CONDENSATION OF N-SUBSTITUTED 5-AMINOOXAZOLES WITH MALEIMIDE: TWO TYPES OF OXAZOLE RING REACTIVITIES

G. Ya. Kondrat'eva, M. A. Aitzhanova,
V. S. Bogdanov, and O. S. Chizhov

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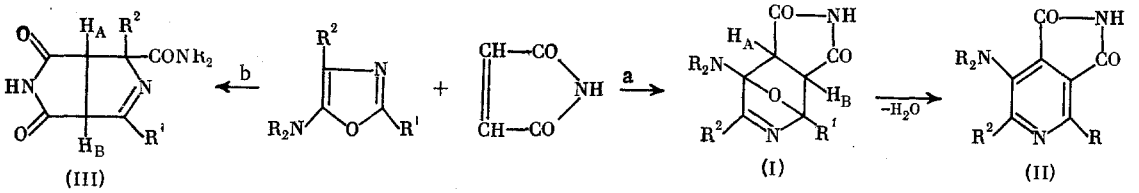
The Diels—Alder reaction is a characteristic cycloaddition of oxazoles [1]. Depending on the properties of the starting components with the ethylenic dienophiles, the reaction either stops at the stage of the 1,4 adduct (endoxotetrahydropyridine) or bypasses this stage and directly leads to the formation of a substituted pyridine; major changes in the direction of the condensation itself are not observed [2, 3].

5-R_2N-Oxazoles have been found to enter into two types of condensation with maleimide. Depending on the R chains in the R_2N group and also on the solvent, the reaction may proceed as a Diels—Alder reaction or by a heretofore unknown 1,3-addition scheme. Heterogeneous synthesis *a* leads to substituted endoxopiperidines (I) and the corresponding pyridines (II) and the competing transformation b leads to substituted Δ^1-pyrrolines (III), but not to addition at the C—N bond as had been proposed previously for the case $R^1 = R^2 = CH_3$ and $R = C_2H_5$ [4].



All the compounds obtained were characterized by elemental analysis and UV and IR spectra which completely correlated with their proposed structures and also by NMR spectroscopy. The PMR spectral data for all the compounds (I)-(III) and (IV) (see below) are given with the description of these compounds; the ^{13}C NMR spectral analysis is published separately.

2-Phenylamino-3,6-endoxo-3,4,5,6-tetrahidropyridine-4,5-dicarboximides (I). Stable endoxypiperidines were described by Naito et al. [5]. They were not isolated in a single case in the condensation of oxazoles with very varied substituents with maleimide [2, 6]. The introduction of the N-phenylamino group to the endoxo bridge apparently leads to enhanced stability of the bicyclic piperidines, and 2,4-dialkyl-substituted 5-methylphenylaminooxazoles react with maleimide in all solvents (except acetic acid) to yield stable endoxopiperidines (Table 1).

All the compounds obtained undergo the retro-Diels—Alder reaction above 120-150°C. As shown by the PMR spectra, the endoxopiperidine $\rightleftarrows$ oxazole + maleimide equilibrium is slowly established in solutions of (I). In benzene, for example, 2,6-dimethyl-3-methylphenylamino-3,6-endoxopiperidine-4,5-dicarboximide undergoes 30% decomposition at 20°C over 30 h; 45% of the original compound remains upon 30 min reflux in this mixture. Upon prolonged storage, (I) is slowly aromatized and the aromatization is accelerated in acid media. Thus, 6-methyl-2-ethyl-3-methylphenylamino-3,6-endoxopiperidine-4,5-dicarboximide is converted into 2-methyl-6-ethyl-3-methylphenylaminopyridine-4,5-dicarboximide in acetic acid solution for 24 h at 20°C with >80% yield.

Molecular ion signals and peaks of the same intensity corresponding to oxazole and maleimide are found in the mass spectra of the endoxopiperideines.

3-Aminopyridine-3,5-dicarboximides (II). The formation of 3-aminopyridines in the condensation of aminooxazoles with maleimide (Table 2) is a typical Diels—Alder reaction. The

N. D. Zelinskii Institute of Organic Chemistry, Academy of Sciences of the USSR, Moscow.
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TABLE 1. 3-Phenylamino-3,6-endoxo-Δ^1-piperidine-4,5-dicarboximides

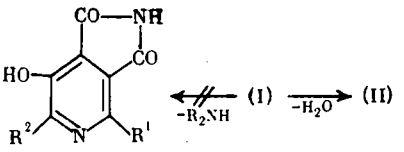
Compound	R	R^1	R^2	mp, °C	PMR spectrum, δ, ppm, J, Hz, TMS standard, in $CDCl_3$
(Ia)	CH_3	CH_3	CH_3	113–115 (decomp.)	1,95 s (6H, 2,6-CH_3), 3,05 s (3H, NCH_3), 3,19 d, 3,48 d (1H, 1H, H_A and H_B, J=7,5), 7,50–7,00m (5H, C_6H_5)
(Ib)	CH_3	CH_3	C_2H_5	112–114 (decomp.)	1,97 s (3H, 6-CH_3), 2,22 q, 1,00 t (2H, 3H, C_2H_5, J=7,0), 3,05s (3H, NCH_3), 3,19 d, 3,48 d (1H, 1H, H_A and H_B, J=7,5), 7,50–6,93 (5H. C_6H_5)
(Ic)	C_6H_5	CH_3	CH_3	140–141 (decomp.)	1,82 s, 2.60 s (3H, 3H, 2.6-CH_3), 3,07 d, 3,30 d (1H, 1H. H_A and H_B, J=7,5), 7.58–6,87 m (10H, C_6H_5)
(Id)	C_6H_5	CH_3	C_2H_5	142–145 (decomp.)	2,02 s (3H, 6-CH_3), 2,20 q, 0,92 t (2H, 3H, C_2H_5, J=7,0), 3.67 d, 3,28 d (1H, 1H, H_A and H_B, J=7,5), 7,55–6,83 m (10H, C_6H_5)

TABLE 2. 3-Aminopyridine-4,5-dicarboximides (II)

Compound	R^1	R^2	NR_2	mp, °C	Color	* (IIi) was identified according to its PMR spectrum
(IIa)	CH_3	CH_3	$N(C_2H_5)_2$	138–139	Light yellow	C_5D_5N: 2,73 s (3H, 2-CH_3), 2,95 s (3-H, 6-CH_3). 3,33 q, 1,00 t (2H, 3H, N-C_2H_5, J=7,0)
(IIb)	CH_3	CH_3	$N(C_4H_9)_2$	151–152	Yellow	$CDCl_3$: 2,70 s, 2,84 s (3H, 3H. 2- and 6-CH_3). 0.85 m 1,35 m 3,20 m (6H, 4H. 4H, C_4H_9)
(IIc)	CH_3	H	$N(CH_3)C_6H_5$	239–240	»	C_5D_5N: 2,93 s (3H, 6-CH_3), 8,70 s (1H, 2-H), 3,50 s (3H, NCH_3), 7,38–6,88 m (5H, C_2H_5)
(IId)	C_6H_5	H	$N(CH_3)C_6H_5$	300–301	»	C_5D_5N: 3,49 s (3H, NCH_3), 8,8 s (1H, 2-H), 8,25–7,05 m (10H, C_6H_5)
(IIe)	CH_3	CH_3	$N(CH_3)C_6H_5$	175–176	Red	C_6D_6+$(CD_3)_2CO$: 2,23 s (3H, 2-CH_3), 2,80 s (3H, 6-CH_3), 3.03 s (3H, NCH_3), 6,22–7,12 m (5H, C_6H_5)
(IIf)	CH_3	C_2H_5	$N(CH_3)C_6H_5$	157–158	»	C_5D_5N: 2,92 s (3H, 6-CH_3), 3,32 s (3H, NCH_3), 1,17 t, 2,70 q (3H, 2H, C_2H_5, J=7,5)
(IIg)	C_6H_5	CH_3	$N(CH_3)C_6H_5$	100–117 (decomp.)	»	DMFA-d_6: 2.38 s (3H, 2-CH_3), 3.33 s (3H, NCH_3). 8,05–6,45 m (10H, C_6H_5)
(IIh) *	CH_3	C_6H_5	$N(CH_3)C_6H_5$	220–221	Dark red	$CDCl_3$: 2,94 s (3H, 6-CH_3), 3,07 s (3H, NCH_3), 6,4–7,7 m (10H, C_6H_5)
(IIi)	CH_3	CH_3	$N(C_6H_5)_2$	–	»	CH_3COOH: 2,28 s (3H, 2-CH_3), 2,74 s (3H, 6-CH_3), 7,38–6,73, (10H, C_6H_5)
(IIj)	CH_3	C_2H_5	$N(C_6H_5)_2$	197–199 (decomp.)	»	CD_3OD: 2,98 s (3H, 6-CH_3), 1,05 t, 2,80 q (3H, 2H, C_2H_5, J=7,5), 7,32–6,77 m (10H. C_6H_5)

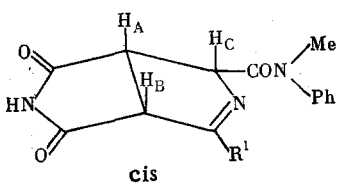
*(IIi) was identified according to its PMR spectrum.

aromatization of (I) proceeds only with the loss of water: and the parallel formation of δ-pyridinols due to the loss of the secondary amine does not occur

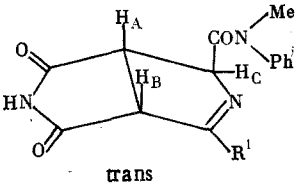


Amides of Δ'-Pyrroline-3,4,5-tricarboxylic Acids (III). 5-Dialkylamino-substituted oxazoles and those 5-methylphenylamino derivatives in which C(4) is not substituted are the most reactive in the 1,3 addition with maleimide. Compound (III) is formed from these compounds in benzene and ether solutions (Table 3) as the predominant and, sometimes, only product. 5-Methylphenylaminooxazoles with the alkyl substituents in the ring react mainly by the Diels–Alder reaction though in benzene solution, both 1,3 and 1,4 additions compete. The 5-diphenyl-substituted derivatives do not give Δ'-pyrrolines under any conditions.

It was possible to establish the spatial configuration of (III) only for compounds (IIIc) and (IIId), in which the arrangement of the three protons may be determined on the basis of the spin–spin coupling constants:



cis



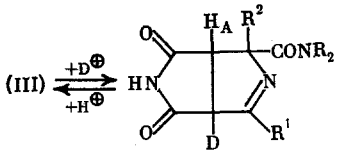
trans

In the spectrum of the cis isomer (IIIc) in $CDCl_3$, we find: a) a doublet of doublets for H_A at 3.23 ppm with $J_{H_A,H_C} = J_{H_A,H_B} = 9.5$ Hz since the dihedral angles between the bonds of the corresponding hydrogens are close to zero, b) a broadened H_B doublet with $\delta H_B = 3.80$ ppm and J = 9.5 Hz as a result of the vicinal spin–spin coupling with H_A (broadening due to a weak coupling with H_C), and c) a quartet of doublets for H_C with $\delta H_C = 4.83$ ppm, $J_{H_C,H_A} = 9.5$, $J_{H_C,CH_3} = 1.5$ Hz (probably the homoallylic constant). In the spectrum of the trans isomer of (IIIc) in $CDCl_3$, we find: a) a doublet of doublets for H_A (3.78 ppm) with $J_{H_A,H_B} = 8.5$ and $J_{H_A,H_C} = 2.5$ Hz, b) doublet of doublets for H_B with $\delta H_B = 4.17$ ppm and $J_{H_B,H_A} = 8.5$ and $J_{H_B,H_C} = 2.5$ Hz, and c) quartet of doublets for H_C (4.95 ppm) with $J_{H_C,H_A} = J_{H_C,H_B} = 2.5$, $J_{H_C,CH_3} = 1.5$ Hz.

The reaction of 2-methyl-5-methylphenylaminooxazole with maleimide in ether yields only the cis isomer of pyrrolinedicarboxiimide, but the pyrroline with trans configuration [trans-(IIId)] forms from 2-phenyl-5-methylphenylaminooxazole in toluene at 110°C.

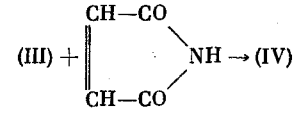
Pyrrolines (III) have a labile hydrogen atom H_B which is capable of:

a) Reversible replacement by deuterium by the action of Cd_3OD (in excess):



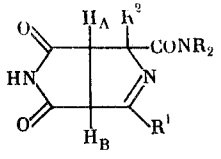
Upon refluxing (IIIe) in CD_3OD, a 3:1 equilibrium of the deuterated and nondeuterated forms is established in 1 h. Under the same conditions, there is 60% deuteration of cis-(IIIc), 50% deuteration of trans-(IIIc), and 27% deuteration trans-(IIId).

b. Electrophilic attack of the double bond of a second molecule of maleimide with the formation of addition products (IV). Adducts (IV) are also formed during the condensation of oxazole with maleimide itself, even if the starting compounds are taken in equimolar amounts; for an excess of maleimide in the reaction mixture, the yield of (IV) increases:

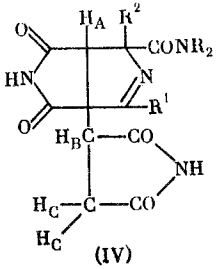


Reversible deuterium exchange with the allylic CH_3 group hydrogen occurs in pyrrolines (III) and (IV) at the ring double bond, which indicates the existence of imine–enamine tautomers:

TABLE 3. Amides of Δ'-Pyrroline-3,4,5-tricarboxylic Acids (III) and (IV)



(III)



(IV)

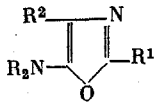
Compound	R^1	R^2	NR_2	mp, °C	PMR spectrum, δ, ppm, J, Hz, TMS standard
(IIIa)	CH_3	CH_3	$N(C_2H_5)_2$	142—143	$CDCl_3$: 1,57 s (3H, 5-CH_3), 2,18 s (3H, 2-CH_3), 1,18 t, 3,38 q (6H, 4H, NC_2H_5, $J = 7,0$), 3,93 d (1H, H_B, $J = 8,5$), 4,75 d (1H, H_A, $J = 8,5$)
(IIIb)	CH_3	CH_3	$N(C_4H_9)_2$	*	C_6H_6: 1,62 s (3H, 5-CH_3), 2,03 s (3H, 2-CH_3), 3,63 d (1H, H_B, $J = 8,5$), 4,82 s (1H, H_A)
(IIIc)	CH_3	H	$N(CH_3)C_6H_5$	236—237 (cis) oil (trans)	$CDCl_3$, trans: 2,17 d (3H, 2-CH_3, $J_{H_C, CH_3} = 1,50$), 3,30 s (3H, NCH_3), 3,78 d.d (1H, H_A, $J_{H_A, H_B} = 8,50$, $J_{H_A, H_C} = 2,50$), 4,17 d.d (1H, H_B, $J_{H_B, H_A} = 8,50$, $J_{H_B, H_C} = 2,50$), 4,95 q.d (1H, H_C, $J_{H_C, H_A} = J_{H_C, H_B} = 2,50$, $J_{H_C, CH_3} = 1,50$), 7,5—7,0 m (5H, C_6H_5). cis: 2,22 d (3H, 2—CH_3, $J_{H_C, CH_3} = 1,5$), 3,24 s (3H, NCH_3), 3,23 t (1H, H_A, $J_{H_A, H_C} = J_{H_A, H_B} = 9,50$), 3,80 d (1H, H_B), $J_{H_A, H_B} = 9,50$, 4,83 q.d (1H, H_C, $J_{H_C, CH_3} = 1,50$), 7,5—7,0 m (5H, C_6H_5)
(IIId)	C_6H_5	H	Same	211—212	$CDCl_3$: 3,25 s (3H, NCH_3), 5,09 d.d (1H, H_C, $J_{H_A, H_C} = J_{H_C, H_B} = 2,7$), 3,93 d.d (1H, H_A, $J = 8,7$), 4,70 d.d (1H, H_B, $J = 8,7$), 8,17—6,92 m (10H, C_6H_5)
(IIIe)	CH_3	CH_3	»	181—182	$CDCl_3$: 1,47 s (3H, 5-CH_3), 1,86 s (3H, 2-CH_3), 3,30 s (3H, NCH_3), 3,58 d (1H, H_B, $J = 9,0$), 4,18 d (1H, H_A, $J = 9,0$)
(IIIf)	CH_3	C_2H_5	»	195—197	$CDCl_3$: 1,82 s (3H, 2-CH_3), 1,00 t, 2,23 q (3H, 2H, C_2H_5, $J = 7,0$), 3,32 s (3H, NCH_3), 3,72 d (1H, H_B, $J = 9,0$), 4,22 d (1H, H_A, $J = 9,0$), 6,87—7,58 m (5H, C_6H_5)
(IIIg)	C_6H_5	CH_3	»	228—229	$CDCl_3$: 1,58 s (3H, 5-CH_3), 3,34 s (3H, NCH_3), 4,35 d, 4,58 d (1H, 1H, $H_A + H_B$, $J = 9,2$), 7,90—7,00 m (10H, C_6H_5)
(IVa)	CH_3	CH_3	$N(C_2H_5)_2$	246—247	C_5D_5N: 2,47 s (3H, 2-CH_3), 1,83 s (3H, 5-CH_3), 1,10 t, 1,22 t, 3,30 m (3H, 3H, 4H, $N(C_2H_5)_2$ nonequiv. $J = 7,0$), 4,10 br.t (1H, H_B, $J = 7,5$), 3,03 br.d (1H, H_C, $J = 7,5$), 5,27 s (1H, H_A)
(IVb)	CH_3	CH_3	$N(C_4H_9)_2$	236—237	C_5D_5N: 2,47 s (3H, 2-CH_3), 1,87 s (3H, 5-CH_3), 3,59 br.t (1H, H_B, $J = 7,5$), 3,03 br.d (1H, H_C, $J = 7,5$), 5,32 c (1H, H_A)
(IVe)	CH_3	CH_3	$N(CH_3)C_6H_5$	292—294	C_5D_5N: 2,37 s (3H, 2-CH_3), 1,92 s (3H, 5-CH_3), 4,13 br.t (1H, H_B, $J = 7,5$), 3,06 br.d (1H, H_C, $J = 7,5$), 3,55 s (3H, NCH_3), 5,19 s (1H, H_A), 7,60—6,68 m (5H, C_6H_5)
(IVf)	CH_3	C_2H_5	Same	>320	C_5D_5N: 2,43 s (3H, 2-CH_3), 1,38 t, 2,37 q (3H, 2H, C_2H_5, $J = 7,0$), 3,58 s (3H, NCH_3), 4,18 br.t (1H, H_B), 3,05 br.d (1H, H_C, $J = 7,5$), 5,22 s (1H, H_A), 6,95—7,67 m (5H, C_6H_5)

*Identified according to the ^1H and ^{13}C NMR spectra.

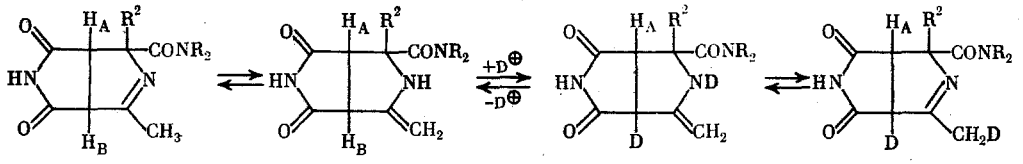
TABLE 4. Yield of the Products of Condensation of 2,4-Dimethyl-5-methylphenylaminooxazole (I) and (III), %

Compound	—	Ether	CCl_4	C_6H_6	Acetone	CH_3OH	DMSO	C_5H_5N	$C_6H_5NO_2$
(I)	100	100	100	50	60	7	70	50	80
(III)	—	—	—	50	—	50	—	—	10

TABLE 5. Yield of the Products of the Condensation of 5-Aminooxazoles in Various Solvents, % (20°C)



R^1	R^2	R_2N	Ether 1,4- (I)	Ether 1,4- (II)	Ether 1,3- (III)	Ether 1,3- (IV)	Benzene 1,4- (I)	Benzene 1,4- (II)	Benzene 1,3- (III)	Benzene 1,3- (IV)	CH_3COOH 1,4- (I)	CH_3COOH 1,4- (II)	CH_3COOH 1,3- (III)	CH_3COOH 1,3- (IV)
CH_3	CH_3	$N(C_2H_5)_2$	—	16	84	—	—	—	100	—	—	20	—	7
CH_3	CH_3	$N(C_4H_9)_2$	—	32	45	—	—	—	50	10	—	40	—	12
CH_3	CH_3	$N(CH_3)C_6H_5$	100	—	—	—	50	—	50	—	—	70	—	3
CH_3	C_2H_5	Same	100	—	—	—	50	—	50	—	—	97	—	2
CH_3	H	»	—	20	80	—	—	20	55	—	—	3	—	—
C_6H_5	H	»	—	1,5	98	—	—	10	40	—	—	3	—	—
CH_3	CH_3	$N(C_6H_5)_2$	50	—	—	—	50	—	—	—	—	20	—	—
CH_3	C_2H_5	Same	50	—	—	—	50	—	—	—	—	24	—	—
CH_3	C_6H_5	$N(CH_3)C_6H_5$	No reaction								—	70	—	—
C_6H_5	CH_3	Same									—	50	29	—



The reaction has a lower rate [especially in the case of compounds (IV)] relative to proton exchange $H_B \rightleftarrows D$: 2,5-dimethyl-5-methylphenylcarbaminopyrroline-3,4-dicarboximide (IIIe) undergoes 85% deuteration over 10 days in CD_3OD, while its derivative (IVe) undergoes only 15% deuteration under the same conditions.

Substituent Effect of the Direction and Yields of the Reaction Products. The reaction direction and yields of the products of the 1,4 and 1,3 addition of maleimide are primarily dictated by the individual structure of the oxazole and, to a lesser extent, by the external conditions. The optimal solvent and temperature mode for obtaining specific compounds should be individually selected though there are some general recommendations. The maximum yield of (III) and (IV) is observed, for example, in condensation in benzene solutions; the Diels–Alder reaction proceeds better in acetone and ether, though 4-H-5-R_2N-oxazoles give 80-100% 1,3 addition also in ether solution (Table 5).

The effect of different types of solvents was studied in greatest detail for 2,4-dimethyl-5-methylphenylaminooxazole. A mixture of equimolar amounts of the starting reagents was maintained for 5 days at 20°C and then analyzed by PMR spectroscopy (Table 4).

The free electron pair of the R_2N group is neutralized in glacial acetic acid, which, to a considerable extent, makes aminooxazoles similar to functionally unsubstituted derivatives; therefore, the reaction with maleimide is mainly directed towards the formation of the 1,4 addition products. In acid medium, the primary products of the condensation [endoxopiperidines (I)] are aromatized and pyridinedicarboximides (II) crystallize from the reaction mixtures. In order to decrease the cleavage and tar formation of many acidophobic aminooxazoles, the reaction is best conducted at 20°C. At higher temperature, the pyridine yield drops. Aminooxazoles unsubstituted at C(4), which are especially sensitive to the action of acids, are decomposed in acetic acid almost completely. 2-Phenyl-4H-5-methylphenylaminooxa-

zole in benzene solution does not react with maleimide, and addition products are obtained only in refluxing toluene. 5-Methylphenylaminooxazoles with a phenyl group on the ring and substituted at C(4) does not enter reaction in benzene, refluxing xylene, or acetic anhydride. A similar ring deactivation by the phenyl group was previously noted by Pfleiderer et al. [2].

EXPERIMENTAL

For the synthesis of the starting aminooxazoles, see our earlier work [7]. The reaction with maleimide was carried out by the standard method and the final products were isolated by various methods described below. All the aminopyridinedicarboximides (II) obtained were recrystallized from 96% ethanol (exceptions are stipulated). The elemental analytic data are given in Table 6.

a. To 0.025 mole oxazole in 100 ml abs. ether, 0.025 mole maleimide powder was added with stirring and the mixture was maintained for 5 days at 20°C. Then, the ether was distilled off in vacuum.

b. To 0.02 mole oxazole in 3 ml benzene, a solution of 0.02 maleimide in 30 ml benzene was added slowly with stirring. The mixture was heated at reflux for 3 h or maintained for 5 days at 20°C and then evaporated in vacuum.

c. To 0.01 mole oxazole in 8 ml acetic acid, 0.01 mole maleimide was added, and the mixture was maintained for 5 days at 20°C and evaporated in vacuum.

Reaction with 2,4-Dimethyl-5-diethylaminooxazole. a. Compound (IIa) was precipitated by 50% ethanol from the residue after distillation of the ether. The filtrate was dried in vacuum and the remaining (IIIa) was washed with cold ethanol.

b. The reaction in benzene at 20° and 80°C leads to the quantitative formation of (IIIa). When maleimide is introduced in a single batch, then, in addition to (IIIa) (30% yield at 80°C), (IVa) is also obtained in 32% yield (at 30°C). The separation was carried out by crystallization from ethanol.

c. Bright orange 2,6-dimethyl-3-diethylamino-4-carboxy-5-carbaminopyridine (V) was precipitated by a 1:1 ethanol—acetone mixture from the residue after distillation of the acetic acid in 10% yield (reaction at 118°C); mp 214-216°C. The PMR spectrum in C_5D_5N solvent, δ, ppm: 2.88 s, 2.94 s (6H, 2- and 6-CH_3), 3.30 q, 0.995 t (2H, 3H, NC_2H_5, J = 7.0 Hz). The mother liquids were evaporated, and (IIa) was precipitated from the residue with 50% ethanol (10% yield, reaction at 118°C). For 1:2 oxazole—maleimide molar ratio (reaction at 20°C), (IVa) precipitated from the mixture in 7% yield.

Reaction with 2,4-Dimethyl-5-dibutylaminooxazole. a. The residue after distillation of the ether was crystalli-ed from 50% ethanol to yield (IIb); the mother liquid was evaporated and the presence of (IIIb) and unreacted oxazole was established by PMR spectroscopy.

b. The residue after distillation of the benzene was washed with ethanol and (IVb) was filtered off; (IVb) was washed with CCl_4. All the filtrates were evaporated in vacuum and (IIIb) was precipitated from the residue by 50% ethanol.

c. Compound (IVb) precipitated from the reaction mixture after 24 h and then was washed with CCl_4. Compound (IIb) was precipitated from the evaporated filtrates with aqueous ethanol.

Reaction with 2,4-Dimethyl-5-methylphenylaminooxazole. a. After evaporation of the ether, pure (Ia) was obtained in the residue, which was recrystallized from ether.

b. Compound (IIIe) was obtained by subjecting the residue after the evaporation of benzene to fractional crystallization from ether; the mother liquid was evaporated, washed with 1:2 acetone—water and the precipitated (Ia) was recrystallized from ether. Compound (IVe) was precipitated from the reaction mixture with excess maleimide in 10% yield, while the yields of (Ia) and (IIIe) were 45% and 45%.

c. Compound (IIe) was precipitated from the residue after distillation of the acid with ethanol; 43% yield at 118°C. The reaction with excess maleimide, in addition, gave 2% (IVe).

Reaction with 2-Methyl-4-ethyl-5-methylphenylaminooxazole. a. As in the previous case (method a), (Ib) was isolated.

TABLE 6. Elemental Analyses of Compounds (II)-(V)

Compound	Formula	Found/calculated, %			Compound	Formula	Found/calculated, %		
		C	H	N			C	H	N
(Ia)	$C_{16}H_{17}N_3O_3$	64,15 64,20	5,79 5,72	13,95 14,04	(IIj)	$C_{22}H_{19}N_3O_2$	73,80 73,93	5,16 5,36	11,26 11,76
(Ib)	$C_{17}H_{19}N_3O_3$	65,25 65,16	6,09 6,11	13,21 13,41	(IIIa)	$C_{13}H_{19}N_3O_3$	58,31 58,85	7,13 7,22	15,88 15,84
(Ic)	$C_{21}H_{18}N_3O_3$	69,76 69,79	5,44 5,30	11,32 11,63	(IIIc)	$C_{15}H_{15}N_3O_3$	63,88 63,15	5,53 5,30	14,39 14,73
(Id)	$C_{22}H_{21}N_3O_3$	70,00 70,38	5,79 5,64	10,99 11,19	(IIId)	$C_{20}H_{17}N_3O_3$	69,26 69,15	4,96 4,93	11,94 12,10
(IIa)	$C_{13}H_{17}N_3O_2$	63,11 63,14	6,90 6,93	16,55 16,99	(IIIe)	$C_{16}H_{17}N_3O_3$	64.09 64,20	5,70 5,72	14,25 14,04
(IIb)	$C_{17}H_{25}N_3O_2$	67,50 67,30	8,26 8,31	13,57 13,85	(IIIf)	$C_{17}H_{19}N_3O_3$	65,00 65,16	6,10 6,11	13,29 13,41
(IIc)	$C_{15}H_{13}N_3O_2$	67,21 67,40	5,03 4,90	15,76 15,72	(IIIg)	$C_{21}H_{19}N_3O_3$	65,20 65,49	4,73 4,84	12,20 12,22
(IId)	$C_{20}H_{15}N_3O_2$	72,61 72,93	4,72 4,59	12,59 12,76	(IVa)	$C_{17}H_{22}N_4O_5$	56,33 56,34	6,21 6.12	15,42 15,46
(IIe)	$C_{16}H_{15}N_3O_2$	67,95 68,31	5,20 5,38	15,20 14,94	(IVb)	$C_{21}H_{30}N_4O_5$	60,00 60,27	7,30 7,23	13,39 13,39
(IIf)	$C_{17}H_{17}N_3O_2$	68,68 69,13	5,92 5,80	14,13 14,23	(IVe)	$C_{20}H_{20}N_4O_5$	61,13 60,60	5,29 5,09	13,82 14,14
(IIg)	$C_{21}H_{17}N_3O_2$	73,60 73,45	4,82 4,99	12,50 12,24	(IVf)	$C_{21}H_{22}N_4O_5$	61,00 61,45	5,25 5,40	13,30 13,65
(IIh)	$C_{21}H_{17}N_3O_2$	73,50 73,45	4,92 4,99	12,38 12,24	(V)	$C_{13}H_{19}N_3O_3$	58,63 58,85	7,15 7,22	15,62 15,84

b. Compounds (Ib) and (IIIf) were separated from the residue after evaporation of benzene by fractional crystallization from ether. Compound (IVf) was isolated in 34% yield, in addition to (Ib) and (IIIf) (in 33% yield), with an excess of maleimide.

c. As in the previous case (method c), (IIf) was isolated, while 3% (IVf) was also obtained with excess maleimide.

Reaction with 2,4-Dimethyl-5-diphenylaminooxazole. a. Compound (Ii) precipitated directly from the reaction mixture and was recrystallized from ether.

b. The residue after evaporation of benzene was treated with 50% ethanol. The reaction at 80°C yields 100% (Ic).

c. After distilling off the solvent, (IIi) was identified by PMR spectroscopy.

Reaction with 2-Methyl-4-ethyl-5-diphenylaminooxazole. a. The PMR spectrum of the residue after removal of the ether showed the presence of (Id) and of the starting compounds.

b. The reaction at 80°C gives a quantitative yield of (Id).

c. Compound (IIj) was isolated by treatment as in the previous case (method b) and the diphenylamide of acetylaminobutyric acid was isolated from the filtrate after the removal of (IIj).

Reaction with 2-Methyl-5-methylphenylaminooxazole. a. The residue after the evaporation of the ether solvent was subjected to fractional crystallization from ethanol which yielded (IIc) and (IIIc).

b. After removal of the benzene, (IIc) and cis-(IIIc) were obtained by fractional crystallization from ethanol; the filtrates were evaporated and PMR spectroscopy showed the presence of trans-(IIIc). The percentage ratio of the isomers varied.

c. The residue after distilling of the acetic acid was treated with ethanol and (IIc) was separated.

Reaction with 2-Phenyl-5-methylphenylaminooxazole. a. The reaction mixture was maintained for 2 weeks at 20°C and then evaporated; (IId) was extracted by a large volume of ether, and (IIId) remained in the residue.

b. After reaction in refluxing toluene, the mixture was evaporated in vacuum and (IId) was extracted with ether; (IIId) was precipitated from the residue after evaporation of the mother liquid with 50% ethanol.

c. Compound (IId) was precipitated from the evaporated reaction mixture (reaction at 118°C) with ethanol.

The Reaction with 2-Methyl-4-phenyl-5-methylphenylaminooxazole. Compound (IIh) was isolated by the same treatment as in the previous case (method c).

The Reaction with 2-Phenyl-4-methyl-5-methylphenylaminooxazole. The reaction mixture obtained by method c was filtered. (IIId) was washed with CCl_4 and the mother liquids were evaporated and (IIg) was precipitated with ethanol.

CONCLUSIONS

1. Substituted 5-aminooxazoles enter two types of condensation with maleimide 1,4 cycloaddition and 1,3 addition at the C(2) and C(4) ring atoms which was observed for the first time for oxazoles. The former reaction leads to the formation of amino-substituted endoxopiperidine-4,5-dicarboximides, while the latter yields amides of Δ^1-pyrroline-3, 4,5-tricarboxylic acids.

2. The predominant condensation reaction depends mainly on the specific features of the starting oxazole and, to a lesser extent, on the solvent used.

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