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Abstract

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Reaction of Oxazoles with Acrylic Acid

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A large number of studies have been devoted to the condensation of unsymmetrical dienophiles with diene hydrocarbons. As a rule, the structural selectivity of such transformations is not high, and although certain empirical rules make it possible to determine the predominant orientation, it is strictly defined only in rare cases. Diene synthesis with the participation of heterodienes has been studied much less, but it is already possible to speak of a structural selectivity characteristic of it. As an example of such directed reactions one may cite the preparation of α-alkoxydihydropyrans from vinyl ethers and unsaturated aldehydes ([1,2]), 4-ethoxyquinolones-2 from aryl isocyanates ([3]), or the synthesis of quinazolines from N-arylacetamido chlorides and nitriles ([4]).

As the present investigation has shown, the interaction of oxazoles with acrylic acid is also subject to a strict spatial orientation. Of the two possible schemes of synthesis,

(scheme of formation of isomeric nicotinic acid adducts from an oxazole and acrylic acid)

only the right-hand one is realized, and the condensation always, irrespective of the nature of R, R′, and R″, leads to the formation of isonicotinic acid. Isomeric nicotinic acids are formed as impurities, in quantities that can be detected only by chromatographic analysis of the crude adducts. If it is assumed that, owing to the acidic character of CH_2=CHCOOH and possible ion formation, the electron cloud of the oxazole ring is displaced toward the nitrogen atom, then the formation of the para-adduct is in complete agreement with the principle of polarity concordance.

For the study of the reaction with acrylic acid, oxazoles with electron-donating (CH_3, OCH_3) and electron-accepting ($COCH_3$, $COOC_2H_5$) substituents in different positions of the ring were selected. Not all oxazoles entered into condensation; some gave only resin, but if the reaction proceeded normally, it was completed at 80° in 3-6 hr, and the crystalline adducts obtained melted only a few degrees lower than the pure samples. 2,4- and 2,5-dimethyloxazoles became resinified under the action of acrylic acid, despite the fact that in other diene condensations, even with maleic acid, they reacted normally ([5]). The activity of oxazole can be retained upon introduction of an electrophilic group, but it depends

strongly on particular structural features. Thus, 4-methyl-5-carbethoxyoxazole reacts successfully with acrylic acid, whereas 4-methyl-5-acetyloxazole and 2,5-dimethyl-4-carbethoxyoxazole do not give adducts with it. The presence of acceptor substituents in diene condensation of the usual type leads to a decrease in the selectivity of the reaction; since the carbethoxy group is a fairly effective directing group, in the condensation of 4-methyl-5-carbethoxyoxazole it was quite probable to expect the formation of a mixture of isomeric adducts —derivatives of 3,4-

and 3,5-pyridinedicarboxylic acids, but in fact here too it was possible to isolate only one of the adducts, the semielher of cinchomeronic acid. Such stability of orientation exceeds all established norms, and to explain it, apparently, references to the "polarity principle" are no longer sufficient.

Condensation with 5-alkoxyoxazoles is accompanied, as in the cases described earlier (6), by cleavage of the alkoxy group and leads to 3-hydroxyisonicotinic acids:

$$\text{5-alkoxyoxazole} + \text{CH}_2{=}\text{CHCOOH} \longrightarrow \text{3-hydroxyisonicotinic acid} + \text{R}''\text{OH}$$

The structure of the adducts obtained was determined chemically—by counter-synthesis or by conversion into compounds of known structure.

The structure of the adduct of 4,5-dimethyloxazole and acrylic acid (2,3-dimethylisonicotinic acid) was proved by the identity of the product of its oxidation with pyridine-2,3,4-tricarboxylic acid, obtained by counter-synthesis in the oxidation of quinine. 2,6-Dimethyl-5-hydroxyisonicotinic acid—the adduct of 2,4-dimethyl-5-methoxyoxazole—was identified by comparison with the diazotization product of 2,6-dimethyl-5-aminopyridine-4-carboxylic acid. The structure of the adduct of 4-methyl-5-carbethoxyoxazole—2-methyl-3-carbethoxyisonicotinic acid—was confirmed by converting it, under the action of NH_2NH_2, into the cyclic pyridopyridazinedione, which is possible only when the $COOH$ and $COOC_2H_5$ groups are in the ortho position. The adduct of 2,4,5-trimethyloxazole and acrylic acid was assigned the structure of 2,3,6-trimethyloxazole and acrylic acid, since depression of the melting point of a mixed sample of the adduct and authentic 2,3,6-trimethylnicotinic acid ruled out their identity. The structures of 2-phenyl-3-methylisonicotinic acid (the adduct of 4-phenyl-5-methyloxazole) and 2-methyl-3-hydroxyisonicotinic acid (the adduct of 4-methyl-5-ethoxyoxazole) were accepted by analogy and confirmed by a number of indirect criteria—the resistance of the CH_3 group of 2-phenyl-3-methylisonicotinic acid to oxidation by potassium permanganate, and the formation of hydantoin from 2-methyl-3-hydroxyisonicotinic acid and hydrazine.

Experimental Part

2,3-Dimethylisonicotinic acid. 2.6 g of 4,5-dimethyloxazole, 3.8 g of acrylic acid, and 0.01 g of hydroquinone are boiled in 5 ml of benzene for 0.5 h. The oil that separates is washed with a mixture of methanol and acetone to give 4.0 g (98%) of a white powder with m.p. 224–226°. After sublimation in vacuo, m.p. 228°.

Found, %: C 63.31; 63.47; H 6.42; 6.23
$C_8H_9NO_2$. Calculated, %: C 63.50; H 6.60

UV spectrum: λ_{max} 271 mμ, $\lg \varepsilon_{max}$3.75 (in 0.1 N HCl); λ_{max} 265 mμ, $\lg \varepsilon_{max}$3.64 (0.1 N NaOH).

Oxidation of 2,3-dimethylisonicotinic acid. To 1.5 g of 2,3-dimethylisonicotinic acid in 50 ml of water is added 6.25 g of $KMnO_4$ in 100 ml of water (100°, over 3 h); the mixture is heated on a water bath for 4 h, then evaporated to 20 ml, and oxalic acid is precipitated with a $BaCl_2$ solution. The filtrate is acidified with H_2SO_4 and evaporated to 10 ml. After dilution with acetone, a small amount of pyridine-2,3,4-tricarboxylic acid with m.p. 248–251° is obtained. A mixed sample with the product of quinine oxidation has m.p. 248–250°. Lit.: m.p. 244–245° (7).

2,3,6-Trimethylisonicotinic acid. 2.0 g of 2,4,5-trimethyloxazole and 4.0 g of acrylic acid are boiled in 5 ml of benzene with hydroquinone for 17.5 h. After washing the precipitate with a mixture of acetone and methanol, 1.4 g (46.7%) of a substance with mp 266–267° is obtained; mp of the analytical sample 270–271° (from aqueous acetone). The mp of a mixed sample with 2,3,6-trimethylnicotinic acid is 181–186°.

Found %:	C 63.58; 63.78; H 6.73; 6.92
$C_9H_{11}NO_2 \cdot 0.25H_2O$. Calculated %:	C 63.68; H 6.34

UV spectrum: λ_{max} 279 mμ; $\lg \varepsilon_{max}$ 3.89 (in 0.1 N HCl), λ_{max} 272 mμ; $\lg \varepsilon_{max}$ 3.63 (in 0.1 N NaOH).

2,6-Dimethyl-3-oxyisonicotinic acid. (a) 2.0 g of 2,4-dimethyl-5-methoxyoxazole and 2.0 g of acrylic acid are boiled in 5 ml of benzene with hydroquinone for 2 h. 1.4 g (60%) of a white powder with mp 290–291° is obtained.

(b) To a hot solution (70°) of 0.33 g of 2,6-dimethyl-3-aminoisonicotinic acid in 10 ml of water, acidified with conc. HCl to pH 2, 0.17 g of $NaNO_2$ is added. The solution is kept for 15 min at 70°, treated with urea, and after cooling neutralized with NH_4OH to pH 4. 0.23 g (85%) of 2,6-dimethyl-3-oxyisonicotinic acid with mp 281–282° precipitates. After crystallization from water, mp 298°. The melting point of a mixed sample with the product of the diene synthesis is 297–300°.

Found %:	C 57.95; 57.96; H 5.66; 5.59
$C_8H_9NO_3$. Calculated %:	C 57.48; H 5.43

UV spectrum: λ_{max} 325 mμ, $\lg \varepsilon_{max}$ 3.88 (in 0.1 N HCl); λ_{max} 242; 315 mμ, $\lg \varepsilon_{max}$ 3.86; 3.79 (in 0.1 N NaOH).

2,6-Dimethyl-3-aminoisonicotinic acid. 1.2 g of 2,6-dimethylpyridine-3,4-dicarboximide is added at −5° over 10 min to a solution of KOCl (from 0.61 g of chlorine and 2.3 g of KOH in 25 ml of water). The mixture is kept for 1 h at 5-20°, then for 30 min at 50-60°, cooled and acidified with HCl to pH 4. After evaporation, 1.2 g (84.5%) of the amino acid is obtained. Mp 269-270.5° (from isopropyl alcohol, acetone, then from alcohol-acetone). Lit.: mp 285-295° (8).

2-Methyl-3-carbethoxyisonicotinic acid. 5.0 g of 4-methyl-5-carbethoxyoxazole, 5.0 g of acrylic acid, and a small amount of hydroquinone are boiled in 5 ml of benzene for 7 h; the precipitate is washed with acetonitrile, yielding 1.8 g (27%) of a white powder with mp 195-198°. The analytical sample melts at 201-201.5° (from alcohol-benzene, acetone-benzene, then from benzene).

Found %:	C 57.13; 57.08; H 5.01; 5.25
$C_{10}H_{11}NO_4$. Calculated %:	C 57.41; H 5.30

UV spectrum: λ_{max} 275 mμ, $\lg \varepsilon_{max}$ 3.76 (in 0.1 N HCl); λ_{max} 270 mμ, $\lg \varepsilon_{max}$ 3.57 (in 0.1 N NaOH).

Reaction of 2-methyl-3-carbethoxyisonicotinic acid with hydrazine. 0.35 g of 2-methyl-3-carbethoxyisonicotinic acid and 0.2 g of hydrazine hydrate are boiled in 2 ml of glycol for 80 min, diluted with water to 10 ml, and acidified with CH_3COOH. 0.06 g (17.7%) of 2-methylpyridin-(3,4-*d*)-pyridazinone with mp 292-294° precipitates. After reprecipitation from aqueous ammonia and sublimation in vacuo, mp 304°.

Found %:	C 53.73; H 4.06
$C_8H_7N_3O_2$. Calculated %:	C 54.23; H 4.00

2-Phenyl-3-methylisonicotinic acid. 4.2 g of 4-phenyl-5-methyloxazole and 2.5 g of acrylic acid are boiled for 4 h in 10 ml of benzene with hydroquinone; the precipitate is washed with tert-butanol, then with acetone. 2.0 g (39.5%) of a white powder with mp 268° is obtained. Purified

A white crystalline sample has m.p. 272-272.5° (from alcohol-benzene, then from benzene).

Found, %: C 72.99; 73.11; H 5.29; 5.20
$C_{13}H_{11}NO_2$. Calculated, %: C 73.21; H 5.26

2-Methyl-3-oxyzonicotinic acid. A mixture of 6.3 g of 4-methyl-5-ethoxyoxazole and 6.3 g of acrylic acid is boiled for 2 h in 10 ml of benzene with addition of hydroquinone. It is evaporated in vacuo to half the volume, cooled, and 2-methyl-3-oxyzonicotinic acid is separated in the form of a white powder with m.p. 312–314°. Yield 7.7 g (80%); m.p. of the pure sample 321° (from water).

Found, %: C 54.39; 54.42; H 4.48; 4.31
$C_7H_7NO_3$. Calculated, %: C 54.89; H 4.62

UV spectrum: λ_{max} 312 mμ; $\lg \varepsilon_{max}$ 3.86 (in 0.1 N HCl); λ_{max} 240; 305 mμ; $\lg \varepsilon_{max}$ 4.26; 4.25 (in 0.1 N NaOH). The same compound is obtained upon condensation with 4-methyl-5-propoxy- and 4-methyl-5-butoxyoxazole (yields 92 and 94.5%).

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