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## Abstract

## Full Text

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# REACTION OF 5-ALKOXYOXAZOLES WITH MALEIC ANHYDRIDE

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It has recently been established that alkyloxazoles are capable of entering into a diene-synthesis reaction with maleic anhydride through the conjugated system C=C−C=N, forming pyridine-3,4-dicarboxylic acids (I). Further study of this reaction, which is at the same time a convenient method for obtaining pyridine compounds, can undoubtedly broaden the limits of application of diene synthesis. The present work describes the diene condensation of maleic anhydride and 5-alkoxyoxazoles with various substituents in positions 2 and 4.

The reaction was carried out under the usual conditions of diene synthesis—heating a benzene solution of the oxazole with an excess (2–4 mol) of maleic anhydride in the presence of hydroquinone or pyrogallol. After boiling the reaction mixture with water and evaporating the solvent, crystalline reaction products separate out; they give the red or blue-violet coloration with ferric chloride characteristic of phenols and $\beta$-hydroxypyridines and have the structure of 5-hydroxypyridine-3,4-dicarboxylic acids.

$$\text{(I)} + \text{maleic anhydride} \longrightarrow [\text{(II)}] \longrightarrow [\text{(III)}] \longrightarrow \text{(IV)}$$

The condensation leads directly to the oxy acids IV; in no case, despite the use of the mildest reaction conditions and the isolation of adducts, was it possible to obtain the intermediate compounds II or III. The results of the work are given in Table 1.

**Table 1**

**Condensation of 5-alkoxyoxazoles with maleic anhydride**

| I–IV | R | R′ | R″ | Yield of IV (%) | I–IV | R | R′ | R″ | Yield of IV (%) |
|---|---|---|---|---|---|---|---|---|---|
| a | $CH_3$ | H | $C_2H_5$ | 54 | zh | $C_6H_5CH$=CH | H | $C_2H_5$ | 0 |
| b | $C_2H_5$ | H | $C_2H_5$ | 47 | z | $CH_3$ | $CH_3$ | $CH_3$ | 36 |
| v | *n*-$C_3H_7$ | H | $C_2H_5$ | 31.5 | i | $C_2H_5$ | $CH_3$ | $CH_3$ | 25 |

Fig. 1. UV absorption spectra of hydroxy acids: 1 –IVa; 2 –IVd; 3 –IVz; 4 –IVk. Solid line–spectrum in 0.1 N HCl; dotted line–spectrum in 0.1 N NaOH.

Figure 1: Fig. 1. UV absorption spectra of hydroxy acids: 1 –IVa; 2 –IVd; 3 –IVz; 4 –IVk. Solid line–spectrum in 0.1 N HCl; dotted line–spectrum in 0.1 N NaOH.

| I-IV | R | R′ | R″ | Yield of IV (%) | I-IV | R | R′ | R″ | Yield of IV (%) |
|---|---|---|---|---|---|---|---|---|---|
| g | *n*-$C_4H_9$ | H | $C_2H_5$ | 42.3 | k | *n*-$C_5H_{11}$ | $CH_3$ | $C_2H_5$ | 15.8 |
| d | *n*-$C_5H_{11}$ | H | $C_2H_5$ | 40 | l | $CH_3$ | $C_2H_5$ | $C_2H_5$ | Resinification |
| e | $C_6H_5$ | H | $C_2H_5$ | 0 | | | | | |

The ultraviolet spectra of the oxy acids IVa, d, z, k, recorded in alkaline solution, are characterized by a well-defined maximum at 312-315 m$\mu$. With the exception of IVk, in acid solution the maximum shifts toward shorter wavelengths (Fig. 1).

To confirm the structure of the products, one of them–2-methyl-5-hydroxypyridine-3,4-dicarboxylic acid (IVa)–was obtained by an independent synthesis from 6-methyl-5-carbethoxypyridine-3,4-dicarboxamide (V), by Hofmann degradation followed by diazotization of the amino derivative (VI):

$$(V) \xrightarrow{KOCl} (VI) \xrightarrow{HNO_2} (IVa)$$

The directed cleavage of the cyclic imide ring is caused in this case by the presence of the pyridine nitrogen atom and the carbethoxy group in position 5, which leads to weakening of the 4-amide bond ([2]).

**Fig. 1.** UV absorption spectra of hydroxy acids:
**1** –IVa; **2** –IVd; **3** –IVz; **4** –IVk. Solid line–spectrum in 0.1 *N* HCl; dotted line–spectrum in 0.1 *N* NaOH.

As is seen from the data of Table 1, lengthening of the carbon chain in position 2 of the oxazole lowers the activity of the heterodiene system. On going from $R = CH_3$ to $R = n\text{-}C_5H_{11}$ (Ia–Id), the yields of pyridine hydroxy acids gradually fall from 54 (IVa) to 40% (IVd), and the same influence of the size of substituent $R$ is observed in the series of 2,4-dimethyl-5-alkoxyoxazoles: in the condensation of Ik ($R = n\text{-}H_5H_{11}$), no more than 16% of hydroxy acid IVk was isolated,

whereas the yields of the hydroxy acids IV and IV from the lower homologs I ($R = C_2H_5$) and I ($R = CH_3$) are, respectively, 25 and 36%.

Changing the substituent in position 4 also has a definite effect on the reactivity of alkoxyoxazoles. Comparison of the results of the condensation of I – I with I –I makes it possible to consider that the 4-methyl group appreciably deactivates alkoxyoxazoles in the reaction with maleic anhydride. 2-Alkyl-4-methyl-5-alkoxyoxazoles (I –I ) give adducts in yields approximately 20% lower than the corresponding 2-alkyl-5-alkoxyoxazoles (I –I ), and 2-methyl-4-ethyl-5-ethoxyoxazole (I ) does not react at all with maleic anhydride.

In contrast to 2-alkyl-5-alkoxyoxazoles, 2-phenyl-5-ethoxyoxazole (I ) and its vinylog, 2-styryl-5-ethoxyoxazole (I ), do not enter into condensation with maleic anhydride in benzene or xylene. After prolonged heating of the components, only products of cleavage of the oxazole ring could be isolated—hippuric acid in the case of I , and the ethyl ester of N-cinnamoylglycine in the case of I .

The 5-oxypyridine-3,4-dicarboxylic acids formed in the diene condensation of alkoxyoxazoles represent a class of very difficultly accessible, but very important, compounds that can be used for the synthetic preparation of vitamin $B_6$ and its analogs. For the synthesis of compounds IV, of which only 5-oxypyridine-3,4-dicarboxylic acid [3] (IV, $R' = R'' = H$) and 6-methyl-5-oxypyridine-3,4-dicarboxylic acid [4–6] (IV, $R = H$, $R' = CH_3$) are currently known, a large number of complex variants have been developed, based mainly on the condensation of cyanoacetamide with dicarbonyl compounds according to Gantzsch [4–7] or on the oxidation of substituted isoquinolines [3,7]. The method proposed by us—condensation of 5-alkoxyoxazoles with maleic anhydride—is the best method for the synthesis of 5-oxypyridine-3,4-dicarboxylic acids, allowing the substituent groups to be varied within broad limits and at the same time being provided with readily accessible starting material.

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## Experimental Part

**2-Methyl-5-oxypyridine-3,4-dicarboxylic acid (IVa).** a) 2.35 g of 2-methyl-5-ethoxyoxazole, 7.3 g of maleic anhydride, and 0.2 g of hydroquinone in 20 ml of benzene are boiled for 8 h. After removal of the benzene with steam, the solution is filtered and evaporated on a water bath to a volume of about 10 ml. 2.25 g (54%) of IVa separates as white crystals, m.p. 239° (decomp.; from water). $\lambda_{max}$ 310 mμ, $\lg \varepsilon_{max}$ 3.70 (0.1 N HCl); $\lambda_{max}$ 315 mμ, $\lg \varepsilon_{max}$ 3.78 (0.1 N NaOH).

Found, %: C 49.23; 49.26; H 3.67; 3.60; N 7.37; 7.47
$C_8H_7NO_5$. Calculated, %: C 48.74; H 3.58; N 7.11

b) To 0.10 g of 2-methyl-5-aminopyridine-3,4-dicarboxylic acid (VI) in 6 ml of water acidified with 1 drop of HCl, a solution of 0.045 g of $NaNO_2$ in 2 ml of water is added. The mixture is heated at 70° until the evolution

of nitrogen ceases, treated with urea, and the solution is evaporated to a volume of 2 ml. The yield of IVa is 0.04 g (40%), m.p. 235.5–236.5°. A mixed sample with the hydroxy acid obtained from I melts at 235.5–236.5°.

**2-Methyl-5-aminopyridine-3,4-dicarboxylic acid (VI).** 1.1 g of 6-methyl-5-carbethoxypyridine-3,4-dicarboximide (V) is introduced over 30 min into 15 ml of a KOCl solution (from 0.39 g of chlorine and 1.7 g of KOH) at 0°. The solution is heated for 1 h on a water bath, the excess KOCl is decomposed with $NaHSO_3$, and then the mixture is acidified with hydrochloric acid to pH 2. After standing for a week in a refrigerator, 0.6 g (65%) of VI precipitates from the solution, m.p. 240–240.5° (from water).

Found, %: C 46.54; 46.74; H 4.36; 4.38
$C_8H_8N_2O_4 \cdot 0.5H_2O$. Calculated, %: C 46.83; H 4.42;

**2-Ethyl-5-oxypyridine-3,4-dicarboxylic acid** (IV ). A mixture of 4.1 g of 2-ethyl-5-ethoxyoxazole, 6.4 g of maleic anhydride, and ~0.05 g of pyrogallol was boiled for 4 h in 15 ml of benzene. Analogously to IVa, 2.9 g (47%) of IV was isolated with m.p. 238° (decomp.). After reprecipitation with hydrochloric acid from aqueous ammonia (to pH 2), m.p. 240–241° (decomp.).

Found, %: C 51.30; 51.07; H 4.48; 4.58
$C_9H_9NO_5$. Calculated, %: C 51.19; H 4.29

**2-*n*-Propyl-5-oxypyridine-3,4-dicarboxylic acid** (IV ). Analogously to IVa, from 2.2 g of 2-*n*-propyl-5-ethoxyoxazole and 4.2 g of maleic anhydride, 1.0 g (31.5%) of IV was obtained with m.p. 216–217° (decomp.).

Found, %: C 53.32; 53.03; H 5.20; 5.32
$C_{10}H_{11}NO_5$. Calculated, %: C 53.29; H 4.88

**2-*n*-Butyl-5-oxypyridine-3,4-dicarboxylic acid** (IV ). Analogously to IVa, from 4.0 g of 2-*n*-butyl-5-ethoxyoxazole and 6.0 g of maleic anhydride, 2.2 g of IV (42.3%) was obtained with m.p. 198–199°.

Found, %: N 5.91; 5.86
$C_{11}H_{13}NO_5$. Calculated, %: N 5.85

**2-*n*-Amyl-5-oxypyridine-3,4-dicarboxylic acid** (IV ). From 3.0 g of 2-*n*-amyl-5-ethoxyoxazole and 6.0 g of maleic anhydride, 1.65 g (40%) of IV was obtained with m.p. 173–174.5°. After recrystallization from water, m.p. 181–183°. $\lambda_{max}$ 315 m$\mu$, $\lg \varepsilon_{max}$ 3.73 (0.1 N HCl); $\lambda_{max}$ 312 m$\mu$, $\lg \varepsilon_{max}$ 3.76 (0.1 N NaOH).

Found, %: N 5.31; 5.40
$C_{12}H_{15}NO_5$. Calculated, %: N 5.53

**2,6-Dimethyl-5-oxypyridine-3,4-dicarboxylic acid** (IV ). From 2.6 g of 2,4-dimethyl-5-methoxyoxazole and 8.8 g of maleic anhydride, 1.5 g (36%) of

IV was obtained with m.p. 269–270° (decomp.). $\lambda_{max}$ 325 m$\mu$, lg $\varepsilon_{max}$ 3.81 (0.1 N HCl); $\lambda_{max}$ 315 m$\mu$, lg $\varepsilon_{max}$ 3.84 (0.1 N NaOH).

Found, %: C 51.00; 50.82; H 4.53; 4.43; N 6.63; 6.80
$C_9H_9NO_5$. Calculated, %: C 51.18; H 4.26; N 6.63

**2-Ethyl-6-methyl-5-oxypyridine-3,4-dicarboxylic acid** (IV ). From 3.0 g of 2-ethyl-4-methyl-5-methoxyoxazole and 6.0 g of maleic anhydride, 1.2 g (25%) of IV was obtained with m.p. 217–221° (decomp.). After reprecipitation from dilute ammonia, m.p. 233.5–234.5°.

Found, %: C 52.78; 52.73; H 4.75; 4.89
$C_{10}H_{11}NO_5$. Calculated, %: C 53.29; H 4.88

**2-*n*-Amyl-6-methyl-5-oxypyridine-3,4-dicarboxylic acid** (IV ). From 2.0 g of 2-*n*-amyl-4-methyl-5-ethoxyoxazole and 4.0 g of maleic anhydride, 0.4 g (15.8%) of IV was obtained with m.p. 213–214° (from water). $\lambda_{max}$ 324 m$\mu$, lg $\varepsilon_{max}$ 3.86 (0.1 N HCl); $\lambda_{max}$ 315 m$\mu$, lg $\varepsilon_{max}$ 3.83 (0.1 N NaOH).

Found, %: C 58.80; 58.70; H 6.67; 6.63
$C_{13}H_{17}NO_5$. Calculated, %: C 58.41; H 6.41

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*Note: Figure translations are in progress. See original paper for figures.*