REACTION OF ALKYL- AND ALKOXYOXAZOLES WITH MALEIC ACID IMIDE

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Abstract

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REACTION OF ALKYL- AND ALKOXYOXAZOLES WITH MALEIC ACID IMIDE

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In our works ([1,2]), the condensation of certain oxazole derivatives with maleic acid and its anhydride was described. These commonly used philodienes showed good activity in reactions with alkyl- and alkoxyalkyloxazoles, but did not react with oxazoles substituted by electron-acceptor groups (2-phenyl-5-ethoxy-, 2-styryl-5-ethoxyoxazoles). Maleic acid imide proved more effective in these cases —a compound little used in diene synthesis, but apparently very reactive ([3–7]). Its condensation with alkyl- and alkoxyoxazoles proceeds with better yields and much more readily than the reaction with maleic anhydride. The final products of the transformation of oxazoles are imides of substituted pyridine-3,4-dicarboxylic acids, and in some cases the half-amides of these acids:

$$\text{A.}\quad \text{(I a–e)} + \text{maleimide} \longrightarrow [\text{(II)}] \longrightarrow \text{(III a–e)}$$

$$\text{B.}\quad \text{(IV a–l)} + \text{maleimide} \longrightarrow [\text{(V)}] \longrightarrow [\text{(VI)}] \longrightarrow \text{(VII a–l)}$$

The intermediate epoxytetrahydropyridine derivatives II and V were not observed in any case. As in the reaction with maleic anhydride, from alkoxyoxazoles there are obtained directly not the pyridine esters VI, but the corresponding oxo compounds.

The general results of the work are presented in Tables 1 and 2. For comparison, the yields of adducts in the reaction with maleic anhydride are also given.

The high activity of maleimide in the reaction with oxazoles is expressed in the fact that it reacts much more rapidly than maleic anhydride: when oxazoles are mixed with the imide, noticeable warming is observed, and after only 10–30 min a precipitate of the adduct begins to separate. In the series of alkyloxazoles (I a–d), the yields of III a–d are 50–98%, i.e., 20 percentage points higher than the yields achieved in the reaction with maleic anhydride. Of interest is the high yield of 5-tert-butylpyridine-3,4-dicarboximide (IIIe), since 4-tert-butyloxazole (Ie) does not react with maleic anhydride. All alkoxyoxazoles, with the exception of the first members of the homologous series (IVa and IV), in condensation with maleimide give high yields of adducts VII a–l, irrespective of the length of the alkyl chain in position 2 and the presen-

which does not have a substituent in position 4. 2-Phenyl-5-ethoxyoxazole (I) and its vinyl analog, 2-styryl-5-ethoxyoxazole, inert in the reaction with the anhydride, readily undergo condensation with maleimide.

The structure of the reaction products was confirmed by reciprocal synthesis, using as examples several pyridinedicarboximides (III –), obtained by heating the corresponding free pyridine-3,4-dicarboxylic acids with urea in ethylene glycol. In some condensation experiments with I , only the product of partial hydrolysis of the cyclic imide ring was isolated–2,5,6-trimethyl-3(4?)-carbamylpyridine-4(3?)-carboxylic acid (IR spectrum λ_{max} 1590, 3152–3176 cm^{-1}) ($CONH_2$). The oxyimide VII formed from IV , on recrystallization from methanol, was converted into 2-ethyl-6-methyl-5-hydroxy-4(3?)-carbomethoxy-3(4?)-carbamylpyridine (IR spectrum λ_{max} 1710–1730 cm^{-1} (COOR); 1637 cm^{-1} ($CONH_2$)). Data on the structure of the oxazole adduct IV will be published later.

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Table 1

Reaction of alkyloxazoles with maleimide
(scheme A)

I–III	R	R′	R″	Yield of III, %	Yield of adduct from maleic anhydride, %
	H	CH_3	CH_3	93	85
	CH_3	CH_3	H	98	78
	CH_3	H	CH_3	81.9	80
*	CH_3	CH_3	CH_3	49.5	52
	CH_3	$-(CH_2)_4$	$-(CH_2)_4$	54.5	35
		–	–		
	H	$(CH_3)_3C$	H	64.3**	0

* In several experiments 2,5,6-trimethyl-3(4?)-carbamylpyridine-4(3?)-carboxylic acid was isolated, yield 93.6%.

** Acid half-amide.

Table 2

Reaction of 5-alkoxyoxazoles with maleimide
(scheme B)

IV–VII	R	R′	R″	Yield of VII, %	Yield of adduct from maleic anhydride, % (2)
	CH_3	H	C_2H_5	43	54
	C_2H_5	H	C_2H_5	80	47
	-C_3H_7	H	C_2H_5	77	31.5
	-C_4H_9	H	C_2H_5	82.8	42.3
	-C_5H_{11}	H	C_2H_5	81.4	40
	C_6H_5	H	C_2H_5	43.5	0
	$C_6H_5CH=CH$	H	C_2H_5	70*	0
	CH_3	CH_3	CH_3	36	36
	C_2H_5	CH_3	CH_3	72.6**	25
	-C_5H_{11}	CH_3	CH_3	68	15.8***
	CH_3	C_2H_5	C_2H_5	84.8	0

* The structure of the adduct will be described separately.
** Acid half-amide.
*** In condensation with maleic anhydride, 2--amyl-4-methyl-5-ethoxyoxazole was used.

Experimental Part

5,6-Dimethylpyridine-3,4-dicarboximide (III). 0.8 g of 4,5-dimethyloxazole, 0.8 g of maleimide, and a small amount of hydroquinone are heated in 5 ml of benzene for 2 hours. The crude reaction product melts at 263–265°. After sublimation in vacuo, m.p. of III 268–270°; m.p. of a mixed sample with the product of reciprocal synthesis 268–270°.

2,6-Dimethylpyridine-3,4-dicarboximide (III) was obtained from 2.0 g of 2,4-dimethyloxazole and 2.0 g of maleimide. M.p. 224–226° (from acetone); m.p. of a mixed sample with the product of reciprocal synthesis 224°.

2,5-Dimethylpyridine-3,4-dicarboximide (III) was obtained analogously to III , m.p. 271–272°. M.p. of a mixed sample with the product of reciprocal synthesis 271–272°.

2,5,6-Trimethylpyridine-3,4-dicarboximide (III). 2.2 g of 2,4,5-trimethyloxazole and 2.1 g of maleimide are heated in benzene

with hydroquinone for 2 hours. Mp of the precipitate 220-221°. Mp of a mixed sample with the product of independent synthesis 220°.

2,5,6-Trimethyl-3(4?)-carbamylpyridine-4(3?)-carboxylic acid. 4.2 g of 2,4,5-trimethyloxazole is heated for 1.5 hours with 3.6 g of maleimide in a benzene–xylene mixture (1 : 1). The precipitated amic acid melts at 180°; a pure

specimen has mp 183.5–185.5° (from acetone–petroleum ether and then from acetone).

Found, %: C 57.95; 58.16; H 5.55; 5.72
$C_{10}H_{12}N_2O_3$. Calculated, %: C 57.68; H 5.77

2-Methyl-5,6-tetramethylenepyridine-3,4-dicarboximide (IIId). From 2.0 g of 2-methyl-4,5-tetramethyleneoxazole and 1.5 g of maleimide, boiling in benzene for 4 hours. Mp of the precipitate 246–247°. Mp of a mixed sample with the product of independent synthesis 245–246°.

5-tert-Butyl-3(4?)-carbamylpyridine-4(3?)-carboxylic acid. 2.0 g of 5-tert-butyloxazole and 2.75 g of maleimide are heated in benzene with hydroquinone for 3 hours; the precipitate is separated, the filtrate is boiled for 5 hours, evaporated, and the residue is washed with water. After recrystallization from ethyl acetate and a mixture of acetone with hexane, mp 176°.

Found, %: C 59.64; 59.38; H 6.31; 6.19
$C_{11}H_{14}N_2O_3$. Calculated, %: C 59.43; H 6.36

2-Methyl-5-oxypyridine-3,4-dicarboximide (VIIa). 4 g of 2-methyl-5-ethoxyoxazole and 3.6 g of maleimide are heated in 10 ml of benzene with hydroquinone for 1.5 hours. The crude adduct melts at 273°; the purified material has mp 308° (from alcohol–benzene).

Found, %: C 54.01; 53.89; H 3.40; 3.50
$C_8H_6N_2O_3$. Calculated, %: C 53.93; H 3.39

2-Ethyl-5-oxypyridine-3,4-dicarboximide (VIIb). 3.0 g of 2-ethyl-5-ethoxyoxazole and 2.2 g of maleimide are heated in 10 ml of benzene with pyrogallol for 4 hours. Mp of the adduct 254°. The pure preparation melts at 258° (from methanol–benzene).

Found, %: C 56.44; 56.50; H 4.13; 4.00
$C_9H_8N_2O_3$. Calculated, %: C 56.25; H 4.18

2-*n*-Propyl-5-oxypyridine-3,4-dicarboximide (VIIv). From 2.0 g of 2-*n*-propyl-5-ethoxyoxazole and 1.4 g of maleimide in 10 ml of benzene with pyrogallol, heating for 3 hours. Mp of the precipitate 247–250°. Mp of pure VIIv 251–252° (from acetone–benzene and methanol–benzene).

Found, %: C 58.03: 53.23; H 4.76; 4.86
$C_{10}H_{10}N_2O_3$. Calculated, %: C 58.24; H 4.89

2-*n*-Butyl-5-oxypyridine-3,4-dicarboximide (VIIg). Obtained analogously to VIIb from 2.5 g of 2-butyl-5-ethoxyoxazole and 1.7 g of maleimide. Mp of the crude adduct 232°; mp of a pure specimen 234.5–235° (from methanol–benzene, acetone–benzene).

Found, %: C 60.37; 60.44; H 5.67; 5.64
$C_{11}H_{13}N_2O_3$. Calculated, %: C 59.98; H 5.49

2-*n*-Amyl-5-oxypyridine-3,4-dicarboximide (VIId). 3.7 g of 2-amyl-5-ethoxyoxazole and 1.95 g of maleimide are boiled in toluene with hydroquinone for 4 hours, and the solution is evaporated in vacuo. Mp of the adduct 231°; mp of the pure preparation 234° (from alcohol, then acetone).

Found, %: N 12.52; 12.53
$C_{12}H_{14}N_2O_3$. Calculated, %: N 11.96

2-Phenyl-5-oxypyridine-3,4-dicarboximide (VIIe). 3.6 g of 2-phenyl-5-ethoxyoxazole are heated for 3 hours with 2.0 g of maleimide.

in xylene with hydroquinone. M.p. of the unpurified adduct 279-282°. The pure preparation has m.p. 286-287° (from methanol—benzene).

Found, %:	C 64.36;	H 3.33
$C_{13}H_{18}N_2O_3$. Calculated, %:	C 65.00;	H 3.36

2,6-Dimethyl-5-oxypyridine-3,4-dicarboximide (VI) was obtained analogously to VII from 2.3 g of 2,4-dimethyl-5-methoxyoxazole and 1.8 g of maleimide. M.p. 275-277° (from alcohol—benzene—methyl ethyl ketone).

Found, %:	C 56.62; 56.74;	H 4.16; 4.13	
$C_9H_8N_2O_3$. Calculated, %:	C 56.25;	H 4.19	

2-Methyl-6-ethyl-5-oxypyridine-3,4-dicarboximide (VII). From 3.1 g of 2-methyl-4-ethyl-5-ethoxyoxazole and 1.95 g of maleimide, boiling in toluene for 6 h. M.p. of the crude adduct 225°; after sublimation and recrystallization from benzene, m.p. 255-257°.

Found, %:	N 13.52; 13.65
$C_{10}H_{10}N_2O_3$. Calculated, %:	N 13.56

2-Ethyl-6-methyl-5-oxy-4(3?)-carbamylpyridine-3(4?)-carboxylic acid. From 2.0 g of 2-ethyl-4-methyl-5-methoxyoxazole and 1.5 g of maleimide in benzene, boiling for 4 h. M.p. 157° (from methanol—benzene, acetone—benzene).

Found, %:	C 55.41; 55.52;	H 6.17; 6.22
$C_{11}H_{14}N_2O_4$. Calculated, %:	C 55.45;	H 5.92

Reaction of 2-styryl-5-ethoxyoxazole with maleimide. 4.2 g of 2-styryl-5-ethoxyoxazole are boiled with 2.1 g of maleimide in a xylene solution for 1 h; the melting point of the precipitate after washing with ether is 245°. The pure adduct melts at 268-268.5° (from acetone—benzene and methanol—benzene).

Found, %:	C 62.16; 62.42;	H 4.75; 4.60
$C_{15}H_{12}N_2O_4$. Calculated, %:	C 61.76;	H 4.46

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