

**4-ETHOXYMETHYLENE-2-PHENYL-5(4H)-OXAZOLONE AS A SYNTHON
FOR THE SYNTHESIS OF SOME FUSED PYRIMIDINES**

Vladimir Kepe, Marijan Kočevár*, and Slovenko Polanc

Department of Chemistry and Chemical Technology,
University of Ljubljana, Askerčeva 5, 61000 Ljubljana,
Slovenia

Abstract - Treatment of 4-ethoxymethylene-2-phenyl-5(4H)-oxazolone with nitrogen-containing heterocycles, having amino group in *ortho* position to the ring nitrogen, leads to the corresponding 4-(arylamino-methylene)-2-phenyl-5(4H)-oxazolones, which can be further converted into different fused pyrimidinones. The (Z)-structure of the oxazolone exocyclic double bond has been determined on the basis of ^{13}C nmr spectroscopy.

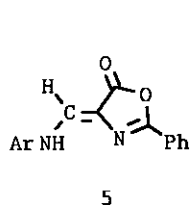
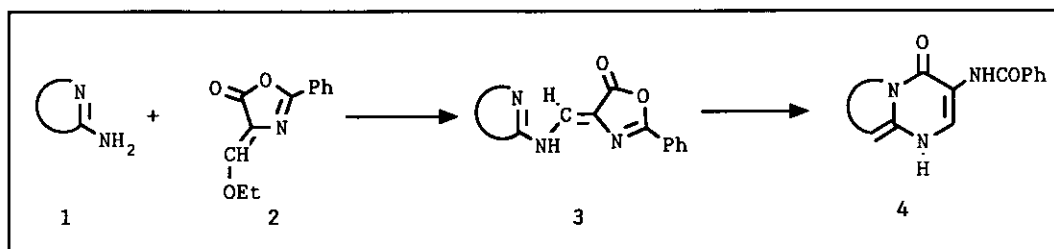
The ethoxy group in 4-ethoxymethylene-2-phenyl-5(4H)-oxazolone (2) has been substituted with different nucleophiles.¹⁻³ These conversions took place under different reaction conditions, neutral, acidic or basic. Tsuge and Noguchi have described the transformations of oxazolone (2) with 1,3-binucleophiles such as 2-aminopyridines, 2-aminothiazole and 2-amino-

Dedicated to Prof. Dr. Edward C. Taylor, Professor of Princeton University, on the occasion of his 70th birthday.

pyrimidine into the corresponding aminomethyleneoxazolones and fused pyrimidinones.⁴

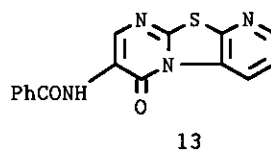
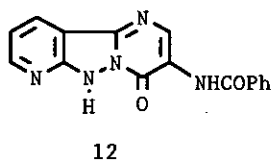
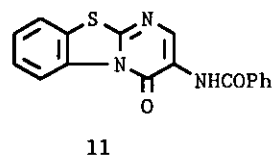
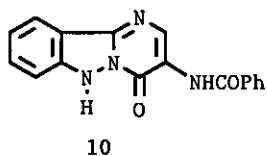
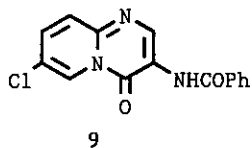
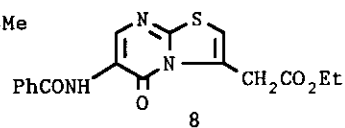
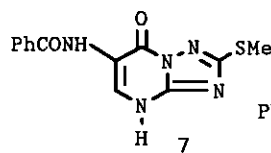
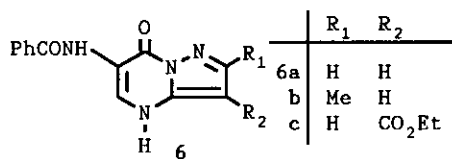
In this paper we report transformations of some aminoheterocycles (1) with ethoxymethyleneoxazolone (2) into 4-(arylaminomethylene)-2-phenyl-5(4*H*)-oxazolones of type 5 and fused pyrimidinones of type 4 (or eventually tautomeric form). We also describe two structure determinations of the exocyclic oxazolone double bonds. In continuation of our work,⁵ we prepared several 4-(arylaminomethylene)-2-phenyl-5(4*H*)-oxazolones (5a-i), starting from different aminoheterocycles and compound (2) in ethanolic solutions in high yields. These compounds can exist in several tautomeric forms and in two types of geometric isomers. They were studied by ¹³C nmr spectroscopy in order to get some data about the configurations of the exocyclic oxazolone double bonds. We used the method in which the magnitude of the coupling constant between the oxazolone carbon 5-C and vicinal proton of the exocyclic CH group was examined.^{5,6} 5-Methyl-1*H*-pyrazolyl derivative (5b) and 1*H*-pyrazolo[3,4-*b*]pyridinyl derivative (5i) were examined by this method. In DMSO-*d*₆ at 80 °C we found the following vicinal coupling constants: for 5b 2.6 Hz at 166.9 ppm and for 5i 2.7 Hz at 167.0 ppm. These values are typical for (*Z*)-isomers and are in accordance with our previous results⁵ and with the X-ray analysis of a compound of this type.⁷ The NH proton in a compound of type 5 could be localized as shown in the structure 5, where in ¹H nmr CHNH fragment appears as two doublets (see 5i: *J*=12.2 Hz). When the signals of this fragment are covered with the signals of the other groups and when they are singlets or broad singlets (instead of doublets), the participation of the tautomeric form having NH proton on the heterocyclic ring can not be excluded.

On the other hand, on heating in acetic acid or in a mixture of pyridine and triethylamine, the starting compounds (1) and (2) have been directly converted into the fused pyrimidinones (6-13), which can also be formed from the intermediates (5) either thermally without any solvent (on the



	Ar
5a	1H-Pyrazolyl-3
b	5-Methyl-1H-pyrazolyl-3
c	4-Ethoxycarbonyl-1H-pyrazolyl-3
d	5-Methylthio-1H-1,2,4-triazolyl-3
e	4-Ethoxycarbonylmethyl-2-thiazolyl

	Ar
5f	5-Chloro-2-pyridinyl
g	1H-Indazolyl-3
h	2-Benzothiazolyl
i	1H-Pyrazolo[3,4-b]pyridin-3-yl



Kofler micro hot stage) or on heating in the previously mentioned solutions (as shown in the case of pyrido[2',3':3,4]pyrazolo[1,5-*a*]pyrimidine derivative (12). All reactions were followed by tlc. We would like to note that in the case of 3-amino-5-methylthio-1*H*-1,2,4-triazole two products might be formed, namely the [1,2,4]-triazolo[1,5-*a*]pyrimidine derivative (7) and isomeric *N*-[3-methylthio-5-oxo-5,8-dihydro-1,2,4-triazolo[4,3-*a*]pyrimidin-6-yl]benzamide. Based on the known results,^{8,9} under our conditions the formation of the compound (7) seems to be more plausible.

EXPERIMENTAL

Melting points were determined on a Kofler micro hot stage. Nmr spectra were recorded with a JEOL JNM FX90Q, Varian EM360L, and Varian VXR 300 instruments, using TMS as internal standard. Mass spectra were recorded with a VG-Analytical AutoSpecEQ instrument. Elemental analyses (C, H, N) were performed with a Perkin Elmer 2400 CHN Analyzer. Tlc was carried out on Fluka silica gel tlc cards. Compound (2),¹⁰ 3-aminoindazol,¹¹ 3-aminopyrazolo[3,4-*b*]pyridine,¹² and 2-aminothiazolo[4,5-*b*]pyridine¹³ were prepared as described in the literature. All other reagents were used as received from commercial sources.

General procedure for the synthesis of 4-(arylaminomethylene)-2-phenyl-5(4*H*)-oxazolones (5a-i). A mixture of the corresponding amino compound (1 mmol) and 4-ethoxymethylene-2-phenyl-5(4*H*)-oxazolone (2) (217 mg, 1 mmol) in 2-4 ml of dry ethanol was heated under reflux for 1 h (in the case of 5b 3 h of heating; in the case of 5c and 5i 4 h at room temperature). After evaporation of the solvent 1 ml of ethanol was added to the residue. Upon cooling the solid product was taken by filtration and washed with a small amount of ethanol.

The following compounds were prepared by this method:

5a: From 3-amino-1*H*-pyrazole and **2** in 90% yield. mp about 250 °C conversion into **6a** (from EtOH); ¹H nmr (90 MHz, DMSO-*d*₆) δ 6.16 (1H, d, *J*=2.2 Hz, 4'-H), 7.53-7.60 (3H, m, Ph), 7.70 (1H, d, *J*=2.2 Hz, 5'-H), 7.96 (3H, m, CH, Ph), 10.9 (1H, br s, NH), 12.56 (1H, br s, NH). Anal. Calcd for C₁₃H₁₀N₄O₂: C, 61.41; H, 3.96; N, 22.04. Found: C, 61.18; H, 3.85; N, 22.07.

5b: From 3-amino-5-methyl-1*H*-pyrazole and **2** in 87% yield. mp about 250 °C conversion into **6b** (EtOH/DMF); ¹H nmr (60 MHz, DMSO-*d*₆) δ 2.23 (3H, s, Me), 5.97 (1H, s, 4'-H), 7.60 (3H, m, Ph), 8.00 (3H, m, CH, Ph), 10.93 (1H, br s, NH), 12.33 (1H, br s, NH). Anal. Calcd for C₁₄H₁₂N₄O₂: C, 62.68; H, 4.51; N, 20.88. Found: C, 62.56; H, 4.48; N, 20.92.

5c: From 3-amino-5-ethoxycarbonyl-1*H*-pyrazole and **2** in 66 % yield. mp about 250 °C conversion into **6c** (EtOH/DMF); ¹H nmr (60 MHz, DMSO-*d*₆) δ 1.37 (3H, t, *J*=7 Hz, OCH₂CH₃), 4.35 (2H, q, *J*=7 Hz, OCH₂CH₃), 7.63 (3H, m, Ph), 7.87-8.12 (3H, m, CH, Ph), 8.37 (1H, s, 5'-H), 10.3 (1H, br, NH), 13.4 (1H, br s, NH). Anal. Calcd for C₁₆H₁₄N₄O₄: C, 58.89; H, 4.32; N, 17.17. Found: C, 58.49; H, 4.29; N, 17.02.

5d: From 3-amino-5-methylthio-1*H*-1,2,4-triazole and **2** in 82% yield. mp 223-225 °C with conversion into **7** (EtOH/DMF); ¹H nmr (90 MHz, DMSO-*d*₆) δ 2.63 (3H, s, Me), 7.58 (3H, m, Ph), 7.87-8.02 (3H, m, CH, Ph). Anal. Calcd for C₁₃H₁₁N₅O₂S: C, 51.82; H, 3.68; N, 23.24. Found: C, 51.83; H, 3.67; N, 23.08.

5e: From 2-amino-4-(ethoxycarbonylmethyl)thiazole and **2** in 82% yield. mp 169-171 °C (EtOH/DMF); ¹H nmr (60 MHz, DMSO-*d*₆) δ 1.22 (3H, t, *J*=7 Hz, CH₃CH₂O), 3.72 (2H, s, CH₂), 4.13 (2H, q, *J*=7 Hz, CH₃CH₂O), 7.08 (1H, s, 5'-H), 7.62 (3H, m, Ph), 7.92-8.17 (3H, m, CH, Ph), 12.07 (1H, br s, NH). Exact Mass Calcd for C₁₇H₁₅N₃O₄S: 357.0783. Found: 357.0773.

5f: From 2-amino-5-chloropyridine and **2** in 77% yield. mp 224-228 °C (MeOH/DMF); ¹H nmr (60 MHz, DMSO-*d*₆) δ 7.37 (1H, d, *J*=9 Hz, 3'-H), 7.62

(3H, m, Ph), 7.93 (1H, dd, $J=9$ Hz and 2.6 Hz, 4'-H), 7.93-8.13 (2H, m, Ph), 8.33 (1H, br s, CH), 8.42 (1H, d, $J=2.6$ Hz, 6'-H). Anal. Calcd for $C_{15}H_{10}ClN_3O_2$: C, 60.11; H, 3.36; N, 14.02. Found: C, 60.31; H, 3.08; N, 13.74.

5g: From 3-amino-1H-indazole and 2 in 93% yield. mp about 250 °C conversion into 10 (EtOH/DMF); 1H nmr (90 MHz, DMSO- d_6) δ 7.13 (1H, deg ddd, 6'-H), 7.40-7.63 (5H, m, 4'-H, 5'-H, 3H of Ph), 7.98-8.24 (4H, m, 7'-H, CH, 2H of Ph), 11.46 (1H, br, NH), 12.74 (1H, br s, NH); ms (m/z) 304 (M^+ , 38%). Anal. Calcd for $C_{17}H_{12}N_4O_2$: C, 67.10; H, 3.97; N, 18.41. Found: C, 66.85; H, 3.92; N, 18.66.

5h: From 2-aminobenzothiazole and 2 in 55% yield. mp 216-219 °C (EtOH/DMF); 1H nmr (90 MHz, DMSO- d_6) δ 7.18-8.13 (10H, m, Ph, 4'-H, 5'-H, 6'-H, 7'-H, CH), 12.2 (1H, br s, NH). Anal. Calcd for $C_{17}H_{11}N_3O_2S$: C, 63.54; H, 3.45; N, 13.08. Found: C, 63.37; H, 3.42; N, 13.07.

5i: From 3-amino-1H-pyrazolo[3,4-b]pyridine and 2 at room temperature in 77% yield. mp above 200 °C conversion into 13 (EtOH/DMF); 1H nmr (60 MHz, DMSO- d_6) δ 7.23 (1H, dd, $J=8$ and 5 Hz, 5'-H), 7.62 (3H, m, Ph), 8.05 (2H, m, Ph), 8.15 (1H, d, $J=12.2$ Hz, CH), 8.55-8.77 (2H, two deg dd, 4'-H, 6'-H), 11.68 (1H, br d, $J=12.2$ Hz, NH), 13.37 (1H, br s, NH). Anal. Calcd for $C_{16}H_{11}N_5O_2$: C, 62.95; H, 3.63; N, 22.94. Found: C, 63.23; H, 3.69; N, 22.94.

General procedure for the synthesis of fused pyrimidines (6-13). A mixture of the corresponding amino compound (2 mmol) and 4-ethoxymethylene-2-phenyl-5(4H)-oxazolone (2) (434 mg, 2 mmol) in 4 ml of acetic acid (or in a mixture of 4 ml of pyridine and 0.2 ml of triethylamine, Py/ NEt_3) was heated under reflux for 4-20 h (see below). After evaporation of the solvent 2 ml of ethanol was added to the residue. Upon cooling the solid product was taken by filtration and washed with a small amount of ethanol.

The following compounds were prepared by this method:

N-[7-Oxo-4,7-dihydropyrazolo[1,5-a]pyrimidin-6-yl]benzamides (6):

a: From 3-amino-1*H*-pyrazole and 2 in AcOH after 4 h in 32% yield; in Py/ NEt_3 , 20 h, 61% yield. mp above 300 °C (EtOH/DMF); ^1H nmr (90 MHz, DMSO-d_6) δ 6.23 (1H, d, $J=2$ Hz, 3-H), 7.55 (3H, m, Ph), 7.90-8.06 (3H, m, 2-H, Ph), 8.35 (1H, s, 5-H), 9.59 (1H, br s, NH). Anal. Calcd for $\text{C}_{13}\text{H}_{10}\text{N}_4\text{O}_2$: C, 61.41; H, 3.96; N, 22.04. Found: C, 61.58; H, 3.95; N, 22.25.

b: From 3-amino-5-methyl-1*H*-pyrazole and 2; AcOH, 4 h, 62%; in Py/ NEt_3 after 20 h a mixture of compounds 6b and 5b is formed in 82% overall yield. mp above 350 °C (DMF); ^1H nmr (60 MHz, DMSO-d_6 , 150 °C) δ 2.32 (3H, s, Me), 6.00 (1H, s, 3-H), 7.57 (3H, m, Ph), 8.01 (2H, m, Ph), 8.42 (1H, s, 5-H), 9.00 (1H, s, NH). Anal. Calcd for $\text{C}_{14}\text{H}_{12}\text{N}_4\text{O}_2$: C, 62.68; H, 4.51; N, 20.88. Found: C, 62.45; H, 4.47; N, 20.99.

c: From 3-amino-5-ethoxycarbonyl-1*H*-pyrazole and 2; Py/ NEt_3 , 4h, 67%. mp about 300 °C (decomp.) (EtOH/DMF); ^1H nmr (90 MHz, DMSO-d_6) δ 1.34 (3H, t, $J=7$ Hz, $\text{CH}_3\text{CH}_2\text{O}$), 4.34 (2H, q, $J=7$ Hz, $\text{CH}_3\text{CH}_2\text{O}$), 7.59 (3H, m, Ph), 7.99 (2H, m, Ph), 8.29 (1H, s) and 8.44 (1H, s) (2-H, 5-H), 9.65 (1H, s, NH). Anal. Calcd for $\text{C}_{16}\text{H}_{14}\text{N}_4\text{O}_4$: C, 58.89; H, 4.32; N, 17.17. Found: C, 58.68; H, 4.31; N, 16.88.

N-[2-Methylthio-7-oxo-4,7-dihydro-[1,2,4]-triazolo[1,5-*a*]pyrimidin-6-yl]-benzamide (7): From 3-amino-5-methylthio-1*H*-1,2,4-triazole and 2; Py/ NEt_3 , 15 h, 66%. mp above 300 °C (DMF); ^1H nmr (60 MHz, DMSO-d_6) δ 2.63 (3H, s, CH_3), 7.60 (3H, m, Ph), 8.02 (2H, m, Ph), 8.43 (1H, s, 5-H), 9.70 (1H, s, NH); ms (m/z) 301 (M^+ , 34%). Anal. Calcd for $\text{C}_{13}\text{H}_{11}\text{N}_5\text{O}_2\text{S}$: C, 51.82; H, 3.68; N, 23.24. Found: C, 51.96; H, 3.49; N, 23.32.

Ethyl 6-Benzoylamino-5-oxo-5*H*-thiazolo[3,2-*a*]pyrimidin-3-acetate (8): From 2-amino-4-(ethoxycarbonylmethyl)thiazole and 2; AcOH, 4 h, 77%; Py/ NEt_3 , 6 h, 70%. mp 194.5-195.5 °C (DMF); ^1H nmr (60 MHz, DMSO-d_6) δ 1.17 (3H, t, $J=7$ Hz, $\text{CH}_3\text{CH}_2\text{O}$), 4.12 (2H, q, $J=7$ Hz, $\text{CH}_3\text{CH}_2\text{O}$), 4.25 (2H, s, CH_2), 7.45 (1H, s, 2-H), 7.64 (3H, m, Ph), 8.06 (2H, m, Ph), 8.68 (1H, s, 7-H), 9.58 (1H, s, NH). Anal. Calcd for $\text{C}_{17}\text{H}_{15}\text{N}_3\text{O}_4\text{S}$: C, 57.13; H, 4.23; N, 11.76.

Found: C, 57.27; H, 3.96; N, 11.71.

N-[7-Chloro-4-oxo-4H-pyrido[1,2-a]pyrimidin-3-yl]benzamide (9):

From 2-amino-5-chloropyridine and 2; AcOH, 4 h, 80%; Py/NEt₃, 20 h, 60%. mp 213-214 °C (DMF); ¹H nmr (60 MHz, DMSO-d₆) δ 7.60 (3H, m, Ph), 7.83-8.15 (4H, m, 8-H, 9-H, Ph), 9.05 and 9.07 (2H, d covered with s, 6-H, 2-H), 9.83 (1H, s, NH). Exact Mass Calcd for C₁₅H₁₀ClN₃O₂: 299.0462. Found: 299.0468.

N-[4-Oxo-4,6-dihydropyrimido[1,2-b]indazol-3-yl]benzamide (10):

From 3-amino-1H-indazole and 2; AcOH, 5 h, 79%; in Py/NEt₃ after 20 h a mixture of compounds 10 and 5g is formed in 74% overall yield. mp above 300 °C (DMF); ¹H nmr (90 MHz, DMSO-d₆, 150 °C) δ 7.23 (1H, m), 7.50-7.62 (5H, m), 7.93-8.13 (3H, m), 8.80 (1H, s, 2-H), 9.15 (1H, broad s, NH). Exact Mass Calcd for C₁₇H₁₂N₄O₂: 304.0960. Found: 304.0964.

N-[4-Oxo-4H-pyrimido[2,1-b]benzothiazol-3-yl]benzamide (11):

From 2-aminobenzothiazole and 2; AcOH, 4 h, 82%; Py/NEt₃, 8 h, 84%. mp 228-230 °C (EtOH/DMF); ¹H nmr (90 MHz, DMSO-d₆) δ 7.51-7.67 (5H, m, 7-H, 8-H, Ph), 7.96-8.15 (3H, m, 9-H, Ph), 8.69 (1H, s, 2-H), 8.95 (1H, dd, J=7.1 and 2.9 Hz, 6-H), 9.62 (1H, br s, NH). Anal. Calcd for C₁₇H₁₁N₃O₂S: C, 63.54; H, 3.45; N, 13.08. Found: C, 63.07; H, 3.41; N, 13.10.

N-[4-Oxo-4,6-dihydropyrido[2',3':3,4]pyrazolo[1,5-a]pyrimidin-3-yl]-

benzamide (12): From 3-amino-1H-pyrazolo[3,4-b]pyridine and 2; AcOH, 4 h, 47%; Py/NEt₃, 20 h, 22%. From compound 5i in Py/NEt₃ after 5 h of heating, 28%. mp above 300 °C (AcOH/EtOH); ¹H nmr (90 MHz, DMSO-d₆, 150 °C) δ 7.07 (1H, dd, J=7.7 and 5.1 Hz, 9-H), 7.51 (3H, m, Ph), 7.95 (2H, m, Ph), 8.50-8.65 (2H, m, 8-H, 10-H), 8.89 (1H, s, 2-H), 9.11 (1H, br, NH). Anal. Calcd for C₁₆H₁₁N₅O₂: C, 62.95; H, 3.63; N, 22.94. Found: C, 63.13; H, 3.77; N, 22.78.

N-[6-Oxo-6H-pyrido[3',2':4,5]thiazolo[3,2-a]pyrimidin-7-yl]benzamide (13):

From 2-aminothiazolo[5,4-b]pyridine and 2; AcOH, 5 h, 68%. mp 215-217 °C (EtOH/DMF); ¹H nmr (60 MHz, DMSO-d₆) δ 7.55-7.87 (4H, m, 3-H, Ph), 8.08 (2H, m, Ph), 8.72 (1H, dd, J=5 and 1.6 Hz, 2-H), 8.77 (1H, s, 8-H), 9.15

(1H, dd, J=8.4 and 1.6 Hz, 4-H), 9.67 (1H, br s, NH). Anal. Calcd for $C_{16}H_{10}N_4O_2S$: C, 59.62; H, 3.13; N, 17.38. Found: C, 59.48; H, 3.09; N, 17.40.

ACKNOWLEDGMENT

We thank the Ministry of Science and Technology for financial support.

REFERENCES

1. J. W. Cornforth, "The Chemistry of Penicillin," ed. by H. T. Clarke, J. R. Johnson, and R. Robinson, Princeton University Press, Princeton, 1949, pp. 730-848.
2. Y. S. Rao and R. Filler, "The Chemistry of Heterocyclic Compounds: The Oxazolones," Vol. 45, ed. by A. Weissberger and E. C. Taylor, Interscience Publ., J. Wiley, New York, 1986, pp. 361-729.
3. V. Kepe, M. Kočevár, A. Petrič, S. Polanc, and B. Verček, *Heterocycles*, 1992, 33, 843.
4. O. Tsuge and M. Noguchi, *Heterocycles*, 1981, 16, 2149.
5. M. Dobnikar, M. Kočevár, S. Polanc, M. Tišler, and B. Verček, *Heterocycles*, 1989, 29, 281.
6. E. P. Prokof'ev and E. I. Karpeiskaya, *Tetrahedron Lett.*, 1979, 737.
7. I. Leban, J. Svete, B. Stanovnik, and M. Tišler, *Acta Cryst.*, 1991, C47, 1552.
8. G. Maury, "The Chemistry of Heterocyclic Compounds: Special Topics in Heterocyclic Chemistry," Vol. 30, ed. by A. Weissberger and E. C. Taylor, Interscience Publ., J. Wiley, New York, 1977, pp. 179-244.
9. L. A. Williams, *J. Chem. Soc.*, 1961, 3046.
10. Ref. 1, p. 803.
11. C. E. Kwartler and P. Lucas, *J. Am. Chem. Soc.*, 1943, 65, 1804.

- 12.T. L. P. Hatt and J. D. R. Vass, *J. Chem. Soc., Chem. Commun.*, 1966, 293.
- 13.A. Petrič, B. Stanovnik, M. Tisler, and B. Verček, *Vest. Slov. Kem. Drus.*, 1978, 25, 31.

Received, 2nd December, 1992