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Synthesis of 4-Pyridoxyacetic Acid *via* a Pyridine N-Oxide Derivative*

HERMEN. J. DEN HERTOG and JULES. MAAS

Laboratory of Organic Chemistry, Agricultural University[1]

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4-Pyridoxyacetic acid, a substance to be used in a study on plant growth substances, cannot be obtained by reacting 4-hydroxypyridine with chloroacetic acid or ethyl diazoacetate, only the N-(4-pyridonyl)acetate or its ester being formed. The desired compound was synthesized from 4-hydroxypyridine 1-oxide by converting the N-oxide with chloroacetic acid into N-(4-pyridonyl)oxyacetic acid and by heating this acid with a solution of ethyl diazoacetate in petroleum ether. Discussion is made on the mechanism of this process by other routes used for its preparation.

Introduction

Thankful to be invited to contribute to this Memorial Issue, the mind of the first author goes to Professor Ochiai as he met him in 1955 during the IUPAC Congress at Zürich in Switzerland. In his memory he sees Prof. Ochiai going round, talking amiably with colleagues and collecting in the segments of a fan he brought with him, the signatures especially of those who were active in the chemistry of aromatic amine oxides the field developed to such an extent by Ochiai and his school. In a conversation between the two of us on the discovery of pyridine N-oxide as a highly suitable substrate in reactions with electrophilic reagents, we agreed that N-oxides are in many respects important compounds from a theoretical as well as from a preparative point of view. Since then this conclusion was affirmed in an avalanche of communications on investigations from all over the world. As another proof we describe in this paper a curious synthesis carried out in our laboratory in the scope of a study on plant-growth substances starting from a derivative of pyridine N-oxide.

Results and Discussion

During the investigation just mentioned we tried to prepare 4-pyridoxyacetic acid from 4-pyridone. It was known that 4-pyridone like 2-pyridone changes when treated with chloroacetic acid only into the N-pyridonylacetic acid.[2,3] Now that 2-pyridone was found to be converted by ethyl diazoacetate into the ethyl 2-pyridoxyacetate as a chief product, together with a small amount of ethyl N-(2-pyridonyl)acetate,[4] we heated 4-pyridone with the same reagent, but here the ester of N-(4-pyridonyl)acetic acid was isolated as the sole product again.

Only in derivatives of 4-pyridone containing bulky groups at positions 2 and 6, ethyl diazoacetate was found to attack the oxygen atom. Thus, we obtained from 2,6-di-*tert*-butyl-4-pyridone exclusively the ethyl 2,6-di-*tert*-butyl-4-pyridoxyacetate.

Then, inspired by previous experience,[5] we decided to use the N-oxide of 4-pyridone (**1b**) as a starting substance. We succeeded in realizing the following reaction sequence.

4-Hydroxypyridine 1-oxide (**1**) was heated with chloroacetic acid in an aqueous solution of sodium hydroxide (molar ratio=1: 1.5: 2.5). By acidifying the reaction mixture, N-(4-

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* Dedicated to the Memory of Prof. Eiji Ochiai.

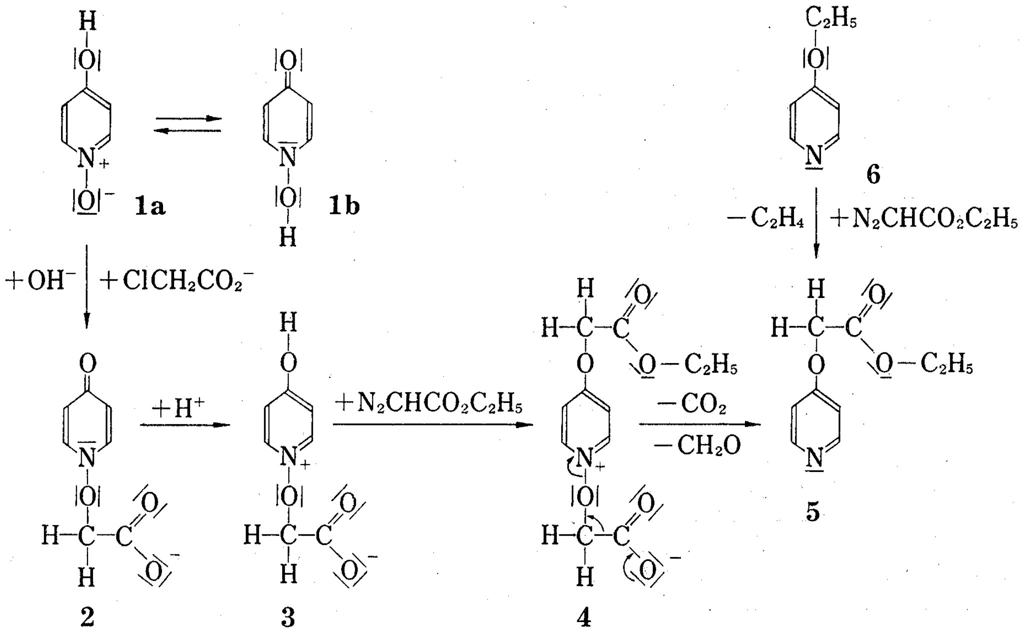
[1] Location: *Wageningen, The Netherlands.*

[2] H.N. Bojarska-Dahlig, *Rocz. Chem.*, **29**, 119 (1955).

[3] A. Kirpal, *Ber.*, **57**, 1954 (1924).

[4] J. Mass, G.B.R. de Graaff, and H.J. den Hertog, *Rec. Trav. Chim. Pays-Bas*, **74**, 175 (1955).

[5] *Cf.* H.N. Bojarska-Dahlig and H.J. den Hertog, *Rec. Trav. Chim. Pays-Bas*, **77**, 331 (1958).



pyridonyl)oxyacetic acid separated out, a tautomeric structure of which, N-(4-hydroxypyridyl)oxyacetate, is given in Chart 1 (**3**). This acid and also the anion (**2**) seem to be stabilized thoroughly by mesomerism.

By boiling an aqueous solution of sodium N-(4-pyridonyl)oxyacetate with an excess of sodium chloroacetate (molar ratio=1: 1.5), the anion (**2**) remains unchanged. The acid (**3**) (N-(4-hydroxypyridyl)oxyacetate) reacts further, however, when heated with ethyl diazoacetate in petroleum ether (bp 185—190°) as a solvent. In the second step of the synthesis this reagent attacks the hydroxy group at the 4-position. The product formed (**4**) is less stable than the acid (**3**); it could not be isolated, apparently losing carbon dioxide and methanal immediately, and yielding ethyl 4-pyridoxyacetate (**5**).

5 was shown to be identical with the ester formed (together with ethene) when reacting 4-ethoxypyridine (**6**) with ethyl diazoacetate and also with the reduction product of one of the ethyl bromopyridoxyacetates obtained by heating 2,4-dibromopyridine with the sodium compound of ethyl hydroxyacetate.

Thus, here again we see that N-oxides are substances with fascinating properties. By treating the N-oxide of 4-pyridone subsequently with the two reagents which convert 4-pyridone into N-(4-pyridonyl) compounds only, the 4-pyridoxy derivative is produced, the first reagent blocking the N-oxide group and the second one thus being directed to attack the hydroxyl group at the 4-position, removing all atoms bound to the nuclear nitrogen atom at the same time.

Experimental

Satisfactory C, H, and N. analyses of all substances isolated were obtained.

Action of Ethyl Diazoacetate on 4-Pyridone——4-Pyridone (16 g) was heated to 145—150° in a dry nitrogen atmosphere, after which 3.5 g of ethyl diazoacetate was dropped into the liquid in 1.25 hr. By extraction of the reaction mixture successively with toluene and EtOH ethyl N-(4-pyridonyl)acetate (1.9 g, mp 130—133°) and unchanged 4-pyridone (13 g) were isolated. The residue consisted of N-(4-pyridonyl)-acetic acid (1.75 g, mp 261—264°) which was formed by saponification when working up the reaction mixture. No depression of the melting points in the products when mixed with authentic specimens.

Action of Ethyl Diazoacetate on 2,6-Di-*tert*-butyl-4-pyridone——The substrate (0.35 g) was treated at 170° with 0.385 g of the reagent in 0.5 hr. By extracting the reaction mixture with petr. ether (bp 40—60°) ethyl 2,6-di-*tert*-butyl-4-pyridoxyacetate was isolated, as an oil which was converted for identification into 2,6-di-*tert*-butyl-4-pyridoxyacetamide (0.125 g, mp 124—126°). The ultraviolet absorption spectrum of the latter compound corresponded with that of 2,6-di-*tert*-butyl-4-ethoxypyridine. An amount of 0.22 g of the substrate was recovered.

Preparation of N-(4-Hydroxypyridyl)oxyacetate (**3**)——4-Hydroxypyridine 1-oxide (**1a**) was synthesized from 4-nitropyridine 1-oxide according to Ochiai *et al.*,[6] and converted into **3** as described by Bojarska Dahlig and den Hertog.[5] **3**, mp 164—165°.

Action of Ethyl Diazoacetate on N-(4-Hydroxypyridyl)oxyacetate (**3**)——A mixture of 4.9 g of ethyl diazoacetate and 9.7 g of petroleume ether (bp 185—190°) was dropped into a solution of 7.3 g of **3** in 23 g of solvent at 140° in 1.25 hr with stirring. During this experiment, 990 ml of N_2 (95% of the theoretical volume) was collected and 1.4 g of CO_2 (75%) in a tube with soda lime. From the reaction mixture by distillation *in vacuo* of the petroleum ether white spirit solution and the benzene extract of the residue, ethyl 4-pyridoxyacetate (**5**) was isolated which for identification was converted with $Ba(OH)_2$ into 4-pyridoxyacetic acid (mp 218—220°) and with NH_4OH into 4-pyridoxyacetamide (mp 145—148°). Yield, —20%. Methanal was found to be formed by preparing its dimedone derivative.

Action of Ethyl Diazoacetate on 4-Ethoxypyridine (**6**)——Into 15 g of **6** heated at 140—145°, a mixture of 9.9 g of ethyl acetate and 5.5 g of **6** was dropped during 1.5 hr, after which the mixture was allowed to react for another 3 hr. By passing the gaseous products formed through bromine, ethene was detected. From the reaction mixture, ethyl 4-pyridoxyacetate (**5**) was isolated by distillation *in vacuo* and converted for identification into the acidamide (mp 145—148°).

Reaction of 2,4-Dibromopyridine (**7**) **with the Sodium Compound of Ethyl Hydroxyacetate** (**8**)——By reacting 70.5 g of **7** with **8** (obtained from 7 g of Na and 31 g of the ethyl ester of glycolic acid), 55 g of an oil was obtained from which by distillation *in vacuo*, ethyl 4-bromo-2-pyridoxyacetate (mp 17—18°, n_D^{20} 1.5342) and ethyl 2-bromo-4-pyridoxyacetate (**10**, an oil, boiling range 128—135°/0.6 Torr) were isolated. These compounds were saponified to the corresponding acids of mp 130—131° and 206—207°, respectively. By shaking the solution of **9** and **10** in EtOH, to which some NaOH was added, in the presence of charcoal with hydrogen, 2-pyridoxyacetic acid (mp 112—113°) and 4-pyridoxyacetic acid were obtained. The latter compound was transformed *via* the methyl ester (by treating it with CH_2N_2 in ether) into 4-pyridoxyacetamide (mp 145—147°).

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[6] *Cf.* E. Ochiai, *J. Org. Chem.*, **18**, 534 (1953).