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AUTOXIDATION OF TERPENIC ALDEHYDES—I[a]

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Abstract—The autoxidation reaction of diterpenic 4-axial-aldehyde torulosal (**1b**) has been studied. Naturally occurring 4-hydroxy-nor-diterpenes have been proved to be artefacts arising in the autoxidation of the corresponding 4-aldehyde. Hydroperoxides (**1d**) and (**2d**), the main autoxidation products of **1b**, have also been postulated as intermediates in the formation of 4-hydroxy-nor-diterpenes (**1a** and **2a**).

Recently, the isolation of a number of 4-hydroxy-nor-diterpenes has been reported[1] and different hypotheses have been proposed concerning their origin. Very recently we isolated two diols (**1a** and **2a**) of the same type from the oleoresin of *Araucaria excelsa*.[2]

This paper deals with the results obtained in a study of the autoxidation of torulosal (**1b**), which suggests such 4-hydroxy-nor-diterpenes are artefacts arising from the 4-aldehyde with the same skeleton almost always isolated together with the diols.

Torulosal (**1b**), present in the oleoresin of *A. excelsa* in a 7% amount, is a rather labile substance,[3] and if oily **1b** is left for some hours, in the air as a thin film† several non-aldehydic substances are formed (TLC and NMR). Among these the only acidic compound is cupressic acid (**1c**), isolated in about 10% yield.‡ The structures of the compounds isolated from the neutral fraction in addition to unreacted aldehyde (40%) are represented by the formulae **1a**, **2a**, **1d**, **2d** and **3**.

Hydroxy-olefins (**3**). The mixture of isomeric hydroxy-olefins **3** (9%) obtained by chromatography were present in the same fraction as the starting aldehyde (**1b**). The isolation of **3** was achieved by immediate LAH reduction of that fraction, in order to avoid further autoxidation of **1b**, and the subsequent chromatographic separation from the resulting torulosol (**1e**). Structure **3**, besides the IR and NMR evidence, was assigned on the basis of the GLC comparison of the acetyl derivatives of **3** with those obtained in the oxidative decarboxylation[4] of acetyl-**1c**.

Nor-diols **2a** *and* **1a**. The crystalline diols (**1a** and **2a**) were compared with the diols isolated from the oleoresin of *A. excelsa*, and found identical in every respect.

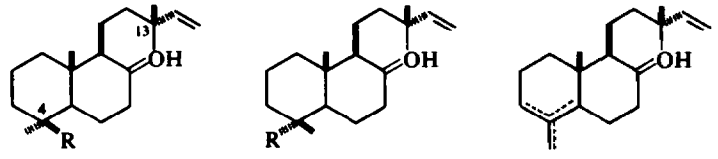
Hydroperoxides (**2d**) *and* (**1d**). The two oily hydroperoxides having $[\alpha]_D + 0{\cdot}9°$ and $[\alpha]_D + 28{\cdot}3°$ were isolated in 14% and 10% yield respectively. Structure **2d** was assigned to the former on the basis of elemental composition, oxidizing character (NaI test)[5] and spectral features. In fact, the IR spectrum only showed an OH absorption and the NMR spectrum presented an olefinic region identical with that of **1b** and three Me singlets at 8·74 τ, 8·93 τ and 9·33 τ respectively. The first two were assigned to the Me's geminal with O atoms at C_{13} and C_4; the last one to the C_{20} angular Me. Acetylation of **2d** yielded an oily monoacetyl derivative (**2f**) whose IR spectrum showed the perester[6] typical C=O band at 1781 cm^{-1}. Finally the reduction of **2d** yielded the diol **2a** almost quantitatively.

To the more dextrorotatory isomer, structure **1d** was assigned on account of its chemical and spectroscopic features which closely resemble those of **2d** and because of its conversion into the diol **1a**. In the NMR spectrum of **1d** two Me singlets were coincident at 8·74 τ (and therefore due to the Me's at C_{13} and C_4) whereas the third one (C_{20} Me) was shifted to 9·22 τ thus confirming[7] the

[a]During the preparation of this manuscript, a paper by Tanaka *et al.*[15] concerning the autoxidation of some 4-axial diterpenic aldehydes and the formation of 4-hydroxy-nor-diterpenes, was published. Prior to this publication in a short communication[16] we reported the isolation and identification of hydroperoxides from the autoxidation reaction, and in addition gave the mechanism of formation. (Chart 2 in the present paper). The formation of 4-hydroxy-nor-diterpenes *via* peracid, as proposed by the Japanese Authors, does not exclude the mechanism we have suggested *via* hydroperoxides (Chart 3 in this paper), the latter being widely supported by the well known facile reducibility[10] of tertiary hydroperoxides. Finally the hypothesis that naturally occurring 4-hydroxy-nor-diterpenes might be artefacts, was also reported in our preliminary communication.

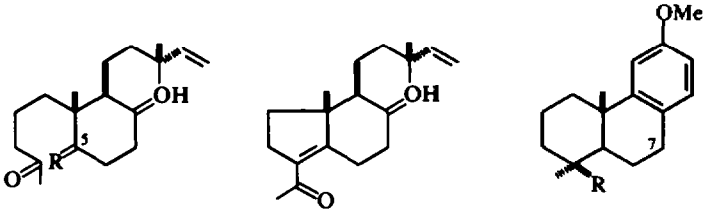
†These experimental conditions have been chosen in order to better reproduce the natural conditions of finding of the oleoresins.

‡All the yields are referred to the starting aldehyde.



1 2 3

a: R = OH
b: R = CHO
c: R = COOH
d: R = OOH
e: R = CH_2OH
f: R = OOAc



4 5 6

a: R = H, βOH
b: R = O

a: R = CH_2OH
b: R = CHO

β-axial configuration assigned to the hydroperoxyl group. Furthermore, **1d** gave a monoacetate under the same conditions as **2d** but this derivative could not be purified by chromatography on alumina or silica-gel owing to quantitative conversion into the oily di-hydroxy-ketone (**4a**). In the IR spectrum of **4a** no acetate absorption was detected but the ketonic CO band was present at 1725 cm^{-1}. Furthermore, the NMR spectrum of **4a** showed, beside an olefinic region identical with that of **1b**, a Me singlet at 7·87 τ (Me-ketone), a multiplet centered at 6·32 τ assigned to a proton geminal with an OH group and finally an unresolved multiplet at about 7·55 τ assigned to a $CH_2\alpha$ to the CO group. The mutual position of CO and OH groups was established by Jones oxidation of **4a** to the oily di-ketone (**4b**) and the subsequent conversion of the latter by alkali into the α,β-unsatured ketone (**5**). Finally, the β-equatorial configuration of the OH group at C_5, which could be predicted on the basis of the mechanism of formation[8] of **4a** from the peracetate **1f** (Chart 1), was confirmed by the value of the width at half height in the NMR signal of the geminal proton (multiplet, $W_{1/2}$ 15 Hz).[9]

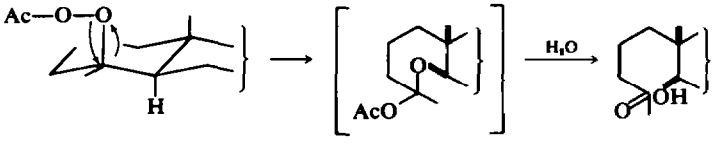
The driving force operating in the rearrangement of the axial peracetate (**1f**) may be reasonably found in the steric relief implied in the transformation **1f** → **7**.

These results suggest a mechanism for the autoxidation of torulosal (**1b**) as shown in Chart 2.

The first step is the usual formation of a radical (**8**) by abstraction of an H· from the formyl group. The radical (**8**) may then undergo either oxygen addition to give **9** or loss of carbon monoxide to give the tertiary radical at C_4 (**10**). The former follows the normal way to the carboxylic acid (**1c**) and the latter reacts with atmospheric oxygen from both the faces of the molecule* giving rise to the peroxy-radicals (**11** and **12**) which, by abstraction of the formyl hydrogen from **1b**, are converted into the hydroperoxides (**1d** and **2d**). The partial reduction of **1d** and **2d**† then gives the

*Mainly from α-face, as expected because of the angular methyl steric hyndrance.

†It is very well known that tertiary hydroperoxides are spontaneously reduced at low temperature to give the corresponding alcohols, being the process assisted by "olefins, aldehydes, ketones, carboxylic acids, alcohols and another molecule of hydroperoxide; furthermore, hydroperoxides decompositions are notoriously sensitive to minute impurities, particularly of metal ions".[10]



1f 7 4a

CHART 1

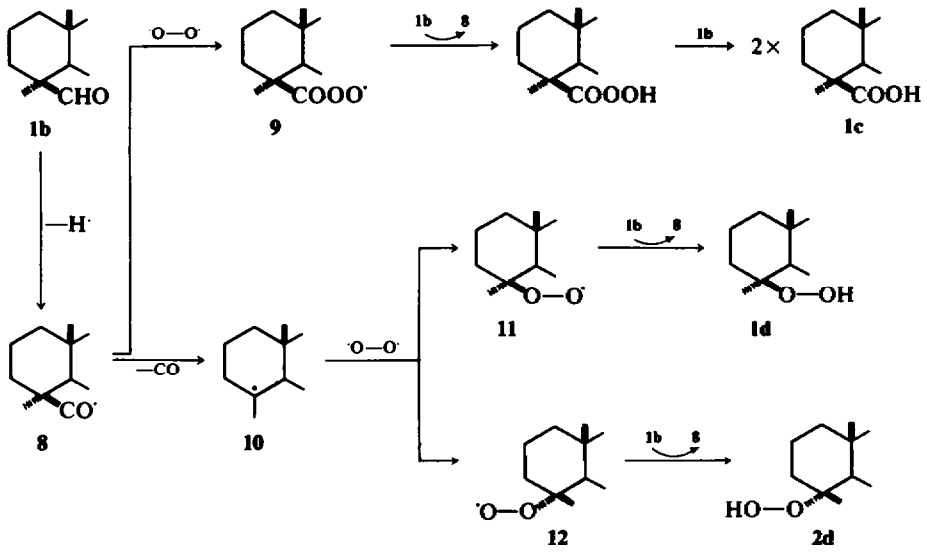


CHART 2

corresponding nor-diols (**1a** and **2a**). The formation of the hydroxy-olefins (**3**) may also be easily rationalized as both **1a** and **2a** are very easily dehydrated to give respectively a mixture of the hydroxy-olefins Δ^3 and Δ^4 and the hydroxy-olefin $\Delta^{*(18)}$ even if they are only absorbed on alumina or silica-gel (Chart 3).

The former was immediately reduced by LAH and the latter was fractioned by chromatography on alumina. Whereas, from this, all the pattern of products described by the above mentioned Authors was obtained, the reduction mixture did not show conclusively the presence either of nor-olefins or of nor-alcohols.

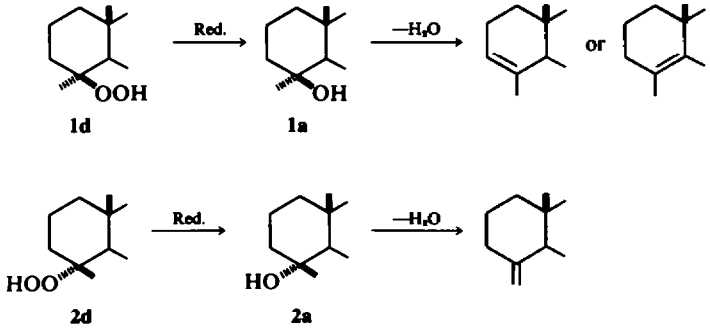


CHART 3

In the light of our results, the scheme proposed by Murray and Martin to explain the presence of small amounts of nor-alcohols and nor-olefins in addition to the 4-aldehyde in the chromic oxidation of eritroxilol A[11] as well as of other 4-hydroxy-methyl-diterpenes[12] is no longer tenable as the formation of the nor-derivatives may be better explained by the partial autoxidation occurring in the working up of the reaction.

In order to prove our point, we carefully repeated the chromic oxidation of O-methyl-podocarpinol (**6a**) the most easily available diterpenic alcohol examined by the Authors.[12] After oxidation, the crude product was divided in two parts.

The oxidation of torulosol (**1e**) under the same conditions gave analogous results: in fact, the working up of the reaction in the usual way did yield, beside torulosal (**1b**), the nor-diols (**1a** and **2a**) and the hydroxy-olefin mixture (**3**) while, as expected, by immediate LAH reduction of the crude product from the chromic oxidation, the starting alcohol was recovered almost quantitatively without any traces of **1a**, **2a** and **3**.

Autoxidation of aldehydes usually leads to the corresponding carboxylic acids. Deformylation of aldehydes to give hydrocarbons *via* a radical process involving the loss of carbon monoxide is also well known[13] and the replacement of a

tertiary aldehyde group by an OH group has been reported in some cases.[14] The present paper, however, is the first example of the isolation and identification of hydroperoxide intermediates in the formation of the nor-alcohols and nor-olefins from aldehydes (Charts 2, 3).

In our case the elimination of carbon monoxide instead of the normal autoxidation pathway is probably due to the peculiar nature of the substrate: the main factors responsible seem to be the quaternary nature of the formyl group and, even more, the 1,3-diaxial interaction between this group and the angular Me. In order to verify this point, the behaviour of a number of aldehydes is being investigated under similar conditions in our laboratory.

EXPERIMENTAL

M.ps are uncorrected. IR spectra were determined on a Perkin Elmer 157 spectrophotometer on $CHCl_3$ solns. NMR spectra were recorded on a Perkin Elmer R 12 A spectrometer, with TMS as an internal standard, in $CDCl_3$ solns. Rotations were taken for $CHCl_3$ solns at r.t. with a Perkin Elmer mod. 141 polarimeter. PLC and TLC were performed on silica-gel F_{254} (Merck). Silica-gel 0·05–0·20 mm (Merck) or alumina (Woelm, grade III) were used for column chromatography. GLC was run on 6′ × 1/4″ glass column with 3% Se-30 on chromosorb G (80 ÷ 100 mesh) using a Perkin Elmer 881 (FID) chromatograph.

Autoxidation of torulosal (**1b**). Pure oily **1b** (1800 mg; $[\alpha]_D$ + 29°) dissolved in hexane was evaporated *in vacuo* in a 500 ml flask to form a thin liquid film, then kept at r.t. for 5 hr. The crude autoxidation product was dissolved in ether and rapidly extracted with 10% Na_2CO_3 aq (2 × 50 ml). Acidification (12N H_2SO_4) of the combined aqueous layers yielded 175 mg of **1c**. The neutral fraction was chromatographed on alumina: elution with benzene (300 ml) gave a less polar fraction A (905 mg) consisting of **1b** and **3**. The subsequent elution then afforded three more polar fractions: B (202 mg with 200 ml benzene/ether 97:3) mainly consisting of **1d**, C (305 mg with 400 ml benzene/ether 94:6) consisting of **1a** and **2d**, D (109 mg with 300 ml benzene/ether 80:20) consisting of **2a**.

13-*Hydroxy-nor-olefins* (**3**). Fraction A, after LAH reduction, was chromatographed on alumina. The elution with 120 ml benzene gave 160 mg of **3**. The subsequent elution with 300 ml benzene/ether (80:20) afforded 720 mg of **1e**. A sample of **3** treated with acetyl chloride/N,N-dimethyl-aniline for 12 hr at r.t. gave the acetyl derivatives identical (GLC analysis) with authentic samples from the oxidative decarboxylation of acetyl-**1c**.

Hydroperoxide **1d**. Fraction B, after repeated chromatographic purification (silica-gel; benzene/ether 99:1), afforded 176 mg of pure oily **1d**: $[\alpha]_D$ + 28·3° (c = 2); MW 308 (MS); (Found: C 74·03; H 10·46. $C_{19}H_{32}O_3$ requires: C 73·98; H 10·46%); τ 9·22 (3H, s, C_{20} Me), 8·74 (6H, s, Me's at C_4 and C_{13}). The purity of **1d** has been shown to be more than 98% by iodometric titration.

Nor-diol (**1a**) *and hydroperoxide* (**2d**). Fraction C was rechromatographed on alumina eluting with benzene/ether 93:7. The first 100 ml eluted 15 mg of crude semi-crystalline **1a** whose purification by PLC afforded 11 mg of pure **1a** m.p. 89·5–90° (from hexane/benzene 7:3): $[\alpha]_D$ + 29·51° (c = 1) compared with an authentic sample.

Further elution (600 ml) then gave 248 mg of the oily **2d** which, after chromatographic purification, had: $[\alpha]_D$ + 0·9° (C = 2); MW 308 (MS); (Found: C 73·97; H 10·38. $C_{19}H_{32}O_3$ requires: C 73·98; H 10·46%); τ 9·33 (3H, s, C_{20} Me), 8·93 (3H, s, Me at C_4), 8·74 (3H, s, Me at C_{13}). The purity of **2d** has been shown to be more than 98% by iodometric titration.

Nor-diol (**2a**). Fraction D, after filtration through alumina with benzene/ether (80:20), gave 98 mg of **2a** m.p. 124–125° (from hexane/benzene 7:3): $[\alpha]_D$ + 14·39° (c = 1) identical with an authentic sample.

Stability of nor-diols (**1a**) *and* (**2a**) *in the chromatographic processes*. The pure **1a**, when absorbed on alumina (or silica-gel) (ratio 1:100) and carefully eluted after 1 hr with hexane, afforded a mixture of Δ^3 and Δ^4 olefins in 24 ÷ 31% amount. The 4-equatorial diol **2a**, under the same conditions, afforded the $\Delta^{4(18)}$ olefin in a 8 ÷ 13% amount.

Reduction of hydroperoxides (**1d**) *and* (**2d**). Reduction of **1d** and **2d** to give respectively **1a** and **2a** were performed by LAH as well as $FeSO_4$ or KI. In the first case solutions of **1d** or **2d** in peroxide-free Et_2O were refluxed for 2 hr and the mixtures then worked up in the usual way. In the second case, the above solns were shaken with sat $FeSO_4$ aq for 3 hr at r.t. In the third way, chloroform solns of **1d** and **2d** were treated with excess KI aq and shaken for few min. The evolved iodine was then destroyed by $Na_2S_2O_4$ and the chloroform layer separated. In all the three ways the yields of **1a** and **2a** were quantitative.

Stability of hydroperoxides (**1d**) *and* (**2d**). Both **1d** and **2d**, when kept at r.t. in benzene soln for 24 hr, spontaneously decomposed to give the diols **1a** and **2a** respectively in 33% and 25% yields. When filtered through alumina with benzene, pure **1d** afforded the diol **1a** in about 20% yield. Under the same conditions, pure **2d** was reduced to **2a** in 16% yield.

Acetylation of **2d**: *peracetate* **2f**. Hydroperoxide **2d** (100 mg) was treated with Ac_2O/pyridine at r.t. for one night and the crude product, chromatographed on silica-gel (benzene/ether 97:3), afforded pure oily **2f** (88 mg): $[\alpha]_D$ − 7·5° (c = 1); MW 350 (MS); (Found: C 72·02; H 9·74. $C_{21}H_{34}O_4$ requires: C 71·96; H 9·78%); ν_{max} 1781 cm^{-1}; τ 9·32 (3H, s, C_{20} Me), 8·83 (3H, s, Me at C_4).

Acetylation of **1d**: *di-hydroxy-ketone* **4a**. Hydroperoxide **1d** (60 mg) was acetylated under the same conditions as **2d**. The crude product (64 mg showing an IR absorption at 1781 cm^{-1}), was then absorbed on alumina and the elution with benzene/ether (70:30) afforded the oily **4a** (45 mg); $[\alpha]_D$ + 26·9° (C = 1·2); MW 308 (MS); (Found: C 74·01; H 10·38. $C_{19}H_{32}O_3$ requires: C 73·98; H 10·46%); ν_{max} 1725 cm^{-1}; τ 9·35 (3H, s, C_{20} Me, 8·73 (3H, s, Me at C_{13}), 7·87 (3h, s, —CO—Me), 6·32 (1H, m, $W_{1/2}$ 15 Hz —CH—OH).

Hydroxy-α,β-unsatured-ketone (**5**). Compound (**4a**) (40 mg), in acetone, was oxidized at 0° by Jones reagent and afforded quantitatively **4b** which was directly dissolved in EtOH (1·5 ml), and 5% K_2CO_3 aq (0·5 ml) added and then refluxed for 3 hr under N_2. Chromatography (silica-gel; benzene) of the crude product afforded pure oily **5** (20 mg): $[\alpha]_D$ + 61·5° (c = 1); MW 288 (MS); (Found: C 79·22; H 9·78. $C_{19}H_{28}O_2$ requires: C 79·12; H 9·78%) ν_{max} 1678 cm^{-1}; λ_{max}^{EtOH} 259 nm (ϵ = 14050); τ 9·16 (3H, s, C_{20} Me), 7·80 (3H, s, CO—Me).

*Oxidative decarboxylation of acetyl-***1c**. Acetyl-**1c**

(1,470 mg) in anhyd C_6H_6 (60 ml) was added to anhyd pyridine (3 ml) and lead tetracetate (2,800 mg) and stirred at r.t. under N_2 for 3 hr. After filtration of the solid, the benzene soln was evaporated and the residue chromatographed on silica-gel. The elution with light-petroleum/ether (95/5) gave acetyl-3 (780 mg); MW 274 (MS); (Found: C 83·01; H 10·93. $C_{19}H_{30}O$ requires: C 83·15; H 11·02%); τ 4·81 (m, vinylic proton at C_3), 5·50 (d, *exo*-CH_2 at C_4), 8·41 (s, vinylic Me at C_4). GLC: three peaks with R_t: 5'30", 6'13", 6'50".

Chromic oxidation of O-methyl-podocarpinol (**6a**). The alcohol **6a** (635 mg) was dissolved in aqueous AcOH[12] (20 ml), CrO_3 soln[12] added (8·4 ml) and stirred at r.t. for 2 hr. After rapid working up, the crude product was divided in two parts (respectively 450 and 70 mg). Chromatographic separation of the former (alumina; mixtures of light-petroleum/ether), afforded **4b** (338 mg), its 7-oxo derivative (11 mg) and the starting alcohol **6a** (67 mg); besides a little polar fraction (4 mg) showing on GLC three peaks identical with those of the olefin mixture from the oxidecarboxylation of O-methyl-podocarpic acid;[17] a fraction (6 mg) with oxidizing character (NaI test) and the crystalline 4α-hydroxy-O-methyl-nor-podocarpane[17] (6 mg) m.p. 106–9° identical with an authentic sample. The second part (70 mg) was, instead, immediately reduced by LAH. The chromatography (alumina; benzene) of the reduction product afforded the starting alcohol **6a** in 96% yield.

Chromic oxidation of torulosol (**1e**). Torulosol **1e** (600 mg) was oxidized under the same conditions as **6a**. The crude product was again divided in two parts (respectively 505 and 50 mg). The former gave, after chromatography, beside the aldehyde **1b** all the autoxidation products **1a**, **2a**, **1d**, **2d** and **3**. The reduction of the second part gave quantitatively torulosol **1e**.

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REFERENCES

[1]P. K. Grant, C. Huntrakul and D. R. J. Sheppard, *Austral. J. Chem.* **20**, 969 (1967); A. Martin and R. D. H. Murray, *J. Chem. Soc.* (C), 2529 (1968); H. H. Quon and E. P. Swan, *Canad. J. Chem.* **47**, 4389 (1969); J. W. Rowe, B. A. Nagasampagi, A. W. Brugstahler and J. W. Fitzsimmons, *Phytochem.* **10**, 1647 (1971); I. T. U. Eshiet, A. Akisanya and D. A. H. Taylor, *Phytochem.* **10**, 3294 (1971); J. W. Rowe, R. C. Ronald and B. A. Nagasampagi, *Ibid.* **11**, 365 (1972).

[2]R. Caputo, L. Mangoni and P. Monaco, *Ibid.* **11**, 839 (1972)

[3]C. Enzell, *Acta Chem. Scand.* **15**, 1303 (1961). For other unstable 4-axial-aldehydes see also: E. Mosettig and W. R. Nes, *J. Org. Chem.* **20**, 884 (1955); E. Mosettig, U. Beglinger, F. Dolder, H. Lichti, P. Quitt and J. A. Waters, *J. Am. Chem. Soc.* **85**, 2305 (1963); W. Herz and R. N. Mirrington, *J. Org. Chem.* **30**, 3195 (1965); E. L. Ghisalberti, P. R. Jefferies and E. J. Middleton, *Austral. J. Chem.* **22**, 455 (1969); R. Caputo and L. Mangoni, *La Chim. e L'Ind.* (Milan), **51**, 1382 (1969)

[4]W. A. Ayer, C. E. McDonald and J. B. Stothers, *Canad. J. Chem.* **41**, 1113 (1963); W. A. Ayer and C. E. McDonald, *Ibid.* **43**, 1429 (1965). See also Ref. 17

[5]A. Nickon and W. L. Mendelson, *Ibid.* **43**, 1419 (1965)

[6]W. H. T. Davison, *J. Chem. Soc.* 2456 (1951)

[7]N. S. Bhacca and D. M. Williams, *Applications of NMR Spectroscopy in Organic Chemistry* p. 19. Holden Day San Francisco (1964)

[8]R. Criegee, *Ber. Dtsch. Chem. Ges* **77**, 722 (1944); D. B. Denney and D. G. Denney, *J. Am. Chem. Soc.* **79**, 4806 (1957)

[9]L. M. Jackman and S. Sternhell, *Applications of NMR Spectroscopy in Organic Chemistry* p. 288. Pergamon Press (1969)

[10]R. Hiatt in D. Swern, *Organic Peroxides* Vol. II. pp. 96 and following. Wiley, Interscience (1971)

[11]A. Martin and R. D. H. Murray, *loc. cit*

[12]A. Martin and R. D. H. Murray, *ibidem* 2023 (1970)

[13]J. O. N. Pitts, Jr. and J. K. S. Wan in S. Patai, *The Chemistry of the carbonyl group* p. 838. Interscience (1966)

[14]M. Ishidate and M. Yoshida, *Chem. Pharm. Bull.* **4**, 43 (1956); J. Binkert, E. Angliker and A. von Wartburg, *Helv. Chem. Acta* **45**, 2122 (1962); A. von Wartburg, J. Binkert and E. Angliker, *ibidem* **45**, 2139 (1962)

[15]O. Tanaka, S. Mihashi, I. Yanagisawa, T. Nikaido and S. Shibata, *Tetrahedron* **28**, 4523 (1972)

[16]R. Caputo, L. Mangoni, L. Previtera and R. Iaccarino, *Tetrahedron Letters* 3731 (1971)

[17]C. R. Bennett and R. C. Cambie, *Tetrahedron* **23**, 927 (1967)