STUDIES ON SOME MONOMETHYL ESTERS OF PYRIDINE DICARBOXYLIC ACIDS

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Abstract – New monomethyl esters of some pyridine dicarboxylic acids have been prepared by novel routes using the appropriate metal chelates as intermediates. Chelation is used to protect a specific carboxyl group or to favour the hydrolysis of a specific ester group.

The acid association constants of these esters and some pyridine dicarboxylic acids as well as the stability constants of the iron(II) and iron(III) complexes of a number of these compounds were determined by various techniques.

INTRODUCTION

OF THE four pyridine dicarboxylic acids, dipicolinic (pyridine 2,6-dicarboxylic) acid, quinolinic (pyridine 2,3-dicarboxylic)acid, lutidinic (pyridine 2,4-dicarboxylic) acid, and isocinchomeronic (pyridine 2,5-dicarboxylic)acid the monomethyl esters of only the first two are known. Mathes *et al.*[1] reported the preparation of monomethyl esters of quinolinic acid. The preparation of both isomeric monomethyl esters of quinolinic acid was claimed by Kirpal[2]. However, Kenyon and Thaker[3] later reinvestigated the preparation and came to the conclusion that both isomers could be formed, but required modifications to the procedure of Kirpal. The procedure was further modified by Norula[4].

A number of attempts to repeat Kenyon and Thaker's experiments was carried out in this laboratory. However, under the conditions described by these workers only the 2-methyl ester was prepared. The procedure failed for the 3-methyl compound.

There is no mention in the literature of the preparation of the monomethyl esters of lutidinic or isocinchomeronic acids.

In an earlier publication, one of the present authors [5] reported on the determination of the stability constants of complexes between some transition metal ions and the anion of 6-hydroxymethyl pyridine-2-carboxylic acid using spectrophotometric and pH titration methods.

This paper reports the preparation of methyl-4-carboxypyridine-2-carboxylate (4-methyl lutidinate), methyl-5-carboxypyridine-2-carboxylate(5-methyl isocinchomeronate) and methyl-2-carboxypyridine-6-carboxylate(2-methyl dipicolinate), and measurements of the association constants and the stability constants of the Fe(II) and Fe(III) complexes.

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EXPERIMENTAL

(a) Preparation of the monomethyl esters

(i) *Preliminary investigations*. A common route for the preparation of the half-ester is through the intramolecular anhydride. However, neither lutidinic nor isocinchomeronic acids can form intramolecular anhydrides, so this route to the half-ester is not available. Both acids, however, form very stable bis-complexes with copper(II), the ring nitrogen and the adjacent carboxyl group in the 2-position being involved in the chelation. As the distal carboxyl group is free, while the 2-carboxyl group is protected through chelation, it was considered a possibility that the distal carboxyl group could be selectively esterified using the copper complex of the acid. The free acid could then be liberated by decomposing the complex with hydrogen sulphide and extraction with an organic solvent. Methylation of the copper complexes of these acids was complicated by the extreme insolubility in solvents. Many esterification techniques were attempted, but success was achieved only through the preparation of the acid chloride with thionyl chloride and subsequent treatment with methanol.

This procedure was satisfactory with lutidinic acid but not with isocinchomeronic acid; the product obtained was the dimethyl ester.

A modified procedure was ultimately found to be successful with isocinchomeronic acid. The dimethyl ester was refluxed with copper nitrate in methanol, when the ester group in the 2 position was selectively hydrolysed yielding the 5-methyl ester.

Neither of the above methods had any success with dipicolinic acid. In this case a new approach was found necessary. The monosilver salt of the acid was formed and this refluxed with methyl iodide to give the mono-ester.

(ii) Methyl-4-carboxypyridine-2-carboxylate(4-methyl lutidinate). The "acid form" of copper(II) lutidinate was prepared from copper(II) acetate and lutidinic acid, as described by Lukes and Jurecek [6].

The copper complex was refluxed with thionyl chloride for 1 hr on a steam bath. A calcium chloride guard tube was attached to the reflux condenser to prevent entry of moisture. Excess thionyl chloride was distilled off, almost to dryness, after which the mixture was chilled in ice and cautiously treated dropwise with methanol previously dried over anhydrous copper sulphate. The reaction was initially extremely vigorous, but gradually subsided after the addition of 20 ml of methanol. A further 150 ml of methanol was added and the mixture refluxed on a steam bath for 1 hr. Excess methanol was removed by distillation until the residual volume was reduced to approximately 20 ml. This concentrated methanol solution was then poured into 250 ml of ice-water mixture from which deep violet-blue crystals of the copper(II) chelate of 4-methyl lutidinate gradually crystallized out on standing over a period of 2-3 days.

The copper chelate gave no reaction with dilute solution of sodium bicarbonate, showing the absence of a free carboxyl group.

It was filtered and washed with water, followed by dilute sodium bicarbonate to remove traces of unreacted copper(II) chelate of lutidinic acid. The washed crystals were suspended in acetone and stirred for $\frac{1}{2}$ hr, followed by a similar treatment with dry ether. This ensured the removal of non-polar impurities. The crystals were filtered off and dried in a vacuum desiccator over concentrated sulphuric acid. (Anal. Calcd. for Cu (C₈H₆NO₄)₂: C, 45·35; N, 2·81. Found: C, 45·30; N, 3·09.)

The free mono-ester, 4-methyl lutidinate, was liberated from the copper chelate by bubbling hydrogen sulphide into its suspension in dioxan. The excess hydrogen sulphide was boiled off on a steam bath. The dioxan extract was filtered and concentrated on the steam bath, after which it deposited crystals of the free ester when treated with a large excess of *n*-hexane. This product, recrystallized from the minimum volume of acetone, had a sharp melting point of 153/154°C. (Anal. Calcd. for $C_8H_7NO_4$: C, 53·03; H, 3·91; N, 7·73. Found: C, 53·15; H, 4·06; N. 7·98.)

(iii) Methyl-5-carboxypyridine-2-carboxylate(5-methyl isocinchomeronate). The method described above for the preparation of the mono-ester of lutidinic acid was used on isocinchomeronic acid, when the product obtained on treating the concentrated methanol solution with ice-water was the dimethyl ester, melting point 163/164°C. A more convenient method of preparing the dimethyl ester was obtained by forming the disilver salt of isocinchomeronic acid and reacting it with methyl iodide.

A solution of the dimethyl ester in methanol was mixed with copper nitrate and refluxed for 1 hr.

Initially, the colour of the solution was light blue, but on refluxing it gradually deepened and

6. R. Lukes and M. Jurecek, Colln Czech. chem. Commun. 13, 131 (1948).

became a deep violet-blue after three quarters of an hour. After 1 hr, deep violet-blue crystals began to deposit. The solution was concentrated, when more crystals were deposited. The crystals were purified by the same procedure as used for the copper complex of 4-methyl lutidinate. (*Anal.* Calcd. for $C_8H_7NO_4$: C, 53·05; H, 3·91; N, 7·73. Found: C, 53·24; H, 4·00; N, 7·33.)

(iv) Methyl-2-carboxypyridine-6-carboxylate(2-methyl dipicolinate). The methods described above for the preparation of 4-methyl lutidinate and 5-methyl isocinchomeronate failed for 2-methyl dipicolinate, possibly because of steric reasons. A number of other methods were investigated and that outlined below gave a good yield of the monomethyl ester and is simpler than the method described by Mathes *et al.*[1].

To 16.7 g (0.1 mole) of dipicolinic acid in boiling water (500 ml) containing 5-10 ml nitric acid, was added slowly with stirring a solution of 17 g silver nitrate (0.1 mole) in water (100 ml). A white crystalline precipitate formed immediately. The solution was boiled for 3 min to coagulate the precipitate and allowed to cool in the dark. The precipitate was filtered and washed with hot water, followed by alcohol and acetone, and dried over concentrated sulphuric acid in a vacuum desiccator (Yield 80 per cent). 10 g of the precipitate were suspended in 150 ml of dry benzene. 3 ml of methyl iodide were added and the mixture refluxed for three hours. The yellow precipitate of silver iodide was filtered and the filtrate allowed to evaporate to dryness in a current of air. The yield of the crude ester was 40 per cent.

As no suitable solvent was found for recrystallization, the crude ester was dissolved in a minimum volume of dioxan. filtered and treated with excess *n*-hexane. Colourless crystals of the monomethyl ester were obtained, which were filtered and dried *in vacuo* over concentrated sulphuric acid. The melting point was 147/148°C. (*Anal.* Calcd. for $C_8H_7NO_4$: C, 53.05; H, 3.91; N, 7.73. Found: C, 52.92; H, 4.09; N, 7.63.)

(b) *Iron(II) and iron(III) perchlorates*

For the determination of the stability constants of the Fe(II) and Fe(III) complexes of the monomethyl ester, the metal perchlorates were used.

Iron(II) perchlorate was prepared by the action of dilute (approx. 30%) perchloric acid on the metal carbonate. The latter was prepared by double decomposition of iron(II) sulphate with sodium hydrogen carbonate in an atmosphere of nitrogen.

The reaction was carried out at 100°C to avoid colloidal precipitation. A slight excess of sodium hydrogen carbonate was used to ensure complete removal of the sulphate ion. The iron(11) carbonate prepared in this way was stable for a few days, if kept dry and in the dark: in practice it was better to use it immediately to form the perchlorate. Iron(11) perchlorate was prepared by strongly heating ferric chloride with 70% perchloric acid in a silica vessel.

Solutions in boiled water, stored under purified nitrogen, were standardized by titration with EDTA for Fe(II) and by titration with dichromate for Fe(II). The Fe(II) perchlorate was further purified immediately before use by passage through a column of Zeocarb 225 cation-exchange resin saturated with Fe(II).

(c) Spectrophotometric measurements

A Hilger Uvispek Spectrophotometer with water-jacketed 1 cm quartz cells was used to measure the optical densities at 25°C.

(d) pH measurements

The pH measurements were made with a Cambridge portable pH-meter with saturated calomel and glass electrodes standardized against 0.05 M potassium hydrogen phthalate (pH 4.00). pH titrations were carried out on solutions of the acid alone and in the presence of excess perchloric acid. The closed titration cell was immersed in a thermostat at 25°C, the solution being stirred with purified nitrogen as required, and the titrant, carbonate-free sodium hydroxide being delivered beneath the surface of the solution from a fine capillary tube connected to a Metrohm piston burette calibrated in divisions of 0.01 ml.

(e) Oxidation potential measurements

These were carried out in a cell similar to the titration cell, which had, in addition to the electrodes for pH measurements, a smooth platinum electrode for measuring the oxidation potential of the solution. The redox potential was measured with a Leeds & Northrup Volt Potentiometer. Model 8687. EMF readings were taken to the nearest 10 μ V.

The solution consisting of the ligand, iron(II) and iron(III) perchlorates, and sufficient sodium perchlorate to make the solution 0.1 M with respect to that salt was adjusted to a pH of 4–5. The solution was about 0.0005 M with respect to both iron(II) and iron(III) and 0.01 M with respect to the ligand. Nitrogen was bubbled into the solution for about half an hour before commencing the titration, which was carried out against dilute perchloric acid, both redox potential and pH being recorded after each addition of acid.

RESULTS

(i) Acid association constants

The association constants of 4-methyl lutidinate, 5-methyl isocinchomeronate and 2-methyl dipicolinate were determined by pH-titration of the ester against standard sodium hydroxide solution. Two sets of titrations were carried out for each ester, one with the acid alone, and the other in the presence of excess perchloric acid, which ensured that points with sufficiently high values of \bar{p} (\bar{p} is the average no. of protons per ligand) required for the calculation of the highest association constant, were obtained.

The value of \bar{p} is determined from an expression of the form

$$\bar{p} = \frac{\sum_{i=1}^{n} i[H_i L]}{\sum_{i=1}^{n} [H_i L]}$$

where *n* is the maximum no. of protons bound by the ligand. When the values of pH and \bar{p}_{expt} are plotted on the same graph, points from both sets of titrations fall on the same curve.

Representative values from the pH, \bar{p}_{expt} curve were then fed into a Silliac digital computer and the curve of best fit determined.

For a system where only mononuclear species are formed, the functional relationship between \bar{p} and [X] is of the form

$$Y = \frac{P_1 X + 2P_2 X^2 + \dots - nP_n X^n}{1 + P_1 X + \dots - P_n X^n}.$$
 (1)

Hence, a computer programme for evaluating P_1 , $P_2 - - - P_n$ from a series of values for (pX, Y) will evaluate acid association constants, if its data represents (pH, \bar{p}) .

The values of acid dissociation constants for 4-methyl lutidinate, 5-methyl isocinchomeronate, 2-methyl dipicolinate, and for comparison, lutidinic, isocinchomeronic and quinolinic acids calculated by the above method are shown in Table 1.

(ii) Stability constants of iron(II) and iron(III) complexes of some pyridine carboxylic acids at $25^{\circ}C$

Iron(II) complexes of 4-methyl lutidinate and 5-methyl isocinchomeronate are intensely coloured and the pH titration technique could not be used for the determination of their stability constants. Instead, these were determined by a study of the variation of their visible spectra with pH. The visible spectra of a

	$\operatorname{Log} \bar{A_1}$	$\log \bar{A_2}$	$Log \bar{A_3}$
4-Methyl lutidinate	3.71		
5-Methyl isocinchomeronate	3.62		
2-Methyl dipicolinate	2.65		
Lutidinic acid	1.60	3.85	8.81
Isocinchomeronic acid	1.5	3.85	8.81
Quinolinic acid	1.3	3.86	8.86

 Table 1. Overall acid association constants of some pyridine carboxylic acids and derivatives

series of solutions of iron(II) perchlorates in the presence of excess ligand were obtained at various pH values above the first proton association constant of the ligand. This permits the absorption peak of the highest complex to be determined.

For each ligand, the molar extinction coefficient (e_M) was plotted against the corresponding pH value. e_M increased to a constant value at high pH. Representative values from the (pH, e_M) curve were then fed into the computer and the curve of best fit computed.

As indicated above when discussing association constants, for a system where only mononuclear species are formed, the function relationship \bar{p} and [X] can be shown to be identical with that between \bar{n} and [L] and of the form indicated in Equation (1). Thus, a computer programme for evaluating $P_1, P_2 - - - P_n$ from a table of values of (pX, Y) will evaluate stability constants, if the data represents (pL, \bar{n}) . The stability constants obtained by this method are shown in Table 2.

	$\log K_1$	Log K ₂	Log K ₃
4-Methyl lutidinate	3.73	6.51	
5-Methyl isocinchomeronate	3.82	6.08	
Lutidinic acid	4.84	8 ·10	
Isocinchomeronic acid	5.91	9.32	10.60

 Table 2. Stability constants of iron(II) complexes of 4-methyl lutdinate and 5-methyl isocinchomeronate

The stability constants of the iron(III) complexes of 4-methyl lutidinate and isocinchomeronic acid were determined from oxidation potentials by the method of curve fitting using the computer. The stability constant of 5-methyl isocinchomeronate could not be obtained because of hydrolysis of the ester group of the ligand. The values obtained are shown in Table 3.

Pyridine dicarboxylic acids function as tribasic acids, while the monomethyl esters function as dibasic acids. Hence the second acidity constant of the acid may be compared with the first acidity constant of its monomethyl ester. On this basis, it would appear that the replacement of the proton of the distal carbonyl group by a methyl group has little or no effect on the dissociation constants. On the other hand, its effect on the stability constants of the iron(II) complexes is

$\log K_1$	$\log K_2$	$\log K_3$
6.11	11.11	23.00
7.77	13.17	23.28
	Log K ₁ 6·11 7·77	$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$

 Table 3. Stability constants of iron(III) complexes of 4-methyl lutidinate isocinchomeronic acid

more marked, reducing their stability considerably, especially in the case of isocinchomeronic acid.

A possible explanation of this is that, in the 5-methyl isocinchomeronate for example, the carboxyl group of the ester is *para* to the coordinating carboxyl group with the result that the inductive effect would tend to withdraw electrons from the coordinating carboxyl group, thereby reducing the stability of the iron(II) complex.