Reaction of *N,N*-bis(chloromethyl)amides with *N,N'*-diacylated alkene(arylene)diamines

O. A. Luk'yanov and T. V. Ternikova*

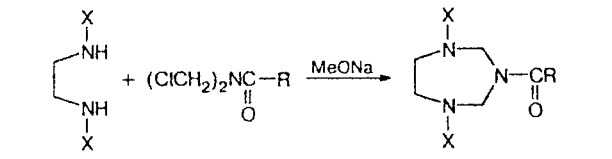
N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 47 Leninsky prosp, 117913 Moscow, Russian Federation. Fax: +7 (095) 135 5328

Reactions of *N,N*-bis(chloromethyl)amides with *N,N'*-diacyl derivatives of ethylenediamine (or *o*-phenylenediamine) result in formation of the corresponding 1,3,5-triacylated perhydro-1,3,5-triazepines (or their benzoanalogs) or 1,3-diacylated imidazolidines (or their benzoanalogs). Reactions of *N,N*-bis(chloromethyl)amides with *N,N'*-ditosylated trimethylenediamine occur in a similar way. The direction of the reactions depends on the type of the acyl substituents and the strength of the bases.

Key words: hexahydro-1,3,5-triazepines, tetrahydrobenzo-1,3,5-triazepines, 3-acetyl-1,2-ditosyloctahydro-1,3,5-triazocyne, imidazolidines, *N,N'*-bis(chloromethyl)amides, alkylenediamides, arylenediamides, *N*-acylimino-bismethylation, methylenation.

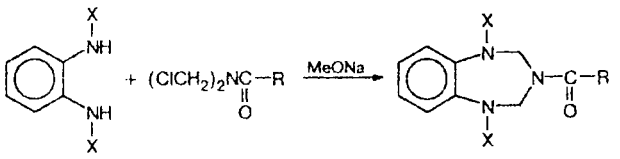
The facile reactions of nucleophilic substitution of the chlorine atom in *N*-(chloromethyl)amides[1] are well known. Several examples of analogous reactions with *N,N*-bis(chloromethyl)amides have also been reported.[2–5] In an attempt to obtain the previously unknown 1,3,5-triacylated hydrogenated 1,3,5-triazepines and their benzoanalogs, we studied the reaction of *N,N*-bis(chloromethyl)acetamide (**1a**) and *N,N*-bis(chloromethyl)formamide (**1b**) with a series of *N,N'*-diacyl derivatives of ethylenediamine (**2**) and *o*-phenylenediamine (**3**) in the presence of bases.

It was found that the direction of reactions between the reagents specified above is determined by the nature of acyl radicals in compounds **2** and **3** and the strength of the bases.



2a–b **1a,b** **4a–c**

2a: X = Ts **1a:** R = Me **4a:** X = Ts, R = Me
2b: X = 3-O_2NTs **1b:** R = H **4b:** X = 3-O_2NTs, R = H
4c: X = 3-O_2NTs, R = Me

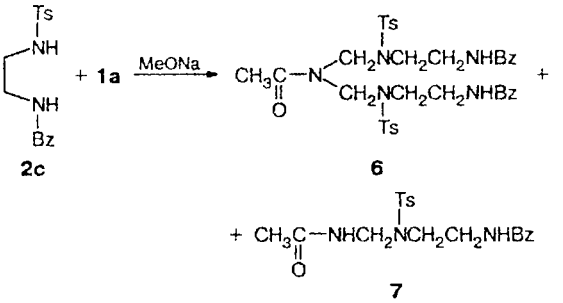


3a,b **1a,b** **5a,b**

3a: X = Ms **5a:** X = Ms, R = Me
3b: X = 3-O_2NTs **5b:** X = 3-O_2NTs, R = H

If arylsulfonyl or alkylsulfonyl groups are used as acyls and alkoxides of alkaline metals are used as bases, the reaction ends in the formation of the required derivatives of 1,3,5-triazepines **4a–c** or **5a–b** (Table 1).

In these cases, the base can be added directly to a mixture of the starting reagents (method *A*), or salts of bisamides **2** or **3** can be obtained beforehand from the same base (method *B*). Compounds **1a** and **1b** play the role of *N*-acylamino-bis-methylating reagents. A similar role can be played by compounds **1a,b** in reactions with *N,N'*-diacyl derivatives **2** or **3**, in which one acyl group is a sulfonic acid residue, and the second one is a carboxylic acid residue. However, in this case the reaction involves only the sulfamide groups, while considerable amounts of triazepine derivatives are not formed.



2c **6**

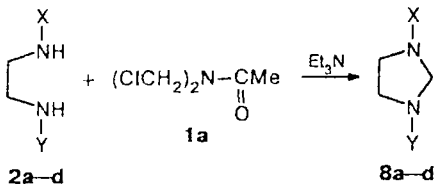
7

If triethylamine is used as the base instead of sodium alkoxide, 1,3-diacylated imidazolidines **8a–d** and **9** are formed rather than triazepines, irrespective of the character of the acyl substituents in compounds **2** or **3**.

It is interesting to note that the reaction result is the same whether it is carried out in the presence of a base (triethylamine) or in the presence of an acid (boron trifluoride etherate).

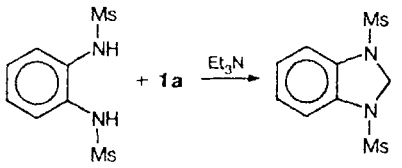
Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya*, No. 11, pp. 2270—2273, November, 1998.

1066-5285/98/4711-2201$20.00



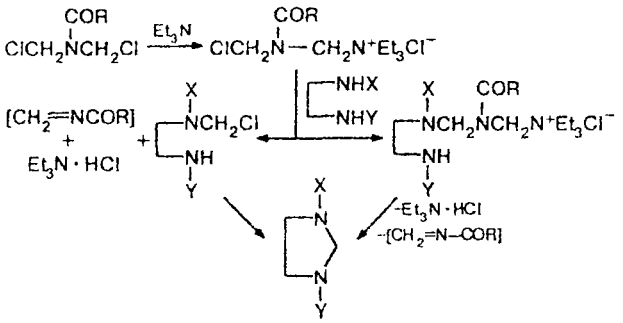
2a–d **1a** **8a–d**

a: X = Y = Ts **c:** X = Ts, Y = Bz
b: X = Y = 3-O_2NTs **d:** X = Y = 4-MeBz



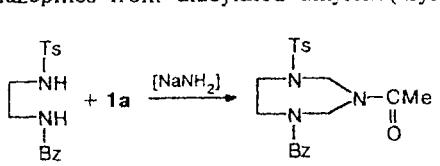
3a **9**

Thus, *N,N*-bis(chloromethyl)amides can act not only as *N*-acylimino-bis-methylating but also as methylenating agents. For example, the following scheme can be suggested as a working hypothesis to explain how methylenating products are formed.

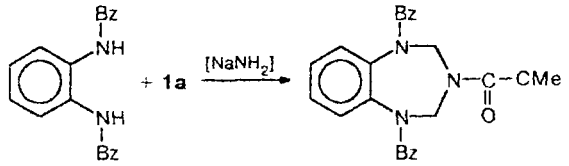


The key stages for the understanding of the final results of the reaction apparently include synchronous cleavage of two C—N bonds, and the role of leaving groups is played by electroneutral compounds CH_2=NCOR and Et_3N.

Analysis of the above laws of formation of triazepines **4** and **5** allowed us to hope that failure in obtaining triazepines from diacylated alkylene(arylene)diamines, in which residues of carboxylic acids served as the acyl groups, can be overcome if independently obtained bis-salts of such diamides are used. In fact, it was found that if ethylene(phenylene)diamides, in which acyl substituents include one or two benzoyl groups, are initially treated with $NaNH_2$, the reaction of such substrates with compounds **1a** or **1b** (method *C*) results in the desired triazepines **4d** or **5c**.

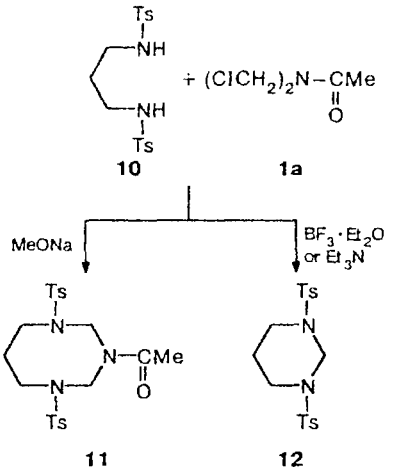


2c **4d**



3c **5c**

It can be inferred from the results of the reaction of *N,N'*-ditosylated trimethylenediamine (**10**) with compound **1a** in the presence of MeONa, Et_3N, or $BF_3 \cdot Et_2O$ that the basic regularities of the reaction of *N,N*-bis(chloromethyl)amides with diacylated ethylenediamines are apparently also valid for the reaction with *N,N'*-diacylated trimethylenediamines.



10 **1a** **11** **12**

Experimental

^{1}H NMR spectra were recorded on a Bruker AM-300 instrument. IR spectra were obtained on a UR-20 spectrophotometer in KBr pellets. Melting poits were determined on a Kofler hot stage. *N,N'*-Diacylated alkylene(arylene)diamines were obtained according to known procedures;[6,7,8] *N,N*-bis(chloromethyl)amides were synthesized according to the method described previously.[2]

Synthesis of 1,3,5-triacylhexahydro-1,3,5-triazepines (4a–d) and 1,3,5-triacyltetrahydro-1,3,5-benzotriazepines (5a–c). Method *A*. A solution of MeONa (2.2 mmol) in 2 mL of MeOH was added at 20 °C with stirring to a solution of alkylenediamide **2** (1.1 mmol) and compound **1a** (1.1 mmol) in 5 ml of DMF. After 12 h, the reaction mixture was poured onto ice, and the precipitate was separated, washed with water, dried, and recrystallized. Compounds **4a** and **4c** were obtained (see Table 1).

Method *B*. Alkylene(arylene)diamide **2** or **3** (1.1 mmol) was added with stirring to a solution of MeONa (2.2 mmol) in 5 mL of MeOH, the reaction mixture was stirred for 0.5 h at 60 °C, the methanol was concentrated, and 5 mL of DMF and 1.1 mmol of compound **1** were added to the residue. After keeping for 3 h at 50 °C, the reaction mixture was processed as in method *A* to give compounds **4b** and **5a,b** (see Table 1).

Method *C*. Alkylene(phenylene)diamide **2** or **3** (1.25 mmol) and then 10 mL of dry toluene were added to a suspension of

Table 1. Conditions of formation and characteristics of 1,3,5-triacylated 1,3,5-triazepines **4a—d** and their benzoanalogs **5a—c**

Compound	Method of preparation	Substituents at positions 1	3	5	Yield (%)	M.p. /°C (solvent)	Found / Calculated (%) C	H	N	S	Molecular formula	IR, ν/cm^{-1}	^{1}H NMR ($CDCl_3$), δ (*J*/Hz)
4a	*A*	Ts	Ac	Ts	40	151—153 (EtOH)	53.16 / 53.20	5.83 / 5.58	9.47 / 9.31	14.06 / 14.20	$C_{20}H_{25}N_3O_5S_2$	1650 (CO), 1350, 1160 (SO_2)	2.37 (s, 3 H, Me), 2.40 (s, 3 H, Me), 2.42 (s, 3 H, Me), 3.35 (s, 4 H, 2 CH_2), 4.71 (s, 2 H, CH_2), 4.95 (s, 2 H, CH_2), 7.32, 7.61 (both d, 2 H each arom., J = 9)
4b	*B*	3-O_2NTs	COH	3-ON_2Ts	40	171—172.5 (EtOH)	43.14 / 43.26	4.11 / 4.01	13.38 / 13.28	—	$C_{19}H_{21}N_5O_9S_2$	1700 (CO) 1535, 1360 (NO_2) 1350, 1170 (SO_2)	2.60 (s, 6 H, 2 Me), 3.50—3.80 (m, 4 H, 2 CH_2), 4.90 (s, 2 H, CH_2), 5.05 (s, 2 H, CH_2), 7.70—8.35 (m, 7 H, CH and arom.)[a]
4c	*A*	3-O_2NTs	Ac	3-ON_2Ts	88	153—155 (EtOH)	44.66 / 44.36	4.60 / 4.28	—	11.38 / 11.84	$C_{20}H_{23}N_5O_9S_2$	1665 (CO) 1540, 1335 (NO_2) 1350, 1160 (SO_2)	2.38 (s, 3 H, Me), 2.70 (s, 6 H, 2 Me), 3.50 (m, 4 H, 2 CH_2), 4.90 (s, 2 H, CH_2), 5.50 (s, 2 H, CH_2), 7.50 (m, 2 H, arom.), 8.35 (s, 2 H, arom.), 7.80 (t, 2 H, arom.)
4d	*C*	Ts	Ac	Bz	20	197—199 (EtOH)	59.51 / 59.83	5.91 / 5.78	—	8.13 / 7.99	$C_{20}H_{23}N_3O_4S$	1650, 1630 (CO) 1350, 1160 (SO_2)	2.40 (s, 3 H, Me), 2.50 (s, 3 H, Me), 3.70 (m, 4 H, 2 CH_2), 5.00 (s, 4 H, 2 CH_2), 7.25—7.75 (m, 9 H, arom.)
5a	*B*	Mz	Ac	Mz	55	296—297 (DMF)	41.78 / 41.49	4.95 / 4.93	—	18.16 / 18.46	$C_{12}H_{17}N_3O_5S_2$	1660 (CO) 1350, 1160 (SO_2)	2.22 (s, 3 H, Me), 3.00 (s, 3 H, Me), 3.35 (s, 3 H, Me), 5.15 (br.s, 4 H, 2 CH_2), 7.30—7.60 (m, 4 H, arom.)[b]
5b	*B*	3-O_2NTs	COH	3-ON_2Ts	31	219—220 (EtOH)	47.92 / 48.00	3.83 / 3.68	12.08 / 12.17	11.10 / 11.14	$C_{23}H_{21}N_5O_9S_2$	1690 (CO) 1540, 1340 (NO_2) 1360, 1170 (SO_2)	2.50 (s, 6 H, 2 Me), 7.20—8.50 (m, 6 H, arom.), 8.20 (s, 1 H, CHO)[a]
5c	*C*	Bz	Ac	Bz	10[c]	178—181	72.42 / 72.17	5.36 / 5.30	—	—	$C_{24}H_{21}N_3O_3$	1652 (CO)	2.10 (s, 3 H, Me), 5.50 (br.s, 4 H, 2 CH_2), 7.00—7.60 (m, 14 H, arom.)

[a] The NMR spectrum was recorded in acetone-d_6.
[b] The NMR spectrum was recorded in DMSO-d_6.
[c] The yield of **5c** with respect to the **3c** consumed is 45 %.

$NaNH_2$ (from 0.15 g of metallic Na) in liquid NH_3. The reaction mixture was heated with stirring to 60 °C, 3.2 mmol of compound **1a** was added, and this temperature was maintained for 1 h. The precipitate was separated, the filtrate was concentrated, and the residue was recrystallized to give compounds **4d** and **5c** (see Table 1).

Reaction of *N*-benzoyl-*N'*-tosylethylenediamine (2c) with compound 1a in the presence of sodium methoxide. A solution of MeONa (2.2 mmol) in 20 ml of MeOH was added at 20 °C with stirring to a solution of compounds **2c** (0.35 g, 1.1 mmol) and **1a** (0.2 g, 1.1 mmol) in 5 ml of DMF, and the mixture was kept for 12 h. The reaction mixture was poured onto ice.

6-Acetyl-1,11-dibenzoyl-4,8-ditosyl-1,4,6,8,11-pentaazaundecane (**6**) and 1-acetyl-6-benzoyl-3-tosyl-1,3,6-triazahexane (**7**) were isolated by PTLC on silica gel. Compound **6**, yield 13 %, m.p. 169—171 °C (from EtOH). Found (%): C, 60.17; H, 5.85; S, 8.76 $C_{36}H_{41}N_5O_7S_2$. Calculated (%): C, 60.07; H, 5.74; S, 8.90. IR, ν/cm^{-1}: 3350 (NH); 1670, 1645 (C=O), 1335, 1160 (SO_2). ^1H NMR ($CDCl_3$), δ: 2.30 (s, 3 H, CH_3CO); 2.40 (s, 6 H, 2 $CH_3C_6H_4$); 3.50 (m, 8 H, 2 NCH_2CH_2N); 4.70 (s, 2 H, NCH_2N); 5.00 (s, 2 H, NCH_2N); 6.95 (br.s, 2 H, NH); 7.10—8.00 (m, 18 H, arom.). Compound **7**, yield 14 %, m.p. 153—155 °C (precipitated with ether from EtOH). Found (%): C, 58.31; H, 6.23; S, 8.53 $C_{19}H_{23}N_3O_4S$. Calculated (%): C, 58.60; H, 5.95; S, 8.23. IR, ν/cm^{-1}: 3340 and 3280 (NH), 1670 and 1640 (C=O), 1340 and 1165 (SO_2). ^1H NMR ($CDCl_3$), δ: 2.00 (s, 3 H, CH_3CO); 2.35 (s, 3 H, $CH_3C_6H_4$); 3.30—3.70 (m, 4 H, NCH_2CH_2N); 4.65 (d, 2 H, NCH_2N, J = 7.2 Hz); 6.60 (br.s, 1 H, $NHCOCH_3$); 7.10—7.90 (m, 9 H, NH + 8 H arom.).

***N,N*-Ditosylimidazolidine (8a).** *A.* Et_3N (1.3 mmol) and compound **1a** (1.3 mmol) were added to a solution of compound **2a** (1 mmol) in 3 mL of dioxane. The reaction mixture was stirred for 3 h at 70 °C, the precipitate was separated, dioxane was evaporated, and the residue was washed with water. The resulting product **8a** was purified by TLC; the yield was 63 %, m.p. 156—160 °C (Ref. 6: m.p. 160 °C). ^1H NMR ($CDCl_3$), δ: 2.20 (s, 6 H, 2 CH_3); 3.00 (s, 4 H, CH_2CH_2); 4.25 (s, 2 H, NCH_2N); 7.00, 7.40 (both d, 2 H each, arom., J = 9.0 Hz).

B. Compound **1a** (0.51 mmol) and a few drops of $BF_3 \cdot Et_2O$ were added to a solution of compound **2a** (0.5 mmol) in 3 mL of dioxane. The reaction mixture was kept for 3 h at 70 °C and filtered; the dioxane was evaporated, and the residue was washed with water. The yield of compound **8a** was 80 %, m.p. 152—157 °C.

***N,N'*-Bis-(3-nitrotosyl)imidazolidine (8b)** was obtained similarly to compound **8a** (with Et_3N), yield 54 %, m.p. 188—190 °C (Ref. 6: 189—192 °C). ^1H NMR (DMSO-d_6), δ: 2.70 (s, 6 H, 2 CH_3); 3.30 (s, 4 H, CH_2CH_2); 4.50 (s, 2 H, CH_2); 7.90, 8.25 (both m, 6 H, arom.).

***N*-Benzoyl-*N'*-tosylimidazolidine (8c)** was obtained similarly to compound **8a** (with Et_3N), yield 49 %, m.p. 118—122 °C (Ref. 6: 120—123 °C). ^1H NMR ($CDCl_3$), δ: 2.30 (s, 3 H, CH_3); 3.10—3.70 (m, 4 H, CH_2CH_2); 4.75 (s, 2 H, NCH_2N); 7.20—7.70 (m, 9 H, arom.).

***N,N'*-Bis(*p*-toluoyl)imidazolidine (8d)** was obtained similarly to compound **8a** (with Et_3N), yield 34 %, m.p. 138—141 °C (Ref. 6: 139—142 °C). ^1H NMR ($CDCl_3$), δ: 2.40 (s, 6 H, 2 CH_3); 3.80 (m, 4 H, CH_2CH_2); 5.10 (s, 2 H, NCH_2N); 7.20, 7.45 (both d, 2 H each, arom., J = 9.0 Hz)

1,3-Dimesylbenzimidazoline (9). Compound **3a** (2 mmol) was dissolved on heating in 5 mL of dioxane. Compound **1a** (2.1 mmol) and Et_3N (2.1 mmol) were added to the solution, and the reaction mixture was heated for 3 h at 70 °C. The precipitate was separated, the filtrate was concentrated, and the residue was washed with water. The yield of compound **9** was 23 %, m.p. 167—170 °C (from EtOH). Found (%): C, 39.06; H, 4.24; S, 22.91. $C_9H_{12}N_2O_4S_2$. Calculated (%): C, 39.12; H, 4.38; S, 23.20. IR, ν/cm^{-1}: 1350 and 1160 (SO_2). ^1H NMR ($CDCl_3$), δ: 2.95 (s, 6 H, 2 CH_3); 5.45 (s, 2 H, NCH_2N), 7.15 and 7.40 (both m, 4 H, C_6H_4).

3-Acetyl-1,5-ditosyloctahydro-1,3,5-triazocyne (11). Sodium (0.05 g) was added to MeOH (5 mL), and *N,N'*-ditosyltrimethylenediamine **10** (0.41 g, 1.1 mmol) was then added with stirring. The reaction mixture was stirred for 0.5 h at 60 °C, and methanol was evaporated. DMF (5 mL) and compound **1a** (0.17 g, 1.1 mmol) were added to the residue. The mixture was stirred for 0.5 h at 50 °C and poured onto ice. The precipitate was separated, washed with water, dried in air, and purified by PTLC on silica gel. The yield of compound **11** was 50 %, m.p. 170—172 °C (from ethanol). Found (%): C, 54.01; H, 5.87; S, 13.57. $C_{21}H_{27}N_3O_5S_2$. Calculated (%): C, 54.17; H, 5.96; S, 13.76. IR, ν/cm^{-1}: 1670 (CO); 1345 and 1175 (SO_2). ^1H NMR ($CDCl_3$), δ: 1.85 (m, 2 H, $CH_2\underline{CH_2}CH_2$); 2.38 (s, 3 H, CH_3CO); 2.46 (s, 6 H, 2 $CH_3C_6H_4$); 3.15 (m, 4 H, 2 NCH_2); 4.78 (s, 2 H, NCH_2N); 4.90 (s, 2 H, NCH_2N); 7.35 and 7.65 (m, 8 H, C_6H_4).

1,3-Ditosylhexahydro-1,3-diazine (12). *A.* A mixture of compounds **10** (0.11 g, 0.287 mmol), **1a** (0.05 g, 0.32 mmol), and Et_3N (0.05 mL, 0.32 mmol) in 3 mL of dioxane was heated for 1.5 h at 70 °C, cooled, and diluted with water. The precipitate was filtered off, dried in air, and recrystallized from EtOH. The yield of compound **12** was 82 %, m.p. 144—146 °C (Ref 7: m.p. 147 °C). ^1H NMR ($CDCl_3$), δ: 1.30 (m, 2 H, CCH_2C); 2.45 (s, 6 H, 2 CH_3); 3.20 (t, 4 H, NCH_2C, J = 7.0 Hz); 4.70 (s, 2 H, NCH_2N); 7.40 and 7.70 (both d, each 4 H, arom., J = 9.0 Hz)

B. A mixture of compounds **10** (0.12 g, 0.31 mmol), **1a** (0.05 g, 0.32 mmol), and several drops of $BF_3 \cdot Et_2O$ in 3 mL of dioxane was heated for 5 h at 70 °C, cooled, the solvent was evaporated, and the residue was washed with water. The yield of compound **12** was 89 %, m.p. 143—145 °C.

References

1. H. E. Zaugg and W. B. Martin, *Organic reactions*, 1967, **14**, 65.
2. H. Bohme and J.-P. Denis, *Liebigs Ann.*, 1979, 1447.
3. H. Bohme and J.-P. Denis, T. Kampchen, *Chem. Ber.*, 1982, **115**, 2947.
4. H. Bohme, J.-P. Denis, *Arch. Pharm.*, 1982, **315**, 227.
5. A. F. Prokof'eva, S. A. Manaev, T. V. Aleshnikova, V. V. Negrebetskii, A. P. Grapov, and N. N. Mel'nikov, *Zh. Org. Khim.*, 1986, **56**, 809 [*J. Org. Chem.*, 1986, 561 (Engl. Transl.)].
6. O. A. Luk'yanov, G. V. Pokhvisneva, and T. V. Ternikova, *Izv. Akad. Nauk, Ser. Khim.*, 1994, 1452 [*Russ. Chem. Bull.*, 1994, **43**, 1376 (Engl. Transl.)].
7. R. Mazurkiewiez, *Monatsh.*, 1988, **119**(11), 1279.
8. H. Steller, *Chem. Ber.*, 1953, **86**, 197.
9. K. Krakowiak, P. Idowski, and B. Kotelko, *Polish. J. Chem.*, 1984, **58**, 251.

Received April 21, 1998;
in revised form May 18, 1998