

## N-Quaternary Compounds

### Part XXV.<sup>1</sup> Ionization Constants of Pyridinium-3-oxides

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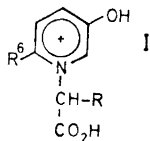
Substituent effects on the ionization constant of 3-hydroxypyridinium derivatives are discussed. The influence of an  $\alpha$ -pyridinium group on the acidity of carboxylic acids has also been investigated.

The ionization constants for hydroxypyridines and the methochloride of 3-hydroxypyridine have been discussed<sup>2,3</sup> but no data are available on substituent effects on the  $pK_a$  value of the hydroxy group in the pyridinium system. In our pyridinium analogues of  $\alpha$ -amino acids we have available suitable compounds for such studies.<sup>4-6</sup>

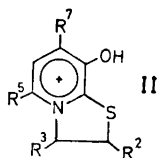
The ionization constants for the phenolic group were determined by the potentiometric method on a semimicro scale using a 0.01 M solution.<sup>2,7</sup> But the ionization constants for the carboxyl groups are less than the negative logarithm of the molar concentration and therefore only approximate values for this group were obtained. Solubility problems prevented increase in molar concentration for accurate determination by this method.

The  $pK_a$  values for the phenolic group in the simple pyridinium acids (Ia - Id) were found to be in the region 5.15 - 5.30 depending slightly on the substituents in the side-chain. The  $pK_a$  for 3-hydroxypyridine methochloride has the value 4.96<sup>2</sup> which is 0.2 - 0.3 units below the above values. The decreased acidity of the phenolic group in the above acid can be ascribed to an inductive effect from the negatively charged carboxylate group. The carboxyl group is by far the stronger acidic group in the molecule and will be fully ionized when the phenolic group is titrated. The inductive effect of the carboxylate group has to be transmitted through the  $\alpha$ -methine carbon before reaching the annular nitrogen of the pyridinium system. The thus partially reduced positive charge in the pyridinium system results in reduced acidity of the phenolic group. A similar decrease in acid strength of the phenolic OH-group is seen by comparing the bicyclic structures IIa and IIc. Thus the former has  $pK_a$  4.70 while the acid (IIc) has the value 4.97. It appears that the inductive effect of the carboxylate group can also be well transmitted through the thioether sulphur since both the 3-carboxyl (IIc) and the isomeric 2-carboxyl (IId) derivatives have the same  $pK_a$  value for the phenolic group.

Table 1. Ionization constants determined in water at 20°.



| I | R <sup>6</sup>  | R  | pK <sub>a2</sub> | pK <sub>a1</sub> |
|---|-----------------|--|------------------|------------------|
| a | H               | CH <sub>3</sub>                                  | 5.34 ± 0.03      | 1.7              |
| b | H               | CH(CH <sub>3</sub> ) <sub>2</sub>                | 5.25 ± 0.03      | 1.8              |
| c | H               | CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>    | 5.22 ± 0.03      | 1.6              |
| d | H               | CH <sub>2</sub> CH <sub>2</sub> SCH <sub>3</sub> | 5.13 ± 0.05      | 1.7              |
| e | CH <sub>3</sub> | CH <sub>3</sub>                                  | 5.77 ± 0.04      | 1.75             |



| II | R <sup>2</sup>    | R <sup>3</sup>    | R <sup>5</sup>  | R <sup>7</sup> | pK <sub>a2</sub> | pK <sub>a1</sub> |
|----|-------------------|-------------------|-----------------|----------------|------------------|------------------|
| a  | H                 | H                 | CH <sub>3</sub> | H              | 4.70 ± 0.02      | —                |
| b  | H                 | CO <sub>2</sub> H | H               | H              | 4.47 ± 0.02      | 1.2              |
| c  | H                 | CO <sub>2</sub> H | CH <sub>3</sub> | H              | 4.97 ± 0.02      | 1.5              |
| d  | CO <sub>2</sub> H | H                 | CH <sub>3</sub> | H              | 4.96 ± 0.02      | 2.0              |
| e  | H                 | CO <sub>2</sub> H | CH <sub>3</sub> | Br             | 2.85 ± 0.03      | 1                |

An *ortho* methyl group in a pyridinium system is chemically highly activated and therefore must be strongly polarized towards the electron deficient pyridinium system. This unusually strong polarization of the methyl group is reflected in a relatively strong effect of this group in the pyridinium system on the phenolic pK<sub>a</sub> value. Thus a comparison of the pairs Ia/Ie and IIb/IIc shows that the *ortho* methyl group increases the pK<sub>a</sub> values 0.4–0.5

units while the increase in the case of the pair phenol/*p*-cresol is only 0.26 units.<sup>8</sup>

Further comparisons between the pairs Ie/IIc and Ia/IIb show that formation of a bicyclic structure through the thioether sulphur has increased the acidic strength by 0.8–0.9 units. About 0.5 increase in phenol acidity has been reported for *meta* and *para* methylthio analogues but no data for the *ortho* isomer were given.<sup>9</sup>

A bromine in *ortho* position to the hydroxyl group (IIe) increases the acidity to a  $pK_a$  value of 2.85 which is 2.1 units lower than in the parent compound (IIc). This should be compared with a 1.6 unit decrease in  $pK_a$  value on going from phenol to *o*-bromophenol.<sup>10</sup>

The pyridinium acids (I) correspond to  $\alpha$ -amino acids where the amino nitrogen is quaternary and exerts a negative inductive effect on the carboxyl group as in *N*-trialkyl glycyl betaines. But the quaternary nitrogen in this case is also part of an aromatic system and the effect of the  $\pi$ -electron system in the pyridine ring is to further increase the inductive effect as reflected in the  $pK_a$  values which lie in the region 1.6–1.8. For comparison the  $pK_a$  value for *N,N,N*-trimethyl glycine has been determined to 1.84<sup>11</sup> while the values for *N,N*-dimethylpiperidinium and *N*-methylquinuclidinium-2-carboxylic acids were also about 1.8.<sup>12</sup>

The effect of forming the bicyclic structure is another drop in the  $pK_a$  to 1.2–1.5 (IIb and IIc).

In I the ionization constants vary slightly in the expected way with the substituents in the side-chain. A pyridyl *ortho* methyl group appears to affect the acidity more in the bicyclic (IIb/IIc) than in the monocyclic (Ia/Ie) system. That a thioaryl sulphur in  $\alpha$ -position, such as in the 2-carboxy isomer (IIId), activates the carboxyl group less ( $pK_a$  2.0) than a quaternary nitrogen is as expected. The strongest acid of all was the 7-bromo derivative (IIe) where the ionization constant for the carboxyl group was close to 1 which corresponds to a fall of 0.5 units. For comparison the bromine in *p*-bromobenzoic acid reduces the  $pK_a$  value of benzoic acid with 0.2 units to 3.97.<sup>13</sup> Despite the lack of conjugation of the carboxyl group with the aromatic system above, the fall in  $pK_a$  is as much as 0.5 units. Therefore the electron deficient pyridinium system must feel the effect of electron attracting substituents more strongly than is normally observed in benzene.

## EXPERIMENTAL

The compounds used in this work were available from other studies.<sup>4–6</sup>

The potentiometric titrations were carried out<sup>2</sup> at 20° using a Beckman model 3H pH-meter with glass and calomel electrodes (standardized to pH 4.00 with 0.05 M potassium hydrogen phthalate and 9.20 with 0.05 M borax). N<sub>2</sub> was used for stirring and maintenance of an inert atmosphere above the solution in deionized water.

19 ml of a 0.01 M solution with respect to the half neutralization point (20 ml) of each dried specimen was first titrated with 0.1 N NaOH (carbonate free). The alkali used (2 ml) in each titration was added in ten equal portions using a micrometer syringe and the pH recorded after each addition. The  $pK_a$  value was then calculated from nine equidistant points on the titration curve:

$$pK_a = \text{pH} + \log \left( \frac{[\text{AH}]}{[\text{H}^+] + [\text{A}^-] + [\text{H}^+]} \right)$$

The solutions were then back-titrated with one equivalent of 1 N HCl (0.2 ml) and further titrated with 0.2 ml 1 N HCl in ten equal portions using a micrometer syringe. The  $pK_a$  values were derived as above from

$$pK_a = \text{pH} - \log \left( \frac{[\text{B}] + [\text{H}^+]}{[\text{BH}^+] - [\text{H}^+]} \right)$$

Before averaging, the nine  $pK_a$  values were converted into the antilogarithmic values.

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Received September 20, 1971.