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Abstract

Full Text

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OXAZOLE DERIVATIVES IN DIENE SYNTHESIS

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Continuing our study of diene synthesis in the oxazole series, we carried out this reaction with some of its derivatives containing electron-acceptor substituents. Such oxazoles are of low activity in diene condensation; they form 1,4-adducts only with a very strong dienophile—maleic acid imide—and do not react with maleic anhydride. At the same time, the nonequivalence of individual compounds—methyl-substituted acetyl-, carbethoxy-, and phenyloxazoles—is also revealed very sharply. Depending on the type of substitution and the relative positions of the substituents in the ring, the adduct with maleimide is formed in good or only moderate yield, and sometimes is not obtained at all. The condensation products, imides of substituted pyridinedicarboxylic acids, in some cases are partially hydrolyzed by the water liberated in the reaction, and then the semiamides of these acids precipitate from the mixture.

Table 1

Reaction of substituted oxazoles with maleic acid imide

Code	R	R′	R″	Yield of adduct, %	Yield of adduct, %
				II	III
a	H	CH_3	$COCH_3$	45.4	–
b	H	CH_3	$CO_2C_2H_5$	37.5	–
c	CH_3	CH_3	$CO_2C_2H_5$	–	–
d	CH_3	$CO_2C_2H_5$	CH_3	–	–
e	C_6H_5	H	CH_3	–	–
f	CH_3	H	C_6H_5	–	–
g	H	C_6H_5	CH_3	–	75.8
h	CH_3	C_6H_5	H	–	68.2
i	CH_3	C_6H_5	CH_3	–	46.7
k	CH_3	C_6H_5	C_6H_5	–	–

Comparing these results with the data obtained in the analogous condensation of methyloxazoles (^{1}), one may note first of all that replacement of one CH_3 group by an acetyl or ester grouping lowers the yield of the adduct with maleimide by approximately 50%. The introduction of one more methyl group, even in the fourth position, which does not play a major role in diene synthesis, leads to complete disappearance of reactivity. Thus, on going from 4,5-dimethyloxazole (I, $R = \text{H}$, $R' = R'' = \text{CH}_3$) to 4-methyl-5-acetyl—(Ia) and 4-methyl-5-carbethoxy derivatives (Ib), the yields of the corresponding adducts change from 93 to 45 and 37%. 2,4-Dimethyl-5-carbethoxyoxazole (Ic) does not react at all with maleimide, whereas 2,4,5-trimethyloxazole (I, $R = R' = R'' = \text{CH}_3$) forms with it more than 90% of the semiamide of trimethylcinchomeronic acid. Does not enter into reaction

and 2,5-dimethyl-4-carbethoxyoxazole (Ig), although the COOC_2H_5 group in it is removed from the terminal atoms of the conjugated system.

$$\text{(I)} + \text{maleimide} \longrightarrow \text{(II)} \quad \text{or} \quad \text{(III)}$$

Within the group of isomeric methylphenyloxazoles, a peculiar and very strong influence of the phenyl group on the reactivity of the diene is observed: 2-methyl-4-phenyloxazole (Iz) and 4-phenyl-5-methyloxazole (Izh) add maleimide in fairly high yield, whereas oxazoles substituted by a phenyl group in the second and fifth positions (Id, e, k) do not react, and only the starting substances are isolated from the reaction mixture. No such dependence exists in the series of conjugated dienes with a purely carbon skeleton: even 1,4-diphenylbutadiene ([2]) and 1,4-diphenylcyclopentadiene ([3]), with two C_6H_5 radicals in the terminal positions, form substituted cyclohexenes with maleic anhydride. The failure of condensations of 2- and 5-phenyl-substituted oxazoles cannot be ascribed to steric hindrance that might be caused by an unfavorable rotation of the phenyl ring, since the complete structural analogue of these compounds, 2-phenyl-5-ethoxyoxazole, successfully enters into reaction with maleimide ([1]).

The influence of the phenyl radical in 2- and 5-phenyloxazoles should apparently be explained by an increase in the aromaticity of their ring in comparison with analogous alkyl derivatives. As a result of the introduction of an effective electrophilic group, the affinity of the heteroatom O for an electron is weakened; this gives rise to a more favorable state for the formation of a delocalized π-electron cloud and leads to an increase in aromaticity and a weakening of the conjugated diene character of the entire heterocyclic system. When substitution occurs in position 4, which is more remote from O, the tendency toward electron delocalization is less pronounced; therefore, 4-phenyl-substituted oxazoles retain diene character to a certain degree and are capable of reacting with maleic imide.

Phenyloxazoles do not react with maleic anhydride, with the exception of the 4-phenyl-5-methyl derivative, from which 5-methyl-6-phenylcinchomeronic acid is obtained in 15.8% yield.

The individual features of the isomeric methylphenyloxazoles are also correspondingly reflected in the spectra of combination scattering of light. Judging by the character of the Raman spectra, 4-phenyl derivatives reproduce alkyl-substituted oxazoles and differ sharply from their 2- and 5-substituted analogues, which in their spectral characteristics approach benzene aromatic systems*.

Comparing the influence exerted by substituents of the oxazole ring on its activity in diene condensation with maleimide, one may apparently arrange these substituents with sufficient confidence in the following series according to decreasing activity of the oxazoles:

$$\mathrm{RO} > \mathrm{R}\ \text{and}\ 4\text{-}C_6H_5 > COCH_3 > COOC_2H_5 \gg 2\text{- and } 5\text{-}C_6H_5.$$

(R –alkyl radical).

Experimental Part

5-Acetyl-6-methylpyridine-3,4-dicarboximide (IIa). 8.0 g of 4-methyl-5-acetyloxazole and 6.5 g of maleimide are heated for 5 hours in 10 ml of xylene with pyrogallol; the mixture is diluted with 10 ml of benzene and vigorously cooled. The filtrate is evaporated; the residue is treated with benzene and methyl ethyl ketone, and a new portion of IIa is isolated. Melting point of the pure substance 222–223° (from methyl ethyl ketone and an acetone–benzene mixture).

Found, %:	C 59.01, 59.13;	H 4.09, 4.10
$C_{10}H_6N_2O_3$. Calculated, %:	C 58.82;	H 3.95

5-Carbethoxy-6-methylpyridine-3,4-dicarboximide (IIb). 3.2 g of 4-methyl-5-carbethoxyoxazole and 2.0 g of maleimide are heated in xylene solution for 3 hours; the precipitate is washed with methyl ethyl ketone. M.p. IIb 183–184° (from benzene, and an acetone-petroleum ether mixture).

Found, %:	C 56.91, 56.78;	H 4.38, 4.29
$C_{11}H_{10}N_2O_4$. Calculated, %:	C 56.41;	H 4.30

5-Methyl-6-phenyl-3(4?)-carbamylpyridine-4(3?)-carboxylic acid (III). 3.34 g of 4-phenyl-5-methyloxazole are boiled in 10 ml of toluene with 2 g of maleimide and hydroquinone for 4 hours. Melting point of the imido acid 158.5–159° (from alcohol, then from acetone).

Found, %:	C 65.71, 65.89;	H 4.78, 4.68
$C_{14}H_{12}N_2O_3$. Calculated, %:	C 65.61;	H 4.71

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* The Raman spectra were recorded and analyzed at the Spectroscopy Commission of the Academy of Sciences of the USSR by V. T. Aleksanyan and E. V. Sobolev.

2-Methyl-6-phenyl-3(4?)-carbamylpyridine-4(3?)-carboxylic acid (III). 3.34 g of 2-methyl-4-phenyloxazole and 2.0 g of maleimide are boiled in toluene for 6 hours; the precipitate (m.p. 163-164°) is recrystallized from alcohol, then from acetone. M.p. 175-176° (pure substance).

Found, %:	N 11.11, 10.98
$C_{14}H_{12}N_2O_3$. Calculated, %:	N 10.93

2,5-Dimethyl-6-phenyl-3(4?)-carbamylpyridine-4(3?)-carboxylic acid (III). 2.6 g of 2,5-dimethyl-4-phenyloxazole and 1.5 g of maleimide are boiled in 10 ml of xylene with hydroquinone for 5 hours. After 24 hours the precipitate is separated; the filtrate is boiled for another 4 hours and evaporated in vacuo. The residue is washed with ether and a second portion of the adduct is obtained, with m.p. 143-144.5°. After crystallization from ethyl acetate-acetone and chloroform-acetone, m.p. 149-149.5°.

Found, %:	N 10.37, 10.10
$C_{15}H_{14}N_2O_3$. Calculated, %:	N 10.36

5-Methyl-6-phenylpyridine-3,4-dicarboxylic acid. 5 g of 4-phenyl-5-methyloxazole and 6 g of maleic anhydride are boiled in 15 ml of toluene with hydroquinone for 7 hours; the precipitate is washed with acetone, giving an acid with m.p. 208-210° (with decomp.). Yield 15.7%. The pure acid melts at 211° (from alcohol).

Found, %:	N 5.39, 5.40
$C_{14}H_{11}NO_4$. Calculated, %:	N 5.44

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