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FORMATION OF 1,2-OXAZINE DERIVATIVES: A NOVEL TYPE OF REACTION BETWEEN 2-AMINOOXAZOLES AND MALEIC ACID IMIDE

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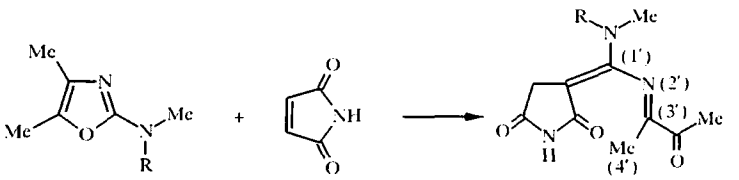
N,N-Disubstituted 2-aminooxazoles in acetic acid at 20°C undergo addition of maleinimide, converting to alkylidene succinimides or 1,2-oxazine derivatives.

Keywords: 2-aminooxazoles, 3-(2-aza-1-amino-3-methyl-4-oxopenten-2-ylidene)-2,5-dioxopyrrolidines, N,N-dimethylamides of 3,4-disubstituted 5,6-hydropyrrolo[3,2-*e*]-1,2-oxazine-2-carboxylic acids, maleinimide.

In continuing our work in [1], we have isolated additional products of the reaction of 2-aminooxazoles **1a-d** with maleic acid imide (**2**) and we have established their structures. The individual oxazoles do not react with maleinimide according to the previously observed directions of heterodiene syntheses and/or 1,3-cycloaddition, but rather after rupture of the $C_{(2)}$–O or $C_{(5)}$–O bond and isomerization they convert to succinimide derivatives or 1,2-oxazine. N,N-Disubstituted 2-aminooxazoles with an unoccupied 5 position do not undergo such conversions, but 4,5-disubstituted derivatives selectively convert to one of the products. These reactions require clearly defined conditions (solvent and temperature) and the direction depends only on the specific substituents on the oxazole ring.



1 a,b **2** **3 a,b**

1,3 a R = Me; **b** Ph

Oxazoles **1a** and **1b** in glacial acetic acid at 20°C reacted with rupture of the $C_{(2)}$–O bond. Such a decomposition of the heterocycle with redistribution of bonds is confirmed by analysis of the ^{1}H NMR spectra (Table 1) and the ^{13}C NMR spectra of compound **3a**: in addition to signals belonging to the methyl groups, in its ^{13}C NMR spectrum we see a signal from a carbonyl carbon atom with chemical shift 210.5 ppm ($CH_3\underline{C}O$), five signals in the 124-178 ppm region (sp^2-carbon atoms and CO of the amide type), and a signal from the methylene

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TABLE 1 Characteristics of Compounds **3** and **5**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	UV spectrum*, λ_{max}, nm	IR spectrum*², ν, cm⁻¹		^{1}H NMR spectrum, δ, ppm, (*J*, Hz)
		C	H	N			C=N	C=O	
3a	$C_{11}H_{14}N_2O_3$	55.55 / 55.63	6.56 / 6.37	17.46 / 17.71	203-204	227	1620-1680	1720, 1770	Pyridine-d_5: 1.98 (3H, s, CH_3); 2.20 (3H, s, $COCH_3$); 2.91 (6H, s, $N(H_3)$); 3.22 and 3.25 (2H, s and s, CH_2)
3b	$C_{16}H_{17}N_3O_3$				>150 (decomp.)	205, 227, 417	1630-1670	1710-1720, 1770	Pyridine-d_5: 1.79 (3H, s, CH_3); 2.01 (3H, s, $COCH_3$); 3.13 (2H, s, CH_2); 3.21 (3H, s, NCH_3); 6.70-7.40 (5H, m, C_6H_5)
5c	$C_{12}H_{17}N_3O_3$	57.43 / 57.35	6.92 / 6.82	16.58 / 16.72	175-176	230	1620, 1675*³	1720, 1770	$CDCl_3$: 1.12 (3H, t, $CH_2\underline{CH_3}$); 2.17 (3H, s, CH_3); 2.37 (2H, q, $\underline{CH_2}CH_3$); 2.92 m 3.00 (6H, s and s, NCH_3 nonequivalent); 3.29 (2H, s, CH_2)
5d	$C_{16}H_{17}N_3O_3$	63.90 / 64.19	5.96 / 5.74	13.86 / 14.04	185-186	203, 249	1610-1630, 1670*³	1720, 1775	$CDCl_3$: 2.17 (3H, s, CH_3); 2.97 (6H, s, NCH_3); 3.40 (2H, s, CH_2); 7.20-8.05 (5H, m, C_6H_5)

* In alcohol.

*² KBr disk.

*³ $\nu_{C=C}$.

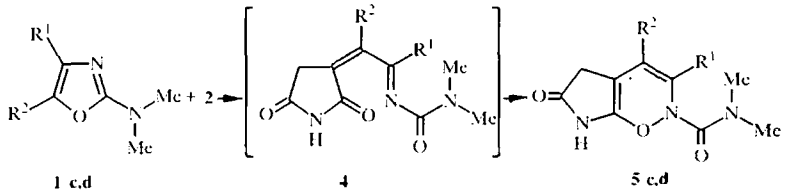
TABLE 2. ^{13}C NMR Spectra, δ, ppm (*J*, Hz)

Compound	Solvent	$C_{(3)}$	$C_{(4)}$	$C_{(4a)}$	$C_{(5)}$	$C_{(6)}$	$C_{(7a)}$	CON<	R^1	R^2	NCH_3
5c	$CDCl_3$	163.2	153.0	121.7	34.0 (t, 136)	174.2 (t, 6)	169.3	173.2	23.6	11.1 (q, 129, CH_3), 27.9 (t, 128, CH_2)	35.7, 37.0 (q, 139)
5d	$CDCl_3$	163.4	145.8	123.9	34.3	174.4	168.2	170.0	128.2, 128.8, 132.0, 134.8	22.0	35.8, 37.3
5d	CD_3COOD	165.5	144.6	126.4	34.8 (t, 136)	178.1 (t, 8)	170.2	172.5	129.2, 129.9, 133.5, 135.2	21.8 (q, 131)	36.2, 37.9 (q, 138)

group which is split into a triplet at 34.3 ppm. The signal in the 149.6 ppm region is split into a quartet with J = 6.0 Hz, which makes it possible to assign it to the $C_{(3')}$ atom. The upfield shift of the $C_{(3)}$ signal is probably due to the effect of the amino group at $C_{(1')}$, which occurs, as we know, for example, for enamines [2]. In the CH_2–$C_{(3)}$=$C_{(1')}$–N=$C_{(3')}$–CH_3 moiety, we observe relatively high coupling constants: $^5J_{C(3),CH_3}$ = 6.0 and $^7J_{CH_2,CH_3}$ = 1.4 Hz.

The less stable compound **3b** was characterized only spectroscopically: according to UV, IR, and ^{1}H NMR spectra, it is completely analogous to **3a**. Compounds **3a,b** are colorless crystals, melt with decomposition, and are unstable in solvents (alcohol, benzene, chloroform, etc.).

In the case of 2-dimethylamino-5-ethyl-4-methyloxazole **1c**, reaction in AcOH occurs with cleavage of the $C_{(5)}$–O bond. This type of ring opening for a 2-aminooxazole is encountered here for the first time; it is not observed also in 5-aminooxazoles [3]. The end product of condensation, however, did not correspond to formula **4**, but rather had the structure of a substituted pyrrolo[3,2-*e*]-1,2-oxazine **5**. The primary adduct **4** was not observed in the mixtures; it underwent complete ring closure of the intramolecular diene synthesis type. 2-Dimethylamino-5-methyl-4-phenyloxazole **1d** reacted similarly, but in ether and benzene solutions.



1 c,d 4 5 c,d

1, 5 c R^1, R^2 = Me, Et; d Ph, Me

The structure of the reaction products, as in the preceding case, was established by ^{13}C NMR spectra. In the spectra of compounds **5c,d** (Table 2), we see triplets from a CH_2 group ($C_{(5)}$) and multiplets from a carbonyl group of the amide type, decoupled from the protons of the dimethylamino group under ^{13}C–^{1}H selective resonance conditions (173.2 ppm for **5c** and 172.5 ppm for **5d**). A cyclic structure for the reaction product is indicated by the magnitude of the chemical shift of the $C_{(4a)}$ atom (121.7 ppm for **5c** and 123.9 ppm for **5d**) occupying the position β to the double bond $C_{(3)}$=$C_{(4)}$ and to the oxygen atom. In compounds **3** with an open chain, such a downfield shift of the $C_{(4a)}$ signal under the influence of the alkyl group is not very likely. Although ^{13}C NMR spectra for such structures are not available in the literature, we know that the effect of an oxygen on a β-carbon atom is significantly greater than for alkyl substituents [4]. Evidence in favor of formula **5** also comes from comparing δ $C_{(3)}$ in adduct **3a** and δ $C_{(4a)}$ in adducts **5**: the closeness of these values is easily explained by the similarity between the moieties N–C=C (**3**) and –O–C=C (**5**). As we know [2,4], the effects of an amino group and an oxygen on a β-carbon atom are rather similar and significantly greater than for alkyl substituents, as would be in the case of alternative formula **4**. The ^{1}H NMR spectra of compounds **5** are shown in Table 1.

EXPERIMENTAL

The ^{13}C NMR spectra were obtained on a Bruker WP-60 spectrometer in pulsed mode; the ^{1}H NMR spectra were obtained on a Varian DA-60-IL spectrometer, internal standard TMS.

3-(2-Aza-1-dimethyleneamino-3-methyl-4-oxopenten-2-ylidene)-2,5-dioxopyrrolidine (3a). A solution of 2-dimethylamino-4,5-dimethyloxazole **1a** (1.40 g, 0.01 mol) and maleinimide **2** (0.97 g, 0.01 mol) in acetic acid (6 ml) was held at 20°C for 5 days and evaporated under vacuum. The residue was diluted with a alcohol–acetone mixture, and the precipitated product **3a** was washed with acetone. Yield 58%. ^{13}C NMR spectrum (CD_3COOD): 17.9 (q, J = 131 Hz, $C_{(4')}$); 29.3 (q, J = 128 Hz, $\underline{C}OCH_3$); 34.3 (t, J = 137 Hz, CH_2); 36.9 (qq, J = 139, ^4J = 3 Hz, NCH_3); 123.7 ($C_{(3)}$); 149.6 ($C_{(3')}$); 162.2 ($C_{(1')}$); 171.2 ($C_{(2)}$); 178.2 (t, ^2J = 6 Hz, $C_{(5)}$); 210.5 ppm ($\underline{C}OCH_3$). From the filtrates after isolation of compound **3a**, we precipitated (with water) 3,4-dicarboximido-2-dimethylamino-5,6-dimethylpyridine, formed from compounds **1a** and **2** according to a heterodiene synthesis scheme. Yield 6%.

3-[2-Aza-3-methyl-1-(N-methyl-N-phenylamino)-4-oxopenten-2-ylidene]-2,5-dioxopyrrolidine (3b). A solution of 4,5-dimethyl-2-(N-methyl-N-phenylamino)oxazole **1b** (2.02 g, 0.01 mol) and imide **2** (0.97 g, 0.01 mol) in acetic acid (6 ml) was held for 5 days at 20°C, and then evaporated under vacuum. A part of the product of heterodiene synthesis – 3,4-dicarboximido-5,6-dimethyl-2-methylphenylaminopyridine – was precipitated with aqueous alcohol. Yield 30%. According to the ^{1}H NMR spectrum, the yellow glassy residue after evaporation of the filtrate under vacuum corresponds to compound **3b**; it decomposes during purification.

Dimethylamide of 4-Ethyl-3-methyl-6-oxo-5,6-dihydropyrrolo[3,2-*e*]-1,2-oxazine-2-carboxylic Acid (5c). A solution of 2-dimethylamino-5-ethyl-4-methyloxazole **1c** (1.54 g, 0.01 mol) and imide **2** (0.97 g, 0.01 mol) in acetic acid (6 ml) were held for 5 days at 20°C, evaporated down under vacuum, and diluted with a 1:1 acetone–ether mixture. Product **5c** gradually precipitated, which was crystallized from alcohol. Yield 40%.

Dimethylamide of 4-Methyl-6-oxo-3-phenyl-5,6-dihydropyrrolo[3,2-*e*]-1,2-oxazine-2-carboxylic Acid (5d). A solution of 2-dimethylamino-5-methyl-4-phenyloxazole **1d** (2.02 g, 0.01 mol) and imide **2** (0.97 g, 0.01 mol) in absolute ether (5 ml) was held for 5 days at 20°C and then evaporated down. The residue was dissolved in a small volume of alcohol and product **5c** was isolated. Yield 10%. A residue which after filtration of the reaction mixture was crystallized from water with addition of a small amount of alcohol was obtained by a similar procedure, but in 5 ml of benzene. Yield 17%.

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