HETERODIENE CONDENSATION OF 4-METHYL-5-PROPOXYOXAZOLE WITH MALEIC ACID

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The ability of oxazoles to function as dienes in the Diels–Adler reaction [1] is currently finding wide application in the synthesis of vitamin B_6 and of derivatives of nicotinic and isonicotinic acids, which are important biologically active compounds.

This paper describes an investigation of the reaction of 4-methyl-5-propoxyoxazole (I) with maleic acid (II), which is one of the most reactive of the dienophiles in heterodiene condensation [1, 2].

The reaction of maleic acid with alkyl-substituted oxazoles to form alkylated pyridinecarboxylic acids has been investigated previously [2]. There is no mention in the literature of the reaction of maleic acid with 4-methyl-5-alkoxyoxazoles, although it occurs also in the list of dienophiles patented by American workers [3].

Reaction of I with II under mild conditions afforded a crystalline product, which was a mixture of pyridinemonocarboxylic acids – 2-methyl-3-hydroxy-5-pyridinecarboxylic (III) and 2-methyl-3-hydroxy-4-pyridinecarboxylic acid (IV) in a ratio of 9:1.

Separation of the mixture of 5- and 4-monocarboxylic acids by recrystallization proved very difficult, and it was effected as follows: the precipitate of mixed carboxylic acids was extracted with the solvent system acetone–dioxan–ammonia (9:9:2), whereupon the pyridine-4-carboxylic acid passed into solution and the 5-isomer remained behind.

The structures of III and IV were confirmed by their UV, PMR, and mass spectra.

In the mass spectra of the monocarboxylic acids III and IV, the molecular ion peaks were the most intense (m/e 153). The following peaks in intensity differed for the 4- and 5-pyridinemonocarboxylic acids: in the case of III fission to the acylium ion (M – 17) was observed such as is typical of carbonyl compounds; IV is capable of eliminating water, and the corresponding peak (M – 18) is observed in the spectrum. Subsequent elimination of carbon monoxide from the acylium ion or dehydrative fragmentation gives ions of mass 108 or 107 which are also observed in the spectra. Other ionic fragments of high intensity are formed by fission of the pyridine ring.

For comparison, the mass spectrum of 2-methyl-3-hydroxy-4,5-pyridinedicarboxylic acid was recorded. The most intense peaks were due to the molecular ion, m/e 197 and to the dehydrated molecule, m/e 179.

The UV spectra of the pyridinemonocarboxylic acids III and IV (see Experimental) corresponded to those described in the literature [4-6].

The PMR spectrum of III showed signals due to the protons of the pyridine ring at 7.92 and 7.19 ppm, which in the case of IV appeared at 7.35 and 6.88 ppm. The signals at lower field, 7.92 and 7.35 ppm, corresponded to the α protons of the pyridine ring. The separation between the signals indicates in the case of III that the second proton is in the γ position (7.19 ppm), and in the case of IV, in the β position (6.88 ppm). More accurate information

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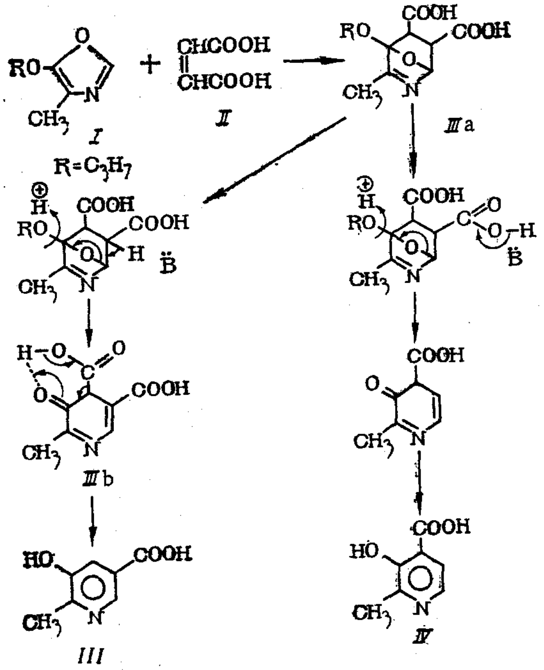
on the mutual interaction of the protons may be obtained from the spin–spin coupling constant, which is 1.5 Hz for III, characteristic of m protons [4, 6], and 5 Hz for IV, characteristic of o protons [5, 6]. The PMR spectra of both III and IV show signals due to the methyl protons (2.40 ppm).

The structures of III and IV may therefore be regarded as proved.

It should be pointed out that 2-methyl-3-hydroxy-4,5-pyridinedicarboxylic acid was absent from the reaction mixture (it was not detected by thin layer chromatography). It was shown in a separate experiment that this compound does not decompose under the reaction conditions. It may therefore be concluded that decarboxylation occurs during the course of the reaction of the stage of aromatization of the intermediate bicyclic adduct (IIIa). Heterodiene condensation adducts of oxazoles with maleic anhydride [3, 7], diethyl fumarate [8, 9], β-acetylacrylic acid [10], aldehydromaleic acid pseudoethyl ester [11], etc. are known to behave similarly.

We suggest that the aromatization of the adduct IIIa proceeds as follows:



Isomerization of the adduct IIIa begins with fission of the C_1–O-bond in the commonly accepted manner [7, 9, 10]. Further stabilization of the transition state is attained by loss of a proton or CO_2 from atoms C_6 or C_5 and elimination of the propoxide anion from the 4-position of the adduct. It appears that fission of the C_1–O bond results in the preferential formation of IIIb, thus giving a higher yield of III.

EXPERIMENTAL

Thin layer chromatography was carried out on Silufol UV-254 in the systems: A) butanol–water–acetic acid (3:1:1), and B) acetone–dioxane–ammonia (9:9:2). Spots were visualized in UV light and by treatment with Gibb's reagent. UV spectra were recorded on a Hitachi R 20A (60 MHz) instrument, and mass spectra on a Jeol JMS-OISG-2 spectrometer.

2-Methyl-3-hydroxy-5-pyridinecarboxylic acid (III). To a solution of 2.75 g (0.024 mole) of II in 25 ml of anhydrous acetone was added 1.75 g (0.012 mole) of I. After 20 h the precipitate was filtered off, washed with acetone, and extracted with solvent mixture B. The insoluble residue was filtered off. Yield 1.35 g (74%). Crystallized from water. Darkens at 322° and sublimes at 330°, leaving a carbonized residue. Literature data [4]: mp 320-325° (with darkening and sublimation, leaving a carbonized residue). Found: C 55.21; H 4.46; N 9.37%. $C_7H_7NO_3$. Calculated, %: C 54.90; H 4.61; N 9.15. UV spectrum: λ_{max}, nm (ε): in 0.1 N hydrochloric acid: 298 (8600), 241 (3700); in 0.1 N sodium hydroxide: 317 (6400), 256 (6200); m/e 153. PMR spectrum: δ, ppm, in D_2O±NaOD: 6-H 7.92; 4-H 7.19; 2-CH_3 2.40. R_f 0.59 (system A); 0.054 (system B).

2-Methyl-3-hydroxy-4-pyridinecarboxylic acid (IV). The reaction of I with II was carried out as above. The precipitate was extracted with mixture B, and the extract after removal of III was evaporated to give 0.17 g (9%) of IV, mp (from water) 310° (decomp.). Literature values: mp 302-308° [5], 321° [6]. UV spectrum: λ_{max}, nm (ε): in 0.1 N hydrochloric acid: 312 (7200); in 0.1 N sodium hydroxide: 307 (5900), 240 (5800), m/e 153. PMR spectrum: δ, ppm, in $D_2O + NaOD$: 6-H 7.35; 5-H 6.88; 2-CH_3 2.40. R_f 0.45 (system B); 0.34 (system A).

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ISOMERIC COMPOSITION OF THE BROMINATION PRODUCTS OF o-XYLENE

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The synthesis of riboflavin (vitamin B_2) requires the use of monobromo-o-xylene, which is obtained by the bromination of o-xylene (I) with bromine. A chromatographic method for the quantitative determination of the bromination products of I has been described, and it has been shown that bromination in the presence of iron activated with iodine leads to the formation of 4-bromo-o-xylene (II) together with only small amounts of 3,4- and 4,5- dibromo-o-xylene (III) and (IV) [1].

The monobromo-o-xylene obtained, however (a narrow fraction boiling over a 2° range) is not the pure isomer II. It is known that the boiling point of the material can be raised slightly, from 211-212° to 214-215°, if it is carefully sulfonated, the barium salt of the resulting sulfonic acid is recrystallized, and the 4-bromo-o-xylene is regenerated by hydrolysis in aqueous solution [2]. Since the boiling points of V and II are 211-212° and 214-215° respectively [3], it may be assumed that the monobromo-o-xylene is a mixture of isomers, rather than pure II.

EXPERIMENTAL

A check on the known methods of synthesis [1, 2] has shown that distilled monobromo-o-xylene, crystallized at −30°, melts at temperatures below −10°, although the melting point of II is −2 to 0° [3]. This shows the presence of appreciable amounts of the by-product isomer V, confirmed by chromatographic analysis. The chromatographic conditions were as follows: Simadzu model GC-1 chromatograph, Silochrome-2 adsorbent of particle size 0.25-0.5 mm, diameter of adsorption column 3 mm, length 2.7 m, thermal conductivity detector, carrier

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