Monatshefte für Chemie 125, 433–439 (1994)

Monatshefte für Chemie
Chemical Monthly

Printed in Austria

Reaction of Benzylidenebenzocyclanones with Dithiocarbamic Acid and Thiourea

P. Perjési[1]*, G. Batta[2], and A. Földesi[1]

[1] Department of Medical Chemistry, University Medical School, H-7601 Pécs, Hungary
[2] Institute of Organic Chemistry, Lajos Kossuth University, H-4010 Debrecen, Hungary

Summary. Reaction of 2-benzylidene-1-benzocyclanones **1** with dithiocarbamic acid afforded open-chain addition products **2A–4B**. Dehydration of the adducts yielded tricyclic 1,3-thiazine-2-thiones **5** and **6**. Treatment of **1** with thiourea under acid conditions gave tricyclic 2-amino-1,3-thiazines **7–9**. IR and ^{1}H NMR spectroscopic investigations showed **7–9** to exist predominantly in the amino tautomeric form both in the solid state and in solution.

Keywords. Benzo[6,7]cyclohepta[1,2-*d*][1,3]thiazines; Benzo[4,5]cyclopenta[1,2-*d*][1,3]thiazines; Naphto[1,2-*d*][1,3]thiazines.

Die Umsetzung von 2-Benzyliden-benzocyclanonen mit Dithiocarbaminsäure und Thioharnstoff

Zusammenfassung. Die Reaktionen der 2-Benzyliden-1-benzocyclanone **1** mit Dithiocarbaminsäure liefern kettenförmige Additionsprodukte **2A–4B**. Die Dehydratisierung der Additionsprodukte führt zu tricyklischen 1,3-Thiazin-2-thionen **5** und **6**. Durch Behandlung von **1** mit Thioharnstoff unter sauren Bedingungen wurden tricyclische 2-Amino-1,3-Thiazine **7–9** gebildet. IR- und ^{1}H-NMR-spektroskopische Untersuchungen zeigten, dass **7–9** sowohl in Substanz als auch in Lösungen überwiegend in der amino-tautomeren Form existieren.

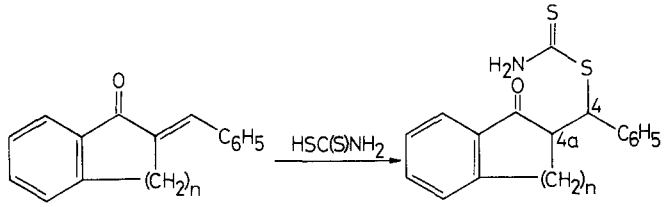
Introduction

The acid-catalyzed reaction of α,β-unsaturated carbonyls with dithiocarbamic acid and thiourea is a versatile route for synthesis of 1,3-thiazines [1–5]. As a continuation of our earlier studies on the reaction of dithiocarbamic acid with chalcones [6] and 2-arylidenecyclohexanones [7–8], as well as *N*-substituted dithiocarbamic acids with 2-arylidenecyclohexanones [9], we report here the results of acid-catalyzed reactions of 2-benzylidene-1-benzocyclanones **1–3** with dithiocarbamic acid and thiourea. These reactions afforded tricyclic 1,3-thiazine derivatives **5–9**, among which **6**, **7**, and **9** were found to be the first representatives of two new condensed tricyclic 1,3-thiazine ring systems.

Discussion

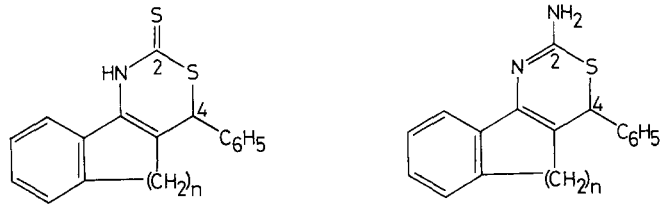
Reaction of 2-benzylidene-1-benzocyclanones **1** with dithiocarbamic acid was carried out treating compounds **1a–c** with ammonium dithiocarbamate in strongly

acid aqueous acetone solution at −5 °C (Method A). Under such conditions, formation of the open-chain adducts **2A**, **3A** and **4A** was observed (cf. Formulae). ^{1}H NMR investigation (cf. experimental part) of the crude products showed formation of only one of the two possible diastereomers in each case.



1a n=1
1b n=2
1c n=3

2A n=1
3A 3B n=2
4A 4B n=3



5 n=2
6 n=3

7 n=1
8 n=2
9 n=3

Formulae

Appearance of the $\nu(NH_2)$ and $\nu(C{=}O)$ signals in their IR spectra gave unambiguous evidence of the progress of the reactions and the open chain structure of the products as well. This was also confirmed by the ^{1}H NMR spectra, which showed a doublet for the benzyl protons (H–C(4)) of the side chains as a proof of the addition reactions (cf. Table 1). The NH_2 protons appear as two separate signals, indicating the open chain structure of the adducts and restricted rotation of the dithiocarbamate moieties in solution.

Changing the amount of hydrochloric acid used in the reactions gave crude products of different composition. Using approximately an equivalent amount of hydrochloric acid compared to ammonium dithiocarbamate (Method B), **1a** yielded adduct **2A** containing some unreacted starting material **1a**. If less hydrochloric acid was used (a quarter of an equivalent compared to ammonium dithiocarbamate, Method C), however, the reaction did not proceed. Analysis (TLC and ^{1}H NMR) of the crude product showed only presence of **1a**.

Reactions of **1b** and **1c** carried out under conditions of Method B or Method C led to formation of mixtures of the corresponding isomeric adducts **3A**, **3B**, and **4A**, **4B**, respectively. In the ^{1}H NMR spectra of the crude products additional benzyl doublets (**3B**: $\delta = 5.74$ ppm, $^3J_{4,4a} = 5.05$ Hz; **4B**: $\delta = 5.70$ ppm, $^3J_{4,4a} = 9.50$ Hz) appeared besides those ones observed for pure **3A** ($\delta = 5.91$ ppm, $^3J_{4,4a} = 3.65$ Hz) and **4A** ($\delta = 5.58$ ppm, $^3J_{4,4a} = 7.30$ Hz). Pure **3B** and **4B** were obtained by fractional crystallization of the respective mixtures obtained with Methods B or C.

The IR and ^{1}H NMR spectra of **3B** and **4B** showed similar features to those of **2A**–**4A**. Thus, two chiral centers developed in the reactions, making formation of two diastereomeric adducts possible. Since **1a** afforded only one of the diastereomeric adducts under all conditions investigated, its structure was determined by X-ray diffraction. X-ray analysis of **2A** showed that the two chiral centers have the same configuration according the C.I.P. rules [10]. Such a stereochemistry is the result of a *cis* addition of dithiocarbamic acid to the α,β-unsaturated system, which was also the case when 2-arylidenecyclohexanones were reacted with dithiocarbamic acid under conditions of Method C [7].

Analysis of the ^{1}H NMR spectra (Table 1) of the diastereoisomers **3** and **4** showed all compounds to have the bulky (dithiocarbamoyl)benzyl group in the preferred *equatorial* position. Based on the $^3J_{4,4a}$ values only **3A** ($J = 3.65$ Hz) seems to have only one preferred conformation around the C(4)–C(4a) axis. Thus, comparison of the ^{1}H NMR spectroscopic parameters of the respective diastereomers could not clarify the relative configurations.

Adducts **3** and **4** were converted into the corresponding 1,3-thiazine-2-thiones **5** and **6** by treatment with *p*-toluenesulfonic acid or trifluoroacetic acid in benzene solution. Similar treatment of **2A**, however, caused decomposition of the compound.

The structures of **5** and **6** were established by IR and ^{1}H NMR methods. In their IR spectra ν(C=C) bands appear instead of the ν(C=O) of compounds **3** and **4**. In the ^{1}H NMR spectra the H–C(4) signals appear as singlets, proving the position of the newly formed double bond.

Besides the well documented pharmacological interest of 1,3-thiazine-2-(thi)ones [11, 12], **5** and **6** could also serve as model compounds for the investigation of tautomeric interconversions of some related 2-amino-1,3-thiazines, which is not a question without contradictions in the literature [13, 14].

Reaction of **1**–**3** with thiourea was performed in boiling ethanol solution using hydrochloric acid as catalyst. Under such conditions the tricyclic 2-amino-1,3-thiazines **7**–**9** were obtained after liberation of the bases from their hydrochloride salts (cf. Formulae). In their IR spectra recorded in KBr $\nu_{as}(NH_2)$ (3475–3450 cm^{-1}) and $\nu_s(NH_2)$ (3280–3270 cm^{-1}) signals appear (cf. experimental part). Similarly, in the spectra taken in $CHCl_3$ solution signals of $\nu_{as}(NH_2)$ (3500–3485 cm^{-1}) and $\nu_s(NH_2)$ (3395–3380 cm^{-1}) can be seen in this region. These characteristics are in accordance with the predominant amino tautomer of the compounds both in the solid state and in solution [15].

In an earlier study on the tautomeric structure of some 2-phenyl-4-aryl-3,4,5,6-tetrahydrobenzo[*h*] quinazolines by NMR spectroscopy, δ(H–C(10)) values were found to be decisive characteristics concerning the two possible tautomers of the compounds [16]. In the ^{1}H NMR spectra of **7**–**9** (cf. experimental part), the characteristic downfield shift of the separated protons H–C(9), H–C(10), and H–C(11) of compounds **7** ($\delta = 7.6$–7.5 ppm), **8** ($\delta = 7.9$–7.7 ppm), and **9** ($\delta = 7.7$–7.5 ppm), respectively, can also be explained by the magnetic anisotropy and conjugation effect of the C=N double bond in the 1,2-position [16, 17]. Thus, the ^{1}H NMR spectra of **7**–**9** also prove predominant existence of the amino tautomer for the compounds in solution.

According to the latest *C.A.* files and the recent edition of *C.A. Ring System*

Table 1. Chemical shifts of compounds **2A–4B** (200 MHz, acetone-d_6)

Compound	N*H* (s, 2 × 1H)	H–C (10) (1H, dd)	Ar*H* (8H, m)	H–C (4) (1H, d)	$^3J_{4,4a}$ (Hz)	H–C (4a) (1H, ddd)	$^3J_{4a,5_{eq}}$ (Hz)	$^3J_{4a,5_{ax}}$ (Hz)	H_{eq}–C (5) (1H, m)	H_{ax}–C (5) (1H, m)	Other
2A	8.85, 8.60		7.92–7.10	5.71	4.00	3.68	8.0	4.7	3.43	3.19[a]	–
3A	8.78, 8.55	7.90	7.55–7.13	5.91	3.65	3.47	4.2	12.4	2.44[b]	1.95[c]	d
3B	8.73, 8.49	7.94	7.57–7.14	5.74	5.05	3.29	4.3	12.5	2.35[e]	1.92[f]	g
4A	8.68, 8.48		7.57–7.13	5.58	7.30	3.79	5.5	10.5	1.87	1.82–1.45[h]	i, j, k
4B	8.79, 8.54		7.46–7.08	5.80	9.50	3.79	5.2	10.9	2.15	1.93–1.52[l]	m, n, o

[a] $^2J(5_{eq}, 5_{ax}) = 17.0$ Hz; [b] $^3J(5_{eq}, 6') = 4.1$ Hz, $^3J(5_{eq}, 6'') = 4.2$ Hz; [c] $^3J(5_{ax}, 6_{ax}) = 10.5$ Hz, $^3J(5_{ax}, 6_{eq}) = 5.5$ Hz, $^2J(5_{ax}, 5_{eq}) = 12.5$ Hz; [d] $^2J(6_{eq}, 6_{ax}) = 12.6$ Hz; [e] $^3J(5_{eq}, 6') = 4.3$ Hz, $^3J(5_{eq}, 6'') = 4.3$ Hz; [f] $J(5_{ax}, 6_{ax}) = 8.9$ Hz, $^3J(5_{ax}, 6_{eq}) = 7.2$ Hz, $^2J(5_{ax}, 5_{eq}) = 13.2$ Hz; [g] $^2J(6_{eq}, 6_{ax}) = 12.4$ Hz; [h] 2H, m, H_{ax}–C(5) + H_{ax}–C(6); [i] 1H, m, $\delta = 2.25$–2.05 ppm, H_{eq}–C(6); [j] 1H, m, $\delta = 2.95$ ppm, H_{eq}–C(7); [k] 1H, m, $\delta = 3.18$ ppm, H_{ax}–C(7); [l] 2H, m, H_{ax}–C(5) + H_{ax}–C(6); [m] 1H, m, $\delta = 2.42$–2.02 ppm, H_{eq}–C(6); [n] 1H, m, $\delta = 3.00$ ppm, H_{eq}–C(7); [o] 1H, m, $\delta = 3.14$ ppm H_{ax}–C(7)

Handbood [18], compounds **6**, **7**, and **9** were found to be the first representatives of two new condensed tricyclic 1,3-thiazine ring systems.

Experimental Part

Melting points were determined on a Boetius apparatus and are uncorrected. IR spectra were taken with a Specord 75 IR spectrophotometer. ^{1}H NMR spectra were recorded with Perkin-Elmer R-12 (60 MHz), Bruker WP 80 SY (80 MHz), and Bruker WP 200 SY (200 MHz) spectrometers. In all NMR measurements tetramethylsilane (TMS) was used as internal standard. Elemental analyses were performed inhouse, at the Central Research Laboratory, University Medical School, Pécs, and at the Department of Organic Chemistry, Eötvös Loránd University, Budapest.

The 2-benzylidene-1-benzocyclanones **1–3** were prepared according to the literature [19]. Their configuration (*E*) was deduced from IR and ^{1}H NMR investigations [20].

The progress of the reactions, as well as the purity of the compounds synthesized, was checked by TLC performed on Kieselgel GF 254 plates (Merck) using benzene and/or benzene:ethanol = 4:1 as eluant.

The isomeric composition of the reaction products was determined by ^{1}H NMR spectroscopy (60 MHz), based on investigation of the well separated signals of H–C(4).

General procedure for the addition of dithiocarbamic acid to 2-benzylidenebenzocyclanones **1–3**

To a solution of 0.175 mol of the ammonium salt of dithiocarbamic acid [21] dissolved in 150 ml of 50% methanol (cooled to −5 °C), 40 ml (Method A), 25 ml (Method B), or 6.5 ml (Method C) of 6.5 *N* hydrochloric acid (cooled to −5 °C) was added dropwise with stirring. Cooling and stirring was continued, and 0.015 mol of unsaturated ketone **1–3** in 250 ml acetone (cooled to −5 °C) was added to the reaction mixture. After stirring at this temperature for 4 h, the precipitate formed was filtered off, washed free of acid with water, dried, and crystallized from benzene/petroleum ether to give colorless crystals.

2-(α-(thiocarbamoylthio)benzyl)-indan-1-one (**2A**)

Yield: 74% (Method A), m.p. 134–137 °C. IR (KBr): $\nu = 3385$, 3245 cm^{-1} (NH_2), 3130 cm^{-1} (NH_2), 1675 cm^{-1} (C=O). $C_{17}H_{15}NOS_2$ (313.44). Calcd. C 65.14, H 4.82, S 20.46; found C 64.87, H 4.85, S 20.40.

2-(α-(thiocarbamoylthio)benzyl)-1-tetralone (**3A**)

Yield: 78% (Method A), m.p. 157–160 °C (benzene). IR (KBr): $\nu = 3380$, 3290 cm^{-1} (NH_2), 3195 cm^{-1} (NH_2), 1665 cm^{-1} (C=O). $C_{18}H_{17}NOS_2$ (327.47). Calcd. C 66.02, H 5.23, S 19.58; found C 65.84, H 5.47, S 19.31.

2-(α-(thiocarbamoylthio)benzyl)-1-tetralone (**3B**)

Yield: 69% (Method C), m.p. 175–178 °C (benzene). IR (KBr): $\nu = 3380$, 3290 cm^{-1} (NH_2), 3195 cm^{-1} (NH_2), 1665 cm^{-1} (C=O). $C_{18}H_{17}NOS_2$ (327.47). Calcd. C 66.02, H 5.23, S 19.58; found C 65.87, H 5.55, S 19.40.

2-(α-(thiocarbamoylthio)benzyl)-1-benzosuberone (**4A**)

Yield: 76% (Method A), m.p. 179–181 °C. IR (KBr): $\nu = 3375$, 3250 cm^{-1} (NH_2), 3165 cm^{-1} (NH_2), 1680 cm^{-1} (C=O). $C_{19}H_{19}NOS_2$ (341.50). Calcd. C 66.83, H 5.61, S 18.78; found C 66.64, H 5.57, S 18.57.

2-(α-(thiocarbamoylthio)benzyl)-1-benzosuberone (**4B**)

Yield: 67% (Method C), m.p. 187–189 °C. IR (KBr): $\nu = 3375$, 3250 cm^{-1} (NH_2), 3165 cm^{-1} (NH_2), 1680 cm^{-1} (C=O). $C_{19}H_{19}NOS_2$ (341.50), Calcd. C 66.83, H 5.61, S 18.78; found C 66.71, H 5.34, S 18.64.

General procedure for dehydration of compounds **2–4**

To the suspension of compounds **2–4** (0.03 mol) in 50 ml of dry benzene a catalytic amount of *p*-toluenesulfonic acid (Method A) or 5–6 drops of trifluoroacetic acid (Method B) was added and the reaction mixture was refluxed for 1–3 h. Then the clear solution obtained was cooled to room temperature, washed free of acid with distilled water, dried (Na_2SO_4), and concentrated. The pale yellow solid was purified by column chromatography (Kieselgel 60, eluant: benzene) and recrystallized from methanol.

4-Phenyl-1,4,5,6-tetrahydro-2H-naphto[1,2-d][1,3]thiazin-2-thione (**5**)

Yield: 89% (Method B), m.p. 186–188 °C. IR (KBr): $\nu = 3125$ cm^{-1} (NH), 2945 cm^{-1} (CH_2), 1655 cm^{-1} (C=C). ^1H NMR (80 MHz, $CDCl_3$): $\delta = 9.2$ (bs, 1H, N*H*), 7.4–7.2 (m, 9H, Ar*H*), 4.66 (s, 1H, H–C (4)), 2.9–2.1 (m, 4H, H–C (5), H–C (6)). $C_{18}H_{15}NS_2$ (309.45). Calcd. C 69.86, H 4.89, S 20.72; found C 69.67, H 4.73, S 20.58.

4-Phenyl-1,4,6,7-tetrahydro-2H,5H-benzo[6,7]cyclohepta[1,2-d][1,3]thiazin-2-thione (**6**)

Yield: 87% (Method B), m.p. 211–214 °C. IR (KBr): $\nu = 3115$ cm^{-1} (NH), 2940 cm^{-1} (CH_2), 1645 cm^{-1} (C=C). ^{1}H-NMR (80 MHz, $CDCl_3$): $\delta = 8.9$ (bs, 1H, N*H*), 7.5–7.2 (m, 9H, Ar*H*), 4.66 (s, 1H, H–C (4)), 2.7–1.5 (m, 4H, H–C (5), H–C (6), H–C (7)). $C_{19}H_{17}NS_2$ (323.48). Calcd. C 70.55, H 5.30, S 19.82; found C 70.32, H 5.54, S 19.67.

General Procedure for acid-catalyzed reaction of thiourea with 2-benzylidene-1-benzocyclanones **1a–c**

A suspension of compounds **1a–c** (5 mmol), thiourea (10.0 mmol), ethanol (20.0 ml), and concentrated hydrochloric acid (4.0 ml) was refluxed for 24 h. Then the reaction mixture was cooled to 0 °C, diluted with an equal volume of water, and alkalized with 10% aqueous ammonia. The mixture was extracted with $CHCl_3$ (3 × 50 ml), the combined organic extract was washed free of base with water, dried (Na_2SO_4), and evaporated. The residue was crystallized from methanol to yield pale yellow (**7**) or colorless crystals (**8**, **9**).

2-Amino-4-phenyl-4,5-dihydrobenzo[4,5]cyclopenta[1,2-d][1,3]thiazine (**7**)

Yield: 64%, m.p. 165–168 °C. IR (KBr): $\nu = 3450$, 3280 cm^{-1} (NH_2), 2900 cm^{-1} (CH_2), 1635 cm^{-1} (C=N). IR ($CHCl_3$): $\nu = 3495$ cm^{-1} (ν_{as} NH_2) 3380 cm^{-1} (ν_s NH_2). ^{1}H-NMR (80 MHz, $CDCl_3$): $\delta =$ 7.6–7.5 (m, 1H, H–C (9)), 7.4–7.2 (m, 8H, Ar*H*), 5.22 (s, 1H, H–C (4)), 5.1 (bs, 2H, NH_2), 2.30 (s, 2H, H–C (5)). $C_{17}H_{14}N_2S$ (278.38). Calcd. C 75.35, H 5.07, N 10.06; found C 75.29, H 5.24, N 9.94.

2-Amino-4-phenyl-5,6-dihydro-4H-naphto[1,2-d][1,3]thiazine (**8**)

Yield: 76%, m.p. 135–137 °C (134–135 °C [4]). IR (KBr): $\nu = 3475$, 3275 cm^{-1} (NH_2), 2905 cm^{-1} (CH_2), 1625 cm^{-1} (C=N). IR ($CHCl_3$): $\nu = 3500$ cm^{-1} (ν_{as} NH_2), 3395 cm^{-1} (ν_s NH_2). ^{1}H-NMR (80 MHz, $CDCl_3$): $\delta = 7.9$–7.7 (m, 1H, H–C (10)), 7.4–7.0 (m, 8H, Ar*H*), 4.8 (bs, 2H, NH_2) 4.57 (s, 1H, H–C (4)), 3.0–2.8 (m, 2H, H–C (6)), 2.5–2.3 (m, 2H, H–C (5)).

2-Amino-4-phenyl-6,7-dihydro-4H,5H-benzo[6,7]cyclohepta[1,2-d][1,3]thiazine (**9**)

Yield: 72%, m.p. 144–146 °C. IR (KBr): $\nu = 3470$, 3270 cm^{-1} (NH_2), 2905 cm^{-1} (CH_2), 1635 cm^{-1} (C=N). IR ($CHCl_3$): $\nu = 3485\,cm^{-1}$ (ν_{as} NH_2), 3380 cm^{-1} ($\nu_s NH_2$). ^{1}H-NMR (80 MHz, $CDCl_3$): $\delta = 7.7$–7.5 (m, 1H, H–C (11)), 7.4–7.1 (m, 8H, Ar*H*), 4.67 (s, 1H, H–C (4)), 4.4 (bs, 2H, NH_2), 2.8–2.5 (m, 2H, H–C (7)), 2.2–1.8 (m, 4H, H–C (5), H–C (6)). $C_{19}H_{18}N_2S$ (306.43). Calcd. C 74.47, H 5.92, N 9.14; found C 74.29, H 5.84, N 9.05.

References

[1] Zimmermann R. (1963) Angew. Chem. **75**: 1025
[2] Garraway J. L. (1964) J. Chem. Soc. 4008
[3] Hoff S., Block A. P. (1973) Recl. Trav. Chim. Pays-Bas **92**: 631
[4] Lóránd T., Szabó D., Földesi A., Osske G. (1984) Pharmazie **39**: 535
[5] Lévai A. (1991) Monatsh. Chem. **122**: 691
[6] Perjési P., Szabó D., Földesi A. (1986) Acta Chim. Hung. **122**: 119
[7] Perjési P., Szabó D., Batta Gy., Földesi A. (1987) Tetrahedron Lett. **28**: 571
[8] Perjési P., Földesi A., Batta Gy., Tamás J. (1989) Chem. Ber. **122**: 651
[9] Perjési P., Sohár P. (1991) Monatsh. Chem. **122**: 1047
[10] Kálmán A., Argay Gy., Perjési P., Szabó D. (1988) Acta Cryst. **C44**: 1955
[11] Hanefeld W., Bercin E. (1981) Arch. Pharm. **314**: 413
[12] Fujisawa Pharmaceutical Co., Ltd. (Umio S., Kariyone K., Kishimoto T., Inv.): a) (1969) Japan 6927, 033; (1970) C.A. **72**: 31823; b) (1969) Japan 69 27, 032; (1970) C.A. **72**: 79068; c) (1970) Japan 70 15, 030; (1970) C.A. **73**: 45525
[13] Cherbuliez E., Baehler, B., Espejo, O., Jindra H., Willhalm B., Rabinowitz, J. (1967) Helv. Chim. Acta **50**: 331
[14] Prókai L., Lóránd T., Földesi A. (1989) Org. Mass. Spectr. **24**: 517
[15] Bellami L. J., Williams R. B. (1957) Spectrochim Acta **9**: 341
[16] Perjési P., Földesi A., Tamás J. (1993) Monatsh. Chem. **124**: 167
[17] Szöllösy Á., Tóth G., Lóránd T., Kónya T., Aradi F., Lévai A. (1991) J. Chem. Soc. Trans. 2489
[18] Chemical Abstract Ring Systems Handbook (1988 Edition) and Cumulative Supplements 1–8 (1989–1992)
[19] Adams R. (1968) Org. React., Vol. 16. Wiley, New York
[20] Azzolina O., Desimoni G., Di Toro V., Ghislandi V., Tacconi G. (1975) Gazz. Chim. Ital. **105**: 971
[21] Gattow G., Hahnkamm V. (1969) Z. Anorg. Allgem. Chem., **364**: 161

Received April 4, 1993. Accepted June 24, 1993