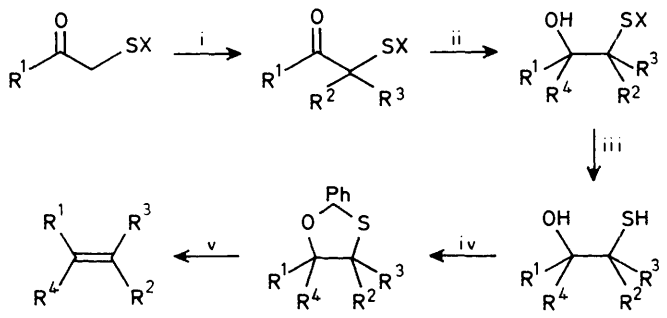
α-Thio-substituted Ketones as Precursors of Olefins *via* Oxathiolanes: α-Methoxybenzyl as Protecting Group

Michael D. Brown, Catherine J. Meunier, and Gordon H. Whitham*
Dyson Perrins Laboratory, South Parks Road, Oxford OX1 3QY

A number of routes to 2-(α-methoxybenzylthio) ketones (**3**) have been explored with a view to their use as precursors of substituted 2-phenyl-1,3-oxathiolanes. The most successful preparation of compounds (**3**; R^1 = Ph) and (**3**; R^1 = Me) involved the *in situ* generation of the appropriate α-mercapto ketone (**10**) from an α-oxo dithiocarbonate and alkylation with α-methoxybenzyl chloride. Lithium aluminium hydride reduction of ketone (**3**; R^1 = Ph) followed by cyclisation to 2,5-diphenyl-1,3-oxathiolane (**11**) provided a prototype for the approach outlined in Scheme 1 but Grignard and organolithium reagents did not react clearly with ketone (**3**) to give a general route to protected β-mercapto alcohols.

Treatment of the β-oxo dithiocarbamate (**13**; R^1 = Ph) with base and alkyl halide under phase-transfer catalysis conditions gave the enol derivative (**14**) by sulphur to oxygen migration followed by alkylation at sulphur.

The work to be described in this and the following paper arose out of our interest in 2-phenyl-1,3-oxathiolanes as precursors of olefins. In a previous paper,[1] we had shown that such oxathiolanes underwent a base-induced cycloreversion to form olefins and thiobenzoate ion even when the product olefin was tetrasubstituted. It seemed possible therefore that a general olefin synthesis might be developed along the lines outlined in Scheme 1. The thiol protecting group, X, would need to be



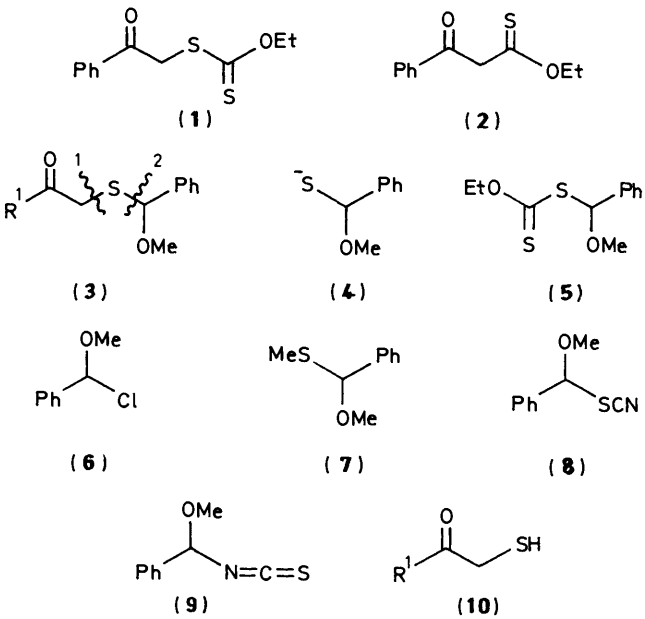
Scheme 1.

stable to the base-catalysed alkylation step(s) (i) and to the organometallic (or hydride) addition step (ii). Subsequent deprotection, step (iii), followed by oxathiolane formation, step (iv), and cycloelimination step (v), complete the sequence. By appropriate choice of alkyl groups R^1—R^4, the regioselective preparation of tri- and tetra-substituted ethylenes should be achievable and if diastereoselectivity could be controlled by the protected thiol SX in (ii), there was the possibility that the olefin could be obtained stereoselectively.

An earlier attempt to use a β-oxo dithiocarbonate (**1**) as starting material was thwarted by the finding that the derived anion underwent sulphur extrusion with formation, after quenching, of the β-oxo *O*-thioester (**2**).[2] α-Thiocyanato ketones (*cf.* Scheme 1, X = CN) were also soon abandoned as possible substrates, when we found in some model experiments with simple thiocyanates that they underwent ready S–CN cleavage on treatment either with lithium di-isopropylamide (LDA) or a Grignard reagent.

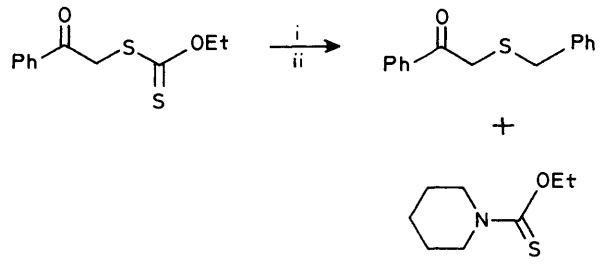
The present paper is concerned with attempts to prepare 2-(α-methoxybenzylthio) ketones and their possible elaboration along the lines indicated in Scheme 1, X = CH(OMe)Ph. Attractive features envisaged for this protecting group were: (a) that steps (iii) and (iv) might thereby be telescoped into a single stage (hemithioacetal cyclisation) and (b) that the extra oxygen function might assist chelation control in step (ii).

We shall discuss attempts to find a general route to compounds of type (**3**) in the order: (a) approaches in which the C–S bond 1, *cf.* (**3**), is formed second and (b) those in which the C–S bond 2 is formed second. Two attempts were made using approach (a). The first was based on the idea that the thiolate ion (**4**) might be alkylated with an α-halogeno ketone to give compound (**3**) directly. The feasibility of generating the thiolate ion (**4**) *in situ* from the substituted dithiocarbonate (**5**), itself obtained from α-methoxybenzyl chloride (**6**) and potassium ethyl dithiocarbonate, was demonstrated by a preparation of the hemithioacetal (**7**) on treatment of the dithiocarbonate (**5**) with sodium methoxide in ether in the presence of methyl iodide. However, alkylation of phenacyl chloride to give (**3**; R^1 = Ph) was not achieved under analogous conditions or variations thereof. The second attempt envisaged a preparation of the methoxythiocyanate (**8**) in order to use it as an



electrophilic thiolating agent of an enolate ion with S–CN cleavage. This attempt foundered on two counts. On the one hand, reaction of the α-halogeno ether (**6**) with potassium thiocyanate gave the isothiocyanate (**9**) by *N*-alkylation, and on the other hand, an authentic thiocyanate, benzyl thiocyanate, was ineffective as a benzyl thiolating agent of acetophenone enolate generated under a variety of conditions.

Turning now to approach (b), involving C–S bond 2 formation (**3**) as the second step, initial attempts to prepare α-mercapto ketones of type (**10**) and to alkylate them with the α-halogeno ether (**6**) were frustrated by the known instability, towards oxidation and dimerisation, of the mercapto ketones.[3] Eventually, in model experiments, it was found possible to generate the mercapto ketone from the dithiocarbonate (**1**) and alkylate it *in situ* with benzyl chloride in the presence of triethylamine according to Scheme 2.[4]

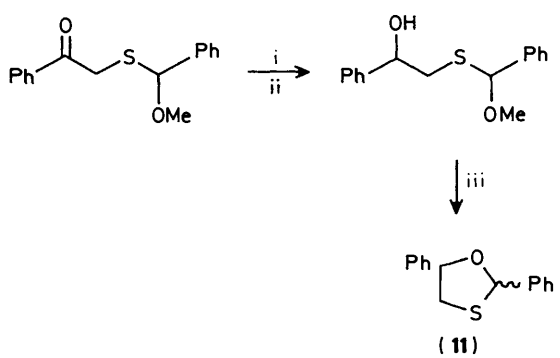


Scheme 2. *Reagents:* i, Piperidine NH–Et_3N–CH_2Cl_2; ii, $PhCH_2Cl$

Using an analogous procedure but alkylating with the halogeno ether (**6**) the desired 2-(α-methoxybenzylthio) ketone (**3**; R^1 = Ph) was obtained in 50% yield. In a variation in which a solution of monomeric α-mercaptoacetone was generated from *S*-acetonyl *O*-ethyl dithiocarbonate and then alkylated with the halogeno ether (**6**), the aliphatic analogue (**3**; R^1 = Me) was also prepared. However, we were unable to find conditions for preparation of 2-(α-methoxybenzylthio)cyclohexanone starting from the cyclohexanone derivative.

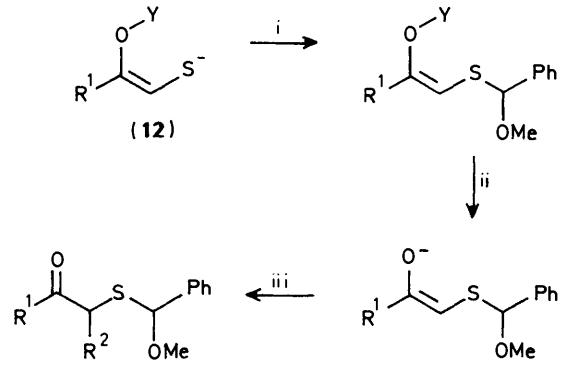
The *in situ* procedure for generation of α-mercapto ketones from β-oxo dithiocarbonates has also been used, in collaboration with other workers in this laboratory, for syntheses of *N*-mono- and *N*-di-alkylated 2-aminothiazoles.[5]

Unfortunately the thioacetal function present in compound (**3**; R^1 = Ph) turned out to be unsuitable for the purposes originally envisaged and attempts either to alkylate α to the carbonyl group or to treat the carbonyl group with an organometallic reagent led either to complex mixtures or to recovery of starting material. However, the feasibility of one of the original ideas was shown by a two-step sequence leading to the substituted oxathiolane (**11**) (Scheme 3).



Scheme 3. *Reagents:* i, $LiAlH_4$–Et_2O; ii, H_3O^+; iii, *p*-TsOH–CH_2Cl_2

In order to circumvent some of the above-mentioned difficulties encountered in attempted alkylation of compound (**3**; R^1 = Ph), a variation on the theme of approach (b) along the lines of Scheme 4 was considered. Here it was hoped that the

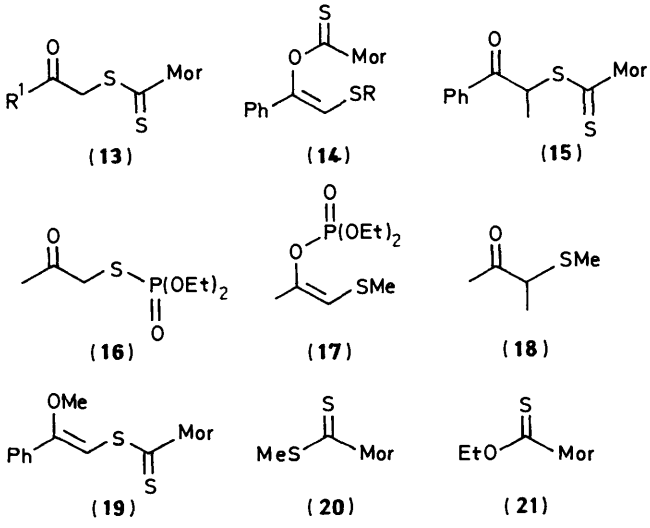


Scheme 4.

thiolate ion (**12**), derived from an appropriately protected enol derivative (Y = protecting group), could be alkylated at sulphur, step (i), and then deprotected step (ii), to uncover an enolate ion which might be alkylated with R^2Hal, step (iii).

It was found that attempted base-catalysed alkylation of the dithiocarbamate (**13**; R^1 = Ph) with methyl iodide or benzyl chloride, using phase-transfer catalysis, gave the rearranged *S*-alkylated products (**14**; R = Me) and (**14**; R = $PhCH_2$), respectively, and it was hoped that this process could be utilised as in Scheme 4. Unfortunately the rearrangement-alkylation reaction did not prove to be sufficiently general to be synthetically useful. For the aliphatic analogue (**13**; R^1 = Me) neither rearranged nor unrearranged alkylation products could be obtained in satisfactory yield on treatment with base–alkyl halide under a range of conditions. Furthermore, attempted alkylation of compound (**13**; R^1 = Ph) under non-hydroxylic conditions, *e.g.* DMF–NaH–MeI, which would be necessary if the α-halogeno ether (**6**) were to be employed as alkylating agent, gave mixtures of rearranged (**14**; R = Me) and unrearranged (**15**) products.

An analogous rearrangement-alkylation has been described for β-oxo thiophosphates,[6] and we confirmed that the thiophosphate (**16**) was converted into the enol phosphate (**17**)



Mor = morphilino

on treatment with sodium hydride in ether followed by methyl iodide. The enol phosphate (**17**) might provide a model for the approach outlined in Scheme 4 if efficient P–O cleavage and alkylation of the enolate produced could be achieved. Unfortunately, treatment of compound (**17**) with a wide variety of reagents designed to encourage P–O cleavage either in the presence of, or followed by, methyl iodide failed to give synthetically useful amounts of the *C*-alkylated product (**18**).

Given the disappointing results outlined above, we did not pursue further the use of α-methoxybenzyl as a protecting group and turned instead to the simpler option of the benzyl group. Some of the results obtained are presented in the following paper.

Experimental

^{1}H N.m.r. spectra were recorded on Perkin-Elmer R24 (60 MHz) or Bruker WH300 (300 MHz) instruments using Me_4Si as internal standard. ^{13}C N.m.r. spectra: $CDCl_3$ solutions on Bruker WH90 (22.63 MHz) or WH300 (75.43 MHz) instruments using solvent (δ_C 77.00) as internal standard.

α-(*Methylthio*)*benzyl Methyl Ether* (**7**).—Potassium *O*-ethyl dithiocarbonate (6 g) was added to a stirred solution of α-chlorobenzyl methyl ether[7] (5 g) in dry ether (100 ml) and the mixture was heated under reflux for 80 min. The solution was washed with water, dried ($MgSO_4$), and evaporated to give a yellow oil (6.7 g). Distillation afforded *O*-ethyl *S*-(α-methoxybenzyl)dithiocarbonate (**5**) (5.5 g, 71%), b.p. 120 °C at 0.03 mmHg; $\delta_H(CCl_4)$ 1.29 (3 H t), 3.4 (3 H, s), 4.51 (2 H, q), 6.43 (1 H, s), and 7.0—7.5 (5 H, complex).

Iodomethane (0.2 ml) was added dropwise to a stirred solution of the dithiocarbonate (0.5 g) in dry ether (50 ml) at 15 °C. After 30 min, sodium methoxide (0.2 g) was added, followed, after a further 5 h, by water. The organic phase was washed with water, dried ($MgSO_4$), and evaporated to give an oil (0.47 g). ^{1}H N.m.r. showed this to be compounds (**5**) and (**7**) in the ratio 1:2. The monothioacetal (**7**) was isolated by distillation and had n.m.r. data in agreement with lit.,[8] $\delta_H(CCl_4)$ 1.71 (3 H, s), 3.4 (3 H, s), 5.33 (1 H, s), and 7.1—7.5 (5 H, complex).

Reaction of α-Chlorobenzyl Methyl Ether with Potassium Thiocyanate.—Dried potassium thiocyanate (0.34 g) was added to a stirred solution of α-chlorobenzyl methyl ether (0.5 g) in dry THF (30 ml) and the mixture was refluxed under nitrogen for 2 h. Most of the THF was evaporated and water and ether were added. The separated organic layer was washed with water and dried ($MgSO_4$). Evaporation gave an oil (0.4 g) which was a mixture of benzaldehyde and α-methoxybenzyl isothiocyanate (*ca.* 5:2 by ^{1}H n.m.r.). Distillation afforded the isothiocyanate (**9**) (with benzaldehyde, 10—15%, as impurity), $\delta_H(CCl_4)$ 3.5 (3 H, s), 5.7 (1 H, s), and 7.3 (5 H, br s); $\nu_{max.}$(film) 2 020 cm^{-1} (NCS).

(α-*Methoxybenzylthio*)*acetone* (**3**; R^1 = Me).—Piperidine (0.83 ml) was added to a solution of *S*-acetonyl *O*-ethyl dithiocarbonate[2] (1.6 g) in dichloromethane (30 ml) in a separating funnel and the mixture was shaken at 20 °C. After 2 min, aqueous sodium hydroxide was added and the mixture was shaken for a further 2 min. The separated aqueous layer was acidified with dilute hydrochloric acid and dichloromethane (20 ml) was added. The mixture was shaken for 90 s, and the organic layer was filtered through $MgSO_4$ into a stirred mixture of α-chlorobenzyl methyl ether (2.8 g) and triethylamine (1.25 ml) in dichloromethane (25 ml) at −78 °C. After addition the mixture was kept under nitrogen. The solution was allowed to warm to 15 °C over 3 h and washed successively with aq. HCl, aq. Na_2CO_3, and brine. The dried ($MgSO_4$) solution was evaporated to give a yellow oil (1.3 g). Chromatography on alumina eluting with graded mixtures of light petroleum–ether gave in earlier fractions benzaldehyde and its dimethyl acetal and later the *title compound* (0.7 g, 37%) as an oil (Found: C, 62.75; H, 6.7; S, 15.0. $C_{11}H_{14}O_2S$ requires C, 62.85; H, 6.7; S, 15.25%); $\delta_H(CDCl_3)$ 2.15 (3 H, s, MeCO), 3.2 (2 H, s), 3.4 (3 H, s, OMe), 5.45 (1 H, s), and 7.2—7.5 (5 H, complex); $\delta_C(CDCl_3)$ 28 (q, MeCO), 39 (t), 56 (q, OMe), 87 (d), 126 (d), 128 (d), 139 (s), and 204 (s, CO).

2-(α-*Methoxybenzylthio*)*acetophenone* (**3**; R^1 = Ph).—Piperidine (1.24 mol) and triethylamine (1.74 ml) were added to a stirred solution of *O*-ethyl *S*-phenacyl dithiocarbonate[2,9] (3 g) in dichloromethane (130 ml) at 20 °C under nitrogen. After 1 h the mixture was cooled (solid CO_2–acetone) and α-chlorobenzyl methyl ether (2 g) in dichloromethane (20 ml) was added dropwise. The mixture was allowed to warm to *ca.* 0 °C over 2 h after which it was diluted with water and the organic layer separated, washed with water, dried ($MgSO_4$), and evaporated to give, on distillation, *O*-ethyl 1-piperidinecarbothioate (**21**) (0.96 g, 45%), b.p. 80 °C at 0.03 mmHg (lit.,[10] b.p. 147—149 °C at 25 mmHg); $\delta_H(CCl_4)$ 1.3 (3 H, t, *J* 7 Hz), 1.64 (6 H, br), 3.5—4.2 (4 H, complex, NCH_2), and 4.42 (2 H, q, *J* 7 Hz); $\delta_C(CDCl_3)$ 14 (q), 24 (t), 25 (t), 25 (t), 46 (t, NCH_2), 50 (t, NCH_2), 67 (t, OCH_2), and 186 (s); followed by 2-(α-methoxybenzylthio)-acetophenone (**3**; R^1 = Ph) (1.7 g, 50%), b.p. 180 °C at 0.03 mmHg; $\delta_H(CCl_4)$ 3.3 (3 H, s, OMe), 3.6 (2 H, ABq, CH_2), 5.4 (1 H, s), 7.05—7.55 (8 H, complex), and 7.6—7.95 (2 H, complex); *m/z* 272 (M^+).

2,5-*Diphenyl*-1,3-*oxathiolane.*—Lithium aluminium hydride (59 mg) was added to a solution of 2-(α-methoxybenzylthio)acetophenone (0.2 g) in dry ether (3 ml) and the mixture heated under reflux for 40 min. A few drops of water were added and the product, 2-(α-methoxybenzylthio)-1-phenylethanol, was isolated as an oil (0.2 g). A portion of the latter (0.1 g) in dichloromethane (5 ml) was stirred with toluene-*p*-sulphonic acid (1 mg) at 20 °C for 1 h. The solution was washed successively with aqueous sodium hydroxide and water, dried ($MgSO_4$), and evaporated to give an oil (0.1 g) shown to be 2,5-diphenyl-1,3-oxathiolane by comparison with an authentic sample,[1] $\delta_H(CDCl_3)$ (mixture of diastereoisomers) 2.9—3.6 (2 H, complex, 4-H), 4.8—5.4 (1 H, complex, 5-H), 6.12 and 6.26 (1 H, both s, 2-H), and 7.1—7.6 (10 H, complex).

1-*Methylthio*-2-*morpholinothiocarbonyloxy*-2-*phenylethylene* (**14**; R = Me).—The dithiocarbamate (**13**; R^1 = Ph)[11] (1.45 g) and methyl iodide (0.9 ml) in dichloromethane (25 ml) were stirred vigorously for 6 h with aqueous sodium hydroxide (50%; 50 ml) containing tetrabutylammonium hydroxide (40%; 0.07 ml). The mixture was diluted with water (25 ml) and the dichloromethane layer separated and combined with the dichloromethane washings of the aqueous layer. Evaporation of the dried organic extracts followed by crystallisation of the residue from ethanol gave the *enol thiocarbamate* (**14**; R = Me) (0.86 g, 54%), m.p. 156—160 °C (Found: C, 57.25; H, 5.9; N, 4.7; S, 21.3. $C_{14}H_{17}NO_2S_2$ requires C, 56.9; H, 5.8; N, 4.75; S, 21.7%); $\delta_H(CDCl_3)$ 2.4 (3 H, s, Me), 3.75—3.93 (4 H, m), and 3.95—4.25 (4 H, m, morpholino group), 6.4 (1 H, s, 2-H), and 7.25—7.38 (5 H, m, ArH).

The enol thiocarbamate structure (**14**; R = Me) rather than the isomeric unrearranged enol methyl ether structure (**19**) was assigned primarily on the basis of ^{13}C n.m.r. comparisons. Thus the thiocarbonyl carbon for compound (**14**; R = Me) showed δ_C 184 compared with 186 for the *O*-thiocarbamate (**21**), see above, and 198 for the dithiocarbamate (**20**).[12] Also S–Me for (**14**; R = Me) absorbed at 17 compared with δ_C of 16[13] and 55[13] for thioanisole and anisole, respectively. Similar considerations

apply to the benzyl derivative (**14**; R = $PhCH_2$) described below.

1-*Benzylthio-2-morpholinothiocarbonyloxy-2-phenylethylene* (**14**; R = $PhCH_2$).—In a similar way the dithiocarbamate (**13**; R^1 = Ph) (3 g) in dichloromethane (50 ml) and aqueous sodium hydroxide (50%; 50 ml), tetrabutylammonium hydroxide (40%; 0.15 ml), and benzyl chloride (1.85 ml) gave the *enol thiocarbamate* (**14**; R = $PhCH_2$) (3.58 g, 96%), m.p. 162—164 °C (from EtOH) (Found: C, 64.45; H, 5.75; N, 3.9; S, 16.95. $C_{20}H_{21}NO_2S_2$ requires C, 64.65; H, 5.7; N, 3.75; S, 17.25%); $\delta_H(CDCl_3)$ 3.67—3.9 (4 H, m), and 3.9—4.2 (4 H, m, morpholino group), 4.0 (2 H, s, $PhCH_2$), 6.38 (1 H, s, 2-H), and 7.2—7.4 (10 H, m, ArH).

Methylation of the Dithiocarbamate (**13**; R^1 = Ph) *Under Non-aqueous Conditions*.—A solution of the dithiocarbamate (1 g, 3.5 mmol) and methyl iodide (0.2 ml, 3 mmol) in dry, redistilled DMF (20 ml) was stirred with a suspension of sodium hydride (50% oil dispersion; 0.18 g, 4 mmol) at 18 °C for 1 h. After addition of a few drops of methanol to the mixture, water was added and the product was isolated with dichloromethane. The n.m.r. spectrum indicated that it was a mixture of the rearranged thiocarbamate (**14**; R = Me) and the *C*-methylated product (**15**) in the ratio 4:3. The product (**15**) was identified primarily on the basis of the methyl doublet (J 7 Hz) at δ 1.6.

Acknowledgements

We thank the S.E.R.C. for a Research Studentship (M. D. B.), Dr. A. E. Derome and his associates for n.m.r. spectra, and Professor M. P. Hartshorn and the Department of Chemistry, University of Canterbury, Christchurch, New Zealand, for hospitality (to G. H. W.) while this paper was written.

References

1 M. Jones, P. Temple, E. J. Thomas, and G. H. Whitham, *J. Chem. Soc., Perkin Trans. 1*, 1974, 433.
2 A. J. Bridges and G. H. Whitham, *J. Chem. Soc., Perkin Trans. 1*, 1975, 1603.
3 F. Asinger, W. Schäfer, G. Herkelmann, H. Römgens, B. D. Reintges, G. Scharein, and A. Wegerhoff, *Justus Liebigs Ann. Chem.*, 1964, **672**, 156; J. M. McIntosh, H. B. Goodbrand, and G. M. Masse, *J. Org. Chem.*, 1974, **39**, 202, and references therein.
4 M. D. Brown, D.Phil. Thesis, University of Oxford, 1983.
5 M. D. Brown, D. W. Gillon, G. D. Meakins, and G. H. Whitham, *J. Chem. Soc., Chem. Commun.*, 1982, 444; *J. Chem. Soc., Perkin Trans. 1*, 1985, 1623.
6 G. Sturtz and M. Baboulene, *Tetrahedron*, 1981, **37**, 3067.
7 T. H. Fife and E. Anderson, *J. Am. Chem. Soc.*, 1970, **92**, 5464.
8 L. Skattebøl, B. Boulette, and S. Solomon, *J. Org. Chem.*, 1967, **32**, 3111.
9 B. Groth, *Ark. Kemi*, 1924, **9**, 63.
10 E. Mameli, K. F. Richter, and F. D'Angeli, *Ann. Chim. (Rome)*, 1956, **46**, 211 (*Chem. Abstr.*, 1957, **51**, 402f).
11 A. Bhai, A. Das, S. Medheker, and K. S. Bopari, *J. Indian Chem. Soc.*, 1981, **58**, 295.
12 F. Stansfield and M. D. Coomassie, *J. Chem. Soc., Perkin Trans. 1*, 1979, 2708.
13 L. F. Johnson and W. C. Jankowski, 'Carbon-13 NMR Spectra,' Wiley, New York, 1972.

Received 27th February 1987; *Paper* 7/371