STUDY OF MICROWAVE IRRADIATION EFFECT ON CONDENSATION OF 6-R-3-FORMYLCHROMONES WITH ACTIVE METHYLENE COMPOUNDS

Renata GASPAROVA and Margita LACOVA*

Department of Organic Chemistry,
Comenius University, 842 15 Bratislava, Slovak Republic

Received February 1, 1995
Accepted May 8, 1995

Condensation of 6-R-3-formylchromones (*I*) with 3,3-dimethyl-1,3-cyclohexanedione (*II*), 1,3-indandione (*III*), 1,2′-biindenylidene-3,1′,3′-trione (bindone, *IV*), 2-oxo-1,4-benzothiazine (*V*) and 3-oxo-2,3-dihydro-1-thia-3a,8-diazacyclopent[*a*]indene (*VI*) by the "classical" method, as well as condensation in a microwave oven, has been studied. Some subsequent reactions of these products are described.

The biological importance of chromone derivatives is well known[1–3]. 3-Formylchromones *I* as α,β-unsaturated reactive aldehydes are suitable agents for preparation of many various compounds. They react with amines or hydrazines with either opening or preserving the pyrone ring[4]. They also can react as Michael acceptors or dienophiles[5,6]. So far only few papers have been devoted to condensation reactions of *I* with active methylene compounds, such as malonic acid derivatives[7], hippuric acid[8], barbituric acid[9] or Meldrum's acid[10]. Products of these syntheses were used in preparation of new heterocyclic systems[11,12] and some of them exhibited interesting biological activities[13].

The aim of this study was to synthesize some new condensation products of 3-formylchromones *I* with active methylene compounds *II–VI* and to compare the results of condensation by the "classical" method with those obtained using microwave irradiation. The latter method is known to shorten the reaction time of various types of reactions[14]. Additionally, we strove to find favourable reaction conditions in order to increase yields of the condensations.

The condensation of 3-formylchromones *I* with active methylene groups of several carbonyl derivatives *II–VI* (Scheme 1) was carried out in acetic anhydride, both under the "classical" and irradiation conditions. The "classical" treatment of compounds *I* with 3,3-dimethyl-1,3-cyclohexanedione (dimedone, *II*) under the conditions described below afforded 2-(6-R-chromon-3-ylmethylidene)-5,5-dimethyl-1,3-cyclohexanediones

* The author to whom correspondence should be addressed.

VIIa–VIId. Compound *VIIa* was prepared either by the "classical" method or by using a microwave oven. Although the yields of both methods were almost the same (60–64%), the reaction with irradiation was considerably shorter (see Table I).

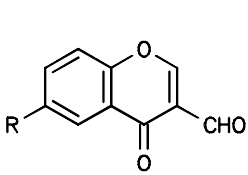
Treatment of the same starting compounds in ethanol gave 3-(3,3,6,6-tetramethyl-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroxanthen-9-yl)chromones as reported by Eiden and Haverland[15]. Under conditions employed by us no such products were obtained.

Reactions of compound *I* with 1,3-indandione *III* were realized only in a microwave oven to give 2-(6-R-chromon-3-ylmethylidene)-1,3-indandiones *VIIIa–VIIIe* in 61–79% yields after 6–10 min of irradiation. When the reaction was carried out in glacial acetic acid and piperidine, the same products *VIIIa–VIIIc* were obtained, as described[16].

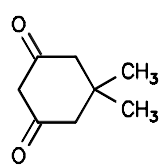
The synthesis of 2-(6-R-chromon-3-ylmethylidene)-1,2′-biindenylidene-3,1,3′-triones *IXa* and *IXb* in microwave oven was not effective. Also the Perkin condensation gave only low yields of compounds *IXa* and *IXb* (20% and 43%, respectively).

2-(6-R-Chromon-3-ylmethylidene)-3-oxo-1,4-benzothiazines *Xa – Xd* were obtained in low yields (15–43%) by reaction of compounds *I* with 3-oxo-1,4-benzothiazine *V* in acetic anhydride in the presence of potassium acetate. Neither an excess of one of the reactants nor prolonged reaction time increased the yields. On the other hand, synthesis of the same compounds in a microwave oven required shorter reaction time and gave higher yields (see Table I).

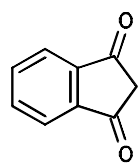
The difference in reaction times of both the condensation methods (with comparable yields) was also evident in the preparation of 2-(chromon-3-ylmethylidene)-3-oxo-2,3-dihydro-1-thia-3a,8-diazacyclopent[*a*]indene (*XI*) from aldehyde *Ia* and 3-oxo-2,3-dihydro-1-thia-3a,8-diazacyclopent[*a*]indene (*VI*).



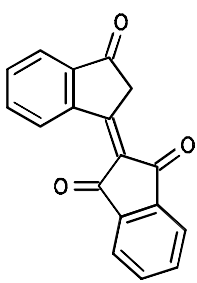
I



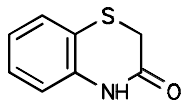
II



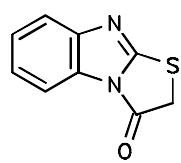
III



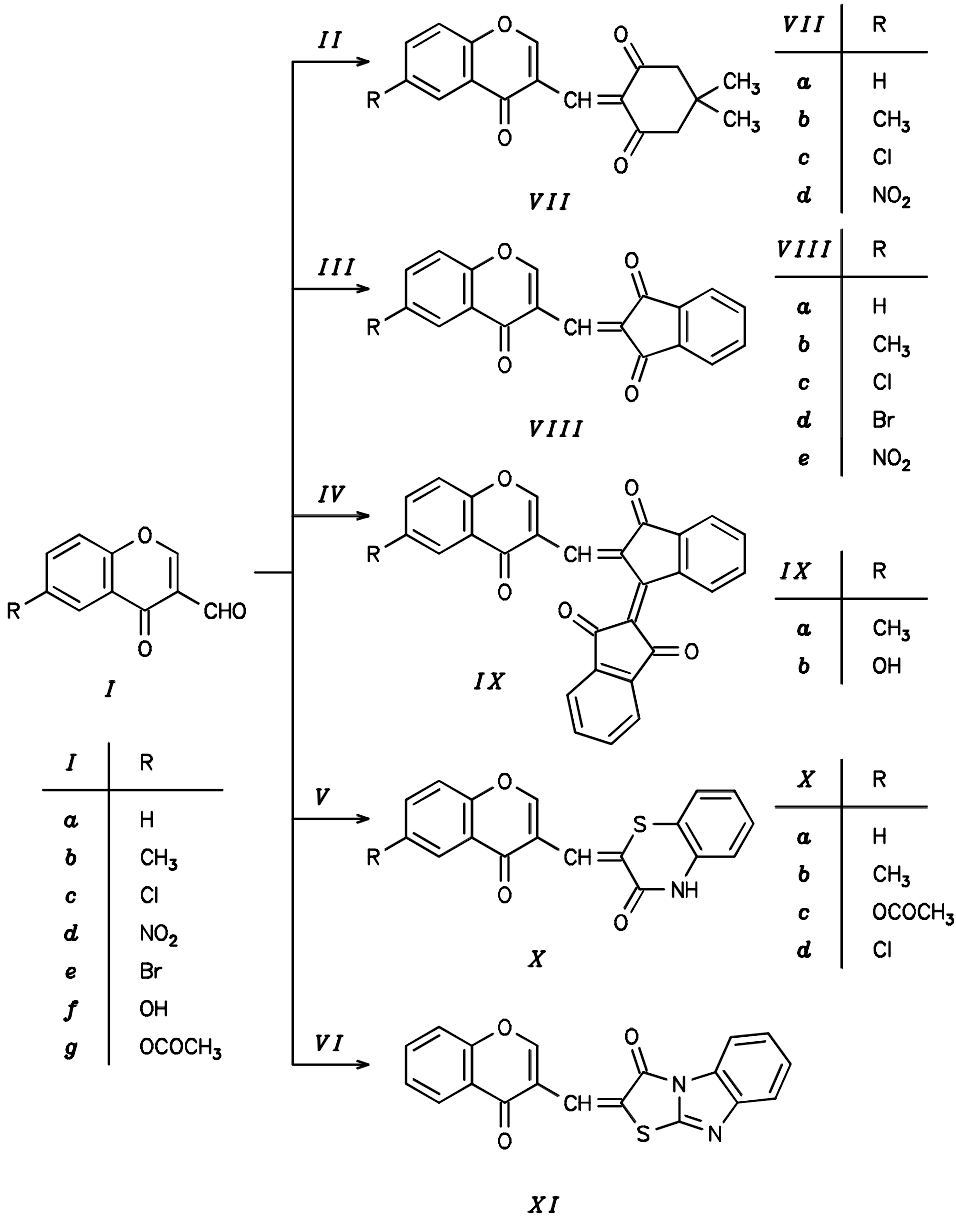
IV



V



VI



I	R
a	H
b	CH_3
c	Cl
d	NO_2
e	Br
f	OH
g	$OCOCH_3$

VII	R
a	H
b	CH_3
c	Cl
d	NO_2

VIII	R
a	H
b	CH_3
c	Cl
d	Br
e	NO_2

IX	R
a	CH_3
b	OH

X	R
a	H
b	CH_3
c	$OCOCH_3$
d	Cl

SCHEME 1

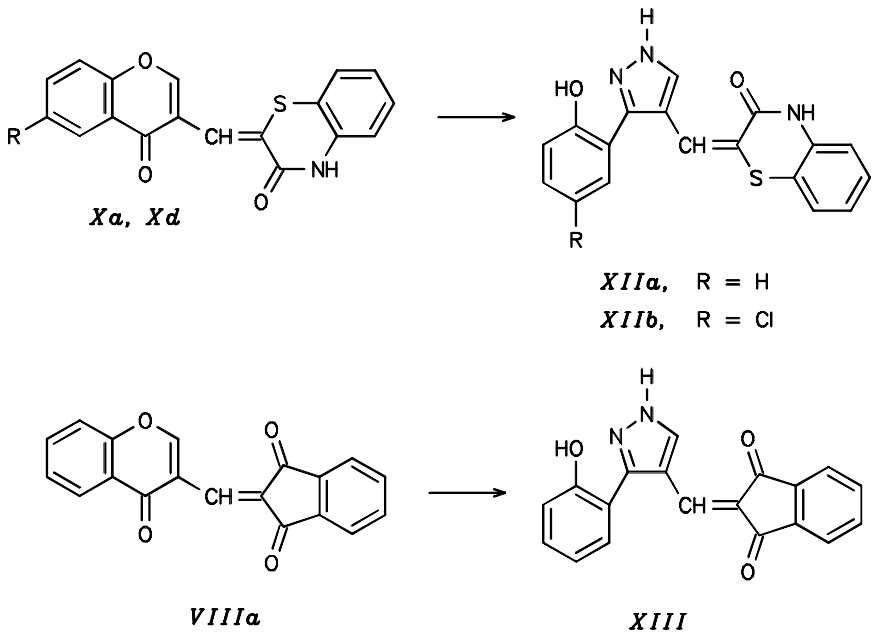
TABLE I
Characteristic data of compounds *VII–XI*

Compound	M.p., °C	Yield[a] %	Reaction time[a] min	Formula M.w.	Calculated/Found			
					% C	% H	% N	% S
VIIa	283–285	60	60	$C_{18}H_{16}O_4$	72.96	5.44	–	–
		64	5	296.3	72.76	5.78	–	–
VIIb	297–298	–	–	$C_{19}H_{18}O_4$	73.53	5.85	–	–
		61	10	310.4	73.43	6.23	–	–
VIIc[b]	173–175	–	–	$C_{18}H_{15}ClO_4$	65.36	4.57	–	–
		54	6	330.8	65.50	4.90	–	–
VIId	196–198	–	–	$C_{18}H_{15}NO_6$	63.34	4.43	4.10	–
		62	4	341.3	62.91	4.39	4.02	
VIIIa	269–271	–	–	$C_{19}H_{10}O_4$	75.49	3.33	–	–
		79	8	302.3	75.33	3.33	–	–
VIIIb	217–219	–	–	$C_{20}H_{12}O_4$	75.94	3.82	–	–
		76	9	316.3	75.70	3.83	–	–
VIIIc[c]	262–264	–	–	$C_{19}H_9ClO_4$	67.77	2.69	–	–
		68	6	336.7	67.19	2.65	–	–
VIIId[d]	256–258	–	–	$C_{19}H_9BrO_4$	60.00	2.39	–	–
		79	10	379.9	60.03	2.45	–	–
VIIIe	305–307	–	–	$C_{19}H_9NO_6$	65.69	2.61	4.03	–
		61	4	347.4	65.48	2.59	3.96	–
IXa	211–213	20	200	$C_{29}H_{14}O_5$	78.37	3.63	–	–
		–	–	444.5	78.01	3.82	–	–
IXb	287–289	43	360	$C_{28}H_{14}O_6$	75.33	3.16	–	–
		–	–	446.4	75.51	3.30	–	–
Xa	283–286	19	360	$C_{18}H_{11}NO_3S$	67.28	3.45	4.36	9.98
		42	20	321.5	67.04	3.32	4.29	9.64
Xb	286–288	15	480	$C_{19}H_{13}NO_3S$	68.05	3.91	4.18	9.56
		33	30	335.4	68.19	3.88	4.17	9.60
Xc	295–297	49	600	$C_{20}H_{13}NO_5S$	63.32	3.45	3.69	8.45
		62	14	379.4	62.97	3.40	3.61	8.44
Xd[e]	350–352	49	360	$C_{18}H_{10}ClNO_3S$	60.76	2.83	3.94	9.01
		57	7	355.8	60.56	2.86	3.89	9.06
XI	315–316	56	120	$C_{19}H_{10}N_2O_3S$	65.89	2.91	8.09	9.26
		60	20	346.8	65.84	2.94	8.12	9.27

[a] The above data are given for the classic condensation, the data below for the condensation in microwave oven; [b] % Cl: calculated 10.72, found 10.93; [c] % Cl: calculated 10.53, found 10.07; [d] % Br: calculated 20.77, found 20.51; [e] % Cl: calculated 9.96, found 9.55.

TABLE II
Characteristic data of compounds *XII–XIII*

Compound	M.p., °C Yield, %	Formula M.w.	Calculated/Found				
			% C	% H	% N	% S	% Cl
XIIa	276–278	$C_{18}H_{13}N_3O_2S$	64.42	3.88	12.52	9.56	–
	42	335.3	64.45	3.98	12.60	9.44	–
XIIb	307–308	$C_{18}H_{12}ClN_3O_2S$	58.45	3.25	11.36	8.65	9.59
	40	369.5	58.87	3.26	11.38	8.39	9.90
XIII	284–286	$C_{19}H_{12}N_2O_3$	72.17	3.82	8.86	–	–
	45	316.1	71.99	3.82	8.46	–	–



SCHEME 2

Reaction of *I* with hydrazine and monosubstituted hydrazines was studied by Ghosh[17]. Treatment with hydrazine or phenylhydrazine converted compounds *I* into hydrazones which on prolonged boiling in ethanol rearranged to give pyrazoles. We studied the reaction of our condensation products *VIIIa*, *Xa* and *Xd* with hydrazine and isolated the respective new pyrazine derivatives 3-(2-hydroxyphenyl)-4-(2*H*,3*H*-3-oxo-1,4-benzothiazine-2,2-diylmethyl)pyrazole (*XIIa*), 3-(5-chloro-2-hydroxyphenyl)-4-(2*H*,3*H*-3-oxo-1,4-benzothiazine-2,2-diylmethyl)pyrazole (*XIIb*) and 3-(2-hydroxyphenyl)-4-(1,3-dioxo-2,2-indandiyl)pyrazole (*XIII*) (Table II). Using thiosemicarbazide instead of hydrazine in the reaction with *Xa* and *Xd* we obtained the same products *XIIa* and *XIIb* (Scheme 2). Upon treatment of compound *VIIa* with hydrazine in ethanol in the presence of sodium ethoxide or *p*-toluenesulfonic acid we isolated only the starting compound *VIIa*. Similar results are described[9] for the reaction of *VIIa* with ammonia.

TABLE III
^{1}H NMR spectral data of synthesized compounds

Compound	δ, ppm; *J*, Hz
VIIa	8.55 s, 1 H (H-2); 8.25 s, 1 H (CH); 7.35–8.04 m, 4 H (Ar-H); 2.50 s, 2 H (CH_2); 2.21 s, 2 H (CH_2); 1.09, 0.98 d, 6 H, *J* = 9.0 (CH_3)
VIId	8.88 s, 1 H (H-2); 8.35–8.50 dd, 2 H, *J* = 3.0 (H-7,H-8); 7.81 s, 1 H (CH); 7.24, 7.35 d, 2 H, *J* = 9.0 (H-5); 2.61 s, 2 H (CH_2); 2.43 s, 2H (CH_2); 1.15 s, 6 H (CH_3)
VIIIa	10.39 s, 1 H (CH); 8.44 s, 1 H (H-2); 7.99–7.61 m, 8 H (Ar-H)
VIIIb	10.37 s, 1 H (CH); 8.45 s, 1 H (H-2); 8.10–7.49 m, 7 H (Ar-H); 2.49 s, 3 H (CH_3)
VIIIc	10.37 s, 1 H (CH); 8.38 s, 1 H (H-2); 8.30–7.57 m, 7 H (Ar-H)
VIIId[a]	10.30 s, 1 H (CH); 8.76 s, 1 H (H-2); 8.03–7.70 m, 7 H (Ar-H)
Xa[a]	11.05 s, 1 H (NH); 8.73 s, 1 H (H-2); 8.71–7.11 m, 9 H (Ar-H,CH)
Xb[a]	11.04 s, 1 H (NH); 8.68 s, 1 H (H-2); 7.92–7.10 m, (Ar-H,CH); 2.45 s, 3 H (CH_3)
Xc[a]	11.03 s, 1 H (NH); 8.75 s, 1 H (H-2); 8.33–7.28 m, 8 H (Ar-H,CH); 2.55 s, 3 H (CH_3)
XI[a]	8.22 s, 1 H (H-2); 8.20–7.29 m, 9 H (Ar-H,CH)
XIIa	13.33 s, 1 H (OH); 10.74 s 1 H (amide NH); 9.92 s, 1 H (H-6); 8.22 s, 1 H (NH); 7.53 s, 1 H (H-5); 7.40–6.90 m, 8 H (Ar-H)
XIIb	13.44 s, 1 H (OH); 10.77 s, 1 H (amide NH); 10.07 s, 1 H (H-6); 8.26 s, 1 H (NH); 7.52 s, 1 H (H-5); 7.30–6.90 m, 7 H (Ar-H)
XIII	13.65 s, 1 H (OH); 10.08 s, 1 H (H-6); 9.23 s, 1 H (NH); 7.91 s, 4 H (indan Ar-H); 7.60 s, 1 H (H-5); 7.50–6.90 m, 4 H (Ar-H)

[a] Measured in hexadeuteriodimethyl sulfoxide.

EXPERIMENTAL

The melting points were determined on a Kofler block. Infrared spectra were recorded on a Specord IR 75 spectrometer in tetrachloromethane (compounds *VII*) or in Nujol (*VIII–XIV*). Proton NMR spectra were measured on a BS-487 (80 MHz) spectrometer in deuteriochloroform or hexadeuteriodimethyl sulfoxide with tetramethylsilane as internal standard. The reaction course was monitored by thin-layer chromatography in ethyl acetate–isohexane.

The ^{1}H NMR spectra of the prepared compounds (except insoluble compounds *VIIa*, *VIIb*, *VIIIe*, *IXa*, *IXb* and *Xd*) are given in Table III, the IR spectra in Table IV.

Synthesis of Compounds *VII–XI* by "Classical" Method

A mixture of compound *I* (2.87 mmol), *II* (or *IV–VI*) (2.87 mmol), dry acetic anhydride (2–3 ml) and freshly fused potassium acetate was refluxed for the time specified in Table I. The deposited solid was filtered off and crystallized from acetone (products *VII*) or ethanol (*VIII*, *X* and *XI*). Products *IX* were chromatographed in isohexane–ethyl acetate (1 : 2) and crystallized from ethanol. Characteristic

TABLE IV
IR spectral data of synthesized compounds

Compound	$\bar{\nu}$, cm^{-1}		
	ν(C=O)$_{pyrone}$	ν(C=O)$_{others}$	ν of other groups
VIIa	1 668	1 701, 1 710	
VIIb	1 668	1 680, 1 683	
VIIc	1 659	1 682, 1 685	
VIId	1 657	1 683, 1 690	
VIIIa	1 655	1 687, 1 731	
VIIIb	1 662	1 690, 1 724	
VIIIc	1 665	1 688, 1 727	
VIIId	1 665	1 687, 1 727	
VIIIe	1 664	1 689, 1 725	
IXa	1 661	1 691, 1 698, 1 723	
IXb	1 651	1 692, 1 700, 1 716	3 300 (OH)
Xa	1 663	1 686	3 169 (NH)
Xb	1 664	1 688	3 168 (NH)
Xc	1 658	1 675	3 167 (NH)
Xd	1 667	1 682, 1 754 (CH_3CO)	3 165 (NH)
XI	1 651	1 721	
XIIa	–	1 654	3 295 (OH)
XIIb		1 667	3 100, 3 190 (NH), 3 290 (OH)
XIII		1 666, 1 714	3 100, 3 180 (NH), 3 234 (OH)

data for these compounds are given in Table I. The published data[16] for compounds *VIIIa–VIIIc* are in accord with ours.

Synthesis of Compounds *VII* and *VIII* in Microwave Oven

A mixture of compound *I* (2.87 mmol), *II* (or *III*) (2.87 mmol) and dry acetic anhydride (2 ml) was irradiated in a microwave oven for the time specified in Table I. The products were isolated in the same manner as described above.

Synthesis of Compounds *X* and *XI* in Microwave Oven

A mixture of compound *I* (2.87 mmol), *V* (or *VI*) (2.87 mmol), dry acetic anhydride (2 ml) and freshly fused potassium acetate was irradiated in a microwave oven for the time specified in Table I. The products *X* or *XI* were filtered off and crystallized from ethanol. For physical characteristics of the products see Table I.

3-(2-Hydroxyphenyl)- (*XIIa*), 3-(5-Chloro-2-hydroxyphenyl)-4-(2*H*,3*H*-3-oxo-1,4-benzothiazine-2,2-diylmethyl)pyrazole (*XIIb*) and 3-(2-Hydroxyphenyl)-4-(1,3-dioxo-2,2-indandiyl)pyrazole (*XIII*)

A mixture of *Xa*, *Xd* or *VIIIa* (2.8 mmol), hydrazine sulfate (or thiosemicarbazide) (2.8 mmol) and pyridine (3 ml) was refluxed for 2 h. After cooling, the mixture was diluted with ethanol (40 ml) and the products *XIIa*, *XIIb* or *XIII* were crystallized from ethanol (Table II).

The authors' thanks are due to Dr E. Greiplova for elemental analyses, Dr E. Solcaniova for measurement of the ^1H NMR spectra and Dr A. Perjessy for the IR spectral measurements (all members of Faculty of Natural Sciences, Comenius University, Bratislava). Financial support for this research by the Slovak Grant Agency is gratefully acknowledged.

REFERENCES

1. Nohara A., Sugihara H., Ukawa K.: Japan. Kokai 78, 111,070; Chem. Abstr. *90*, 54828 (1979).
2. Jerome F. F.: Phyton *21*, 133 (1964); Chem. Abstr. *62*, 13718 (1965).
3. Bradel-Gay J., Guiroy P., Bourillet F.: Therapie *17*, 1211 (1962); Chem. Abstr. *62*, 3296 (1965).
4. Fitton A. O., Kosmirak M., Suschitsky H., Suschitsky J. L.: Tetrahedron Lett. *23*, 3953 (1982).
5. Saegchantara S. T., Wallace T. W.: J. Chem. Soc., Chem. Commun. *1986*, 1592.
6. Saegchantara S. T., Wallace T. W.: J. Chem. Soc., Perkin Trans. 1 *1986*, 789.
7. Nohara A., Ishiguto T., Sanno Y.: Tetrahedron Lett. *13*, 1183 (1974).
8. Fitton A. O., Frost J. R., Suschitsky H., Houghton P. G.: Synthesis *1977*, 133.
9. Haas G., Stanton J. L., von Sprecher A., Wenk P.: J. Heterocycl. Chem. *18*, 607 (1981).
10. Prousek J. : Collect. Czech. Chem. Commun. *56*, 1361 (1991).
11. Ghosh C. K., Khan S.: Synthesis *1981*, 903.
12. Jones W. D., Albrecht W. L.: J. Org. Chem. *41*, 706 (1976).
13. Polyakov V. K., Babich J., Shevtsova R. G., Trusevitch N. D., Lavrushkin V. F.: Khim. Tekhnol. *30*, 42 (1987); Chem. Abstr. *108*, 112324 (1988).
14. Toma S.: Chem. Listy *87*, 627 (1993).
15. Eiden F., Haverland H.: Arch. Pharm. *360*, 806 (1967).
16. Polyakov V. K., Shevtsova R. G., Tsukerman S. V.: Ukr. Khim. Zh. *47*, 85 (1981).
17. Ghosh C. K., Mukhopadhyay K. K.: J. Indian Chem. Soc. *55*, 386 (1978).