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Synthesis and Spectroscopic Evidences of *N*-Arylmaleimides and *N*-Aryl-2,3-dimethylmaleimides

Dragutin Fleš,[a,*] Radivoje Vuković,[a] Ana Erceg Kuzmić,[a] Grozdana Bogdanić,[a] Vlasta Piližota,[b] Damir Karlović,[c] Krešimir Markuš,[d] Kristina Wolsperger,[e] and Dražen Vikić-Topić[e,*]

[a]*INA-Industrija nafte d.d., Strategic Development, Research and Investment Sector, Lovinčićeva bb, P. O. Box 555, HR-10002 Zagreb, Croatia*

[b]*Faculty of Food Technology, The Josip Juraj Strossmayer University, Kuhačeva 18, 31000 Osijek, Croatia*

[c]*Faculty of Food Technology and Biotechnology, University of Zagreb, Pierottijeva 6, 10000 Zagreb, Croatia*

[d]*Dr. Ivana Ribara 13, 44250 Petrinja, Croatia*

[e]*Ruđer Bošković Institute, NMR Center, P. O. Box 180, HR 10002 Zagreb, Croatia*

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A series of *N*-arylmaleimides (*N*-aryl-MI) and ***N***-aryl-2,3-dimethylmaleimides (*N*-aryl-DiMeMI) were prepared by condensation of primary amines with maleic anhydride (MAn) and 2,3-dimethylmaleic anhydride (DiMeMAn), respectively. Preparation of *N*-aryl-MI proceeded through the formation of *N*-arylmaleamic acid, which subsequently cyclized to *N*-aryl-MI. In the reaction of *N*-arylamines with DiMeMAn, cyclic condensation products were formed in one step. By means of one- and two-dimensional ^{1}H and ^{13}C NMR spectroscopy it was proven that *N*-aryl-DiMeMI and not isomaleimides were formed by a one step reaction.

Keywords
N-supstituted maleimides
arylamines condensation
maleic anhydride
NMR, IR spectra

INTRODUCTION

N-substituted maleimides represent an important group of electron acceptor monomers capable to form charge-transfer-complexes with various vinyl monomers. Free-radical-initiated copolymerisation of maleimides with electron donors often forms alternating copolymers. Some examples from our previous work are described in Refs. 1–5. Besides being of interest as monomers for the preparation of various polymers and copolymers, N-substituted maleimides are interesting as biologically active compounds. For instance, *N*-ethymaleimide is a diuretic and potentially nephrotoxic agent in dogs.[6]

In the present paper, we wish to compare the mechanism of condensation of arylamines with maleic anhydride and with 2,3-dimethylmaleic anhydride. The following primary amines were used in the condensation reactions: aniline, *p*-biphenylamine, *p*-phenoxyphenylamine, *p*-aminohippuric acid and 4-*N*-(aminobenzo-15-crown-5).

EXPERIMENTAL

Materials

Maleic anhydride; *p*-aminobiphenil, 98 %; *p*-aminohippuric acid, 98 %; 2,3-dimethylmaleic anhydride, Aldrich Chemical

* Authors to whom correspondence should be addressed. (E-mail: dfles@irb.hr and vikic@irb.hr)

Corporation, USA; *p*-phenoxyphenylamine, 95 %; 4-(aminobenzo-15-crown-5), Fluka Chimica-Biochimica, Switzerland.

Physicochemical Measurements

IR spectra were measured with a Perkin-Elmer 421 spectrophotometer using the nujol technique. The ^{1}H and ^{13}C one- and two-dimensional NMR spectra were recorded with a Varian Gemini 300 spectrometer, operating at 75.5 MHz for the ^{13}C nucleus. All samples were measured from $CDCl_3$ solutions at 20 °C in 5 mm NMR tubes. Chemical shifts, in ppm, are referred to TMS. Digital resolution in ^{1}H NMR spectra was 0.20 Hz, while it was 0.63 Hz per point in ^{13}C NMR spectra. The following spectra were recorded: standard ^{1}H, ^{13}C broadband proton decoupled, ^{13}C gated proton decoupled, COSY-45 and HETCOR. In all experiments, the proton decoupled spectrum was performed by Waltz-16 modulation. In two-dimensional experiments, standard pulse sequences were used. The COSY-45 spectra were measured in the magnitude mode using 1024 points in F_2 dimension and 256 increments in F_1 dimension, subsequently zero-filled to 1024 points. Each increment was obtained with 16 scans, 3000 Hz spectral width and relaxation delay of 1 s. The corresponding digital resolution was 5.9 Hz/point and 11.7 Hz/point in F_2 and F_1 dimensions, respectively. The HETCOR spectra were recorded with 2048 points in F_2 dimension and 256 increments in F_1 dimension, zero-filled to 512 points. Increments were recorded with 64 scans, relaxation delay of 1 s and spectral width of 20 000 Hz in F_2 and 4500 Hz in F_1 dimensions. The corresponding digital resolution was 19.53 and 17.6 Hz/point in F_2 and F_1 dimensions, respectively.

Preparation of Monomers

Synthesis of N-*Arylmaleimides and* N-*Aryl-2,3-dimethylmaleimides*. – Synthesis of *N*-arylmaleimides (RMI) proceeds by a two-step mechanism. In the first step, arylamines (RNH_2) react with maleic anhydride (MAn) by forming maleamic acid: RNHCOCH=CHCOOH, which in the second step cyclizes by heating in acetic anhydride in the presence of anhydrous NaOAc under elimination of water. Arylamines used in this work are presented in Scheme 1. Different results were obtained in the reaction of the same RNH_2 with 2,3-dimethylmaleic anhydride (DiMeMAn). Under the same experimental conditions, in all studied reactions *N*-aryl-2,3-dimethylmaleimides were obtained in one step.

Syntheses of *N*-arylmaleimides and *N*-aryl-2,3-dimethylmaleimides are illustrated by the reaction of MAn and DiMeMAn with *p*-biphenylamine.

Synthesis of N-*Biphenylmaleimid in Two Steps*. – In the first step, *N*-biphenylmaleamic acid is prepared. To a solution of 8.46 g (0.05 mol) of *p*-biphenylamine in 40 mL of $CHCl_3$, a solution of 5.0 g (0.05 mol) of MAn in 60 mL of $CHCl_3$ was added under stirring at room temperature and the reaction mixture was left overnight at room temperature. The crystalline product was filtered off, yielding 10.85 g of crude biphenylmaleamic acid, which after recrystallization from 35 mL of DMF gave 8.48 g (62.5 %) of *N*-biphenylmaleamic acid, melting at 290 °C (under sublimation at 225 °C).

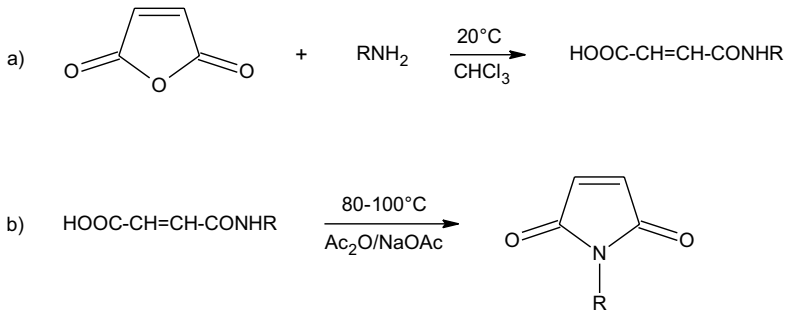
Anal. Calcd. for $C_{16}H_{13}NO_3$ (M_r = 267): C 71.91, H 4.37, N 5.24 %; found: C 71.89, H 5.04, N 5.32 %.

N-biphenylmaleimide is prepared by dehydration of *N*-biphenylmaleamic acid (second step). *N*-biphenylmaleamic acid (4 g) was heated for 1 h at 90–100 °C in 10 mL of acetic anhydride in the presence of 200 mg of anhydrous NaOAc. Acetic anhydride was hydrolyzed with iced water and the reaction mixture was left overnight at room temperature. The crystalline product was filtered off yielding 3.54 g (95 %) of *N*-biphenylmaleimide melting at 191–192 °C. The sample for analysis was recrystallized from dioxane, m.p. 198–200 °C.

Anal. Calcd. for $C_{16}H_{11}NO_2$ (M_r = 249): C 77.11, H 4.42, N 5.62 %. found: C 77.45, H 4.75, N 5.54 %.

N-phenylmaleimide,[6] *N*-(*p*-phenoxyphenyl) maleimide,[7] *N*-maleimidohippuric acid,[6] and *N*-maleimido-(benzo-15-crown-5)[8] were prepared in a similar way.

Synthesis of N-*Biphenyl-2,3-dimethylmaleimide in One Step.* – *p*-Biphenylamine (3.38 g; 0.02 mol) dissolved in 10 mL of $CHCl_3$ was mixed at room temperature with a solution of 2.52 g (0.02 mol) of DiMeMAn and left overnight at room temperature. The solvent was evaporated, yielding 5.14 of crude crystalline product, which was recrystallized from 60 mL of isopropanol yielding 3.86 g (70 %), m.p. 172–173 °C (under formation of fine needles melting at 155 °C).



Scheme 1. R: phenyl, biphenyl, phenoxyphenyl, hippuric acid, benzo-15-crown-5.

Anal. Calcd. for $C_{18}H_{15}NO_2$ (M_r = 277): C 77.98, H 5.42, N 5.05 %. found: C 78.07, H 5.54, N 5.07 %.

By applying a similar experimental procedure, the following RNH_2 were condensed with DiMeMAn:

(i) Aniline (1.86 g; 0.02 mol) and 2.52 g (0.02 mol) of DiMeMAn in $CHCl_3$ yield 3.28 g (82 %), m.p. 90–91 °C.

Anal. Calcd. for $C_{12}H_{11}NO_2$ (M_r = 201): C 71.61, H 5.51, N 6.96 %. found: C 71.55, H 5.63, N 6.94 %.

(ii) *N-p*-phenoxyphenylamine (3.70 g, 0.02 mol) and 2.52 g (0.02 mol) of DiMeMAn in $CHCl_3$ gave a quantitative yield of the crude product, which was recrystallized from 25 mL of iso-propanol yielding 4.55 (78 %) of crystalline product, m.p. 115–116 °C.

Anal. Calcd. for $C_{18}H_{15}NO_3$ (M_r = 293): C 73.72, H 5.12, N 4.78 %. found: C 73.58, H 5.27, N 4.73 %.

(iii) Amino-(benzo-15-crown-5) (0.564 g; 0.002 mol) and 0.252 g (0.002 mol) of DiMeMAn in 3 mL $CHCl_3$ was left overnight at room temperature. Evaporation of solvent gave 0.8 g of crystalline product, which was recrystallized from isopropanol yielding 0.72 g (92 %) of analytically pure cyclic compound melting at 140–142 °C.

Anal. Calcd. for $C_{20}H_{25}NO_7$ (M_r= 391): C 61.38, H 6.38, N 3.58 %. found: C 61.25, H 6.39, N, 3.65 %.

(iv) 4-Aminohippuric acid (1.95 g; 0.01 mol) and 1.26 g (0.01 mol) of DiMeMAn in 4 mL of DMF was left overnight at room temperature. The yellow solution was diluted with 150 mL of water; the pale yellow crystalline product was filtered off, yielding 2.65 g (88 %) of cyclic maleimide. The analytical sample was recrystallized from THF under addition of petroleum ether (b.p. 40–60 °C); m.p. 218–219 °C.

Anal. Calcd. for $C_{15}H_{14}N_2O_5$ (M_r = 302): C 59.60, H 4.64, N 9.27 %. found: C 59.55, H 4.87, N 9.98 %.

Preparation of *N*-(2,3-dimethylmaleimido) hippuric acid was described in Ref. 6 under different experimental conditions. Yield 50 %; m.p. 206–209 °C.

RESULTS AND DISCUSSION

As shown in the Experimental part, *N*-arylamides are prepared by a two-step mechanism. In the first step, addition of primary amines (RNH_2) to MAn results in the formation of maleamic acids, which subsequently cyclize by heating in acetic anhydride in the presence of NaOAc (Scheme 1).

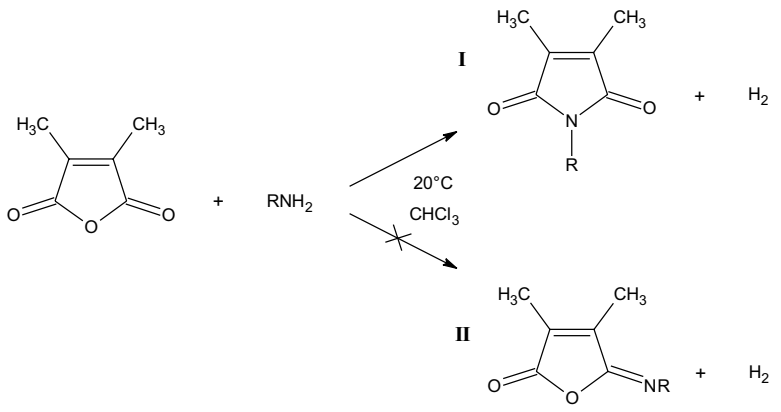
It is well known from our previous work and from many examples described in the literature that symmetrical *N*-arylmaleimides and not isomaleimides are prepared the two-step mechanism.

On the other hand, the condensation of DiMeMAn with RNH_2, which proceeds by the one-step mechanism, has not been systematically studied and it is not known whether the one-step reaction results in the formation of symmetrical 2,3-dimethylmaleimide (**I**) or 2,3-dimethylisomaleic anhydride (**II**), (Scheme 2).

In order to prove the structures **I** or **II** (in Scheme 2), the compounds obtained by condensation of DiMeMAn with RNH_2, were analyzed by IR, ^1H and ^{13}C NMR spectroscopy. The IR spectra of the condensation product of Ph-NH_2 with DiMeMAn in Figure 1 clearly show the groups of signals between 1068 cm^{-1} and 1120 cm^{-1}, which could be attributed to the isomaleimide group,[9] =C–O–C=. However, signals which belong to C=N group could not be identified in the spectra, because of the strong C=O group absorption (1702 cm^{-1}).[10] It is obvious that IR spectra could not unambiguously distinguish between symmetrical and isomaleimide structures of *N*-aryl-DiMeMAn.

^1H and ^{13}C NMR spectra corraborate that the reaction of primary amines with MAn proceeds in two steps. In the first step, the formation of maleamic acids was confirmed by the existence of COOH signal as well as by the increase in the number of proton and carbon signals. Cyclization in the second step was proven by the disappearance of some signals and by changes of chemical shifts of the remaining ones. The number of carbon signals is in agreement with the symmetrical structure of *N*-arylmaleimides obtained (Table I).

In the condensation of DiMeMAn with primary amines, ^1H NMR spectroscopy showed that immediately after mixing amine and anhydride in $CDCl_3$ the cyclic compound was formed, under elimination of water. Spectra revealed the signal of H_2O but not that of COOH. The ^1H spectra did not change for 24 hours, as long as mea-



Scheme 2. R: phenyl, biphenyl, phenoxyphenyl, hippuric acid, benzo-15-crown-5.

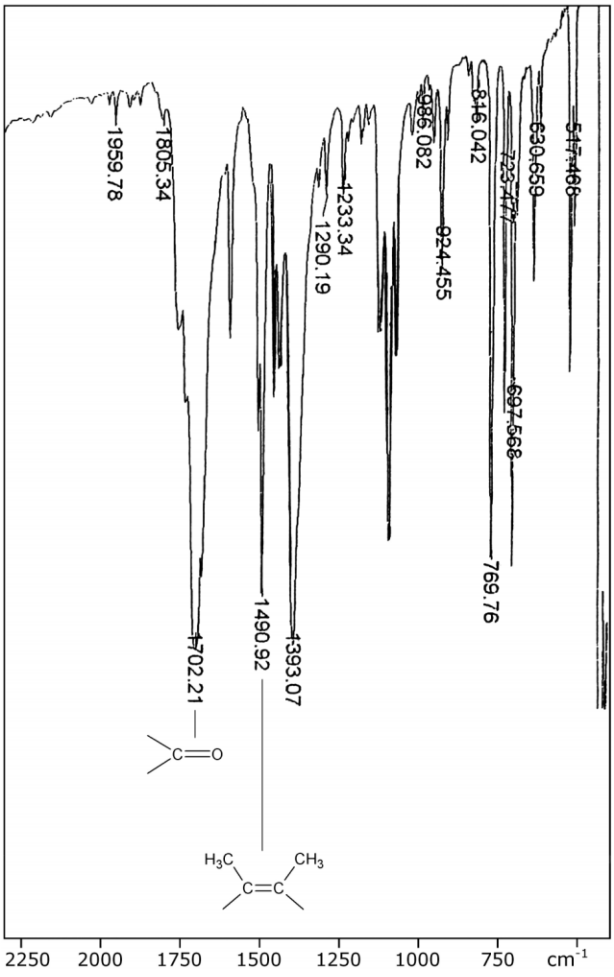


Figure 1. IR spectrum of the condensation product of aniline and DiMeMAn.

surements were performed, confirming that the condensation proceeds by the one-step mechanism. However, it was not possible to conclude on the basis of ^{1}H NMR spectra if symmetrical or unsymmetrical products were formed. The ^{13}C NMR spectra were in agreement with the one-step mechanism, since no existence of maleamic acid was found. Moreover, the ^{13}C NMR analysis clearly showed that one can discard the formation of isomaleimides as condensation products, *i.e.*, it was revealed that only symmetrical *N*-aryl-2,3-dimethylmaleimides were formed. This was concluded from the number of ^{13}C signals as well as from their chemical shifts. Namely, in the hypothetical ^{13}C spectra of *N*-aryl-2,3-dimethylisomaleimides (Scheme 2, **II**) there would always be three ^{13}C signals more than in the spectra of the corresponding *N*-aryl-2,3-dimethylmaleimides (Scheme 2, **I**) due to the unsymmetrical substitution in the former and symmetrical in the latter. Also, the typical chemical shift of the imino carbon atom should be observed in isomaleimides, but this signal was not revealed, in the compounds investigated additionally proving that only maleimides were present.

Since the recorded ^{13}C NMR spectra of the products of one-step reactions showed a reduced number of ^{1}H and ^{13}C signals as well as the absence of imino carbon signal, one can unambiguously prove the formation of only symmetrical *N*-aryl-2,3-dimethylmaleimides. The ^{13}C NMR data of the selected *N*-arylmaleimides and *N*-aryl-2,3-dimethylmaleimides are given in Table I. The assignment of ^{13}C NMR spectra was performed using ^{13}C substituent induced chemical shifts and C-H spin-spin couplings and it was confirmed by HETCOR spectra.

In Figures 2 and 3, the ^{13}C NMR spectrum and two-dimensional HETCOR spectrum of the *N*-(*p*-phenoxyphenyl)-2,3-dimethylmaleimide are shown. The number of ^{13}C signals and their chemical shifts substantiated the symmetrical structure of the compounds formed.

TABLE I. ^{13}C chemical shifts (δ/ppm)[a] of selected *N*-arylmaleimides (**1**, **3** and **5**)[b] and *N*-aryl-2,3-dimethylmaleimides (**2**, **4** and **6**)[c]

Molecule	δ / ppm					
C-atom	**1**	**2**	**3**	**4**	**5**	**6**
C-2,5	169.31	170.75	169.35	170.72	169.43	170.67
C-3,4	133.94	137.26	134.04	137.33	133.99	137.11
C-1'	130.99	131.79	130.12	130.92	125.69	126.54
C-2',6'	125.86	125.60	126.09	125.73	127.47	127.02
C-3',5'	128.92	128.83	127.68	127.53	118.72	118.58
C-4'	127.72	127.23	140.71	140.14	156.86	156.36
C-1"			139.96	140.09	156.28	156.16
C-2",6"			126.99	126.95	119.26	118.98
C-3",5"			128.68	128.63	129.71	129.55
C-4"			127.47	127.30	123.70	123.40
CH_3		8.74		8.74		8.60

[a]Recorded in $CDCl_3$ solution. Chemical shifts referred to TMS. Digital resolution ±0.63 Hz.
[b]*N*-arylmaleimides: **1,** *N*-phenylmaleimide; **3**, *N*-biphenylmaleimide; **5**, *N*-phenoxyphenylmaleimide.
[c]*N*-aryl-2,3-dimethylmaleimides: **2,** *N*-phenyl-2,3-dimethylmaleimide; **4**, *N*-biphenyl-2,3-dimethylmaleimide; **6**, *N*-phenoxyphenyl-2,3-dimethylmaleimide.

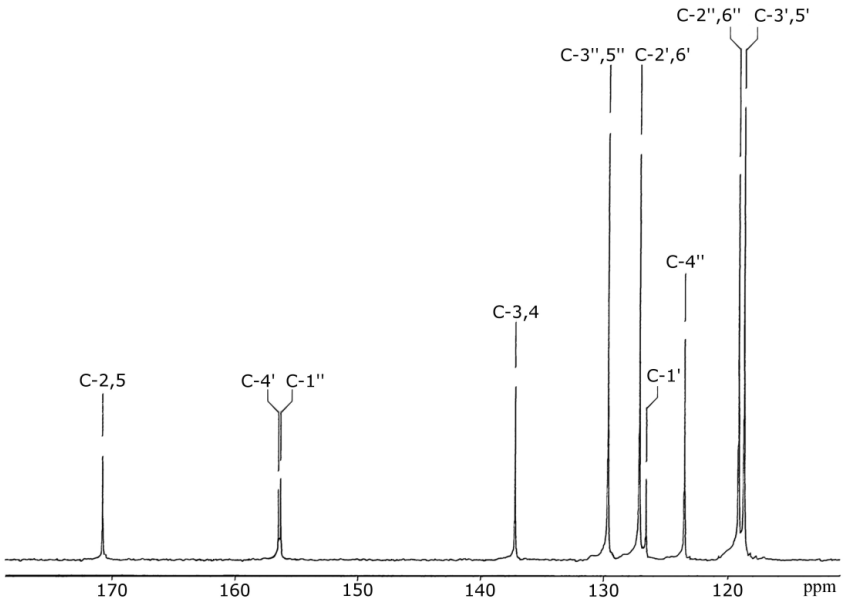


Figure 2. ^{13}C NMR spectrum of *N*-(*p*-phenoxyphenyl)-2,3-dimethylmaleimide, confirming the symmetrical structure of the condensation product.

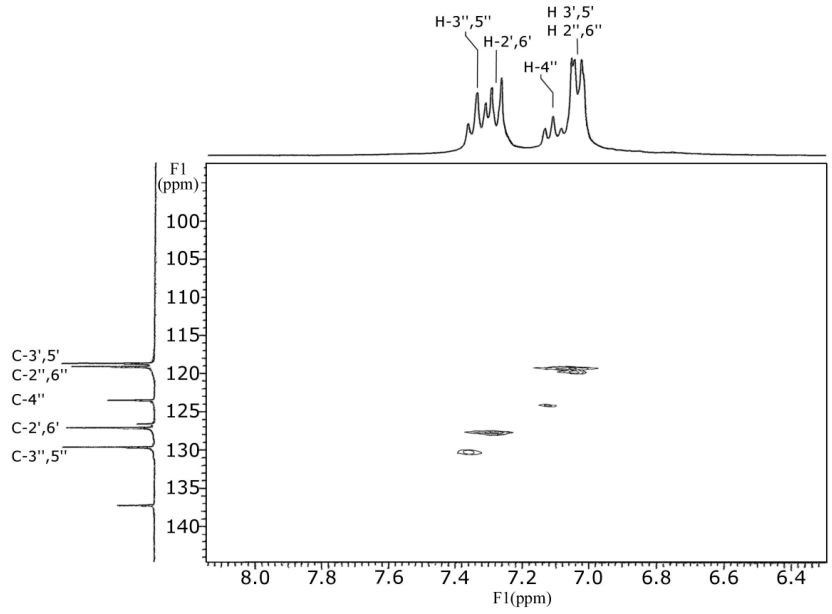


Figure 3. Two-dimensional heteronuclear ^{13}C-^{1}H chemical shift correlation spectrum (HETCOR) of *N*-(*p*-phenoxyphenyl)-2,3-dimethylmaleimide. Chemical shifts and the number of protons and carbon signals corraborate the symmetrical structure of the molecule.

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REFERENCES

1. D. Fleš, Rad. Hrv. Akad. Znan. Umjet., Kem. **10** (1993) 23–47.
2. D. Fleš, R. Vuković, F. Ranogajec, and D. D. Fleš, *J. Macromol. Sci., Chem.* **27** (1990) 1621–1630.
3. D. Fleš and R. Vuković, *J. Macromol. Sci., Pure Appl. Chem.* **32** (1995) 1461–1469.
4. A. Erceg, R. Vuković, G. Bogdanić, and D. Fleš, *J. Macromol. Sci., Pure Appl. Chem.* **37** (2000) 513–524.
5. D. Fleš, D. Hace, F. Ranogajec, and R. Vuković, *Polym. Bull.* **29** (1992) 153–157.
6. D. A. Koechel, J. B. Tarloff, and G. Rankin, *J. Med. Chem.* **26** (1983) 85–90.
7. M. P. Cava, A. A. Deana, K. Muth, and M. J. Mitchell, *N-phenymaleimide*, in: J. D. Roberts (Ed.), *Organic Synthesis 41*, John Wiley and Sons, New York, 1961, pp. 93–95.
8. R. Vuković, D. Fleš, and A. Erceg, *J. Macromol. Sci., Pure Appl. Chem.* **34** (1997) 1619–1628.
9. E. Hedaya, R. L. Hinman, and S. Theodoropulos, *J. Org. Chem.* **31** (1966) 1311–1316.
10. I. Simionescu and M. Grigoros, *J. Polym. Sci., Polym Lett.* **28** (1990) 39–45.

SAŽETAK

Sinteza i spektroskopski dokazi *N*-arilmaleimida i *N*-aril-2,3-dimetilmaleimida

Dragutin Fleš, Radivoje Vuković, Ana Erceg Kuzmić, Grozdana Bogdanić, Vlasta Piližota, Damir Karlović, Krešimir Markuš, Kristina Wolsperger i Dražen Vikić-Topić

Serija *N*-arilmaleimida (*N*-aril-MI) i *N*-aril-2,3-dimetilmaleimida (*N*-aril-DiMeMI) priređena je kondenzacijom primarnih amina s maleinskim anhidridom (MAn) i 2,3-dimetilmaleinskim anhidridom (DiMeMAn). Priprava *N*-aril-MI provedena je u dva stupnja. U prvom stupnju nastaje *N*-arilmaleiminska kiselina, koja zagrijavanjem u anhidridu octene kiseline uz NaOAc prelazi u *N*-aril-MI. U reakciji *N*-arilamina s DiMeMAn nastaje u jednom stupnju ciklički *N*-aril-DiMeMI. Priređeni su slijedeći *N*-aril-DiMeMI: *N*-fenil-DiMeMI, *N*-bifenil-DiMeMI, *N*-fenoksifenil-DiMeMI, *N*-[(benzo-15-kruna-5)-DiMeMI], *N*-hipuril-DiMeMI. Primjenom IR spektroskopije i jedno- i dvodimenzijske ^{1}H i ^{13}C NMR spektroskopije utvrđeno je da svi ciklički spojevi pripadaju skupini simetričnih maleimida, a ne izomaleimida.