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AUTOXIDATION OF TERPENIC ALDEHYDES—II[1]

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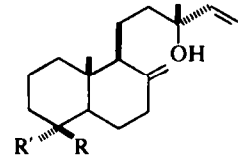
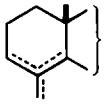
Abstract—The influence of steric factors on the autoxidation of aldehydes having tertiary formyl groups has been investigated. These afford nor-derivatives by loss of carbon monoxide, and carboxylic acids. Steric interactions have been shown to affect strongly the ratio between carboxylic acid and nor-derivatives and, in addition, to increase the autoxidation rate. For the first time, formation of formates from aldehydes by autoxidation conditions, has been demonstrated.

Very recently we have reported[1] that the autoxidation of the 4-axial diterpene aldehyde torulosal (**1a**) leads, to the acid **1b** and to nor-compounds **1c**, **1d**, **1e**, **1f** and **2**.

The presence of nor-compounds was explained in considering the formation of the tertiary radical at C_4 (**3**), through loss of carbon monoxide from **1g** which is the first step of autoxidation.[2] Subsequent reaction of **3** with atmospheric oxygen and abstraction of H· from a second aldehyde molecule then produces the hydroperoxides **1c** and **1d**. Reduction of **1c** and **1d** affords the alcohols **1e** and **1f** and dehydration of these latter leads to the olefins **2**.





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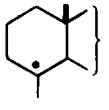


3

1a R = CHO R′ = CH_3
1b R = COOH R′ = CH_3
1c R = OOH R′ = CH_3
1d R = CH_3 R′ = OOH
1e R = OH R′ = CH_3
1f R = CH_3 R′ = OH
1g R = CO R′ = CH_3

Furthermore, we suggested the tertiary nature of the formyl group and the 1,3 diaxial interaction between this group and angular methyl group as main factors responsible for the behaviour of **1a**. The tertiary nature of the formyl group could favour the formation of the stable radical **3**, by loss of carbon monoxide from **1g**. Moreover, the 1,3 diaxial interaction between formyl and angular methyl group could be directly responsible for the loss of carbon monoxide. In fact, the formation of the planar radical **3** leads to a large steric relief of the molecule owing to the elimination of the above-mentioned interaction. In order to check the role played by such interaction we have now examined the autoxidation of a number of aldehydes having a tertiary formyl group: dehydroabietic aldehyde (**4a**), a diterpene 4-aldehyde having an equatorial formyl group; the conformationally mobile 1-methylcyclohexancarboxy-aldehyde (**9a**); the acyclic pivalaldehyde (trimethylacetaldehyde).

RESULTS

Dehydroabietic aldehyde (**4a**)† was found to be much more stable than torulosal (**1a**), when kept in contact with air without solvent.‡ Working up of autoxidation crude product after 24 hr led to the isolation of starting aldehyde **4a** (45%),§ of the related acid **4b** (20·4%) and of other several neutral compounds:¶ **4c** (1·8%), **4d** (9·6%), **6a** (4·5%), **4e** (1·2%), **6b** (0·6%) and **5**[1] (4·8%).

Nor-olefins **5**. Structure **5** was assigned on the basis of elemental composition, of spectroscopic characteristics and through gas-chromatographic comparison with the olefins from the oxidative decarboxylation[3] of dehydroabietic acid (**4b**).

Formate **4c**. The oily formate $[\alpha]_D + 27·9°$ was assigned structure **4c** on the basis both of elemental composition and of spectroscopic properties. In addition the alkaline hydrolisis of **4c** quantitatively led to the alcohol **4e**.

Nor-alcohols **6b** *and* **4e**. Both **6b** and **4e** were crystalline, m.p. 64–66°, $[\alpha]_D + 51°$ and m.p. 89–91°,

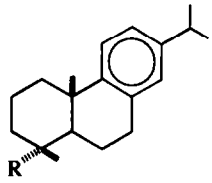
†Prepared from commercially available **4b**, by LAH reduction to **4f** and controlled Jones oxidation.

‡The autoxidation reactions were performed under the same experimental conditions as used for **1a**.

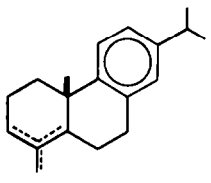
§All the yields are referred to the starting aldehydes.

¶In addition, a small amount (2·8%) of more polar compounds, which exhibited the characteristic absorptions (IR, UV) of aromatic ketones, was observed. This fraction therefore consists of a mixture of 7-oxo-compounds which however, was not further examined because of its complexity.

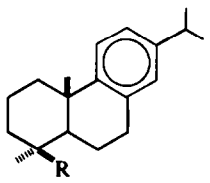
‖Actually, the olefins **5** were obtained, after chromatography, together with the unreacted starting aldehyde. The subsequent LAH reduction of the mixture allowed the separation of **5** from the dehydroabietinol (**4f**) formed.



4a R = CHO; **4e** R = OH
4b R = COOH; **4f** R = CH_2OH
4c R = OCHO; **4g** R = OOAc
4d R = OOH; **4h** R = OAc



5



6a R = OOH
6b R = OH
6c R = OOAc

$[\alpha]_D+45°$ respectively. Both were identified by comparison with authentic samples.[3,4]

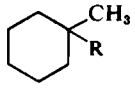
Hydroperoxides **6a** *and* **4d**. The crystalline hydroperoxide **6a** had m.p. 103–105°, $[\alpha]_D+77·7°$ while the oily one **4d** had $[\alpha]_D+14·5°$. The above structures, besides the elemental composition were based on chemical and spectroscopic properties. Both **6a** and **4d** were easily transformed by reduction into the corresponding alcohols **6b** and **4e**.*

Autoxidation of the aldehyde **9a** was carried out until its complete consumption (3 days) in order to prevent experimental difficulties depending on the presence of starting aldehyde among the autoxidation products.†

The crude autoxidation material, after removal of a polymeric, ether-insoluble fraction, readily afforded crystalline **9c**[8] (61·2%) m.p. 38–39° and a neutral fraction. The neutral components **9d** (0·7%), **9e** (7·1%), **9f** (9·1%) and **10** (1·1%) were identified by comparison (GLC, NMR) with authentic samples.[9–13]

The amount of hydroperoxide **9d** was directly determined by iodometric titration[14] of a portion of the neutral fraction. The remaining part was treated with excess $FeSO_4$, to reduce the hydroperoxide **9d** to alcohol **9e**, and then used to determine the olefins **10**, the formate **9f** and the alcohol **9e** separately.

The amount of **10** was determined on a portion by measuring the volume of hydrogen absorbed by the mixture when subjected to catalytic hydrogenation according to Brown.[15]



9

10

9a R = CHO
9b R = CH_2OH
9c R = COOH
9d R = OOH
9e R = OH
9f R = OCHO

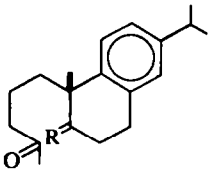
Chromatography of another portion allowed the separation of the crystalline alcohol **9e** m.p. 24–25° from the olefins **10** and from the formate **9f**. The weight of **9e** was then corrected for the quantity due to the previous reduction of the hydroperoxide **9d**.

Finally, formate **9f** was determined by treatment of a third portion with an excess of LAH, followed by chromatographic isolation of the alcohol **9e**. The increase in the weight of **9e** as compared with that previously determined gave the amount of **9f**.

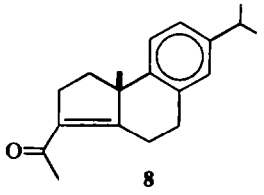
The autoxidation of volatile pivalaldehyde was carried out in a closed flask connected with a rubber balloon full of air. The autoxidation was found to be very slow: after seven days starting aldehyde was still present in 24% amount. NMR examination of the crude product showed peaks corresponding to trimethylacetic acid, t-butyl alcohol and t-butyl formate. The eventual presence of t-butyl hydroperoxide could not be demonstrated by NMR because of overlapping peaks. On the other hand, iodometric titration[14] of the mixture showed that oxidizing substances such as t-butyl hydroperoxide were present in less than 0·6% amount. Integration of the NMR spectrum of the mixture showed the three major products to be in a 7·5:1:1 ratio.‡

The identity of all the products was also confirmed by gas-chromatographic comparison with authentic samples. Furthermore, the mixture was reduced by LAH and the reduction product was

*Both **4d** and **6a** could be easily acetylated to give the related peresters. However, only the equatorial perester **4g** $[\alpha]_D-2·6°$ could be obtained as a pure compound. The axial perester **6c**, instead, spontaneously rearranged to the hydroxy-ketone **7a**. Structure **7a** was confirmed by transforming this latter into the α,β-unsatured ketone **8**.[1]



7a R = H, βOH
7b R = O



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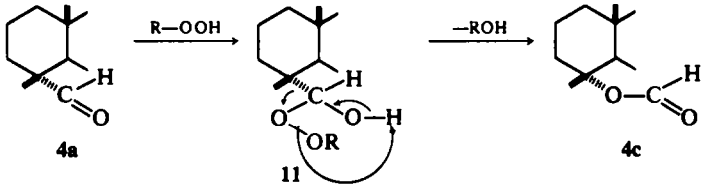
†The preparation of aldehyde **9a** has been reported.[5] Nevertheless, we found more convenient to prepare it from the alcohol **9b*** using dicyclohexylcarbodi-imide and dimethylsulphoxide.[7]

‡This value is not very accurate because of the partial overlapping of Me-signals.

found to consist of a mixture of neopentyl alcohol and t-butyl alcohol in a 5·4:1 ratio (NMR, GLC).

The autoxidation rates exhibited by the aldehydes considered in this paper, are generally lower than that of torulosal (**1a**). In addition, a main difference between the behaviour of torulosal (**1a**) and of aldehydes **4a**, **9a** and pivalaldehyde lies in the presence of formates (**4c**, **9f** and t-butyl formate) among the autoxidation products. The formation of formates is not common in the autoxidation reactions of aldehydes, and can be interpreted (Scheme 1) in a way similar to that suggested[16] for the formation of formates from aldehydes and hydrogen peroxide. The retention of configuration in the case of **4c** suggests a Baeyer-Villiger type mechanism which should lead to the formate, through the intermediate hydroxy-peroxide **11**. This view also accounts for the absence of formate among the autoxidation products of torulosal (**1a**). In fact, in this case initial attack of an R-OOH species, with the consequent tetrahedrization of the formylic carbon, appears to be much more hindered because of the axial position of formyl group.



SCHEME 1

All the results obtained have been summarized in Table 1, in which previously reported results[1] concerning the autoxidation of torulosal (**1a**) have been also included, with two significant percentages for each aldehyde. In the "normal" column the percentages of carboxylic acid and of formate (when present) were reported; in the "anomalous" column, we instead reported the percentages of all the products formed in the autoxidation process by loss of carbon monoxide (hydroperoxides, tertiary alcohols and olefins). Examination of these results shows that the "anamalous" behaviour of aldehydes in the autoxidation reaction should be considered rather general, at least for aldehydes having a tertiary formyl group. It is evident, however, that this behaviour is dramatically enhanced when conformationally rigid aldehydes, with the formyl group affected by marked steric interactions, are considered. Furthermore, in this case the autoxidation rate rapidly increases, thus accounting for the well known lability[1] of 4-axial diterpene aldehydes.

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 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 unless otherwise specified) were used for column chromatography. GLC was run on a Perkin Elmer 881 (FID) chromatograph.

Autoxidation of dehydroabietic aldehyde (**4a**). A hexane solution of pure **4a** (2·3 g) was evaporated in a 500 ml flask to give a thin crystalline layer, kept 24 hr at r.t. The crude autoxidation product was subsequntly dissolved in Et_2O and rapidly extracted with 2*N* Na_2CO_3 (3×50 ml). Acidification (12*N* H_2SO_4) of the combined alkaline layers gave dehydroabietic acid (**4b**) (470 mg) m.p. 180–181° (from benzene). The neutral fraction was then absorbed on alumina: the elution with benzene (130 ml) yielded a less polar fraction A (1·15 g) consisting of olefins **5** and unreacted **4a**, whereas the elution with absolute Et_2O yielded a complex mixture (499 mg) which, subsequently rechromatographed on silica-gel (15 g), afforded four fractions: **B** (50 mg; hexane-Et_2O 98:2; 85 ml) consisting of formate **4c**; **C** (324 mg; hexane-Et_2O 97:3; 300 ml) mainly consisting of hydroperoxides **4d** and **6a**; **D** (58 mg; hexane–Et_2O 8:2; 85 ml) consisting of alcohols **4e** and **6b**; **E** (55 mg; hexane–Et_2O 7:3; 120 ml) a complex mixture (TLC): ν_{max} 1685 cm^{-1}, λ_{max}^{EtOH} 253, 303 nm.

Nor-olefins **5**. Fraction A was reduced by $LiAlH_4$ and the crude product chromatographed on alumina (35 g).

Table 1*

aldehyde	"normal" carboxylic acid	"normal" formate	"anomalous"
torulosal (**1a**)	16·7	—	65·1
dehydroabietinal (**4a**)	37·1	3·3	37·6
1-methyl-cyclohexan carboxy-aldehyde (**9a**)	61·2	9·1	8·9
pivalaldehyde	78·9	10·6	10·6

*Yields are based on unrecovered aldehyde.

The elution with hexane (140 ml) gave the mixture of isomeric olefins **5** (112 mg): (Found: C 89·52; H 10·36. $C_{19}H_{26}$ requires: C 89·70; H 10·30%); MW 254 (MS) identical (GLC: 6′ × ¼″ glass column with 3% SE-30 on chromosorb G 80 ÷ 100 mesh) with the olefins from oxidative decarboxylation[3] of the acid **4b**. Subsequent elution with hexane–Et_2O 8:2 (350 ml) then gave dehydroabietinol (**4f**) $[\alpha]_D$ +53° (c 1·7) (1033 mg) identical with an authentic sample.

Formate **4c**. Rechromatography of fraction **B** on silica-gel (3 g) with hexane–Et_2O 98:2 (30 ml) gave the pure oily formate **4c** (39 mg): $[\alpha]_D$ +27·9° (c 1); MW 300 (MS); (Found: C 79·98; H 9·20. $C_{20}H_{28}O_2$ requires: C 79·95; H 9·39%); ν_{max} 1195 cm^{-1}; τ 2·00 (1H, s, —OCHO), 8·44 (3H, s, methyl at C_4). The hydrolisis of **4c** by 10% ethanolic KOH for 2 hr quantitatively afforded the corresponding alcohol **4e** m.p. 89–91°.

Hydroperoxides **6a** *and* **4d**. Fraction **C** was rechromatographed on silica-gel (10 g) with hexane–Et_2O (98:2). The first 200 ml eluted the crystalline axial hydroperoxide **6a** (104 mg) m.p. 103–105° (from hexane): $[\alpha]_D$ +77·7° (c 1·2); MW 288 (MS); (Found: C 79·18; H 9·63. $C_{19}H_{28}O_2$ requires: C 79·12; H 9·79%); ν_{max} 3500 cm^{-1}; τ 8·73 (3H, s, C_{20} methyl), 8·64 (3H, s, methyl at C_4). Further elution with 300 ml of the same solvent then gave oily equatorial hydroperoxide **4d** (220 mg): $[\alpha]_D$ +14·5° (c 2); MW 288 (MS); (Found: C 78·89; H 9·65. $C_{19}H_{28}O_2$ requires: C 79·12; H 9·79%); ν_{max} 3500 cm^{-1}; τ 8·81 (3H, s, C_{20} methyl), 8·84 (3H, s, methyl at C_4). The purity of both **6a** and **4d** was shown to be more than 98% by iodometric titration.[14] The pure **4d**, when treated with pyridine–acetic anhydride at r.t. overnight, gave the oily perester **4g**: $[\alpha]_D$ −2·6° (c 2).

Nor-alcohols **6b** *and* **4e**. Fraction **D** was absorbed on silica-gel (2 g) and elution with hexane–Et_2O (85:15 24 ml) afforded the crude **6b** whose purification by PLC gave the pure crystalline alcohol (14 mg) m.p. 64–66°, $[\alpha]_D$ +51° (c 1·8) identical with a specially prepared[4] sample. Subsequent elution with hexane–Et_2O (8:2) (20 ml) gave the crystalline alcohol **4e** (30 mg) m.p. 89–91° (from hexane), $[\alpha]_D$ +45° (c 1·9) identical with a sample coming, by alkaline hydrolysis, from the acetate **4h** obtained in the oxidative decarboxylation[3] of **4b**.

Reduction of the hydroperoxides **6a** *and* **4d**. The reduction of both **6a** and **4d**, to give respectively the alcohols **6b** and **4e**, was performed by either $LiAlH_4$ or $FeSO_4$. In the first way, solutions of either **6a** or **4d** in peroxides-free Et_2O were refluxed with an excess of reagent for 2 hr and the reaction mixtures then worked up in the usual way. In the second way, the above solutions were shaked with an excess of sat. $FeSO_4$ for 3 hr at r.t. In both ways, reductions were quite quantitative.

Acetylation of **6a**: *hydroxyketone* **7a**. The hydroperoxide **6a** was acetylated in the same conditions as **4d**. The crude product (70 mg showing an IR absorption at 1789 cm^{-1}) was absorbed on silica-gel and the elution with benzene–Et_2O (92:8) (25 ml) led to the oily hydroxyketone **7a** (38 mg): $[\alpha]_D$ +40·3° (c 1); MW 288 (MS); (Found: C 78·99; H 9·68. $C_{19}H_{28}O_2$ requires: C 79·12; H 9·79%); ν_{max} 1712 and a broad band at 3450–3550 cm^{-1}).

α,β-unsaturated ketone **8**. The hydroxyketone **7a** (57 mg), in acetone, was oxidized at 0° by Jones reagent. The usual work up quantititatively yielded the diketone **7b** which was directly dissolved in EtOH (1 ml), added of 5% K_2CO_3 (1 ml) and refluxed for 3 hr under N_2. Chromatography (silica-gel; benzene–Et_2O; 94:6) of the crude product afforded the pure oily **8** (29 mg): $[\alpha]_D$ +151·8° (c 1·3); MW 268 (MS); (Found: C 85·33; H 8·89. $C_{19}H_{24}O$ requires: C 85·02; H 9·01%); ν_{max} 1678 cm^{-1}; λ_{max}^{EtOH} 256 nm (ϵ 13570); τ 8·69 (3H, s, C_{20} methyl), 7·68 (3H, s, —$COCH_3$).

Preparation of the aldehyde **9a**. The alcohol **9b** (16 g), dissolved in anhydrous benzene (480 ml) and dimethyl sulfoxide (480 ml), was added of dicyclohexylcarbodi-imide (88·8 g), anhydrous pyridine (11·5 ml), trifluoroacetic acid (7·7 ml) and stirred at 70° for 3 hr under N_2. A white crystalline solid precipitated. The suspension, after cooling, was diluted with benzene (500 ml) and the solid filtered off. The clear solution was severally washed with water and the most of the solvent evaporated. Distillation of the oily residue under r.p. gave a main fraction boiling at 76°/15 mm Hg consisting of aldehyde **9a** (10 g): MW 126 (MS); (Found: C 76·02; H 11·31. $C_8H_{14}O$ requires: C 76·14; H 11·18%); ν_{max} 1720, 2650 cm^{-1}; τ 0·53 (1H, s, —CHO), 9·00 (3H, s, —CH_3).

Autoxidation of **9a**. The liquid aldehyde **9a** (8 g) was kept, without any solvent and with slow magnetic stirring, in a large flask until the aldehyde disappeared (NMR after 72 hr). The crude autoxidation product was then treated with Et_2O and 1350 mg of polymeric substances remained dissolved in the flask. The ethereal solution was rapidly extracted with 2*N* Na_2CO_3 and, after evaporation of the solvent under r.p., gave a neutral fraction (1680 mg). Acidification (12*N* H_2SO_4) of the alkaline layers then gave the crystalline acid **9c** (4·9 mg) m.p. 38–39° (subl.) compared with an authentic sample. the neutral fraction consisted of **9d**, **9e**, **9f** and **10** which were identical with authentic samples (NMR, GLC: 6′ × ¼″ glass column with 10% diethylene glycol succinate on chromosorb W HMDS 80 ÷ 100 mesh).

Hydroperoxide **9d**. Part of the neutral fraction (300 mg) dissolved in AcOH (4 ml) was added to a little sat $NaHCO_3$ and KI soln and shaken for few min in the dark; the iodine evolved was then titrated with 10^{-2}*N* $Na_2S_2O_4$ (15·2 ml) corresponding to 10 mg of **9d**. The dosages of the other neutral compounds were performed on a mixture in which the hydroperoxide **9d** had been pre-reduced by shaking the neutral fraction in Et_2O with sat $FeSO_4$ at r.t. for 1 hr.

Part of the above **9d**-free mixture (300 mg) dissolved in glacial CH_3COOH (3 ml) was hydrogenated in a Brown microhydrogenator using PtO_2 as catalyst. H_2 was absorbed (3·46 ml) corresponding to 15 mg of **10**. No presence of olefinic protons was detected (NMR) in the hydrogenated product. 300 mg of the above **9d**-free mixture were absorbed on neutral alumina (grade IV): elution with light petrol. (50 ml) gave a fraction (179 mg) consisting of olefins **10** and formate **9f**. Further elution with light petrol–Et_2O (95:5) (60 ml) afforded the alcohol **9e** (118 mg) m.p. 24–25° identical with an authentic sample. Deduction of the weight corresponding to the reduction of **9d** (= 10 mg) from the total, gave for **9e** a yield of 7·1%. In such conditions, pure samples of **9f** and **9e** were quantitatively recovered. Part of the **9d**-free mixture (200 mg) was reduced, by excess $LiAlH_4$, and the crude product absorbed on neutral alumina (grade IV). Light petrol–Et_2O (95:5) (30 ml) eluted the alcohol **9e** (166 mg). Deduction of both the weight due to the reduction of **9d** (= 6 mg) and that of the alcohol **9e** already present in the mixture (= 73 mg), gave for **9f** a yield of 9·1%.

Autoxidation of pivalaldehyde. Pure liquid pivalaldehyde (5 g) was kept, with slow magnetic stirring, in a flask connected with a rubber balloon full of air. After seven days, the NMR spectrum of the product showed unreacted aldehyde (24%) and peaks respectively

attributable to trimethyl-acetic acid (s, 8·79 τ), to t-butyl alcohol (s, 8·73 τ) and to t-butyl formate (s, 8·51 τ and s, 2·06 τ) in a 7·5:1:1 ratio. $LiAlH_4$ reduction of the mixture, followed by continuous extraction with Et_2O afforded a mixture (1:5·4) (NMR, GLC) of t-butyl and neopentyl alcohols. Part of the autoxidation mixture (1·5 g) was titrated as described for **9d**. The iodine evolved consumed $10^{-2}N$ $Na_2S_2O_4$ (20 ml) corresponding to 9 mg of t-butyl hydroperoxide.

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