*[d]
 VI		275–300	33% 2-*d* 26% 6-*d*
			31% 2,6-*d*[c] 41% 3-*d*

[a] From NMR analysis

[b] Range of values found from several experiments

[c] An average percentage for both positions

[d] Although some deuterium is present at each position, the samples do not contain any molecules with five D atoms.

peratures exceeding 275°. Deuteration at the site previously occupied by the carboxylic acid group is achieved in this second step, Fig. 1.

$$C{-}COOH \xrightarrow{D_2O} C{-}COOD \xrightarrow{\Delta} C{-}D + CO_2$$

FIG. 1

The location and amount of deuterium in the product was measured by a combination of NMR and low voltage mass spectrometry. Results are summarized in Table 1. The chemical shifts of all the unlabeled products have been published.[7] Assignment of sites of deuteration is possible since all non-equivalent positions have clearly separated signals. In spite of the low degree of deuteration at each position in some of these examples, there can be little doubt that the analyses are correct. The NMR and mass spectral data are in surprisingly good agreement. The Appendix illustrates the method by which NMR data were correlated with the mass spectra.

Lack of complete deuteration probably reflects incomplete conversion to COOD in the first step of the reaction. Only a single exposure to D_2O was carried out on acid starting materials. Repeated exposure to fresh D_2O should result in a higher conversion to COOD and a product with more deuterium.

DISCUSSION

Deuterodecarboxylation is a simple, convenient method for the selective introduction of deuterium into the 2- and 6-positions of a pyridine ring. The mechanism of decarboxylation is believed to involve the formation of an ylid intermediate.[8] Capture of a deuteron by the ylid leads to labeled product, Fig. 2.

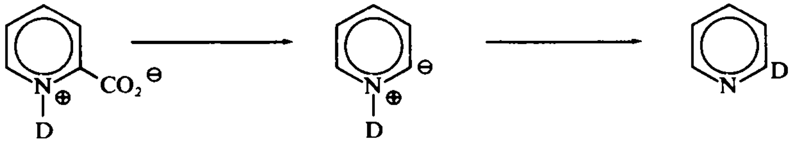


Fig. 2.

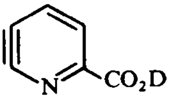
As the reaction conditions for decarboxylation become progressively more severe, a loss in the specificity of the deuterium labeling occurs. Accompanying deuterodecarboxylation at higher temperatures is a H—D exchange reaction. The preferred sites for this exchange are the 2 and 6 positions. A comparison of the results from isomeric monocarboxylic acids I and VI and dicarboxylic acids II and IV makes this conclusion evident. That complete scrambling of the deuterium label is possible, is indicated by the product from the decarboxylation of 4-carboxylic acid V. It is important to note that this acid was subjected to the most severe reaction conditions for the series of compounds investigated.

H—D exchange precedes rather than follows decarboxylation in the case of 3-carboxylic acid VI. The decarboxylation of this acid, which was interrupted prior to completion, gave recovered acid containing deuterium at positions 2,6 and pyridine labeled at the 2,3,6-positions. Since the recovered acid and pyridine each have the same deuterium content at the 2,6-positions, it seems likely that this polydeuterated acid is the precursor to the trideuterated pyridine.

Since the favored positions for hydrogen-deuterium exchange are positions 2,6, we suggest that these exchange reactions proceed by way of ylidic intermediates. The ylid is generated by base-catalyzed deprotonation of a pyridinium ion. The observation that pyridine undergoes exchange only at positions 2,6 in neutral D_2O supports this hypothesis.[2] The latter exchange is believed to occur by means of an ylidic intermediate.[2]

Although a 2,3-pyridyne intermediate such as VII might result from the loss of

CO_2 and bromide ion from bromodicarboxylic acid III, no significant quantities of bromide ion were detected in the reaction mixture.



VII

We think that the deuterodecarboxylation reaction can be readily extended to 5- and 6-membered heterocyclic ring systems.[9] The positional specificity found for pyridine-2-carboxylic acids may well be found in the wide variety of heterocyclic carboxylic acids which decarboxylate readily. In choosing acids for the selective introduction of a hydrogen label, one should primarily consider the ease of decarboxylation. Heteroatoms such as O and S, though less able to accept a proton than N, are known to facilitate decarboxylation at an adjacent center. Furthermore, a radioactive H label may be introduced by the use of tritium-enriched water in place of D_2O. The method, therefore, would appear to have considerable generality.

EXPERIMENTAL

Materials. All pyridine carboxylic acids, with the exception of 3-bromopyridine-2,6-dicarboxylic acid (Found: C, 34·42; H, 1·78; N, 5·66. $C_7H_4BrNO_4$ requires: C, 34·18; H, 1·64; N, 5·69 %), were commercially available. The latter acid was prepared by the permanganate oxidation of 3-bromo-2,6-dimethylpyridine[10] according to a general procedure for the oxidation of dimethylpyridines.[11] This method was modified by the use of *t*-butyl alcohol as a co-solvent.

Measurement of deuterium content. NMR spectra were obtained on a Varian A-60-A spectrometer. Samples were dissolved in CCl_4. t-Butyl alcohol was used as an internal reference standard, except for those products which contained a non-exchanging hydrogen. Data represents the average of several integrations; uncertainty in the degree of deuteration is about ±3%. Mass spectra were obtained with a Hitachi Perkin–Elmer RMU-6E spectrometer. Spectra were obtained at sufficiently low electron energies to eliminate fragmentation, particularly that giving rise to M-1 species.[12]

Pyridine-2-d from pyridine-2-carboxylic acid. A mixture of 15 g of pyridine-2-carboxylic acid and 5 g of D_2O was heated to soln in a distillation apparatus. When the D_2O had distilled and the pot temp reached 170–180°, pyridine distilled. When the product was dissolved in a little ether, dried with $MgSO_4$, and redistilled, 7 g (73 %) of pyridine-2-*d*, b.p. 113·5–115·5° (lit.[13] b.p. of pyridine is 115·5°) was obtained. Mass spectral analysis showed: $d_0 = 0{\cdot}258$; $d_1 = 0{\cdot}742$.

Pyridine-3-carboxylic acid-2-d from pyridine-2,3-dicarboxylic acid. A mixture of 5 g of pyridine-2,3-dicarboxylic acid and 5 g of D_2O was heated to soln with the aid of a little Et_3N. The liquid was removed under vacuum and the solid was placed in a Monel bomb. After heating at 200–220° for 45 min, the contents of the bomb were recrystallized from dil AcOH, then sublimed at 150°/0·05 torr to give 2 g (54 %) of pyridine-3-carboxylic acid-2-*d*, m.p. 230–234°, (lit.[13] m.p. of pyridine-3-carboxylic acid is 236°). This acid was converted to the methyl ester, m.p. 39·5–40·5° (lit.[13] m.p. of methyl pyridine-3-carboxylate is 38°) for NMR and mass spectral analysis by treatment with $SOCl_2$, then MeOH. Mass spectral analysis showed d_0 -0·215; $d_1 = 0{\cdot}785$.

Pyridine-3-carboxylic acid-2,6-d_2 from pyridine-2,5-dicarboxylic acid. A stirred suspension of 5 g of pyridine-2,5-dicarboxylic acid and 18 g of D_2O was heated at reflux for 12 hr. Following removal of the D_2O under vacuum, the solid was placed in a sealed Monel bomb and heated at 250–270° for 30 min. Recrystallization of the contents of the bomb from dil AcOH followed by sublimation at 150°/0·05 torr gave 1·5 g (40 %) of pyridine-3-carboxylic acid-2,6-d_2, m.p. 233–237°. This acid was converted to its methyl ester for analysis by the method described above. Mass spectral analysis showed: $d_0 = 0{\cdot}138$; $d_1 = 0{\cdot}714$; $d_2 = 0{\cdot}148$.

Pyridine-3-carboxylic acid-2,6-d_2 and pyridine-2,3,6-d_3 from pyridine-3-carboxylic acid. A stirred suspension of 5 g of pyridine-3-carboxylic acid and 20 g of D_2O was heated at reflux for 20 hr. After the D_2O

had been removed under vacuum the solid was heated in a sealed Monel bomb at 275–300° for 30 min. The contents of the bomb were added to about 20 cc of ether, and the suspension was filtered. The filtrate was dried with $MgSO_4$ and distilled to give 1·5 g (48 %) of pyridine-2,3,6-d_3, b.p. 113·5–115·5°. Mass spectral analysis showed: $d_0 = 0{\cdot}317$; $d_1 = 0{\cdot}442$; $d_2 = 0{\cdot}219$; $d_3 = 0{\cdot}050$.

The solid filtered from the ether suspension was recrystallized from dil AcOH and sublimed at 150°/0·05 torr to give 1·9 g (38 %) of pyridine-3-carboxylic acid-2,6-d_2, m.p. 235–237°. This acid was converted to its methyl ester as described above. Mass spectral analysis showed: $d_0 = 0{\cdot}502$; $d_1 = 0{\cdot}400$; $d_2 = 0{\cdot}098$.

Pyridine-d_5 from pyridine-4-carboxylic acid. A 5 g sample of pyridine-4-carboxylic acid was heated to soln in 25 cc of $SOCl_2$. The excess $SOCl_2$ was distilled, and the residue was neutralized with a 25 % NaOD soln. The D_2O was then removed under vacuum, and the solid residue was heated to 320° for 2 hr. in a Monel bomb. The contents of the bomb were added to a little ether, and filtered. The filtrate was dried with $MgSO_4$, and distilled to give 1·7 g (52 %) of pyridine-d_5, b.p. 113·5–115·5°. Mass spectral analysis showed: $d_0 = 0{\cdot}367$; $d_1 = 0{\cdot}409$; $d_2 = 0{\cdot}180$; $d_3 = 0{\cdot}039$; $d_4 = 0{\cdot}005$.

3-Bromopyridine-2,6-d_2 from 3-bromopyridine-2,6-dicarboxylic acid. The recrystallization of 7 g of 3-bromopyridine-2,6-dicarboxylic acid, m.p. 178°, from 15 cc D_2O gave 6·5 g of the deuterated acid III. This was dried and added to 50 cc of diethylene glycol diethyl ether which had been freshly distilled (b.p. 188°) from sodium. The soln was refluxed for 4 hr, then added to 100 cc of H_2O. Aqueous $HgCl_2$ was added until no additional ppt formed. The precipitated mercurichloride was filtered and decomposed in 100 cc 10N KOH. The salts were filtered, and rinsed with ether. The filtrate was extracted 4 times with 50 cc of ether, and the combined extracts were concentrated to 25 cc. After drying with Na_2SO_4, the soln was distilled to give 2·7 g (65 %) of 3-bromopyridine-2,6-d_2, b.p. 168–173° (lit.[13] b.p. of 3-bromopyridine is 173°). Mass spectral analysis showed: $d_0 = 0{\cdot}061$; $d_1 = 0{\cdot}362$; $d_2 = 0{\cdot}577$.

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[14] Ref. 12, pp. 227–231 contains relevant worked examples.

APPENDIX

The following illustrates a method based upon probability considerations for calculating the mass distribution for a mixture of partially deuterated pyridines from observed NMR data. The sample resulted from the deuterodecarboxylation of acid V. The NMR data have units of per cent D per position (%D), while the units of mass distribution are per cent d_i per mole (%d_i).

First, the NMR data are converted to a form giving positional isotope distribution, Table 2. Relative amounts of d_1 and d_2 for the α and β positions which have two *equivalent* sites each are calculated from the amount of deuteration as indicated by the NMR data and from the probability of two consecutive reactions. Secondary isotope effects are assumed to be negligible. The method of calculation is illustrated for the α position only.

Second, the probable mass distribution resulting from deuteration of two or more chemically *non-equivalent* positions are calculated. The %d_i is given by the product of the positional isotope distribution.[14]

The results of such calculations are given in Table 3. The agreement between the mass distribution calculated from the NMR analysis and the observed mass spectrum strongly supports the NMR analysis.

TABLE 2. POSITIONAL ISOTOPE DISTRIBUTION CALCULATED FROM OBSERVED NMR DATA

γ Position		α Position		β Position	
NMR	Isotope distribution	NMR	Isotope distribution	NMR	Isotope distribution
14·7 %D	14·7 % d_1	26·9 %D	$d_2 = (26{\cdot}9\%)^2 = 7{\cdot}2\%$	11·2 %D	1·2 % d_2
85·3 %H	85·3 % d_0	73·1 %H	$d_1 = 2(26{\cdot}9\% \times 73{\cdot}1\%) = 39{\cdot}4\%$	88·8 %H	20 % d_1
			$d_0 = (100\% - 39{\cdot}4\% - 7{\cdot}2\%) = 53{\cdot}4\%$		78·8 % d_0

TABLE 3. COMPARISON OF CALCULATED AND OBSERVED MASS DISTRIBUTION FOR A MIXTURE OF PARTIALLY DEUTERATED PYRIDINES

Calculated mass distribution		
Positions deuterated		Observed mass distribution
$\alpha \times \gamma$	$\alpha \times \beta \times \gamma$	
45·6 % d_0	35·9 % d_0	36·7 % d_0
41·4 % d_1	41·7 % d_1	40·9 % d_1
11·9 % d_2	18·2 % d_2	18·0 % d_2
1·1 % d_3	3·8 % d_3	3·9 % d_3
	0·3 % d_4	0·5 % d_4