

THIOPHENE CHEMISTRY—XX*

C- AND O-METHYLATION OF THALLIUM(I)-SALTS OF 3-THIOLENE-2-ONES

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Abstract—Thallium(I) salts of thiole-2-ones with no substituent in the 3-position on treatment with MeI underwent C-methylation in the 3-position. O-, Di- and trimethylation reactions were also observed. Analogous treatment of a 3-substituted 3-thiole-2-one with thallium(I) ethoxide produced in addition to the expected thallium salt, a salt due to ring-opening. The tautomeric properties of 3,5-dimethyl-3-thiole-2-one have been investigated.

INTRODUCTION

RECENTLY Taylor *et al.*¹ described a method for monoalkylation of β -dicarbonyl compounds, yielding C-alkylated product in almost quantitative yield under neutral conditions. The thallium(I) salt of the β -dicarbonyl compound was heated with an excess of an alkyl iodide, the thallium(I) iodide removed, and the product isolated by simple distillation. No O-alkylated product was observed. Strangely enough, alkylation of thallium(I) salts of phenols has not been reported, but treatment of the thallium(I) salts at room temperature with an acyl or aroyl halide in ether produced almost quantitative yields of phenol esters.² In the heterocyclic field, the thallium(I) salt of phenanthridone³ afforded the N-alkylated product on treatment with an alkyl halide. Consequently, the thallium(I) salts of potential 2-hydroxythiophenes (3-thiole-2-ones) were prepared in order to study alkylation reactions. As potential 2-hydroxythiophenes give dimeric products⁴ in the presence of a base, the corresponding thallium(I) salts should give different products under the neutral conditions used. This is shown to be the case in the present communication.

Synthesis of starting materials

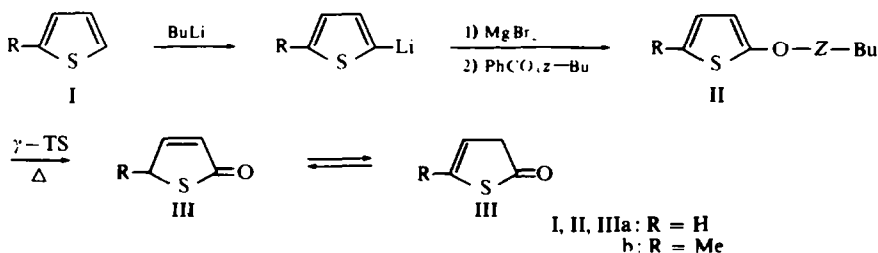


FIG 1

* Part XIX. J. Z. Mortensen, B. Hedegaard and S.-O. Lawesson, Tetrahedron 27, 3853 (1971).

Compounds IIIa and IIIb were prepared by dealkylation of IIa and IIb,^{5,6} respectively (Fig 1). In the preparation of the *t*-butylethers (Experimental) the procedure has been changed to avoid time-consuming separation difficulties, but yields were as high as claimed earlier.^{5,6}

The thallium(I) salts of IIIa and IIIb were readily prepared by addition of thallium(I) ethoxide to IIIa or IIIb in an inert solvent.

Treatment of the thallium(I) salts with methyl iodide

In the methylation of thallium(I) phenoxide, a 20% yield of anisole was produced after a reaction time of 24 hr but this yield was increased to 75% after one week. No C-methylation was observed. This alkylation reaction was too slow for preparative purposes. In the thiophene field if compound IV (Table 1) was heated under reflux with methyl iodide for 17 hr according to Taylor *et al.*,¹ the main product, 3-methyl-3-thiolen-2-one (VII), was isolated together with high-boiling materials. The yield of the monomeric material was increased (50%) by Soxhlet extraction of IV with methyl iodide diluted with light petroleum.

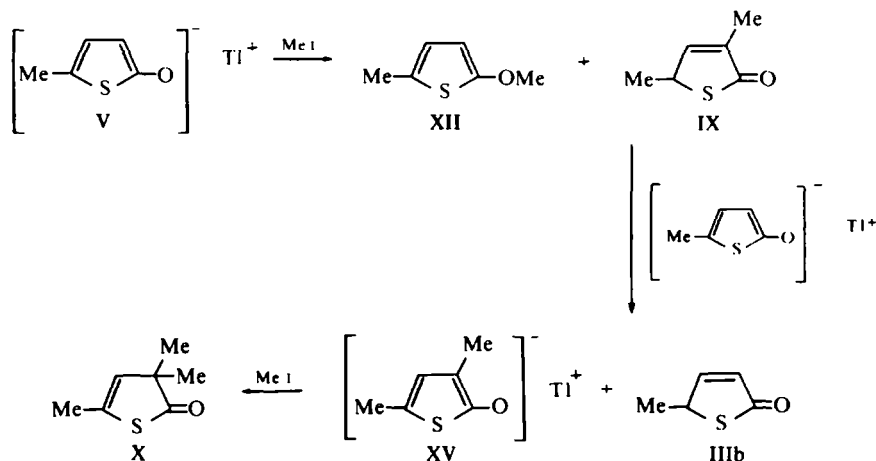
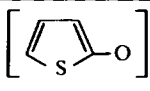
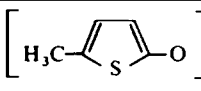
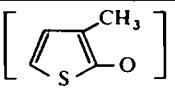
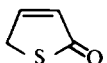
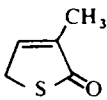
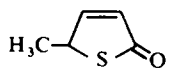
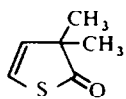
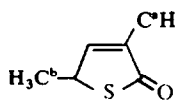
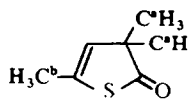
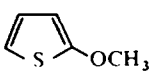
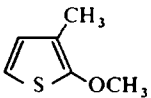
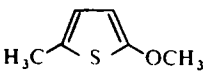
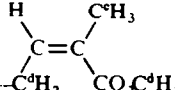


FIG. 2.

As seen from Table 1, treatment of the thallium(I) salts with methyl iodide produced a complex mixture of products which with the exception of VIII and X, could be separated by unidimensional multiple chromatography (UMC).⁹ O- and C-alkylation in position 3 were observed (in the ratio $\frac{1}{4}$ and $\frac{1}{8}$ with compounds IV and V, respectively). Methylation in the 5-position of IV and VI was less than in the 3-position, in accordance with the greater π -electron density at the 3-position relative to the 5-position of the anion of III (MO-calculations¹⁰ and protonation experiments of the anion⁸), indicating the greater nucleophilicity of the 3-position. Furthermore, di- and trimethylated products were formed and in addition the original compound, from which the thallium(I) salt was prepared, was recovered. The mechanism of formation of these compounds is suggested in Fig 2, which gives the simpler product distribution of all investigated salts. It is assumed that V can undergo a Tl⁺(I) exchange with IX initially formed, thereby producing IIIb and XV. Subsequent

TABLE 1. THE RELATIVE PRODUCT DISTRIBUTION FROM TREATMENT OF THALLIUM(I)-SALTS WITH MeI (IN PERCENT)

Products	Salts		
			
	IIIa	10	
	VII	73	50
	IIIb		6*
	VIII	1	11
	IX	4	76
	X	1	9
	XI	11	
	XII		9
	XIII		9
	XIV		18

* NMR showed that this fraction was a mixture of IIIb and XIX (9:1)^{6,8}

methylation of XV would then yield X. Dimethylation via organic thallium(I) compounds has not been observed hitherto, and is probably due to the insolubility of these salts.¹

Compound VI under similar conditions, produced very low yields of products substituted at the 3-position. Furthermore, treatment of VII with (TIOEt)₄ partly caused ring opening with formation of XVI, which in the presence of methyl iodide

gave XIV (Fig. 3). The competitive formation of XVI was probably due to the lower acidity of VII as compared with III. Substitution at the 3-position prevented stabilization of this anion by a close contact between the partly negative charged 3-position of VI and Tl^+ (I).

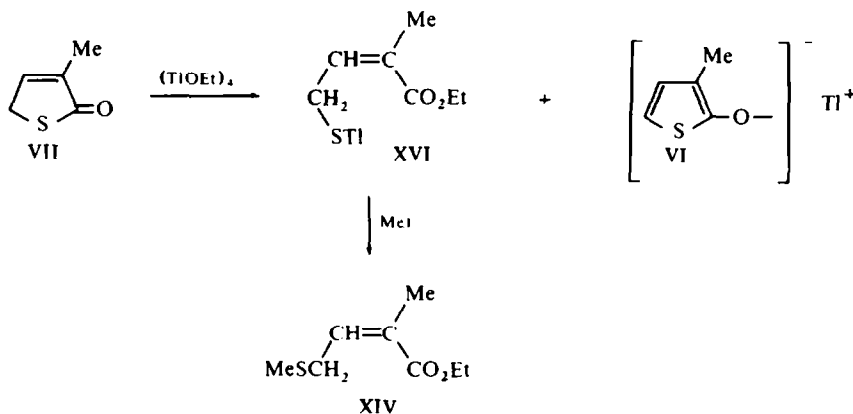


FIG 3

Spectroscopic studies

3,3,5-Trimethyl-4-thiolene-2-one (X); NMR (δ): 1.22 (C^aH_3), 2.10 (C^bH_3), 5.48 (H^4), and $J_{4-C^bH_3} = 1.6$ c/s. The NMR spectrum does not permit elucidation of the structure of this compound as X or XVII (Fig 4). However, the IR spectrum shows the following characteristic bands: A strong absorption, due to the $C=O$ group, at 1715 cm^{-1} and weak absorptions at 1685 cm^{-1} and 1635 cm^{-1} , due to the $C=C$ group. Because $C=O$ absorptions of 4-thiolene-2-ones are $1715\text{--}1740\text{ cm}^{-1}$, while for 3-thiolene-2-ones they are $1670\text{--}1695\text{ cm}^{-1}$,^{6,7,11} the correct structure must be X; UV (EtOH): $\lambda_{max} = 271\text{ nm}$ ($\log \epsilon = 3.09$).

3,3-Dimethyl-4-thiolene-2-one (VIII). Compound VIII could not be separated from X. However, the concentrations of VIII relative to X, obtained by methylation of IV and VI were different. As X was obtained as a pure product by methylation of V, it was easy to establish the following NMR spectrum of VIII: 1.23 δ (Me), 5.85 δ (H^4), 6.48 δ (H^3), and $J_{4,5} = 7.5$ c/s. The coupling constant, which is 1.5 c/s greater than the corresponding $J_{4,5}$ of thiophene, is also found in other 3-substituted 4-thiolene-2-ones.¹² The chemical shift of H^4 at lower field in VIII than in X (the difference 0.37 δ is due to the change of substitution at the 5-position) and is in good agreement with the additive rules for the chemical shifts of olefinic protons.¹³

The IR spectrum of a mixture of VIII and X (1:1) shows the following absorptions: strong $C=O$ stretching vibrations at 1715 cm^{-1} due to VIII and X, weak $C=C$ stretchings at 1685 cm^{-1} and 1635 cm^{-1} due to X, and weak $C=C$ stretchings at 1650 cm^{-1} due to VIII.

3,5-Dimethyl-3-thiolene-2-one (IX); NMR (δ): 1.55 (C^bH_3), 1.90 (C^aH_3), 4.33 (H^5), 7.07 (H^4), $J_{4-C^aH_3} = 1.4$ c/s, $J_{5-C^bH_3} = 2.0$ c/s, $J_{4,5} = 2.8$ c/s and $J_{5-C^bH_3} = 7.2$ c/s. The IR spectrum shows weak $C=C$ stretching vibrations at 1650 cm^{-1} and strong $C=O$ stretching vibrations at 1675 cm^{-1} , which again indicates that the correct

structure is IX and not XVIII,^{6, 8, 11} UV (EtOH): $\lambda_{\max} = 264$ nm ($\log \epsilon = 3.33$). In order to investigate the tautomeric equilibrium between IX and XVIII, the preparation of XVIII was attempted by extracting IX with 20% NaOH from ether and then acidifying the basic solution of the formed anion, (compare the preparation of 4-thiolen-2-ones from 3-thiolen-2-ones⁸). This procedure, in two successive runs,

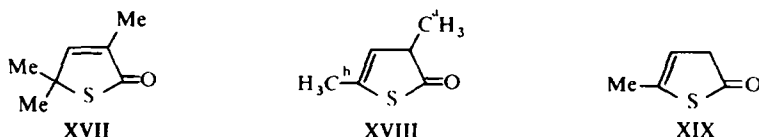


FIG 4

produced only a very low yield of a mixture of IX and XVIII (3:1 and 5:1). The NMR (δ) of XVIII: 1.28 (C^aH_3), 2.10 (C^bH_3), 3.38 (H^3), 5.53 (H^4), $J_{34} = 2.5$, $J_{3-C^aH_3} = 7.6$, $J_{3-C^bH_3} = 2.4$, and $J_{4-C^bH_3} = 1.6$.

This low yield (mixture of IX and XVIII) was probably due to the lower acidity of IX relative to IIIa, on account of the Me group at the partly negatively charged 3-position. The relative acidities of these two compounds are in accordance with the effect of an α -alkyl group in 2,4-pentanedione and acetoacetic ester.²² The NMR spectrum of a deuteriochloroform solution of a mixture of IX and XVIII (5:1) after 24 hr shows less than 2% of XVIII relative to IX. This experiment demonstrated that the tautomeric equilibrium mixture of IX and XVIII contained less than 2% of the latter.

The tautomeric equilibrium between 3-thiolen-2-ones and 4-thiolen-2-ones with alkyl substituents at the 5-position is well-known.^{6, 8, 11} Therefore, a tautomeric equilibrium mixture of IIIb and XIX, contained 19% of the latter, whereas the unsubstituted thiolen-2-one existed exclusively as 3-thiolen-2-one.⁶ It is generally accepted that 4-thiolen-2-ones are stabilized relative to 3-thiolen-2-ones by hyperconjugation to an alkyl group at the 5-position.¹⁰ If we compare the equilibrium system of IIIb and XIX with that of IX and XVIII, we see that the Me group at the 3-position and the 5-position almost neutralize each other, concerning the position of the equilibrium between the two thiolen-2-one forms, and this gives a rough estimation of the effect of a 3-substituted Me on the positions of this sort of equilibrium.

Ethyl 2-methyl-4-methylthiocrotonate (XIV) (Z-form): NMR (δ): 1.30 (C^bH_3), 1.93 (C^cH_3), 2.02 (C^eH_3), 3.53 (C^dH_2), 4.20 (C^fH_2), 5.95 (H), $J_{H-C^eH_3} = 1.5$, $J_{H-C^fH_2} = 8.0$, $J_{C^eH_2C^fH_2} = 1.1$, and $J_{C^eH_2C^bH_3} = 7.2$.

The IR spectrum shows strong C=O stretching vibrations at 1705 cm^{-1} and weak C=C stretching vibrations at 1640 cm^{-1} ; UV (EtOH): $\lambda_{\max} = 223$ nm ($\log \epsilon = 3.85$) and shoulder at 255 nm.

2-Methoxy-3-methylthiophene (XII): NMR (δ): 2.05 (Me), 3.85 (OMe), 6.52 and 6.60 (H^4 and H^5) and $J_{45} = 5.8$; UV (EtOH): shoulder at 247 nm.

Compounds IIa,⁵ IIb,⁶ IIIa,⁵ IIIb,⁶ VII,¹⁴ XI,¹⁵ XIII,¹⁶ and XIX⁶ have been characterized^{5, 6, 8, 14-17} and need no comment.

CONCLUSION

The usual way of preparing 3-substituted 3-thiolene-2-ones has been dealkylation of the corresponding 2-*t*-butoxythiophenes¹⁸ or oxidative cleavage of the corresponding thiopheneboronic acids with hydrogen peroxide.¹⁴ Thus 3-methyl-3-thiolene-2-one was synthesized by hydrogen peroxide cleavage of 3-methyl-2-thiopheneboronic acid, prepared from 3-methyl-2-thienylmagnesium bromide and butyl borate.

Methylation of the thallium(I) salts of 3-thiolene-2-ones produced in each case mixtures of products. However, the main products were the 3-substituted 3-thiolene-2-ones, when starting from compounds IV or V. This method is general and provides a direct synthetic route to otherwise not easily available structures. Extended and general studies in thiophene chemistry as well as in other heterocyclic systems support this statement.¹⁹ As to methylation of the thallium(I) salt of phenol our results offer very little scope.

EXPERIMENTAL

NMR spectra were recorded in CDCl₃ at 60 Mc/s on a Varian A-60 spectrometer. The temps of the 14–16% (w/w) solns were 33° ± 1. TMS was used as internal reference standard and the chemical shifts are expressed in ppm from TMS taken as 0.00 (δ units) and are believed to be correct within ±0.02 ppm. The coupling constants were measured with an accuracy of ±0.2 c/s on the 50 c/s scale. Numerical AB analysis has been carried out on H⁴ and H⁵ in compounds VIII and XII. In all other cases the spin pattern is considered to be approximately first order. IR spectra were recorded as films on a Perkin-Elmer infrared 137 and the UV spectra on a Bausch & Lomb Spectronic 505 spectrophotometer with EtOH as solvents. B.ps are uncorrected. Analyses were made by Løvens Kemiske Fabrik—Copenhagen. UMC (j, k : l) was carried out on Kieselgel PF₂₅₄₊₃₆₆ (Merck) support (20 × 40 cm and 3 mm thick) and eluted j times with ether—light petroleum in the ratio k : l. The light petroleum (b.p. 37–50°) was distilled before use. *R_f* values were obtained from the pure products using the same support (0.3 mm thick) and solvent for elution.

Methylation of Tl(I) phenoxide. 29.2 g of Tl(I) salt of phenol was refluxed for 7 days with 25 ml MeJ in 200 ml light petroleum (b.p. 40–60°). Each day an additional 5 ml of MeI was added. The yellow TlJ was filtered off and 8 g (75%) of pure anisole (b.p. 48°/14 mm) was obtained and characterized.

2-t-Butoxythiophene (IIa). 2-Thienyllithium²⁰ was prepared under N₂ from 115 g (1.4 mole) thiophene and 700 ml 1.5 N (1.0 mole) *n*-BuLi in hexane. After stirring for 1 hr, the soln was cooled to –70°. An ethereal soln of anhyd MgBr₂ (prepared by dropping 62 ml (1.1 mole) Br₂ on to 30 g (1.3 mole) Mg in 400 ml anhyd ether) was added rapidly under N₂. The mixture was allowed to warm up to –15° and 190 ml (0.94 mole) *t*-butyl perbenzoate in 200 ml anhyd ether was added dropwise to the Grignard reagent at –15°. After stirring for 2 hr at room temp the mixture was cooled to –20° and a thick oil separated. The ethereal soln was decanted off, extracted with dil NaOH aq, dried (Na₂SO₄) and the ether removed. As there was no absorption in IR at 1750 cm⁻¹, this fraction contained no unreacted *t*-butyl perbenzoate, which is, however, easily removed by reaction with EtMgBr,²¹ b.p. 67–70°/10 mm Hg, yield 105 g (72%) of IIa.⁵

2-t-Butoxy-5-methyl-thiophene (IIb). IIb was prepared analogously to IIa from 37 g (0.38 mole) 2-methylthiophene, 260 ml 1.5 N (0.39 mole) *N*-BuLi in hexane, 12 g (0.5 mole) Mg, 21 ml (0.39 mole) Br₂, and 62 ml (0.31 mole) *t*-butyl perbenzoate, b.p. 87–89°/15 mm Hg, yield 33 g (51%).⁶

3-Thiolene-2-one (IIIa)⁵ and a mixture of IIIb and XIX (IIIb)⁶ was prepared by dealkylation of IIa and IIb, respectively.

Thallium(I) salt of 3-thiolene-2-one (IV). 74 g of (TlOEt)₄ was added at once to 35 g IIIa, dissolved in 200 ml C₆H₆. IV precipitated immediately and after washing with light petroleum, it was dried in air and then used, yield 90 g (100%). The thallium salts V and VI were prepared in the same way in 94% and 84% yields, respectively. The precipitation of VI was completed by addition of light petroleum to the benzene solution.

Methylation of IV. 30 g of freshly prepared IV was extracted for 17 hr with 30 ml MeI in 450 ml light

petroleum in a Soxhlet extraction apparatus. The light petroleum was evaporated off, and the residue distilled, b.p. 60–110°/15 mm Hg, yield 7 g; UMC (2, 20:80) gave:

(1) A band ($R_f = 0.67$) (0.80 g) was a mixture of VIII, X, and XI, and the yields were 0.5%, 0.5%, and 5%, respectively. UMC (2, 0:100) of this mixture gave:

(a) A band ($R_f = 0.19$) was XI.

(b) A band ($R_f = 0.07$) was a mixture of VIII and X (1:1).

(2) A band ($R_f = 0.32$) (0.24 g) was IX; yield 2%.

(3) A band ($R_f = 0.21$) (4.16 g) was VII; yield 37%.

(4) A band ($R_f = 0.10$) (0.49 g) was IIIa; yield 5%.

Methylation of V. 24 g was treated as above with 25 ml MeI in 400 ml light petroleum. Distillation, b.p. 80–110°/15 mm Hg, gave 7 g, UMC (1, 20:80) gave:

(1) A band ($R_f = 0.67$) (1.10 g) was a mixture of X and XIII, and the yields (calculated from NMR) were 5% and 5%, relatively, UMC (2, 2:98) of this mixture gave:

(a) A band ($R_f = 0.46$) was XIII.

(b) A band ($R_f = 0.35$) was X, which on distillation at 10 mm Hg gave: $n_D^{25} = 1.4925$; (Found: C, 59.06; H, 7.11; S, 22.19. $C_7H_{10}OS$ requires: C, 59.14; H, 7.09; S, 22.52%).

(2) A band ($R_f = 0.32$) (4.6 g) was IX; yield 48%. Distillation 95–97°/12 mm Hg; $n_D^{25} = 1.5241$; (Found: C, 56.02; H, 6.30; S, 24.95. C_8H_8OS requires: C, 56.24; H, 6.29; S, 24.98%).

(3) A band ($R_f = 0.16$) (0.35 g) was IIIb (see footnote to Table 1); yield 4%.

Treatment of VI with MeI. 16 g VI was treated as above with 25 ml MeI in 450 ml of light petroleum. Distillation at 60–120°/15 mm Hg gave 1.3 g, UMC (2, 10:90) gave:

(1) A band ($R_f = 0.66$) (0.08 g) was XII; yield 1%.

(2) A band ($R_f = 0.50$) (0.14 g) was a mixture of VIII and X, and the yields (calculated from NMR) were 1.5% and 0.5%, relatively.

(3) A band ($R_f = 0.41$) (0.22 g) was XIV, which was, however, only about 90% pure, due to overlapping between band 3 and the tail of band 2; yield 2.5%. XIV was purified by use of UMC (1, 5:95), which gave pure XIV as a band at $R_f = 0.25$. XIV was distilled at 14 mm Hg; (Found: C, 55.20; H, 8.30; S, 18.05. $C_8H_{14}O_2S$ requires: C, 55.16; H, 8.10; S, 18.37%).

(4) A band ($R_f = 0.22$) (0.07 g) was IX; yield 1%.

(5) A band ($R_f = 0.17$) (0.41 g) was VII; yield 7%.

3,5-Dimethyl-4-thiolen-2-one (XVIII). 2.4 g of IX was taken up in ether and extracted several times with cold 20% NaOH aq. The water phase was immediately acidified with 2N H_2SO_4 under cooling and at once extracted with ether. The ether phase was immediately washed with water, dried (Na_2SO_4), evaporated and distilled at 14 mm Hg; yield 30 mg; an NMR spectrum was immediately recorded which showed the fraction to be a mixture of IX and XVIII (3:1). The ether was evaporated from the ether phase containing IX. It was then attempted to extract the very liquid IX with cold NaOH aq and work up as above. Distillation at 89–94°/14 mm Hg yielded 200 mg of a mixture of IX and XVIII (5:1).

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REFERENCES

- 1 E. C. Taylor, G. H. Hawks and A. McKillop, *J. Am. Chem. Soc.* **90**, 2421 (1968)
- 2 E. C. Taylor, G. W. McLay and A. McKillop, *Ibid.* **90**, 2422 (1968)
- 3 E. C. Taylor and A. McKillop, *Accounts Chem. Res.* **3**, 338 (1970)
- 4 A.-B. Hörnfeldt, *Arkiv Kemi* **28**, 363 (1968)
- 5 S.-O. Lawesson and C. Frisell, *Ibid.* **17**, 393 (1961)
- 6 H. J. Jakobsen, E. H. Larsen and S.-O. Lawesson, *Tetrahedron* **19**, 1867 (1963)
- 7 S. Gronowitz, *Arkiv Kemi* **16**, 363 (1960–61)
- 8 S. Gronowitz and R. A. Hoffman, *Ibid.* **15**, 499 (1960)
- 9 G. Goldstein, *Analyt. Chem.* **42**, 140 (1970)
- 10 A.-B. Hörnfeldt, *Inaugural dissertation*. Lund, Sweden (1968)
- 11 A.-B. Hörnfeldt, *Arkiv Kemi* **22**, 211 (1964)
- 12 E. B. Pedersen and S.-O. Lawesson, *Tetrahedron* **26**, 2959 (1970)
- 13 C. Pasqual, J. Meier and W. Simon, *Helv. Chim. Acta* **49**, 164 (1966)
- 14 A.-B. Hörnfeldt and S. Gronowitz, *Arkiv Kemi* **21**, 239 (1963)

- ¹⁵ J. Sicé, *J. Am. Chem. Soc.* **75**, 3697 (1953)
- ¹⁶ R. A. Hoffman and S. Gronowitz, *Arkiv Kemi* **16**, 563 (1960-61)
- ¹⁷ S. Gronowitz and R. A. Hoffman, *Ibid.* **13**, 279 (1959)
- ¹⁸ E. B. Pedersen and S.-O. Lawesson, *Synthesis* **1**, 170 (1970) and refs cited
- ¹⁹ E. B. Pedersen and S.-O. Lawesson, to be published
- ²⁰ H. Gilman and D. A. Shirley, *J. Am. Chem. Soc.* **71**, 1871 (1949)
- ²¹ H. J. Jakobsen and S.-O. Lawesson, *Tetrahedron* **23**, 871 (1967)
- ²² R. G. Pearson and J. M. Mills, *J. Am. Chem. Soc.* **72**, 1692 (1950)