CROATICA CHEMICA ACTA CCACAA 63 (2) 215—224 (1990)

CCA-1937

YU ISSN 0011-1643
UDC 547.787
Original Scientific Paper

Preparation of 2-Alkyl-4-methyl-5-amidooxazoles[1]

Nedjeljko Kujundžić and Berislav Glunčić

Research Institute PLIVA, Zagreb, Croatia, Yugoslavia

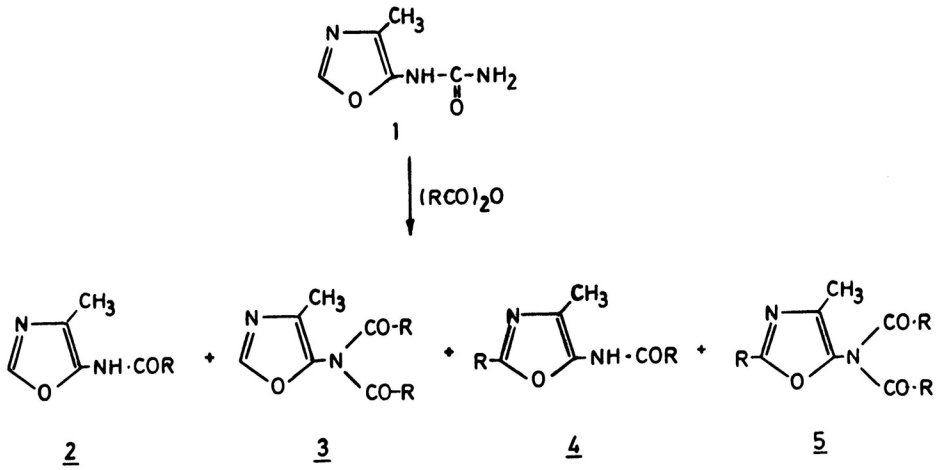
Received Oktober 13, 1989

2-Alkyl-4-methyl-5-amidooxazoles (*7*, *8*) were prepared by reaction of 4-methyl-5-amidooxazoles (*6*) with acylanhydrides. It was proposed that alkylation occurred with an opening of oxazole ring, rotation of C_4—N bond, and recyclization.

In the course of acylation of 4-methyl-5-aminooxazoles, it was detected that acylation was followed by partial alkylation of the oxazole ring; this result is reported here.

In general, 5-acylaminooxazoles can be prepared either by acylation of 5-aminooxazole, obtained *in situ* by cyclization of 2-formamidoproprionitril[2], or by transformation of a suitable functional group on oxazole ring. We used the latter method, reported by D'Olieslager[3], i.e. an acylation of oxazolylurea with acylanhydride. 5-Oxazolylurea was prepared from 4-methyl-5-oxazolylcarboxamide by the Hofmann reaction with amines[4].

The acylation of 4-methyl-5-oxazolylurea (*1*) with acetic anhydride gave 4-methyl-5-acetylaminooxazole[5] (*2*, R = CH_3) in high yield (80%), with *N*,*N*-



R = CH_3 ; C_2H_5

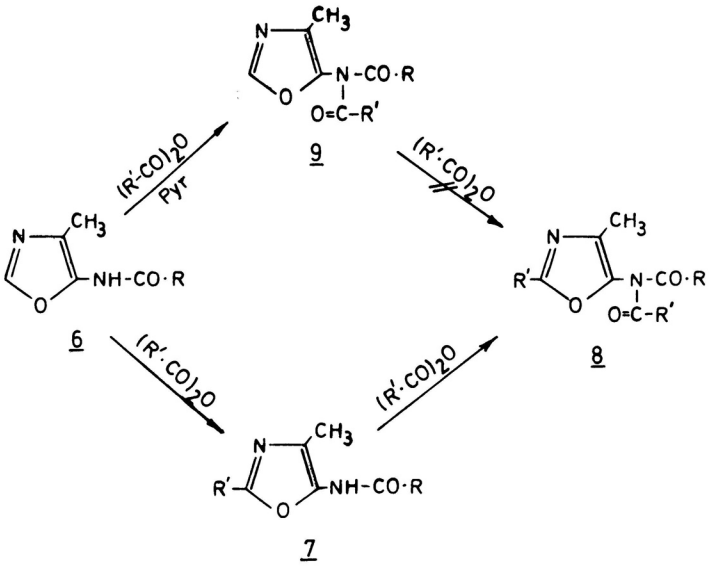
SCHEME 1

-diacetylderivate *3* (R = CH_3) as byproduct. However, in the reaction solution, two additional compounds were detected. Since alteration in the molar ratio of urea und anhydride gave higher yields of these compounds on account of product *2*; they were isolated and identified.

The isolated compounds were identified as C_2-methyl derivatives *4* and *5* (R = CH_3) of *N*-acyl and *N,N*-diacyl 4-methyl-5-aminooxazole, based on spectroscopic data and elemental analysis.

The ^1H NMR spectra of *4* and *5* resemble those recorded in *2* and *3*, except for the C—H band at δ 8.04 and δ 8.48, respectively, which was missing, and the presence of singlet at δ 2.35, attributed to methyl group.

Additional evidence for the proposed structure was obtained by synthesis of *4* and *5* from 2,4-dimethyl-5-oxazolylurea *7* (R = NH_2, R' = CH_3) in reaction with acetic anhydride. The obtained compounds were identical to those isolated in reaction of *1* with Ac_2O. Urea *7* (R = NH_2, R' = CH_3) was prepared by the same procedure as urea *1*.



SCHEME 2

Further study revealed that, when propionylanhydride was used, instead of acetylanhydride, a mixture of 2-ethyl *4* and *5* (R = C_2H_5) derivatives was obtained. Moreover, the acylation of 4-methyl-5-acetylamiooxazole (*6*, R = CH_3) with acylanhydride gave a mixture of C_2-alkylated products. Acylation with acetylanhydride gave *7* and *8* (R = R' = CH_3), whyle acylation with propionylanhydride gave *7* and *8* (R = CH_3, R' = C_2H_5). It follows that the acyl group of anhydride molecules was incorporated into the oxazole ring during acylation. Contraty to that, succinyl or phtalyl andydride gave, in the reac-

tion with 5-oxazolylurea *1*, under the same reaction conditions, only succinimido or phtalimido derivative. It can be concluded that the presence of proton on amide nitrogen is necessary for the alkylation to take place.

In a similar way, 4-methyl-5-oxazolylcarbamates[6] (*6*, R = OC_2H_5) with acetylanhydride gave C_2-alkyl *N*-acetylcarbamates *7* and *8* (R = OC_2H_5, R' = = CH_3). Similar results, obtained in an analogous reaction of acylation of 4--methyl-5-oxazolylcarbamate, indicate that C_2-alkylation is a common reaction to oxazoles having a NH—COR group at C_5-position.

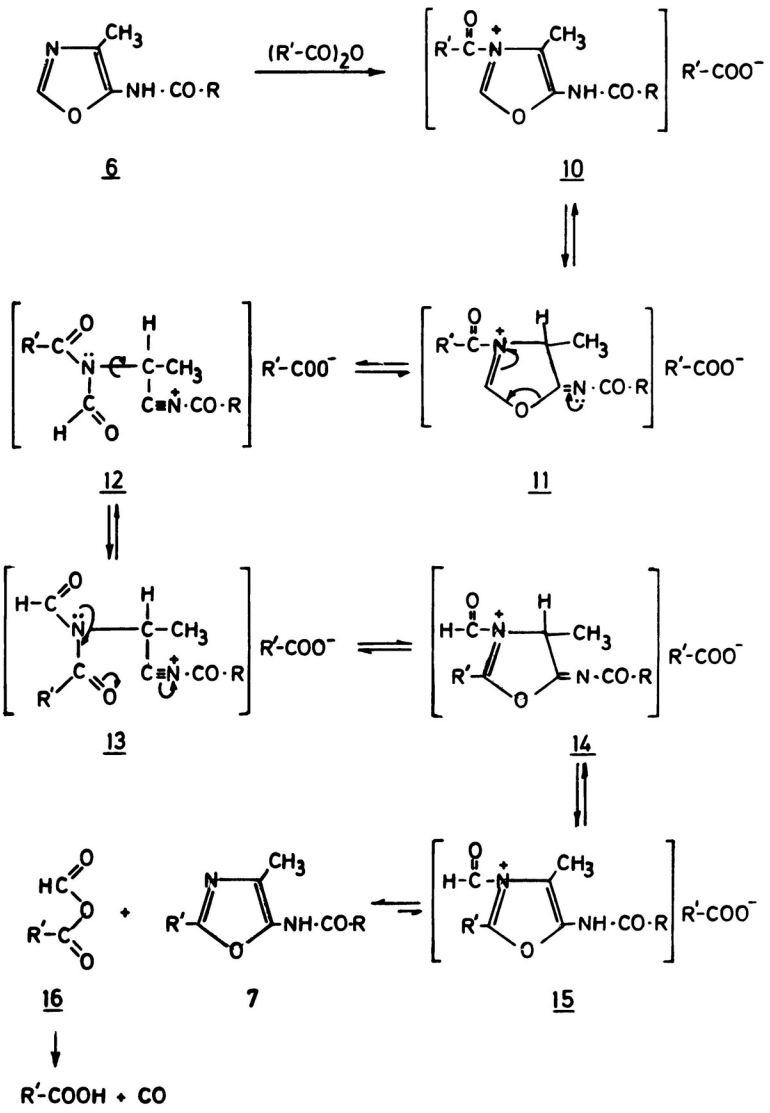
Apparently, the course of acylation reaction does not depend only on NH—COR group but also on the presence of a base or acid in the reaction solution. Results of this study are presented in the Table 1.

It can be seen that, at a constant ratio of *6* (R = CH_3) and Ac_2O, *N,N*--diacyl derivate 9 (R = R' = CH_3) was formed predominantly when a terciary base was present, while acid (AcOH) favoured the formation of alkylated product *7* (R = R' = CH_3).

TABLE I

Results of the reaction of 0.0035 mol of 4-methyl-5-acetylaminooxazole (2, R = = CH_3) and 0.053 mol acetic anhydride in the presence of various quantities of pyridine, triethylamine or acetic acid by heating the reaction mixture in a sealed tube at 80 °C and 140 °C.

Exp.	Pyridine ml	Et_3N ml	CH_3COOH ml	Temp. react. °C	YIELD		
					3 (R = CH_3) %	4 (R = CH_3) %	5 (R = CH_3) %
1	10.0	-	-	140	80.06	2.24	14.44
2	5.0	-	-	140	75.49	3.12	19.22
3	1.0	-	-	140	61.54	4.61	32.65
4	0.5	-	-	140	47.63	6.33	44.89
5	-	-	-	140	36.39	7.28	54.27
6	-	-	-	80	82.97	4.79	8.46
7	-	1.73	-	140	65.43	4.02	28.22
8	-		1.0	140	9.63	7.63	71.70



SCHEME 3

The mechanism of alkylation of oxazole at C_2-position during reaction with acylanhydrides can be explained by the opening of oxazole ring, followed by free rotation of a single C_4—N bond, and recyclization.

The process leading to the opening of oxazole ring probably involves 3-acyl-5-acylaminooxazolium salt *10*, generally formed in the reaction of oxa-

zoles with acylanhydrides. The next reaction step occurred only with 3-acyl--5-*mono*acylaminooxazolium salt *10* which can exist in tautomeric form *11* and may lead to the opening of oxazole ring. The formed open chain intermediate *12* can occure with one of the acyl groups. Cyclization of the nitrilium group with formyl would yield the starting oxazolium salt *11*, while reaction with other acyl group would give 3-formyloxazolinium product *14*, alkylated at C_2-position. Deacylation of *15* resulted in 7 and mixed anhydride *16*, which upon decomposition yielded carbon monoxide.

So far, no direct evidence of the existance of the given intermediates has been obtained. However, the proposed mechanism may be supported by the fact that *N,N*-diacyl derivatives do not undergo alkylation and that the acyl group, as a part of acylanhydride molecule, is incorporated in the oxazole ring at C_2-position. The presence of carbonmonoxide in the reaction product, detected by GC, can explain decomposition of mixed anhydride *16*.

Since the results of the application of this method for C_2-alkylation of 5-amidooxazoles are promising, further work in this direction is in progress.

EXPERIMENTAL

Melting and boiling points are uncorrected. The IR spectra were recorded with a Model 257 G Perkin-Elmer spectrometer. The ^1H NMR measurements were taken with an A-60 Varian, with TMS as the internal standard. GC was done on a GC-900 Perkin-Elmer with the flame-ionization detector. A glass 3 mm by 200 cm column with 3% OV-225 on Chromosorb G-HP was used for *N*-acetyl and *N,N*-diacetyl 4-methyl- and 2,4-dimethyl-5-aminooxazole separation. Column temperature was 150 °C. For carbonmonoxide separation, a column with a molecular sieve of 5 Å in diameter was used. Column temperature was 25 °C and the temperature of the injection block 100 °C. The detector was on thermal conductivity. TLC was conducted on orginal plates (Merck-Kieselgel HF_{254}), followed by detection with iodine vapour and UV absorption in a chloroform-methanol 9:1 solvent system.

4-Methyl-5-oxazolylurea (1)

In sodium hypochlorite water solution (80 ml; 0.1 mol: containing 10.2 g NaOCl in 100 ml of solution), sodium hydoxide (4.0 g; 0.1 mol) was dissolved, and to the obtained solution 4-methyl-5-oxazolecarboxamide (12.6 g; 0.1 mol) was added in portions at a temperature of 15 °C, the separated crystals were filtered and dissolved in 25% water solution of ammonia (80 ml; 1.08 mol). The solution was heated at 80 °C for 1 h and then cooled to 0 °C. The crystals formed were filtered and recrystallized from ethanol: Yield: 7.6 g (53%) of *1;* m.p. 218—220 °C.

Anal. $C_5H_7N_3O_2$ (141.13) calc'd: C 42.55; H 5.00; N 29.78%
found: C 42.74; H 4.79; N 29.93%.

IR spectrum (KBr): 3370(s), 3260(s), 3170(s), 3110(m), 1675(vs), 1580(w), 1525(m), 1495(vs), 1229(m), 1145(s), 1075(m) cm^{-1}.

^1H NMR spectrum (DMSO-d_6) δ: 1.93 (s, CH_5), 6.01 (s, NH_2), 7.96 (s, NH), 8.05 (s, C_2—H).

2,4-Dimethyl-5-oxazolylurea (7; $R = NH_2$, $R' = CH_3$)

A mixture of ethyl 2,4-dimethyl-5-oxazolecarboxylate (10.75 g; 0.063 mol) and 25% water solution of ammonia (50 ml; 0.67 mol) was mixed at room temperature for 5 hrs and then cooled to 0 °C. The crystals formed were fitered and recrystallized from ethanol, yielding 2,4-dimethyl-5-oxazolecarboxamide (5.1 g; 57 %), m.p. 223—225 °C.

Anal. $C_5H_8N_2O_2$ (140.14) calc'd: C 51.42; H 5.57; N 19.99%
found: C 51.53; H 5.59; N 19.74%.

IR spectrum (KBr): 3350(s), 3150(vs), 1675(vs), 1610(vs), 1550(s), 1420(vs), 1260(s), 1165(vs), 1110(s) cm^{-1}.

Acording to the procedure for proparation of *1*, 2,4-dimethyl-5-oxazolecarboxamide gave 2,4-dimethyl-5-oxazolylurea (21 %), m.p. 220—222 °C.

Anal. $C_6H_9N_3O_2$ (155.076) calc'd: C 46.44; H 5.85; N 27.08%
found: C 46.61; H 6.03; N 27.22%.

IR spectrum (KBr): 3290(s), 3130(s), 1670(vs), 1656(w), 1475(s), 1420(s), 1285(vs), 1240(s), 1115(m), 1070(m) cm^{-1}.

4-Methyl-5-acetylaminooxazole (2; R = CH_3)

A mixture of 4-methyl-5-oxazolylurea (14.1 g; 0.1 mol), acetic anhydride (12.2 g; 0.1 mol) and dry pyridine (90 ml) was heated under reflux for 3 hrs. After pyridine had evaporated, the residue was distilled under reduced pressure. Distillation at b.p. 120—125 °C/26.6 Pa gave viscous oil (11.4 g), which was rexrystallized from benzene-ethanol (8:1).

Yield: 9.7 g (69 %) of *2* (R = CH_3); m.p. 70—75 °C.

Anal. $C_6H_8N_2O_2$ (140.17) calc'd: C 51.42; H 5.57; N 19.99%
found: C 51.63; H 5.68; N 19.97%.

IR spectrum (KBr): 3170(m), 3120(m), 1710(vs), 1655(s), 1645(m), 1500(s), 1130(s) cm^{-1}.

^1H NMR (DMSO-d_6) δ: 1.95 (s, CH_3), 2.02 (s, $COCH_3$), 8.04 (s, C_2—H), 9.67—10.0 (broad s, NH).

4-Methyl-5-propionylaminooxazole (2; R = C_2H_5)

According to the above procedure, 1 treated with propinylanhydride gave 48 % of *2* (R = C_2H_5); b.p. 95—100 °C/26.6 Pa.

Anal. $C_7H_{10}N_2O_2$ (154.17) calc'd: C 54.53; H 6.54; N 18.17%
found: C 54.33; H 6.75; N 17.99%.

IR spectrum (100%): 3250(m), 3318(m), 3120(w), 1660(vs), 1490(s), 1225(s), 1125(s), 1070(s) cm^{-1}.

^1H NMR (DMSO-d_6) δ: 1.07 (t, CH_2—CH_3), 2.34 (q, CH_2), 1.95 (s, CH_3), 8.03 (s, C_2—H), 9.5—10.0 (broad s, NH).

4-Methyl-5-(3',4',5'-trimethoxybenzylamino)-oxazole
(2; R = 3,4,5-(CH_3O)$_3$—C_6H_2)

According to the above procedure, *1* treated with 3,4,5-trimethoxybenzoic anhydride gave, after evaporation of pyridine, a residue which was suspended in water, and the crystalls formed were filtred. The filtrate was extracted with chloroform (3 × 20 ml), chloroform extract washed with saturated sodium bicarbonate solution (40 ml), chloroform layer dried and evaporated to dryness. The residue was recrystallized from benzene.

Yield: 22% of *2* (R = 3,4,5-(CFH_3O)$_3$—C_6H_2); m.p. 142—144 °C.
Anal. $C_{14}H_{16}N_2O_5$ (292,28) calc'd: C 57.53; H 5.52; N 9.59%.
found: C 57.81; H 5.73; N 9.72%.

IR spectrum (KBr): 3190(m), 3130(w), 1680(m), 1650(s), 1580(vs), 1500(s), 1235(vs), 1125(vs) cm^{-1}.

4-Methyl-5-diacetylaminooxazole 3; *(R = CH_3)* (9; *R = R' = CH_3)*

a.

A mixture of 4-methyl-5-oxazolylurea (1.0 g; 0.0071 mol), acetic anhydride (7.2 g; 0.071 mol) and dry pyridine (10 ml) was heated under reflux for 3 hrs. After evaportion of pyridine, the residue was dissolved in chloroform (20 ml), the solution washed with saturated solution of sodium bicarbonate (20 ml), dried and evaporated to dryness. The oily residue was submitted to chromatography on silica gel column in the solvent system chloroform-methanol 9:1. Eluation with the same solvent gave an oily residue which was distilled under reduced pressure.

Yield: 0.72 g (56%) of *3* (R = CH_3); m.p. 38—40 °C; R_f = 0.85.

Anal. $C_8H_{10}N_2O_3$ (182.18) calc'd: C 52.74; H 5.53; N 15.38%
found: C 52.19; H 5.79; N 15.15%.

IR spectrum (100%): 3110(m), 1725(vs), 1605(s), 1500(s), 1420(s), 1400(s), 1370(vs), 1270(vs), 1230(vs), 1195(vs), 1145(s), 1070(s), 1020(s) cm^{-1}.

^1H NMR (DMSO-d_6) δ: 2.04 (s, CH_3), 2.3 (s, 2 CO—CH_3), 8.46 (s, C_2—H).

b.

A mixture of 4-methyl-5-acetylaminoxazole (2.0 g; 0.014 mol), acetic anhydride (10.8 g; 0.105 mol) and dry pyridine (10 ml) was refluxed for 1 hrs. After evaporation of the solution to dryness, an oily residue was obtained which was dissolved in chloroform (20 ml). The solution was washed with saturated solution of $NaHCO_3$, treated with active charcoal, dried and the chloroform was evaporated.

Yield: 1.97 g (75%) of 3 (R = CH_3); m.p. 38—40 °C.
IR spectrum was identical with those obtained under *a.*

4-Methyl-5-dipropionylaminooxazole 3; *(R = C_2H_5)* (9; *R = R' = C_2H_5)*

According to the above procedure *(a)*, *1* treated with propionylanhydride gave 45% of *3* (R = C_2H_5); b.p. 95—105 °C/20 Pa; R_f = 0.85.

Anal. $C_{10}H_{14}N_2O_3$ (210.20) calc'd: C 57.14; H 6.70; N 13.32%
found: C 57.45; H 6.35; N 13.68%.

IR spectrum (100%): 3120(m), 2940(s), 2880(m), 1760(m), 1715(vs), 1645(s), 1550(m), 1495(s), 1455(s), 1345(s), 1135(vs), 1070(s), 865(m), 810(m) cm^{-1}.
^1H NMR (DMSO-d_6) δ: 1.13 (t, CH_2—CH_3), 2.07 (s, CH_3), 2.63 (q, CH_2), 7.88 (s, C_2—H).

4-Methyl-5-succinimidooxazole (3; *R—R = CH_2—CH_2)*

According to the above procedure *(a)*, *1* treated with succinic anhydride gave 47% of *3* (R—R = CH_2—CH_2); m.p. 107—108 °C (ethanol).

Anal. $C_5H_8N_2O_3$ (180.16) calc'd: 53.33; H 4.48; N 15.55%
found: 53.52; H 4.43; N 15.80%.

IR spectrum (KBr): 3120(m), 1790(m), 1725(vs), 1660(m), 1500(s), 1410(s), 1155(s) cm^{-1}.
^1H NMR (DMSO-d_6) δ: 2.0 (s, CH_3), 2.85 (s, CH_2—CH_2), 8.36 (s, C_2—H).

4-Methyl-5-phthalimidooxazole (3; *R—R = o—C_6H_4)*

According to the above procedure *(a)*, *1* treated with phthalic anhydride gave 19% of *3* (R—R = o—C_6H_4); m.p. 220—222 °C (ethanol).

Anal. $C_{12}H_8N_2O_3$ (228.2) calc'd: C 63.16; H 3.35; N 12.28%
found: C 63.10; H 3.35; N 12.02%.

IR spectrum (KBr): 3125(m), 1790(s), 1740(vs), 1665(m), 1610(w), 1375(vs), 1115(s) cm^{-1}.

2,4-Dimethyl-5-acetylaminooxazole (4; R = CH_3) and 2,4-Dimetil-5-diacetylaminooxazole (5; R = CH_3)

a.

A mixture of 4-methyl-5-oxazolylurea (*1*) (2.82 g; 0.02 mol) and acetic anhydride (20.2 g; 0.2 mol) was heated under reflux for 3 hrs. The solution was evaporated under reduced pressure to dryness. The residue was dissolved in chloroform (20 ml) and chloroform solution extracted with water (4 × 10 ml). Aqueous layers were evaporated to dryness and the residue distilled under reduced pressure.

Yield: 0.51 g (17%) of *4* (R = CH_3); b.p. 100—105 °C / 26.6 Pa; R_f = 0.6.

Anal. $C_7H_{10}N_2O_2$ (154.11) calc'd: C 54.51; H 6.54; N 18.18%
found: C 54.30; H 6.79; N 18.38%.

IR spectrum (100%): 3240(m), 3160(m), 1665(vs), 1570(s), 1500(s), 1430(w), 1355(m), 1270(vs) cm^{-1}.

^1H NMR ($CDCl_3$) δ: 2.0 (s, C_4—CH_3), 2.15 (s, CO—CH_3), 2.35 (s, C_2—CH_3), 9.07 (s, NH).

The chloroform layer was dried ($MgSO_4$), the solvent evaporated and the residue distilled under reduced pressure.

Yield: 2.42 g (62%) of *5* (R = CH_3); b.p. 90—92 °C / 26.6 Pa; R_f = 0.9.

Anal. $C_9H_{12}N_2O_3$ (196.1) calc'd: C 55.07; H 6.16; N 14.28%
fornd: C 55.32; H 6.28; N 14.07%.

IR spectrum (100%): 1670(vs), 1570(m), 1415(w), 1315(s), 1270(vs), 1230(vs), 1200(vs), 1100(m), 1020(s) cm^{-1}.

^1H NMR ($CDCl_3$) δ: 2.02 (s, C_4—CH_3), 2.33 (s, CO—CH_3), 2.45 (s, C_2—CH_3).

b.

A mixture of 4-methyl-5-acetylaminooxazole (*3*; R = CH_3) (2.0 g; 0.014 mol), acetic anhydride (21.86 g; 0.214 mol) and acetic acid (4 ml) was heated under reflux for 1 h. The solution was evaporated under reduced pressure to dryness. The oily residue was submitted to chromatography on silica gel column in the solvent system chloroform-methanol (9:1). Eluation with the same solvent gave 0.34 g (15%) of *4* (R = CH_3) with R_f = 0.6 ($CHCl_3$—MeOH = 9:1) and 1.25 g (45%) of *5* (R = CH_3) with R_f = 0.9.

IR and ^1H NMR spectral data were identical with those obtained under *a.*

c.

A mixture of 2,4-dimethyl-5-oxazolylurea (*7*; R = NH_2) (0.6 g; 0.0038 mol), acetic anhydride (2.37 g; 0.0232 mol) and dry pyridine (2.5 ml) was heated under reflux for 3 hrs. Evaporation of the solution under reduced pressure gave an oily residue which was submitted to chromatography on silica gel column in the solvent system chloroform-methanol (9:1). Eluation with the same solvent gave 0.245 g (41%) of *4* (R = CH_3), with R_f = 0.6 ($CHCl_3$—MeOH = 9:1) and 0.43 g (57%) of *5* (R = CH_3) with R_f = 0.9.

IR and ^1H NMR spectral data were identical with those obtained under *a.*

2-Ethyl-4-methyl-5-propionylaminooxazole (4; R = C_2H_5) and 2-Ethyl-4-methyl--5-dipropionylaminooxazole (5; R = C_2H_5)

According to the above procedure (a), *1* treated with propionic anhydride gave an oily residue which distilled under reduced pressure. Distillation at b.p. 107—110 °C / 53.3 Pa gave 24% of *5* (R = C_2H_5); R_f = 0.9.

Anal. $C_{12}H_{18}N_2O_3$ (238.16) calc'd: C 60.64; H 7.26; N 11.76%
found: C 60.43; H 7.89; N 11.88%.

IR spectrum (100%): 2980(s), 2940(s), 2880(m), 1725(vs), 1665(m), 1570(s), 1460(m), 1410(m), 1350(s), 1285(m), 1255(s), 1195(vs), 1130(vs), 1070(s), 990(m), 950(m) cm^{-1}.
^1H NMR ($CDCl_3$) δ: 1.02 (t, CO—CH_2—CH_3), 1.12 (t, CH_2—CH_3), 1.92 (s, CH_3), 2.28 (q, CO—CH_2—CH_3), 2.80 (q, CH_2—CH_3).

Further distillation at b.p. 115—120 °C / 53.3 Pa yielded 61% of *4* (R = C_2H_5); R_f = 0.6.

Anal. $C_9H_{14}N_2O_2$ (182.22) calc'd: C 59.32; H 7.74; N 15.37%
found: C 59.53; H 8.00; N 15.85%.

IR spectrum (100%): 3250(s), 3170(s)- 2970(vs), 2940(s), 2880(m), 1690(s), 1655(vs), 1570(s), 1500(s), 1460(s), 1370(s), 1325(m), 1285(m), 1235(vs), 1195(m), 1100(m), 1080(s) cm^{-1}.
^1H NMR ($CDCl_3$) δ: 1.15 (t, CO—CH_2—CH_3), 1.24 (t, CH_2—CH_3), 2.02 (s, CH_3), 8.3—8.6 (broad s, NH).

2-Ethyl-4-methyl-5-acetylaminoxazole (7; R = CH_3; R' = C_2H_5) and 2-Ethyl-4-methyl-5-acetylpropionylaminooxazole (8; R = CH_3; R' = C_2H_5)

A mixture of 4-methyl-5-acetylaminooxazole *2* (R = CH_3) (3.0 g; 0.021 mol), propionic anhydride (39.0 g; 0.3 mol) and propionic acid (3.0 ml) was heated under reflux for 1 h. After evaporation of unreacted propionic anhydride and propionic acid the oily residue (4.0 g) was obtained which was submitted to chromatography on silica gel column in the solvent system chloroform-methanol (9:1). Eluation with the same solvent gave a fraction with R_f = 0.9 which upon distillation under reduced pressure gave 2.9 g (58.7%) af *8* (R = CH_3; R' = C_2H_5); b.p. 90 °C / 53.3 Pa.

Anal. $C_{11}H_{16}N_2O_3$ (224.25) calc'd: C 58.91; H 7.19; N 12.49%
found: C 59.19; H 7.36; N 12.20%.

IR spectrum (100%): 2990(s), 2950(vs), 2885(m), 1730(vs), 1575(s), 1460(m), 1355(s), 1255(s), 1195(vs), 1130(vs), 1075(s), 1015(m), 990(m), 955(w), 870(m) cm^{-1}.

Further eluation gave a fraction with R_f = 0.6, which upon distillation under reduced pressure gave 0.39 g (8.9%) of *7* (R = CH_3; R' = C_2H_5); b.p. 100 °C / 53.3 Pa.

Anal. $C_8H_{12}N_2O_2$ (168.19) calc'd: C 57.13; H 7.14; N 16.66%
found: C 57.26; H 7.16; N 16.62%.

IR spectrum (100%): 3260(m), 2994(s), 2990(s), 2870(m), 1660(vs), 1525(vs), 1460(s), 1370(s), 1325(m), 1280(m), 1230(s), 1150(m), 1095(w), 1070(m), 1010(w), 990(w) cm^{-1}.

Ethyl N-Acetyl-4-methyl-5-oxazolylcarbamate (9; R = OC_2H_5; R' = CH_3)

A mixture of ethyl 4-methyl-5-oxazolylcarbamate (1.0 g; 0.0059 mol), acetic anhydride (1.2 g; 0.012 mol) and dry pyridine (7 ml) was heated under reflux for 3 hrs. The solution was evaporated and an oily residue distilled under reduced pressure.

Yield: 1.05 g (84%) of *9* (R = C_2H_5; R' = CH_3); R_f = 0.9.

Anal. $C_9H_{12}N_2O_4$ (212.11) calc'd: C 50.94; H 5.70; N 13.20%
found: C 51.00; H 5.60; N 13.44%.

IR spectrum (100%): 3130(w), 2930(m), 1795(m), 1760(vs), 1730(vs), 1660(m), 1500(s), 1395(s), 1370(s), 1270(vs), 1240(vs), 1180(m), 1125(s), 1090(vs), 1025(m), 995(s), 935(m), 915(m) cm^{-1}.

Ethyl 2,4-Dimethyl-5-oxazolylcarbamate (7; R = OC_2H_5; R' = CH_3) and Ethyl N-Acetyl-2,4-dimethyl-5-oxazolylcarbamate (8; R = OC_2H_5; R' = CH_3)

A mixture of ethyl 4-methyl-5-oxazolylcarbamate (1.0; 0.0059 mol) and acetic anhydride (5.4 g; 0.053 mol) was heated under reflux for 1 h. The solution was evaporated to an oily residue which was submitted to chromatography on silica

gel column in the solvent system chloroform-methanol (9:1). The fraction containing substance with $R_f = 0.6$ upon distillation under reduced pressure gave 0.47 g (43.5%) of 7 (R = OC_2H_5; R' = CH_3); b.p. 90 °C / 66.6 Pa.

Anal. $C_8H_{12}N_2O_3$ (184.19) calc'd: C 52.16; H 6.57; N 15.21%
found: C 52.00; H 6.85; N 15.00%.

IR spectrum (100%): 3265(m), 3175(m), 2970(m), 2930(m), 1740 (vs), 1680(vs), 1590(s), 1510(s), 1445(m), 1385(m), 1310(m), 1280(s), 1240(vs), 1175(w), 1095(s), 1060(vs), 960(m), 910(m) cm^{-1}.

^1H NMR ($CDCl_3$): 1.26 (t, CH_2—CH_3), 2.03 (s, C_4—CH_3), 2.34 (s, C_2—CH_3), 4.32 (q, CH_2), 6.56—6.8 (broad s, NH).

The fraction containing substance with $R_f = 0.9$ upon distillation under reduced pressure gave 0.39 g (29%) of *8* (R = C_2H_5; R' = CH_3); b.p. 80 °C/66.6 Pa.

Anal. $C_{10}H_{14}N_2O_4$ (226.23) calc'd: C 53.09; H 6.24; N 12,38%
found: C 53.19; H 6.19; N 12.10%.

IR spectrum (100%): 2975(m), 2920(m), 1795(w), 1755(vs), 1730(vs), 1670(m), 1575(s), 1445(m), 1370(s), 1345(m), 1310(s), 1280(vs), 1245(vs), 1220(vs), 1170(vs), 1090(s), 1030(m), 1000(s), 960(m), 920(m) cm^{-1}.

^1H NMR ($CDCl_3$) δ: 1.24 (t, CH_2—CH_3), 1.95 (s, C_4—CH_3), 2.27 (s, C_2—C_3), 2.52 (s, CO—CH_3), 4.26 (q, CH_2)

b.

A solution of 2,4-dimethyl-5-oxazolecarboxylic acid azide (0.5 g; 0.0035 mol) in anhydrous ethanol *(15 ml)* was heated under reflux for 5 hrs. The solvent was evaporated and the oily residue was distilled under reduced pressure to give 0.55 g (89%), b.p. 90 °C/66.6 Pa of ethyl 2,4-dimethyl-5-oxazolylcarbamate (7; R = OC_2H_5; R' = CH_3).

A mixture of ethyl 2,4-dimethyl-5-oxazolylcarbamate (0.3 g; 0.00163 mol) and acetic acid anhydride (7 ml) was heated under reflux for 2 hrs. The solvent was evaporated and the oily residue was distilled under reduced pressure to give 0.32 g (87%) of ethyl N-acetyl-2,4-dimethyl-5-oxazolylcarbamate (*8*; R = C_2H_5; R' = CH_3); b.p. 80 °C/66.6 Pa.

IR and ^1H NMR spectral data were identical with those obtained under a.

Acknowledgements. — The authors thank Dr. Rudolf Novina and Mrs. Dubravka Smojver for GC measurements.

REFERENCES

1. Taken in part from N. Kujundžić, (1981) *Ph. D. thesis.*
2. S. Schimada, *J. Heterocyclic Chem.* **24** (1987) 1237.
3. W. D'Olieslager, and I. De Aguirre, *Bull. Soc. Chim. Fr.* 1967, 179.
4. N. Kujundžić, and B. Glunčić, *Yugoslav Patent Appl. (to PLIVA)* P-2205/79 (1979).
5. N. Kujundžić, and B. Glunčić, *Yugoslav Patent Appl. (to PLIVA)* P-7/81 (1981).
6. M. Hoffer, US Patent *(to Hoffman-La Roche)* 3,290,326 (1966).

SAŽETAK

Priprava 2-alkil-4-metil-5-amidooksazola

Nedjeljko Kujundžić i Berislav Glunčić

2-Alkil-4-metil-5-amidooksazoli (*7*, *8*) pripravljeni su reakcijom 4-metil-5-amidooksazola (*6*) s anhidridima karboksilnih kiselina. Pretpostavljeno je da se alkiliranje odvija uz otvaranje oksazolskog prstena, rotaciju veze C_4—N i ponovnu ciklizaciju.