THE MECHANISM OF THE DIENE SYNTHESIS WITH 5-ALKOXYOXAZOLES

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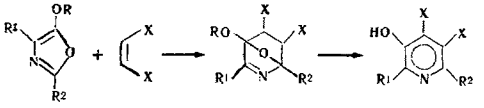
The reaction of 5-ethoxyoxazole with β-acetylacrylic acid and its ethyl ester is examined, and the most probable mechanism for the heterodiene synthesis with oxazoles is suggested on the basis of the experimental results and on the calculation of the π-electron densities for these molecules.

The discovery, ten years ago, of the ability of oxazoles to function as dienes in the Diels-Alder reaction [1] has subsequently found wide application in the synthesis of various pyridine bases.

The formation of the pyridine ring in the heterodiene condensation of 5-alkoxyoxazoles proceeds in at least two separate stages: the actual diene synthesis, i. e., the reaction of the oxazole with the dienophile to give unstable adducts and the isomerization of these adducts according to the scheme (1). The final reaction



products are always substituted 3-hydroxypyridines.

This paper considers theoretically and experimentally the most essential features of the mechanism of each of these stages.

Since the azadiene system of oxazoles is strongly polarized, the heterodiene synthesis will proceed most quickly by a two-stage mechanism involving charge separation in the transition state. If this hypothesis is correct, then the orientation of unsymmetrical dienophiles in their reaction with 5-alkoxyoxazoles must be determined completely by the distribution of electron densities on the carbon atoms participating in bond formation, and should be independent of the distribution of free valency indices.

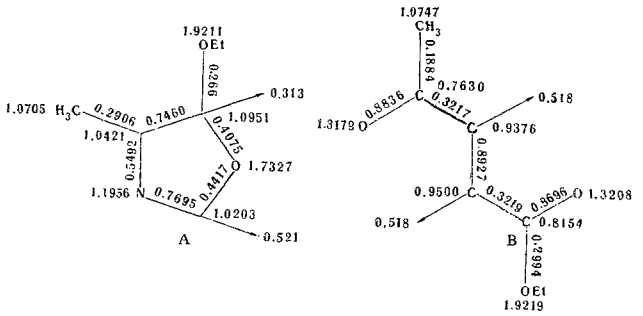


Fig. 1. Diagram of π-electron charge distribution, π-bond orders and free valency indices for the molecules of 4-methyl-5-ethoxyoxazole (A) and ethyl β-acetylacrylate (B).

In order to test this theory experimentally, the dienophile chosen was β-acetylacrylic acid (I). It will be seen from Fig. 1 that the π-electron densities on the C-2 and C-3 atoms differ substantially, while the free valency indices

are the same (the calculations were carried out by the molecular orbital method using Hückel's approximation, including allowance for the effect of hyperconjugation of the methyl groups).

Comparison of the indices of the electronic structures I and 4-methyl-5-ethoxyoxazole (II) shows that the main reaction product should be 2-methyl-3-hydroxy-4-acetyl-5-ethoxycarbonylpyridine (III). In fact, reaction of I with II gave only one product. Thin-layer chromatography of the reaction product demonstrated the absence of other pyridine compounds in appreciable amounts.

The NMR spectrum showed one proton in the pyridine ring, the position of which (8.41 ppm) is characteristic for an α-hydrogen atom. The signals of the two methyls (2.51 and 2.47 ppm) and one ethyl group (CH_2 quartet at 4.30 ppm and a CH_3 triplet at 1.34 ppm) are found at fields corresponding to alkyl substituents linked to unsaturated, electron-withdrawing groups. The IR spectrum shows C=O valency stretching bands at 1728 and 1660 cm^{-1}. The first of these is due to the ester grouping not participating in hydrogen bonding, and the second is characteristic for a ketone. The shift of 30 cm^{-1} toward lower frequencies indicates the presence of hydrogen bonding of medium strength, which is possible only if the acetyl group occupies the 4-position in the pyridine ring.

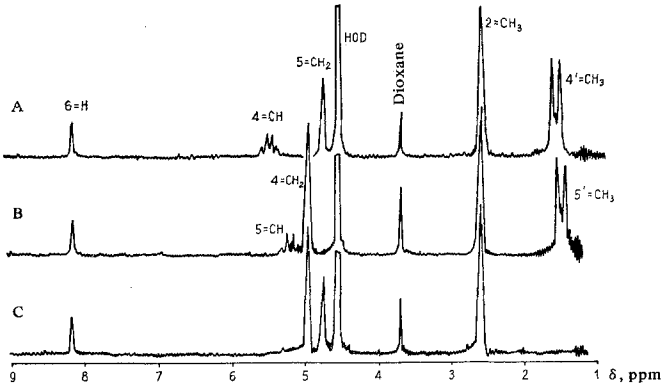
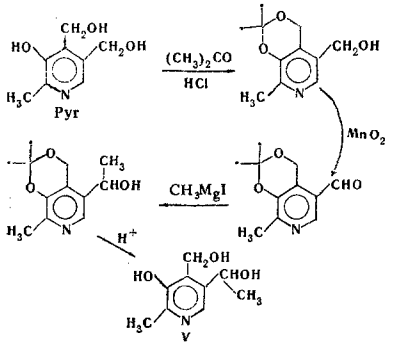
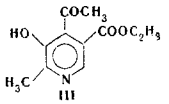


Fig. 2. NMR Spectra (hydrochlorides in D_2O): A) 2-methyl-3-hydroxy-4-α-hydroxyethyl-5-hydroxymethylpyridine (IV); B) 2-methyl-3-hydroxy-4-hydroxymethyl-5-α-hydroxyethylpyridine (V); C) Pyridoxine.

In order to prove conclusively the structure of this compound, it was reduced with lithium aluminum hydride. If the structure is in fact III, then the reduction product must be 2-methyl-3-hydroxy-5-hydroxymethyl-4-α-hydroxyethylpyridine (IV). It has previously been shown [2] that the NMR spectrum of pyridoxine after selective deuteration gives a signal due to the 4-hydroxymethyl group at 4.99 ppm, and the 5-hydroxymethyl group at 4.76 ppm. Fig. 2 shows the NMR spectra of the reduction product III, pyridoxine, and the isomeric 2-methyl-3-hydroxy-4-hydroxymethyl-5-α-hydroxyethylpyridine (V), obtained by route 2. The position of the signal due to the methylene group in V corresponds exactly with that of the 4-hydroxymethyl group in pyridoxine, while the CH_2 signal in the reduction product lies at 4.76 ppm. It may, therefore, be regarded as proved the compound in question has the structure III.

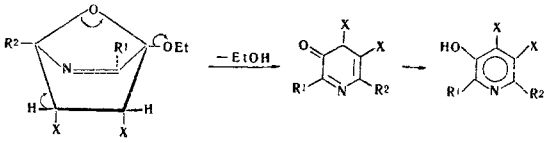




III

In just the same way, reaction of II with cyclopentene-3-one affords, in agreement with the electron density distribution, 5-methyl-4-hydroxy-6-azahydrindene-3-one, the structure of which was confirmed by its IR and NMR spectra. The IR spectrum of this compound showed a strong absorption band at 1736 cm^{-1} attributed to valency stretching of the carbonyl group of the cyclic ketone. The NMR spectrum showed a signal due to the 5-CH_3 group (a singlet at 2.62 ppm), two methylene groups (multiplets at 2.62 and 2.86 ppm), and the α-hydrogen of the pyridine ring (8.27 ppm). The latter was split (J = 1.8 Hz) as a result of distant spin-spin coupling with the methylene group. Such coupling is possible only for compounds with a CH_2 group in the 1-position, thus confirming our proposed structure.

As has already been pointed out, the reaction of 5-ethoxyisoxazoles with dienophiles leads to the formation of an unstable intermediate adduct, 4-ethoxy-7-oxa-2-azabicyclo[1, 2, 2]hept-2-ene, which aromatizes readily in acid media (scheme 3). The formation of



the adduct has been proved rigorously in [3, 4].

In our opinion, the isomerization of the adduct involves initial breaking of the 1-C—O bond. This conclusion is based on the following considerations.

1. It is precisely the 1-C—O bond which is most weakened by σ-π-conjugation with the 3-C=N bond. In anhydrous media (anhydrous HCl in ethanol), the nitrogen atom of the adduct is protonated, resulting in still greater ease of heterolysis of the 1-C—O bond.

2. Rupture of the 4-C—O bond followed by hydrolysis is improbable because both the diene synthesis and the isomerization often occur in anhydrous media. The correctness of this argument is supported by a consideration of the diene synthesis with 4-methyl-5-ethoxythiazole [5], the products from which are always 3-alkoxypyridines, despite the fact that the isomerization conditions (heating in conc HCl) favor hydrolysis.

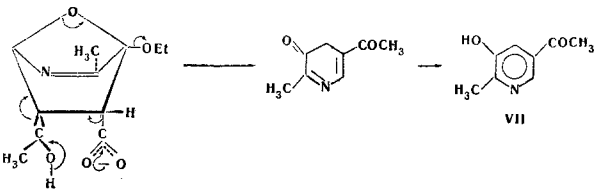
3. Finally, if rupture of the 4-C—O bond did occur, it would be difficult to explain the exclusive formation of 3-hydroxypyridines on reaction of dienophiles with 5-cyano-oxazoles [6].

After fission of the 1-C—O bond, stabilization of the transition state occurs by loss of a proton from the 6-C atom and elimination of the ethoxide anion from the 4-position of the adduct.

This mechanism offers an explanation of the fact, recorded in the literature [7, 8], that 5-unsubstituted oxazoles react with dienophiles in a similar way in the presence of oxidizing agents.

In this case, aromatization is brought about by elimination of a hydride ion from the 4-position of the adduct, which is energetically disfavored. The reaction will of course be greatly facilitated by the presence of hydride ion acceptors such as hydrogen peroxide or nitrobenzene.

In order to confirm experimentally the suggested mechanism, we examined the condensation of 4-methyl-5-ethoxyoxazole (II) with β-acetylacrylic acid. It follows from the π-electron density distribution (Fig. 3) in the adduct that the carboxyl group must be at the 5-position, and the acetyl group at the 6-position. If this mechanism is the correct one, then aromatization of the adduct must be accompanied by decarboxylation because there will then occur the more energetically-favored loss of a proton from the enol (scheme 4). Irrespective of the reaction conditions (heating at 80° C, or at room temperature), only one reaction product was obtained.



VII

Examination of the IR spectra showed the absence of carboxyl groups. The position of the C=O valency-stretching band (1698 cm^{-1}) was characteristic for nonhydrogen-bonded keto-groups, and this was confirmed by the absence of ν_{O-H} hydroxyl bands participating in chelate hydrogen bonds at 3300–3200 cm^{-1} (ν_{OH} for phenol is at 2650 cm^{-1}). These results permit the elimination of the possibility that the phenolic hydroxyl and the acetyl group are vicinal. The deformation stretching frequencies for the methyl groups are shifted towards the lower wave-number region (1440 and 1374 cm^{-1}) which is characteristic of alkyl substituents attached to electron-attracting unsaturated groups.

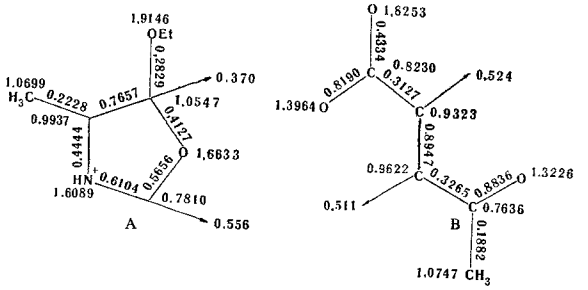


Fig. 3. Diagram of π-electron density distribution, π-bond orders and free valency indices in the molecules of the 4-methyl-5-ethoxyoxazole cation (A) and the β-acetylacrylate anion (B).

The greatest amount of information on the structure of the compound was obtained from its NMR spectrum. The signals due to the two methyl groups occurred at 2.86 and 2.89 ppm, indicating that these substituents are attached to electron-attracting, unsaturated groups (the pyridine nucleus and the carbonyl group), and the proton signal at the lowest fields (8.81 ppm) agrees with the α-proton of the pyridine ring. The position of the signal due to the second proton (8.57 ppm) suggests that it is in the γ-position. More precise information on the relative positions of the two protons is obtained from the spin-spin coupling constant J, which is equal to 2.2 Hz. It is known from the literature [9] that J for ortho-protons lies between 6 and 10 Hz, for meta- between 1 and 4 Hz, and for para- between 0 and 1 Hz.

The results obtained agree well with the proposed heterodiene synthesis reaction scheme and allow structure **VII** to be assigned to the compound under consideration, with a high degree of probability.

EXPERIMENTAL

The compounds obtained were chromatographed on silica-coated plates, using the method described previously [10]. Two systems were used: A) ethyl acetate–acetone–25% ammonia (20 : 10 : 1.5); B) butanol–25% ammonia–water (40 : 9 : 1). UV spectra were recorded in layers of thickness 1 mm and in concentrations of 10^{-4} moles/l, using an SF-4 instrument (Optica Milano). The IR spectra were taken on a UR-10 instrument for solids (KBr discs). The NMR spectra were taken on a JEOL JNM-4H-100 (100 MHz) instrument.

2-Methyl-3-hydroxy-4-acetyl-5-ethoxycarbonylpyridine (III). To a solution of 17.9 g (0.14 mole) of ethyl β-acetylacrylate [11] in 20 ml of anhydrous ethanol was added 8.87 g (0.07 mole) of 4-methyl-5-ethoxyoxazole [12], 1 ml of glacial acetic acid and 200 mg of hydroquinone. The resulting solution was kept in the dark for one week at room temperature. The crystals which separated were filtered off and washed with ether, giving 8 g (51%), mp 151–152° C (from heptane). Found, %: C 59.09; H 6.00. Calculated for $C_{11}H_{13}NO_4$, %: C 59.18; H 5.87. UV spectrum λ_{max}, nm (ε), in 0.1 N KOH: 250 (5800); 826 (6500). NMR spectrum, δ, ppm, in $CDCl_3$: 6-H 8.41; 2-CH_3 2.47; $COCH_3$ 2.51; $COOC_2H_5$ quartet 4.30 and triplet 1.34. R_f in system A, 0.107 in system B, 0.745.

2-Methyl-3-hydroxy-5-acetylpyridine (VII). A solution of 2.5 g (20 mM) of 4-methyl-5-ethoxyoxazole and 3.42 g (30 mm) of β-acetylacrylic acid [11] in 40 ml of absolute ether were kept with a calcium chloride guard tube for five days. The precipitate which separated was filtered off and washed with dry acetone to give 0.64 g (21%) of VII, mp 253–254° C (decomp., from methanol). Found, %: C 63.58; H 5.98. Calculated for $C_8H_9NO_2$, %: C 63.56; H 6.01.

UV spectrum, λ_{max}, nm (ε), in 0.1 N KOH: 265 (5000) and 345 (5500). NMR spectrum, δ, ppm, in CF_3COOH: 6-H 8.81; 4-H 8.57; 2-CH_3 2.86; $COCH_3$ 2.89. R_f in system A, 0.47; and in system B, 0.77.

2-Methyl-3-hydroxy-4-α-hydroxyethyl-5-hydroxymethylpyridine (IV). To a suspension of 1.14 g (30 mM) of lithium aluminum hydride in 50 ml of dry tetrahydrofuran was added dropwise with stirring and cooling a solution of 2.1 g (10 mM) of 2-methyl-3-hydroxy-4-acetyl-5-ethoxycarbonylpyridine (III) in 50 ml of dry tetrahydrofuran. The mixture was boiled gently for 6 hr and kept overnight at room temperature. To the stirred, cooled mixture was added 100 ml of water, and the mixture was saturated with carbon dioxide. The precipitate was filtered off, mixed with 100 ml of a mixture of water and ethanol (1:1), and again saturated with carbon dioxide. After filtration, the solid was washed with 2 × 50 ml of hot ethanol, and the combined filtrates evaporated in vacuo to dryness at 45–50° C. The residue was extracted with hot ethanol (5 × 20 ml). The combined alcoholic extracts were concentrated to a small volume and treated with 2 ml of a 25% solution of anhydrous hydrogen chloride in absolute ethanol, followed by anhydrous ether until crystallization began. The mixture was kept overnight in the refrigerator, filtered, and the crystals of IV hydrochloride washed with ether. Yield 1.74 g (79%), mp 172–173° C (from alcohol–ether). R_f in system A, 0.107; in system B, 0.67. Found, %: C 48.85; H 6.53. Calculated for $C_9H_{14}ClNO_3$, %: C 49.20; H 6.42.

2-Methyl-3-hydroxy-4-hydroxymethyl-5-α-hydroxyethylpyridine (V). To a solution of the Grignard reagent (prepared from 0.5 g of magnesium and 2.92 g of methyl iodide in 20 ml of ether) was added slowly with stirring and cooling a solution of 4 g (0.0193 mole) of α^4, 3-O-isopropylideneisopyridoxal [13] in 20 ml of dry ether. When the addition was complete, the mixture was boiled for 2 hr, cooled, and decomposed by adding 10 g of ice. The ether layer was separated and the aqueous layer extracted with 3 × 10 ml of ether. The combined ether extracts were dried and evaporated to dryness. The residue was dissolved in 100 ml of 10% HCl, and the solution boiled for 30 min, then evaporated to dryness in vacuo. The residue was thoroughly triturated with dry acetone, and filtered. The yield of V hydrochloride was 2.3 g (54%), mp 159–160° C (from alcohol–ether). Lit. mp [13], 160° C.

5-Methyl-4-hydroxy-6-azahydrindene-3-one. A mixture of 0.8 g (0.098 mole) of cyclopentene-3-one [14], 0.63 g (0.005 mole) of 4-methyl-5-ethoxyoxazole and 0.1 g of pyrogallol was heated for 2 hr at 110° C. The mixture was cooled and treated with 1 ml of 25% anhydrous hydrogen chloride in ethanol, followed by the careful addition of 70 ml of dry ether, and kept overnight in the refrigerator. The crystals which separated were filtered off and washed with ether, giving 0.22 g (20%) of product. The compound decomposed without melting at temperatures above 170° C (from alcohol–ether). Found, %: C 54.51; H 5.20. Calculated for $C_9H_{10}ClNO_2$, %: C 54.16; H 5.05.

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