THE ACTION OF DIAZOACETIC ESTER ON PYRIDONE-2.

A new synthesis of 2-pyridoxyacetic acid

BY

J. MAAS, G. B. R. DE GRAAFF, and H. J. DEN HERTOG
(Laboratory of Organic Chemistry of the Agricultural University, Wageningen).

Ethyl 2-pyridoxyacetate is obtained as chief product, together with a small amount of N-(2-pyridonyl) acetic ester, by reacting pyridone-2 with ethyl diazoacetate.

Some time ago Kharasch, Rudy, Nudenberg, and Büchi have shown that cyclohexanone (I) was converted readily into cyclohexene-1-oxyacetic ester (II) by reacting the ketone with ethyl diazoacetate 1).

\[ \text{I} \xrightarrow{\text{H}_2\text{NC-CO}_2\text{CH}_3} \text{II} \]

In this connection we have reacted pyridone-2 (III) with diazoacetic ester. It is known that III exists predominantly in the pyridone structure, and so we were interested to find whether the analogous reaction (2) would proceed.

\[ \text{III} \xrightarrow{\text{H}_2\text{NC-CO}_2\text{CH}_3} \text{IV} \]

Thus far pyridoxyacetic acid (V) has not been synthesized from III as a starting substance. Kirpal reacted III with chloroacetic acid, and boiled the addition product with a concentrated aqueous solution.

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of sodium hydroxide. He only isolated N-(2-pyridonyl)acetic acid (VI) from the reaction mixture.\(^2\)

![Chemical structures](image)

We expected the formation of the ester of VI and V to proceed simultaneously when III was treated with diazoacetic ester at an elevated temperature, since the carbethoxymethylene radical, which originates from the decomposition of the reagent, might add in its polar form (VII) to the lone pair of electrons of the nitrogen atom just as well as to those of the oxygen atom. As the ratio of the electron densities at the oxygen and nitrogen atoms of the molecule III reacting according to equation (2) is larger than that of the anion reacting according to (3), it seemed probable that the formation of the O-derivative would not be surpassed by that of the N-compound. When we dropped ethyl diazoacetate slowly into an excess of pyridone-2 (III) which was heated to 140°, it appeared that 2-pyridoxy-acetic ester (IV) was formed, even in a yield of about 60%, the isomer N-(2-pyridonyl)acetic ester (VIII) in a yield of 8—9%\(^3\).

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\(^3\) The yields are calculated on the amount of pyridone consumed.
Absorption spectra of $10^{-4}$ molar solutions in 50% aqueous ethanol.

1 = 2-Pyridoxacetamide (X)
2 = N-(2-Pyridonyl)acetamide (IX)
3 = 2-Methoxypyridine
4 = N-Methylpyridone-2
The ethyl ester of N-(2-pyridonyl)acetic acid (VIII) has not been mentioned before in the literature. It was converted for identification into the amide IX. This amide did not lower the melting point of a specimen prepared according to Kirpal\(^2\). Ethyl 2-pyridoxyacetate (IV) has been recorded only once, as far as we know. It was synthesized by Hill and McGraw from 2-bromopyridine by reacting this compound with the sodium alkoxide of ethyl glycolate\(^4\). When we repeated the experiment of Hill and McGraw, we obtained an oil of the same refractive index as was shown by the product which resulted from the action of diazoacetic acid ester on III. We converted both specimens of IV into the corresponding acids (V) and amides (X), and showed by mixed melting point determination that they were identical. As Hill and McGraw gave no further proof for the structure of IV besides its synthesis, we measured the ultraviolet absorption spectra of the corresponding acid (V) and amide (X), and also that of the isomeric amide IX. The result confirmed IV to be the O-derivative, the spectra of V and X corresponding very well with that of 2-methoxypyridine (see the diagram), while the curve of IX coincided with that of N-methylpyridone-2\(^5\).

The investigation is being continued.

**Experimental part\(^6\).**

a. *Action of ethyl diazoacetate on pyridone-2 (III).*

12 g of III (0.125 mole) were heated up to 140° in a flask placed in an oil bath. While the liquid was kept at this temperature, 3 g of ethyl diazoacetate (0.025 mole) were added in 2 h with vigorous stirring. After the reaction mixture had been heated for 1½ h to 160°, it was cooled down, and dissolved in benzene. By gradually evaporating the solvent, several portions of crystalline matter consisting of unchanged III (8.85 g = 74%) were precipitated. The residue, an oily liquid, was distilled *in vacuo*. The following fractions were collected:

- fraction 1 (3.5 g of a viscous colourless liquid), boiling range 96—97° at 4 mm mercury pressure, \(N^\text{D}_{20} = 1.4970\):
- fraction 2 (0.5 g of a pale-yellow thick liquid), boiling range 142—147° at 4 mm mercury pressure; a residue (0.25 g of a tarry mass).

Fraction 1 appeared to be practically pure ethyl 2-pyridoxyacetate (IV); it was analysed without further purification.

\(^5\) See also the table in the Experimental part.
\(^6\) The melting points are corrected.
Ethyl 2-pyridoxyacetate (IV).

**Analysis**:  
Found: C 59.57; H 5.96; N 7.94.  
Calc. for $C_9H_{11}NO_3$: C 59.66; H 6.12; N 7.73.

Hill and McGraw recorded the distillation temperature of IV as 83—84° (0.5 mm mercury pressure), $n^D_0 = 1.4970$. The conversion of our preparation of IV into 2-pyridoxyacetic acid (V) and 2-pyridoxyacetamide (X) is described in sections b and c.

Fraction 2 contained N-(2-pyridonyl)acetic ester (VIII), as is shown in section e. The residue has not been investigated any further.

Yield of IV, calculated on the amount of III consumed: 55—60%; yield of VIII: 8—9%.

b. 2-Pyridoxyacetic ester (IV) → 2-Pyridoxyacetic acid (V).

1.10 g of IV (= fraction 1, mentioned in section a) were saponified by boiling with 1.00 ml of a 5.915 N aqueous sodium hydroxide solution and 1 ml of ethanol for 5 h. The reaction mixture was neutralized with 0.93 ml of a 0.114 N aqueous solution of sulphuric acid. Equivalent weight of IV: 189 (calc. for $C_9H_{11}NO_3$: 181).

After distilling off the greater part of the solvent, the residue was continuously extracted with ether. From the ethereal solution 0.83 g of crude V was obtained.  
Yield: 85—90%.

2-Pyridoxyacetic acid (V), m.p. 111.5—112.5°, colourless crystalline needles (from benzene).

**Analysis**:  
Found: C 55.07%; H 4.59%; N 9.19%.  
Calc. for $C_7H_8NO_2$: C 54.90; H 4.61; N 9.15.

c. 2-Pyridoxyacetic ester (IV) → 2-pyridoxyacetamide (X).

0.56 g of IV was shaken with 20 ml of concentrated aqueous ammonia for 3 days at room temperature. After evaporating the liquid to dryness in vacuo, 0.385 g of colourless crystals (X) remained as a residue. Yield: 80—85%.

2-Pyridoxyacetamide (X), m.p. 63—64°, colourless crystals (from a mixture of diethyl ether and petroleum ether).

**Analysis**:  
Found: C 55.54; H 5.63.  
Calc. for $C_9H_{16}N_2O_2$: C 55.25; H 5.30.

d. Preparation of ethyl 2-pyridoxyacetate (IV) from 2-bromopyridine and the sodium alkoxide of ethyl glycolate.

IV was prepared by reacting the compounds mentioned above according to Hill and McGraw. We obtained IV as an oil, distilling at 96—97° at 6 mm mercury pressure: $n^D_0 = 1.4990$. The yield amounted to 15—20% (Hill and McGraw recorded a yield of 26%). For identification, this preparation of IV was transformed into 2-pyridoxyacetic acid (V) and 2-pyridoxyacetamide (X), which compounds did not lower the melting point of specimens obtained as described in sections b and c.

7) This analysis was carried out by Messrs. P. J. Hubers and H. Pieters, Microchemical Department of the Laboratory for Organic Chemistry of the Municipal University of Amsterdam.

8) Microanalysis by Mr. W. P. Combé of this laboratory.
e. N-(2-Pyridonyl)acetic ethyl ester (VIII) → N-(2-pyridonyl)acetamide (IX).

0.4 g of crude VIII (= fraction 2, mentioned in section a) was converted into IX analogously to the procedure described in section c. 0.28 g of IX (melting at 233—234°) was obtained.

Analysis *):

Found: C 55.65; H 5.19.
Calc. for C₇H₈N₂O₂: C 55.25; H 5.30.

Mixed melting point with a preparation of IX, synthesized according to Kirpal *), (m.p. 233—234°): no depression. Yield: 80—85%.

f. Ultraviolet absorption spectra.

Absorption spectra of 10⁻⁴ molar solutions in 50% aqueous ethanol of the compounds recorded in the table were measured in a Unicam Quartz SP 500 Spectrophotometer.

<table>
<thead>
<tr>
<th>Ultraviolet Absorption Spectrum</th>
<th>Maxima</th>
<th>Minima</th>
</tr>
</thead>
<tbody>
<tr>
<td>wavelength (m/λ)</td>
<td>log ε</td>
<td>wavelength (m/λ)</td>
</tr>
<tr>
<td>2-Pyridoxyacetic acid (V)</td>
<td>212</td>
<td>3.94</td>
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<tr>
<td></td>
<td>270</td>
<td>3.67</td>
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<tr>
<td>2-Pyridoxyacetamide (X)</td>
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<td>3.82</td>
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<td></td>
<td>269</td>
<td>3.58</td>
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<tr>
<td>2-Methoxypyridine</td>
<td>214</td>
<td>3.82</td>
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<td></td>
<td>271</td>
<td>3.60</td>
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<tr>
<td>N-(2-Pyridonyl)acetamide (IX)</td>
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<td>301</td>
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<tr>
<td>N-Methylpyridone-2</td>
<td>226</td>
<td>3.94</td>
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<tr>
<td></td>
<td>300</td>
<td>3.74</td>
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</tbody>
</table>

We are indebted to Mr. D. J. Buurman for his assistance in measuring the spectra.

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