Oxidation of Unsaturated Aliphatic and Arylalkyl Alcohols by Peroxydisulphate. Intramolecular Cyclization of Alkoxyl Radicals

By **Angelo Clerici** * and **Ombretta Porta**, Istituto di Chimica del Politecnico, 39 Via Golgi, 20133 Milano, Italy

Oxidation of unsaturated aliphatic and arylalkyl alcohols by the sodium peroxydisulphate–silver salt system has been studied. Both classes of alcohols lead to cyclic ethers through different pathways. The ratio of five- to six-membered cyclic ethers was established reliably by trapping the corresponding cyclic radicals with heteroaromatic bases. Since a general preference for the formation of the five-membered ring was observed, comparison has been made with other oxidizing systems. The products obtained are also interesting from the synthetic point of view.

THE possibility of hydrogen abstraction [1] as the primary step in the oxidation of alcohols by peroxydisulphate has recently been reconsidered by Caronna *et al.*[2] who investigated the oxidation of saturated aliphatic alcohols both in the presence and absence of silver salt. Their results clearly showed that an alkoxyl radical is formed in the presence of silver salt (Scheme 1) while hydrogen abstraction occurs in its absence (Scheme 2).

$$S_2O_8^{2-} + Ag^+ \longrightarrow SO_4^{2-} + SO_4^{-\cdot} + Ag^{2+}$$
$$CH_3{-}OH + Ag^{2+} \longrightarrow CH_3{-}O\cdot + Ag^+ + H^+$$

SCHEME 1

Recently, Mihailovic *et al.*[3,4] have made a thorough study of the oxidation of unsaturated aliphatic alcohols using lead tetra-acetate, although no conclusive evidence was achieved regarding the preferred size of cyclization, owing to the further oxidation of the cyclic radical and subsequent rearrangement. Also, Surzur and his co-workers [5] examined in detail the photolysis of the nitrites of unsaturated aliphatic alcohols and have drawn interesting conclusions on the mechanism involved by trapping the cyclic radicals formed by means of the e.s.r. technique.[6]

We have previously [7] investigated the oxidation of unsaturated aliphatic alcohols by sodium peroxydisulphate and silver salt: this study allowed us to link up the alkoxyl radical formation with its interaction with the double bond and clarify the mechanism involved.

Now we report new results on the oxidation of various classes of alcohols (unsaturated aliphatic with and without a heteroatom in the aliphatic chain and saturated aryl-alkyl alcohols) using sodium peroxydisulphate in the

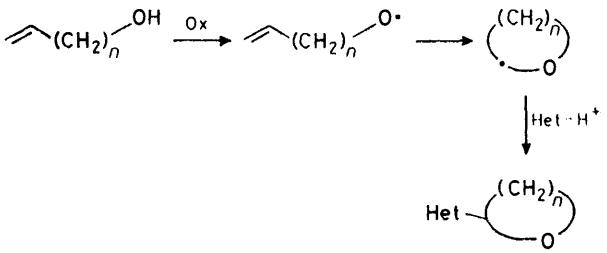
$$S_2O_8^{2-} \xrightarrow{\text{Heat}} 2\ SO_4^{-\cdot}$$
$$CH_3{-}OH + SO_4^{-\cdot} \longrightarrow \cdot CH_2{-}OH + HSO_4^-$$

SCHEME 2

presence and absence of silver(I) and copper(II) salts. Most reactions were carried out in the presence of protonated 4-methylquinoline and 4-cyanopyridine, since heteroaromatic bases have proved to be a very valuable trap for alkyl radicals.[8,9] As the addition rate constant of the alkyl radicals to the protonated bases was shown [10] to be very high, the cyclic radicals formed can be fully trapped before their further oxidation and the corresponding alkylation products of these bases completely account for them (Scheme 3).

Unsaturated Alcohols.—(1) *Influence of the chain length* (*Scheme* 4). When $n = 3$ the cyclization leads to the formation of both tetrahydrofuranyl (90%) and tetrahydropyranyl (10%) ethers. This selectivity is in agreement with the stereochemical rules of Baldwin [11] which also apply to the homolytic processes and parallels previous work on the oxidation of pent-4-en-1-ol with lead tetra-acetate [12,13] but is somewhat in contrast with the photolysis of the corresponding nitrite.[5,14] It is clear that the major product is the kinetically-controlled one since the five-membered ring arises from the thermodynamically less stable primary radical. The kinetic preference for the five-membered transition state over the six-membered one is frequently observed in organic reactions.

However, it was rather surprising to find that when



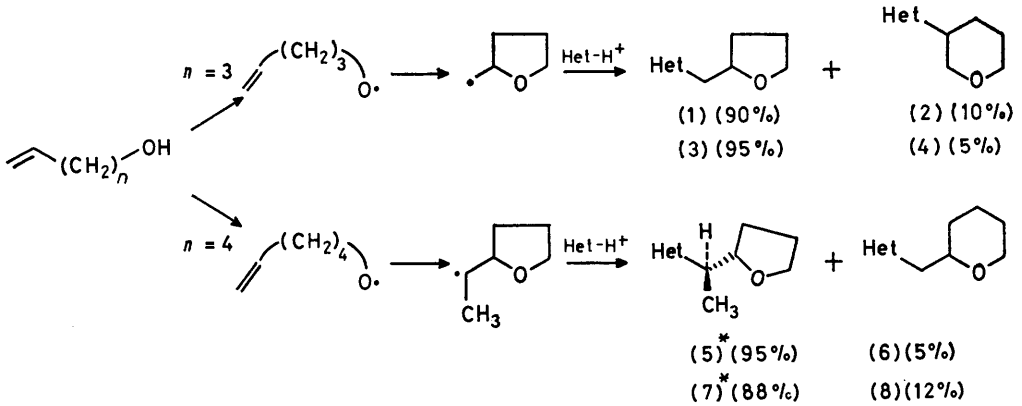
SCHEME 3 Het–H^+ = protonated heteroaromatic base

$n = 4$ the sole reaction products are again five- and six-membered ethers, whereas one would expect the six-membered ring to predominate. At present we think that the most plausible explanation is rearrangement of hex-5-en-1-ol to the most stable internal olefin (hex-4-en-1-ol) under the reaction conditions (aqueous sulphuric acid) followed by almost exclusive cyclization of this olefin to the five-membered-ring ether as the major product (Scheme 5). Evidence for such isomerization was also noted in the reaction of hex-5-en-1-ol with pyridinium chloride and bromide.[15] Moreover, in the presence of silver salt, the equilibrium constant for complex formation of several unsaturated alcohols indicated [16] that the equilibrium constant is largest when the double bond is δ to the hydroxy-group.

(2) *Influence of a heteroatom in the aliphatic chain* (*Scheme* 6). By replacing a CH_2 group with an oxygen atom in the aliphatic chain of the unsaturated alcohol the product obtained is quite different: the radical which attacks the heteroaromatic base is that resulting from β-

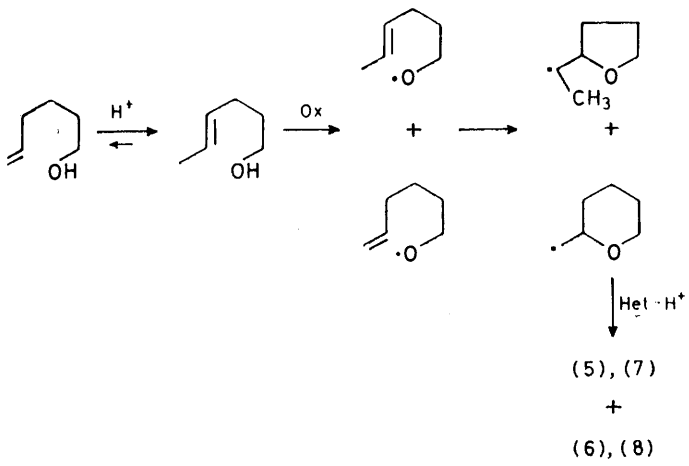
scission. Clearly, under the present reaction conditions, the β-scission process is faster than cyclization or δ-hydrogen abstraction: this is in contrast with the photolysis of the corresponding nitrite.[17]

peroxydisulphate. It gave a high yield of γ-lactone at high conversion in a very clean reaction. The transformation was considered to proceed by initial formation of a radical cation, as indicated in Scheme 7,



SCHEME 4 Het = 4-methylquinolinyl for (1), (2), (5), and (6) and 4-cyanopyridinyl for (3), (4) (7), and (8). * Mixture of two diastereoisomers (40 and 60%).

When the heteroatom was sulphur, no product of attack on the heteroaromatic base was isolated. This is probably due to the high oxidation potential of the



SCHEME 5

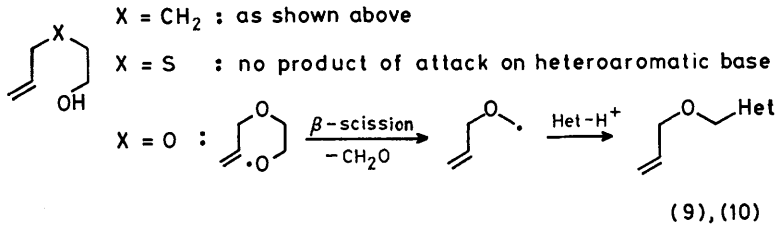
sulphur atom, which becomes the first target for oxidation. Also, the alkyl radical formed from β-scission would almost certainly not be able to attack the base.

through an electron-transfer process since normal peroxydisulphate oxidation of the carboxy group would lead to decarboxylation, and initial hydrogen abstraction from the benzyl carbon atom would not be expected to give complete selectivity of attack.

On this basis we have now investigated the oxidation of 4-phenylbutan-1-ol. In this case the oxidation with peroxydisulphate, both in the presence and absence of silver salt, leads to the same secondary benzyl radical (13) (Scheme 8). So it seems to us likely that the formation of an alkoxyl radical (11), followed by hydrogen abstraction, is the primary step in the presence of silver salt, while an electron-transfer process on the aromatic ring (12) would account for the primary step in its absence.

It was not unexpected that the use of a heteroaromatic protonated base to trap the cyclic radical formed was unsuccessful: in fact the very high oxidation potential of the secondary benzyl radical prevents attack on the base. In order to make the oxidation to the corresponding cation quantitative copper(II) salt was added and thus 2-phenyltetrahydrofuran (14) was the sole product of the reaction.

Similar conclusions on the mechanism involved have recently been reported by Walling *et al.*[19] who recon-



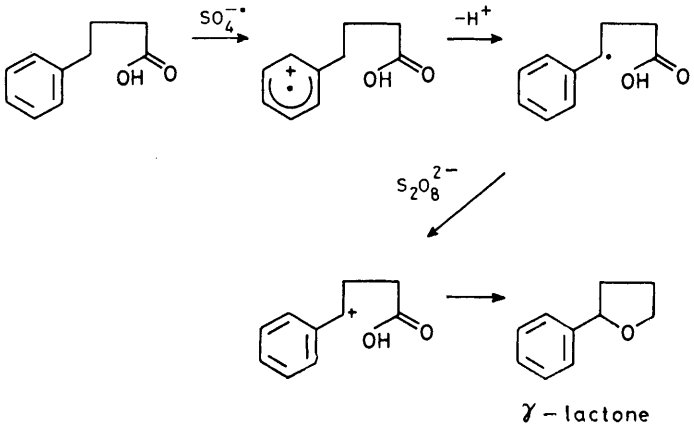
SCHEME 6

Arylalkyl Alcohols.—Aromatic substrates with side-chain CO_2H and OH groups show two main points of attack by an oxidizing agent. In a previous paper[18] we reported the oxidation of 4-phenylbutyric acid with

sidered the oxidation of aromatic substrates with side-chain groups by peroxydisulphate both in the presence and absence of silver salt.

Work is in progress on homologous alcohols (*e.g.* 5-

phenylpentan-1-ol) which should be of more interest in this connection because the different mechanisms of oxidation would clearly differentiate the final ring-ethers:



SCHEME 7

in the presence of silver salt, the five-membered ring ether is expected to be the major product (δ-hydrogen abstraction by the alkoxyl radical) while in its absence the six-membered-ring ether would result from the electron-transfer process on the aromatic nucleus.

It is worth noting that all the compounds obtained are new and could probably be prepared only with difficulty by other methods, so these reactions, besides their bearing on the mechanism of oxidation of alcohols and the effect of ring size on cyclization, are also interesting from the synthetic viewpoint.

EXPERIMENTAL

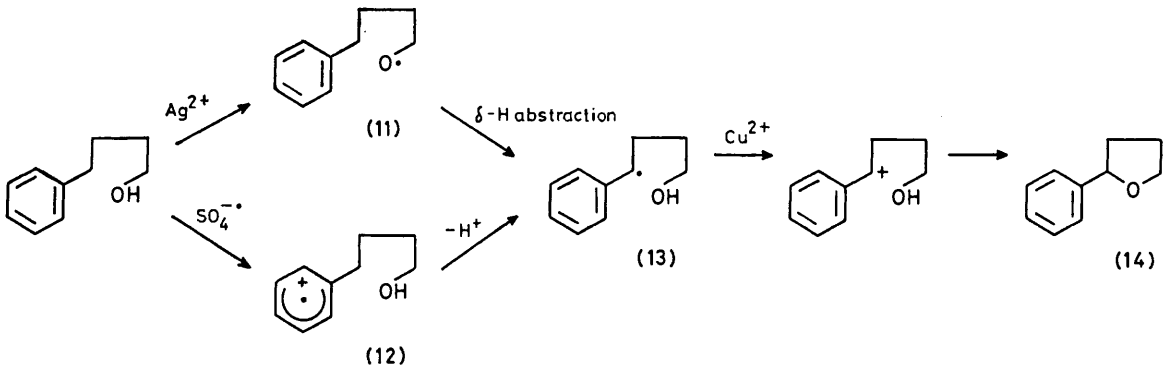
Reagents.—Sodium peroxydisulphate was recrystallized from water. Reagent grade silver(I) nitrate and copper(II) acetate were used as received. The purity of all organic reagents was checked by g.l.c. and they were redistilled when necessary. Reference compounds were either purchased or synthesized by known methods.

Analysis.—^{1}H N.m.r. spectra were recorded on a Varian A–90 instrument. For i.r. spectra a Perkin-Elmer 177 spectrometer was used. G.l.c. analysis were performed on a Hewlett–Packard 5750 G instrument with a flow rate of 30 ml min^{-1} N_2. Mass spectra were taken on a Hitachi–Perkin-Elmer RMU–6D spectrometer at 70 eV.

Alkylation of Heteroaromatic Bases with Unsaturated Aliphatic Alcohols. General procedure. To a solution of heteroaromatic base (0.025 mol), concentrated H_2SO_4 (0.0125 mol), the alcohol (0.125 mol), and $AgNO_3$ (0.001 25 mol) in H_2O (10 ml) and CH_3CN (10 ml), a solution of $Na_2S_2O_8$ (0.025 mol) in H_2O (10 ml) was slowly added (30 min) with stirring and refluxing at 85 °C and kept for an additional 4 h. The mixture was then cooled, diluted with H_2O, carefully basified with 3M-NaOH with stirring and cooling, and extracted with ether. After removal of the solvent, the residue was analysed by g.l.c. (using 5-ft × ⅛-in columns in 10% UCC W–982 and 3% OV–17 on Chromosorb W DMCS, 80—100 mesh) and fractionated by column chromatography (eluant hexane–ethyl acetate, 8 : 2). All the alkyl derivatives of the heteroaromatic bases were isolated as pure samples by p.l.c. (2-mm Merck Kieselgel GF 254).

2-*Tetrahydrofurfuryl*-4-*methylquinoline* (1). This compound had δ($CDCl_3$) 1.7—2.2 (4 H, CH_2CH_2, β to O, m), 2.6 (3 H, CH_3, s), 3.15 (2 H, CH_2, d), 3.6—4.0 (2 H, CH_2, α to O, m), 4.3—4.5 (1 H, α to O, m), 7.2 (1 H, ArH, β to N, s), and 7.4—8.1 (4 H, C_6H_4, m), *m/e* 227 ($M^{+\bullet}$), 157 (major peak), 143, 84, 71, and 43, $\nu_{max.}$ 3 050 (CH aromatic), 2 950—2 850 (CH_2 aliphatic), and 1 060 (C–O–C) cm^{-1}.

2-(*Tetrahydropyran*-3-*yl*)-4-*methylquinoline* (2). Despite the difficulty of its separation from (1), the use of g.l.c.–m.s.* allowed us to differentiate the two products clearly on the basis of the relative abundance of ions in the different fragmentation paths.[20] Compound (1) yielded a major peak of *m/e* 157, (2) of *m/e* 170. Compounds (1) (90%) and (2) (10%) were obtained in 95% yield based on converted base (38%).



SCHEME 8

2-*Tetrahydrofurfuryl*-4-*cyanopyridine* (3). This compound had δ($CDCl_3$) 1.6—2.1 (4 H, CH_2CH_2, β to O, m), 3.0—3.1 (2 H, CH_2, d), 3.6—4.0 (2 H, CH_2, α to O, m), 4.15—4.35 (1 H, α to O, m), 7.35 (1 H, β to N, d), 7.55 (1 H, β to N, s), and 8.7 (1 H, α to N, d), *m/e* 188 ($M^{+\bullet}$), 118 (major peak), 104, 71, and 43, $\nu_{max.}$ 3 040 (CH aromatic), 2 960—2 850 (CH_2 aliphatic), and 1 060 (C–O–C) cm^{-1}.

2-(3-*Tetrahydropyranyl*)-4-*cyanopyridine* (4). G.l.c.–m.s.* was used to differentiate (4) from (3). Compound (4) had *m/e* 188 ($M^{+\bullet}$), 157, 131 (major peak), 71 and 43; δ($CDCl_3$) 1.8 (4 H, CH_2CH_2, β and γ to O, m), 3.5 (4 H, CH_2–O–CH_2, α to O, m), 4.7 (1 H, CH, β to O, m), 7.5 (1 H, β to N, s), and 8.65 (1 H, α to N, d). Compounds (3)

* Instrument: Varian Mat 111, 80 eV, columns packed with 5% E–30 and 5% OV–225, 5-ft × ⅛-in.

(95%) and (4) (5%) were obtained in 98% yield based on converted base (43%).

2-[α-(2-*Tetrahydrofuryl*)*ethyl*]-4-*methylquinoline* (5). Compound (5) had δ($CDCl_3$) 1.36 and 1.46 (3 H, CH_3, 2 d), 1.75—2.2 (4 H, CH_2CH_2, β to O, m), 2.7 (3 H, CH_3, s), 2.9—3.25 (1 H, CH, m), 3.6—3.9 (2 H, CH_2, α to O, m), 3.95—4.25 (1 H, CH, α to O, m), 7.25 (1 H, β to N, s), and 7.4—8.0 (4 H, C_6H_4, m), *m/e* 241 ($M^{+\cdot}$), 171 (major peak), 157, 143, and 71, $\nu_{max.}$ 3 080 (aromatic CH), 3 000—2 840 (aliphatic CH_2), and 1 065 (C–O–C) cm^{-1}.

2-[(*Tetrahydropyranyl*-2-*yl*)*methyl*]-4-*methylquinoline* (6). G.l.c.–m.s.* analysis was used to differentiate this product from (5) on the basis of the relative abundance of ions in different fragmentation paths. Compound (5) yielded a major peak of *m/e* 171, (6) of *m/e* 157. Compounds (5) (95%) and (6) (5%) were obtained in 98% yield based on converted base (52%).

2-[α-(*Tetrahydrofuran*-1-*yl*)*ethyl*]-4-*cyanopyridine* (7). Compound (7) had δ($CDCl_3$) 1.3 and 1.38 (3 H, CH_3, 2 d), 1.5—2.2 (4 H, CH_2CH_2, β to O, m), 2.85—3.25 (1 H, CH, m), 3.6—3.9 (2 H, CH_2, α to O, m), 3.9—4.2 (1 H, CH, α to O, m), 7.35 (1 H, β to N, d), 7.5 (1 H, β to N, s), and 8.7 (1 H, α to N, d), *m/e* 202 ($M^{+\cdot}$), 132 (major peak), 104, 71, and 43, $\nu_{max.}$ 3 080 (aromatic CH), 3 000—2 850 (aliphatic CH_2), 2 240 (CN), 1 065, and (C–O–C) cm^{-1}.

2-(*Tetrahydropyran*-2-*yl*)*methyl*-4-*cyanopyridine* (8). G.l.c.–m.s.* analysis was used to differentiate (8) from (7). Compound (8) had *m/e* 202 ($M^{+\cdot}$), 118 (major peak), 104 and 85. Compounds (8) (88%) and (8) (12%) were obtained in 96% yield based on converted base (55%).

2-*Allyloxymethyl*-4-*methylquinoline* (9). Compound (9) had δ($CDCl_3$) 2.7 (3 H, CH_3, s), 4.1 (2 H, CH_2O, d), 4.8 (2 H, $ArCH_2O$, s), 4.9—5.4 (2 H, CH_2=CH, m), 5.7—6.1 (1 H, CH_2=CH, m), 7.2 (1 H, α to N, s), and 7.4—8.2 (4 H, C_6H_4, m), *m/e* 213 ($M^{+\cdot}$), 184, 157 (major peak), 143 and 115, $\nu_{max.}$ 3 050 (aromatic and olefinic CH), 2 950—2 850 (aliphatic CH_2), 1 630 (CH_2=CH), 1 060 (C–O–C), and 850 (CH out-of-plane) cm^{-1}.

2-*Allyloxymethyl*-4-*cyanopyridine* (10). Compound (10) had δ($CDCl_3$) 4.15 (2 H, CH_2O, d), 4.7 (2 H, $ArCH_2O$, s), 5.2—5.45 (2 H, CH_2=CH, m), 5.8—6.2 (1 H, CH_2=CH, m), 7.35—7.45 (1 H, β to N, d), 7.75 (1 H, β to N, s), and 8.65—8.75 (1 H, α to N, s), *m/e* 174 ($M^{+\cdot}$), 146, 118 (major peak), 104 and 70, $\nu_{max.}$ 3 050 (aromatic and olefinic CH), 2 960—2 840 (aliphatic CH_2), 2 230 (CN), 1 630 (CH_2=CH–), and 1 060 (C–O–C) cm^{-1}. Compounds (9) and (10) were obtained in very poor yield (conversion 10%).

Oxidation of 4-*Phenylbutan*-1-*ol*. To a solution of the alcohol (0.03 mol), $AgNO_3$ (0.005 mol), and $Cu(CH_3COO)_2$ (0.002 mol) in H_2O (10 ml) and CH_3CN (10 ml) vigorously stirred and refluxed, was slowly added over 30 min a solution of $Na_2S_2O_8$ (0.02 mol) in H_2O (10 ml). Stirring and refluxing were continued for a further 4 h. The mixture was diluted with H_2O after cooling and extracted (×3) with ether. After removal of the solvents under reduced pressure, the crude oil (3.96 g, 88% overall yield) was analysed by g.l.c. (using 5-ft × ⅛-in column packed with 10% Carbowax 20M on Chromosorb W DMCS, 80—100 mesh). Only two compounds were detected, 4-phenylbutan-1-ol (62.5%) and 2-phenyltetrahydrofuran (37.5%) (conversion 49.7%, yield based on converted alcohol 66%). 2-Phenyltetrahydrofuran (14) was isolated on a silica gel column (eluant hexane–ethyl acetate, 8 : 2), δ($CDCl_3$) 1.8—2.4 (4 H, CH_2CH_2, β to O, m), 3.8—4.2 (2 H, CH_2, α to O, m), 4.75—4.9 (1 H, CH, α to O, t), and 7.2 (5 H, C_6H_5, s), *m/e* 148 ($M^{+\cdot}$), 147, 105 ($Ph–CO^+$), 104 ($Ph–\overset{+}{C}H=CH_2$), 91 ($Ph–CH_2^+$), 71 and 43, $\nu_{max.}$ 3 040 (aromatic CH), 2 970—2 830 (aliphatic CH_2), and 1 060 (C–O–C) cm^{-1}.

* Instrument: Perkin-Elmer RMU-6D, 70 eV, column packed with 3% OV-17, 5-ft × ⅛-in.

We thank Professor J.-M. Surzur, Université des St. Jerome, Marseille, for helpful discussions. We also thank Dr. P. Traldi, C.N.R. Department, Polytechnic of Milan, and Mrs. M. Charlot, Organic Chemistry Department, Université des St. Jerome, for g.l.c.–m.s. measurements.

[9/1563 *Received*, 2*nd October*, 1979]

REFERENCES

[1] J. E. Isaac and J. O. Edwards, *J. Org. Chem.*, 1969, **34**, 2565.
[2] T. Caronna, A. Citterio, L. Grossi, F. Minisci, and K. Ogawa, *Tetrahedron*, 1976, **32**, 2741.
[3] M. Mihailovic and R. E. Partch, 'Selected Organic Transformation,' Wiley–Interscience, New York, vol. 2, 1972.
[4] M. Mihailovic, *J. Heterocyclic Chem.*, 1976, *Supplement Lectures Heterocyclic Chem.*, **3**, 5—111.
[5] J.-M. Surzur and M.-P. Bertrand, *Bull. Soc. chim. France*, 1973, 1861, 2393.
[6] P. Tordo, M.-P. Bertrand, and J.-M. Surzur, *Tetrahedron Letters*, 1970, 3399.
[7] A. Clerici, F. Minisci, K. Oagawa, and J.-M. Surzur, *Tetrahedron Letters*, 1978, 1149.
[8] F. Minisci and O. Porta, *Adv. Heterocyclic Chem.*, 1974, **16**, 123.
[9] F. Minisci, *Topics Current Chem.*, 1976, **62**, 1.
[10] A. Citterio, F. Minisci, O. Porta, and G. Sesana, *J. Amer. Chem. Soc.*, 1977, **99**, 7960.
[11] J. E. Baldwin, *J.C.S. Chem. Comm.*, 1976, 734.
[12] S. Moon and J. M. Lodge, *J. Org. Chem.*, 1964, **29**, 3453.
[13] M. Mihailovic, Z. Cekovic, J. Stankovic, N. Pavlovic, S. Konstantinovic, and S. Djokic-Mazinmamin, *Helv. Chim. Acta*, 1973, **56**, 3056.
[14] R. D. Rieke and N. A. Moore, *J. Org. Chem.*, 1972, **37**, 413.
[15] D. Dauzanne, P. Demerseman, J. Egjed, C. Lang, N. Platzer, and R. Rojer, *Tetrahedron*, 1977, **33**, 19.
[16] D. Gray, R. A. Wies, and W. D. Classon, *Tetrahedron Letters*, 1968, 5639.
[17] J.-M. Surzur, M.-P. Bertrand, and R. Nougier, *Tetrahedron Letters*, 1969, 4197.
[18] A. Clerici, F. Minisci, and O. Porta, *Tetrahedron Letters*, 1974, 4183
[19] C. Walling and D. Camaioni, *J. Org. Chem.*, 1978, **43**, 3266.
[20] K. Biemann, 'Mass Spectrometry: Organic Chemical Applications, McGraw–Hill Book Co., New York, 1962, pp. 98—100.