Monatshefte für Chemie 121, 45–50 (1990)

Monatshefte für Chemie
Chemical Monthly

Synthesis of Substituted 4 *H*-Thieno[2,3-b][1]benzothiopyran-4-ones as Possible Schistosomicidal Agents

Mohamed M. El-Kerdawy[1], **Ali A. El-Emam**[1,*], **Hussein I. El-Subbagh**[1], and **Elie Abushanab**[2]

[1] Department of Medicinal Chemistry, Faculty of Pharmacy, University of Mansoura, Mansoura, Egypt

[2] Department of Medicinal Chemistry, College of Pharmacy, University of Rhode Island, Kingstone, RI 02881, USA

Summary. A new series of thiophenic isosters of thioxanthones, namely: 2-substituted-4 *H*-thieno-[2,3-b][1]benzothiopyran-4-ones and 5-substituted-2-nitro-8-methyl-4 *H*-thieno[2,3-b][1]benzothiopyran-4-ones were synthesized as potential schistosomicidal agents. The synthesized compounds were characterized by their ^{1}H-NMR data.

Keywords. Synthesis; 4 *H*-Thieno[2,3-b][1]benzothiopyran-4-ones.

Synthese von substituierten 4 *H*-Thieno[2,3-b][1]benzothiopyran-4-onen als mögliche schistosomicide Wirkstoffe

Zusammenfassung. Es wurde eine neue Serie von thiophenischen Isosteren des Thioxanthons, nämlich 2-substituierte 4 *H*-Thieno[2,3-b][1]benzothiopyran-4-one und 5-substituierte 2-Nitro-8-methyl-4 *H*-thieno[2,3-b][1]benzothiopyran-4-one als potentielle schistosomicide Wirkstoffe synthetisiert. Die synthetisierten Verbindungen wurden mittels ihrer ^{1}H-NMR Daten charakterisiert.

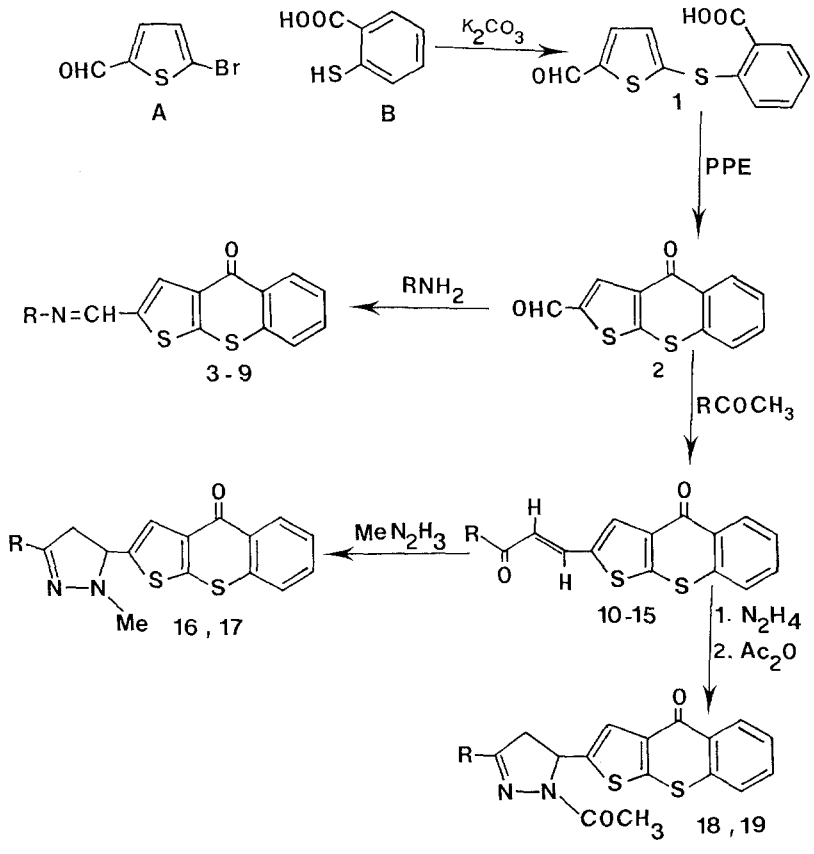
Introduction

The first major series of nonantimonial compounds with schistosomicidal activity were the thioxanthones. Lucanthone [1] and its metabolite Hycanthone [2] were successfully used in the treatment of schistosomiasis. Other thioxanthone derivatives [3–5] were also reported to possess potent schistosomicidal activity. In addition, certain thioxanthones were proved to possess carcinostatic activity [6, 7]. The pyrido isosters of thioxanthones, azathioxanthones [8, 9], were also reported to be of great schistosomicidal acitivity. The present work describes a convenient synthesis of certain substituted-4 *H*-thieno[2,3-b][1]benzothiopyran-4-ones, as the thiophenic isosters of thioxanthones, for evaluation as schistosomicidal agents.

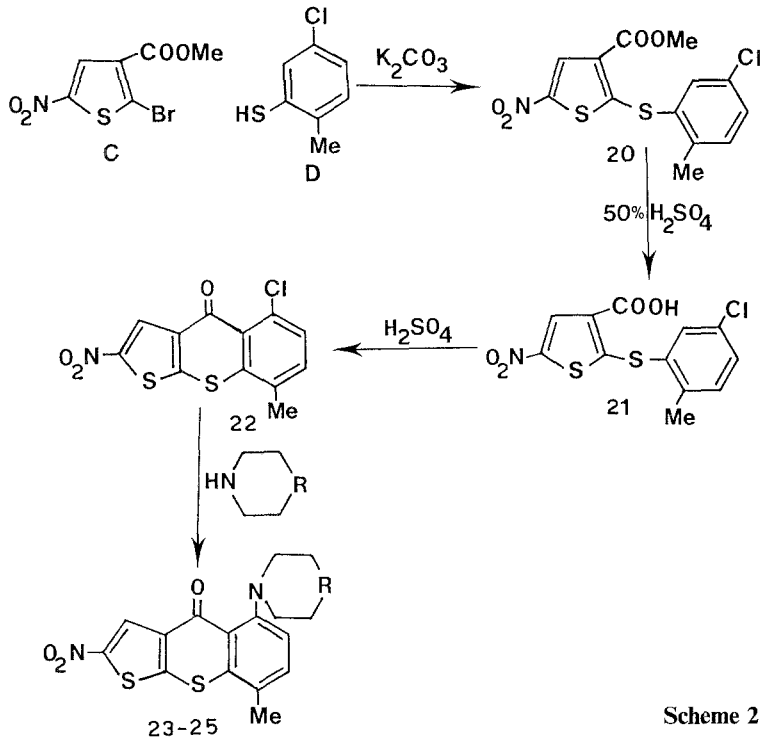
Results and Discussion

A literature survey has revealed that a limited number of publications have been reported for the synthesis of isomeric thieno-benzothiopyranones [10–15]. 2-Formyl-4 *H*-thieno[2,3-b][1]benzothiopyran-4-one (**2**), required as a starting material, was prepared by interaction of 5-bromo-2-thenaldehyde **A** and thiosalicylic acid **B** in dimethylformamide in presence of potassium carbonate to furnish 2-[(5-formyl-2-thienyl)thio]benzoic acid (**1**), which was cyclized by the action of polyphosphoric acid ethyl ester (*PPE*) [16] to yield **2**. Compound **2** was condensed with some substituted anilines or phenylhydrazines to give the corresponding anils **3–9**. Interaction of compound **2** with a variety of aromatic ketones in ethanolic sodium hydroxide solution furnished the chalcone analogues **10–15**. The ^{1}H-NMR assignment proved that the two olefinic protons of compounds **10–15** were in *E* position to each other. Compounds **10** and **15** were allowed to react with methylhydrazine to afford the pyrazoline derivatives **16** and **17**. The acetylpyrazolines **18**, **19** were obtained by interaction of compounds **10**, **15** with hydrazine hydrate followed by acetylation with acetic anhydride in presence of few drops of pyridine (Scheme 1).

Interaction of methyl 2-bromo-5-nitrothiophene-3-carboxylate (**C**) with 2-methyl-5-chlorothiophenol (**D**) in dimethylformamide in presence of potassium carbonate afforded methyl 5-nitro-2-[(5-chloro-2-methylphenyl)thio]-3-thiophenecarboxylate (**20**) at ambient temperature. Compound **20** was hydrolyzed by the action of 50% sulphuric acid to afford the corresponding carboxylic acid **21**,



Scheme 1



Scheme 2

which was subsequently cyclized by the action of sulphuric acid to yield compound **22**. Trials to replace the chlorine atom at position 5 with a variety of cyclic secondary amines in polar solvents even at room temperature led to an immediate decomposition of the compound. In nonpolar solvents, the reaction proceeded very slowly as detected by TLC, however, the compounds **23–25** were obtained in poor yields (Scheme 2).

The structures of the synthesized compounds were assigned on the basis of elemental analysis and ^{1}H-NMR spectral data.

Experimental

Melting points were determined on a Thomas-Hoover melting point apparatus. ^{1}H-NMR Spectra were obtained on a Varian EM-390 90 MHz spectrometer using *TMS* as an internal standard. Mass spectra were recorded on a Hewlett Packard GC-MS, 5987 A mass spectrometer at 70eV. Elemental analyses were performed by M-H-W laboratories, Phoenix, Arizona, USA. 2-Methyl-5-chlorothiophenol was prepared by the method described in Ref. [17], methyl 2-bromo-5-nitro-3-thiophenecarboxylate was prepared from 3-thenoic acid by the methods cited in Refs. [18–20].

The microanalytical data were in full agreement with the molecular formulae. Compounds where no ^{1}H-NMR data are listed were insufficiently soluble in common NMR solvents.

2-[(5-Formyl-2-thienyl)thio]benzoic acid (**1**)

A mixture of thiosalicylic acid (1.54 g, 0.01 mol), 5-bromo-2-thenaldehyde (1.9 g, 0.01 mol) and anh. K_2CO_3 (2.8 g, 0.02 mol), in *DMF* (20 ml) was heated under reflux for 4 h. The solvent was then removed in vacuo, the residue was dissolved in water, filtered and acidified with HCl. The precipitated

crude product was filtered, washed with water, dried and crystallized. Yield 81%. M.p. (benzene): 158–60°C. $C_{12}H_8O_3S_2$. NMR (*DMSO*-d_6): 6.8–7.6 (4 H, m, *Ar*-H), 7.8–8.0 (1 H, dd, Thiophene-H at 4-), 8.0–8.2 (1 H, m, Thiophene-H at 3-) and 9.9 (1 H, s, CHO).

2-Formyl-4 H-thieno[2,3-b][1]benzothiopyran-4-one (**2**)

A solution of **1** (2.6 g, 0.01 mol) and 70% *PPE* in $CHCl_3$ (300 ml), was heated under reflux for 3 h. The solvent was then removed in vacuo and the obtained oily residue was poured onto crushed ice (100 g). The precipitated product was filtered, washed with 10% $NaHCO_3$, dried and crystallized. Yield 76%. M.p. (Acetic acid): 240–2°C. $C_{12}H_6O_2S_2$. NMR ($CDCl_3$): 7.5–7.7 (3 H, m, *Ar*-H), 8.4 (1 H, s, *Ar*-H at 3-), 8.5–8.7 (1 H, m, *Ar*-H at 5-) and 9.9 (1 H, s, CHO).

2-(Arylazomethine)-4 H-thieno[2,3-b][1]benzothiopyran-4-ones **3–9**

Compound **2** (0.25 g, 0.001 mol), was added to a solution of the appropriate amino compound (0.001 mol) in acetic acid (20 ml) and the mixture was heated under reflux for 1 h. On cooling, the separated solid was filtered and crystallized.

3: R = *o*-$CH_3C_6H_4$. Yield 60%. M.p. (*DMF*): 248–50°C. $C_{19}H_{13}NOS_2$. NMR (CF_3COOH): 2.4 (3 H, s, CH_3), 7.3–7.8 (7 H, m, *Ar*-H), 8.5–8.8 (1 H, m, *Ar*-H at 5-), 9.1 (1 H, s, *Ar*-H at 3-) and 9.4 (1 H, s, CH = N).

4: R = *o*-EtC_6H_4. Yield 30%. M.p. (*DMF*): 173–5°C. $C_{20}H_{15}NOS_2$. NMR (CF_3COOH): 1.1–1.4 (3 H, t, CH_3), 2.5–2.8 (2 H, q, CH_2), 7.3–7.8 (7 H, m, *Ar*-H), 8.5–8.8 (1 H, m, *Ar*-H at 5-), 9.1 (1 H, s, *Ar*-H at 3-) and 9.4 (1 H, s, CH = N).

5: R = 2,4-$Cl_2C_6H_3$. Yield 30%. M.p. (*DMF*): 305–7°C. $C_{18}H_9Cl_2NOS_2$.

6: R = *p*-BrC_6H_4. Yield 45%. M.p. (*DMF*): 254–6°C. $C_{18}H_{10}BrNOS_2$.

7: R = C_6H_5NH. Yield 55%. M.p. (*DMF*): 280–2°C. $C_{18}H_{12}N_2OS_2$.

8: R = *p*-$NO_2C_6H_4NH$. Yield 40%. M.p. (*DMF*): 340–2°C. $C_{18}H_{11}N_3O_3S_2$.

9: R = *p*-ClC_4H_6NH. Yield 35%. M.p. (*DMF*): 288–90°C. $C_{18}H_{10}ClN_2OS_2$.

E-2-(3-Aryl-3-oxo-1-propenyl)-4 H-thieno[2,3-b][1]benzothiopyran-4-ones **10–15**

Compound **2** (0.25 g, 0.001 mol) was added portionwise to a solution of the appropriate ketone (0.001 mol) in 2.5% ethanolic NaOH solution (10 ml). The mixture was stirred at ambient temperature for 1 h. The precipitated solid product was filtered, washed with water, dried and crystallized.

10: R = *p*-$CH_3OC_6H_4$. Yield 60%. M.p. (*DMSO*): 188–9°C. $C_{21}H_{14}O_3S_2$. NMR (CF_3COOH): 3.5 (3 H, s, CH_3), 6.4–6.6 (1 H, d, olefinic CH, J = 9 Hz), 6.8–7.8 (9 H, m, *Ar*-H and olefinic CH) and 8.1–8.3 (1 H, m, *Ar*-H at 5-).

11: R = *o*-$NO_2C_6H_4$. Yield 45%. M.p. (*DMF*): 234–6°C. $C_{20}H_{11}NO_4S_2$.

12: R = *p*-ClC_6H_4. Yield 65%. M.p. (*DMF*): 263–5°C. $C_{20}H_{11}ClO_2S_2$.

13: R = *p*-BrC_6H_4. Yield 55%. M.p. (*DMF*): 242–4°C. $C_{20}H_{11}BrO_2S_2$.

14: R = *p*-$CH_3CONHC_6H_4$. Yield 40%. M.p. (*DMF*): 314–6°C. $C_{22}H_{15}NO_3S_2$. NMR (CF_3COOH): 2.3 (3 H, s, CH_3), 7.1–7.3 (1 H, d, olefinic CH, J = 14 Hz), 7.4–8.1 (9 H, m, *Ar*-H and olefinic CH), 8.4–8.7 (1 H, m, *Ar*-H at 5-) and 8.9 (1 H, s, NH).

15: R = 2-thienyl. Yield 60%. M.p. (Acetic acid): 235–7°C. $C_{18}H_{10}O_2S_3$. NMR (CF_3COOH): 7.0–8.1 (9 H, m, *Ar*-H and CH = CH) and 8.5–8.7 (1 H, m, *Ar*-H at 5-).

2-(4,5-Dihydro-1-methyl-3-aryl-1H-pyrazol-5-yl)-4 H-thieno[2,3-b][1]benzothiopyran-4-ones **16, 17**

A solution of methylhydrazine (0.18 g, 0.004 mol) and compound **10** or **15** (0.001 mol) in ethanol (30 ml), was heated under reflux for 3 h. The solvent and the excess methylhydrazine were removed in vacuo and the residue was extracted with $CHCl_3$, dried over $MgSO_4$, evaporated to dryness and the remaining crude product was crystallized.

16: $R = p\text{-}CH_3OC_6H_4$. Yield 30%. M.p. (*Et*OH/$CHCl_3$): 190–2°C. $C_{22}H_{18}N_2O_2S_2$. NMR ($CDCl_3$): 2.8 (3 H, s, CH_3), 2.9–3.6 (2 H, double ABq, pyrazoline CH_2), 3.75 (3 H, s, OCH_3), 4.2–4.5 (1 H, dd, pyrazoline CH), 6.7–7.7 (8 H, m, *Ar*-H) and 8.5–8.7 (1 H, m, *Ar*-H at 5-).

17: R = 2-Thienyl. Yield 35%. M.p. (aqu. *Et*OH): 125°C. $C_{19}H_{14}N_2OS_3$. MS (m/z): 382 (68%, M^+), 383 (15), 384 (9). NMR ($CDCl_3$): 2.9 (3 H, s, CH_3), 2.9–3.7 (2 H, double ABq, pyrazoline CH_2), 4.3–4.7 (1 H, dd, pyrazoline CH), 6.9–8.8 (7 H, m, *Ar*-H) and 8.5–8.8 (1 H, m, *Ar*-H at 5-).

2-(1-Acetyl-4,5-dihydro-3-aryl-1 H-pyrazol-5-yl)-4 H-thieno-[2,3-b][1]benzothiopyran-4-ones **18, 19**

A solution of hydrazine hydrate (0.2 g, 0.004 mol) and compound **10** or **15** (0.001 mol) in ethanol (30 ml) was heated under reflux for 3 h. The solvent and the excess hydrazine were removed in vacuo. Acetic anhydride (10 ml) and few drops of pyridine were added to the remaining residue and the mixture was heated under reflux for 1 h. On cooling, the mixture was poured onto crushed ice (50 g), the precipitated solid was filtered, washed with water and crystallized.

18: $R = p\text{-}CH_3OC_6H_4$. Yield 40%. M.p. (aqu. *Et*OH): 198–200°C. $C_{23}H_{18}N_2O_3S_2$. NMR ($CDCl_3$): 2.3 (3 H, s, $COCH_3$), 3.2–3.7 (2 H, double ABq, pyrazoline CH_2), 3.8 (3 H, s, OCH_3), 5.7–5.9 (1 H, dd, pyrazoline CH), 6.7–8.2 (8 H, m, *Ar*-H) and 8.4–8.8 (1 H, m, *Ar*-H at 5-).

19: R = 2-Thienyl. Yield 35%. M.p. (aqu. *Et*OH): 225°C. $C_{20}H_{14}N_2O_2S_2$. NMR ($CDCl_3$): 2.3 (3 H, s, $COCH_3$), 3.3–3.9 (2 H, double ABq, pyrazoline CH_2), 5.7–5.8 (1 H, dd, pyrazoline CH), 6.7–7.7 (8 H, m, *Ar*-H) and 8.5–8.7 (1 H, m, *Ar*-H at 5-).

Methyl 5-nitro-2-[(5-chloro-2-methylphenyl)thio]-3-thiophenecarboxylate (**20**)

A mixture of methyl 2-bromo-5-nitro-3-thiophenecarboxylate (0.27 g, 0.001 mol), 5-chloro-2-methylthiophenol (0.2 g, 0.0012 mol) and anh. K_2CO_3 (0.14 g, 0.001 mol) in *DMF* (10 ml), was stirred at ambient temperature for 3 h. The solvent was then distilled in vacuo and the residue was dissolved in $CHCl_3$, dried over $MgSO_4$ and evaporated. The remaining crude product was crystallized. Yield 85%. M.p. (*Et*OH): 165–6°C. $C_{13}H_{10}ClNO_4S_2$. NMR ($CDCl_3$): 2.4 (3 H, s, *Ar*-CH_3), 3.9 (3 H, s, $COOCH_3$), 7.3–7.65 (3 H, m, *Ar*-H) and 8.1 (1 H, s, Thiophene-H).

5-Nitro-2-[(5-chloro-2-methylphenyl)thio]-3-thiophenecarboxylic acid (**21**)

A mixture of compound **20** (0.35 g, 0.001 mol) and 50% H_2SO_4 (20 ml), was heated under reflux for 5 h. The mixture was diluted with water (100 ml) and the separated solid product was filtered, washed with water and crystallized. Yield 62%. M.p. (aqu. *Et*OH): 218–20°C. $C_{12}H_8ClNO_4S_2$. NMR (*DMSO*-d_6): 2.4 (3 H, s, CH_3), 7.6–7.8 (3 H, m, *Ar*-H) and 8.1 (1 H, s, thiophene-H).

2-Nitro-5-chloro-8-methyl-4H-thieno[2,3-b][1]benzothiopyran-4-one (**22**)

A mixture of compound **21** (0.3 g) in 98% H_2SO_4 (10 ml) was heated at 90°C for 3 h. The mixture was then poured onto crushed ice (50 g), the separated crude product was filtered, washed with water and crystallized. Yield 71%. M.p. (benzene): 275°C. $C_{12}H_6ClNO_4S_2$. MS (m/z): 311 (100%, M^+), 312 (13) and 313 (41).

2-Nitro-5-substituted-8-methyl-4 H-thieno[2,3-b][1]benzothiopyran-4-ones **23–25**

A mixture of compound **22** (0.1 g, 0.3 mmol) and the appropriate secondary amine (0.4 mmol) in benzene (10 ml), was heated under reflux for 8 h. The mixture was distilled in vacuo and the remaining crude products were purified by elution from a silica gel column using the eluents: $CHCl_3$ (**23**), $CHCl_3$/*Et*O*Ac*, 5 : 1 (**24**) and $CHCl_3$/*Me*OH/*Et*O*Ac*, 2 : 2 : 1 (**25**).

23: $R = CH_2$. Yield 36%. M.p. (*Et*OH): 134–6°C. $C_{17}H_{16}N_2O_3S_2$. NMR ($CDCl_3$): 1.6–1.9 (6 H, m, 3 CH_2), 2.4 (3 H, s, CH_3), 3.0–3.2 (4 H, m, CH_2NCH_2), 6.9–7.3 (2 H, dd, *Ar*-H) and 8.4 (1 H, s, *Ar*-H at 3-).

24: R = O. Yield 48%. M.p. (*Et*OH): 223–4°C. $C_{16}H_{14}N_2O_4S_2$. NMR ($CDCl_3$): 2.4 (3 H, s, CH_3), 3.0–3.2 (4 H, m, CH_2NCH_2) 3.9–4.1 (4 H, m, CH_2OCH_2), 6.9–7.4 (2 H, dd, *Ar*-H) and 8.4 (1 H, s, *Ar*-H at 3-).

25: R = NCH_3. Yield 28%. M.p. (*Et*OH): 160–2°C. $C_{17}H_{17}N_3O_3S_2$. NMR ($CDCl_3$): 2.38 (3 H, s, *Ar*-CH_3), 2.4 (3 H, s, NCH_3), 2.6–2.7 [4 H, m, $(CH_2)_2NCH_3$], 3.0–3.2 (4 H, m, CH_2NCH_2), 6.9–7.3 (2 H, dd, *Ar*-H) and 8.4 (1 H, s, *Ar*-H at 3-).

References

[1] Mauss H. (1948) Ber. **81**: 19
[2] Rosi D., Peruzotti G., Dennis E. W., Berberian D. A., Freele H., Archer S. (1956) Nature (London) **208**: 1005
[3] Archer S., Suter C. M. (1952) J. Am. Chem. Soc. **74**: 4296
[4] Elslager E. F. (1975) Ger. Offen 2,433,988; (1975) Chem. Abstr. **83**: 43318
[5] Elslager E. F., Worth D., Donald E. (1975) U. S. Pat. 3,904,631; (1976) Chem. Abstr. **84**: 44151
[6] Blanz E., French F. (1963) J. Med. Chem. **6**: 185
[7] Archer S., Zayed A., Rej R., Rujino A. (1983) J. Med. Chem. **26**: 1240
[8] Brener Z., Pelligrino J. (1958) J. Parasitol. **44**: 659
[9] Druey J., Meier K. (1961) Ger. Offen 1,037,458; (1961) Chem. Abstr. **55**: 3619
[10] Steinkopf W., Schmitt H. F., Fielder H. (1937) Ann. **527**: 237
[11] Steinkopf W., Schmitt H. F. (1938) Justus Liebigs Ann. Chem. **523**: 264
[12] Sandoz Ltd. (1962) Belg. Pat. 616,813, Oct. 24; (1963) Chem. Abstr. **58**: 13919 h
[13] Sandoz Ltd. (1965) Neth. Appl. 6,411,477, April 9; (1965) Chem. Abstr. **63**: 13265
[14] Rudorf W. D. (1978) Tetrahedron **34**: 725
[15] Watthey J. W. H., Desai M. (1982) J. Org. Chem. **47**: 1755
[16] Rajsner M., Svatek E., Metys J., Provita M. (1974) Collect. Czech. Chem. Commun. **39**: 1366
[17] Sharp T. M. (1951) J. Chem. Soc.: 2961
[18] Campaigne E., Bourgois R. (1954) J. Am. Chem. Soc. **76**: 1445
[19] Rinkes I. J. (1934) Rec. Trav. Chim. **53**: 643
[20] Spenelli D., Consiglio G., Noto R., Corrao A. (1975) J. Chem. Soc. Perkin II: 620

Received December 22, 1988. Accepted March 27, 1989