Deoxidation studies with cyclopropylcarbinol

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The liquid products from the deoxidation with cyclopropylcarbinol in KOH–$CHBr_3$ were identified as cyclopropylcarbinyl, cyclobutyl, and allylcarbinyl alcohols, bromides, and the various ethers, with dicyclopropylcarbinyl ether as the most abundant product. In addition, small amounts of methylene bromide, cyclopropanecarboxaldehyde, and cyclobutanone were also found. The deoxidation with cyclopropylcarbinol-α-^{14}C gave rise to isotopically scrambled cyclopropylcarbinol-x-^{14}C, with about 22% of the ^{14}C-label rearranged from C-α to the cyclopropyl group.

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In a 1964 review on carbonium ions, Deno (1) briefly stated that deoxidation with cyclopropylcarbinol-α,α-d_2 (**1**-OH-α-d_2) gave principally 1,3-butadiene-1,1-d_2, indicating that no isotopic scrambling has occurred in the cyclopropylcarbinyl cation produced under the conditions of very short life expected for deoxidation. A more detailed analysis of the hydrocarbon products from the alkaline deoxidation of **1**-OK with bromoform was reported by Bayless *et al.* (2). Among the 11% yield of hydrocarbon products, 1,3-butadiene, bicyclobutane, cyclobutene, methylenecyclopropane, ethylene, and acetylene were found and their formation was attributed to processes involving highly energetic intramolecular cationic paths, such as carbon–hydrogen insertion, carbon-skeleton rearrangement, and fragmentation. In these earlier studies, the nature of the liquid products apparently has not been investigated. In the present work, the liquid products from deoxidation studies with **1**-OH were examined. The reaction was carried out in concentrated KOH (3, 4), since in this medium the presence of excess hydroxide ions may allow for the formation of rearranged alcohols such as cyclobutanol (**2**-OH) and allylcarbinol (**3**-OH). Moreover, Lee and Hahn (5) have found that the deoxidation with 2-phenyl-1-^{14}C-ethanol in KOH–$CHBr_3$ gave rise to some isotope position rearranged 2-phenyl-2-^{14}C-ethanol. Analogously, deoxidation studies with **1**-OH-α-^{14}C in KOH-$CHBr_3$ should be capable of yielding data on the extents of isotopic scrambling, if any, in the recovered **1**-OH-x-^{14}C.

The liquid products from the deoxidation with **1**-OH using a **1**-OH:$CHBr_3$ molar ratio of 1.0:0.5 or 1.0:1.0 are given in Table 1. The identifications of the various products were based on peak enhancement in the vapor phase chromatogram utilizing authentic samples and by examination of their n.m.r. spectra (the spectra of some of the authentic compounds, namely, the isomeric bromides, **1**-Br, **2**-Br, and **3**-Br, and the isometric ethers, **1**-O1, **1**-O2, and **1**-O3 are shown in Fig. 1). The **1**-OH-α-^{14}C (6) was subjected to a similar deoxidation using an equimolar amount of $CHBr_3$ and the recovered **1**-OH-x-^{14}C was degraded by oxidation to cyclopropanecarboxylic acid, followed by conversion to cyclopropylamine (6). The resulting activity data, showing the extents of isotopic scrambling from C-α to the cyclopropyl group, are summarized in Table 2.

The results in Tables 1 and 2 demonstrate that cationic processes do play important roles in deoxidation reactions. As originally suggested by Skell and Starer (7, 8), highly energetic carbonium ions may be formed via intermediate carbenes, eq. 1. In the cyclopropylcarbinyl

$$[1]\quad RO^- + CBr_2 \xrightarrow{-Br^-} ROCBr \rightarrow R^+ + CO + Br^-$$

system, interconversions between cyclopropylcarbinyl, cyclobutyl, and allylcarbinyl cations are well known (6, 9), and reactions between these ions and the available nucleophiles (OH^-, Br^-, and the various RO^-) would account for

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TABLE 1

Liquid products from deoxidation with cyclopropylcarbinol (1-OH)

Products*	Composition (%)† Experiment 1‡	Experiment 2‡
Two unidentified peaks	1.1	2.0
Allylcarbinyl bromide§	0.5	0.9
Cyclobutyl bromide§	1.5	5.2
Cyclopropylcarbinyl bromide§	0.1	0.2
Diallylcarbinyl ether‖	0.2	0.4
Allylcarbinyl cyclobutyl ether‖	0.2	0.2
Methylene bromide	0.4	0.9
Allylcarbinyl cyclopropylcarbinyl ether	1.6	2.5
Dicyclobutyl ether‖	0.1	0.3
Cyclobutyl cyclopropylcarbinyl ether¶	7.1	10.8
Allylcarbinol	0.3	0.8
Dicyclopropylcarbinyl ether	34.7	34.2
Cyclobutanol	0.6	4.3
Cyclopropylcarbinol	51.4	37.4

*Listed in the order of increasing retention times which ranged from 16 to 172 min under the conditions used for the v.p.c. analyses by the analytical column.

†Based on the relative areas of the various peaks in the v.p.c.

‡Experiments 1 and 2 were carried out using 1-OH:$CHBr_3$ molar ratios of 1.0:0.5 and 1.0:1.0, respectively.

§The actual amounts of these isomeric bromides formed in the deoxidation reaction may be different from the composition shown because 1-Br was found to undergo some rearrangement to 2-Br and 3-Br in the v.p.c. column under the conditions employed (see preparation for 1-Br in the Experimental section).

‖Authentic samples of these ethers were not synthesized and their tentative identifications were based on their n.m.r. spectra.

¶Containing small quantities of cyclobutanone and cyclopropanecarboxaldehyde, which amounted to about 0.1 and 0.2% respectively, in experiment 2.

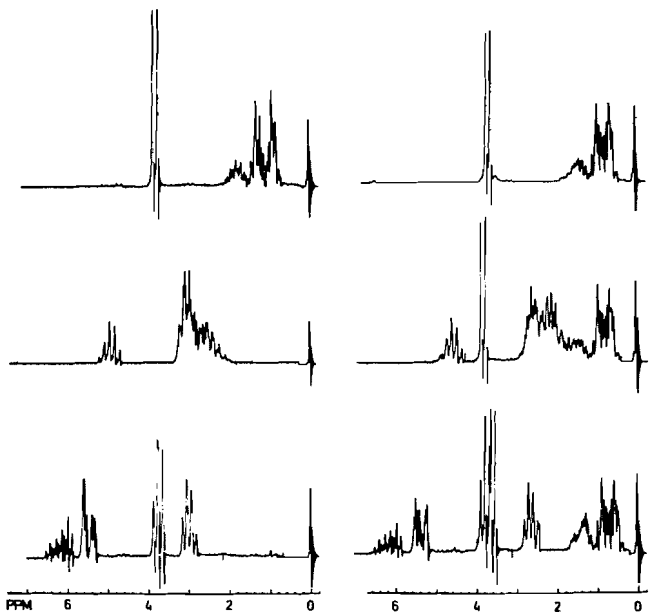

FIG. 1. The n.m.r. spectra. Left column, top to bottom, respectively, are the spectra of cyclopropylcarbinyl, cyclobutyl, and allylcarbinyl bromides; right column, top to bottom, respectively, are the spectra of dicyclopropylcarbinyl, cyclobutyl cyclopropylcarbinyl, and allylcarbinyl cyclopropylcarbinyl ethers.

TABLE 2

Activity data and isotopic scrambling in the recovered cyclopropylcarbinol-x-^{14}C from deoxidation with cyclopropylcarbinol-α-^{14}C

Compound assayed	Specific activity* (c.p.min/mmole)		Rearrangement (%)	
	Run 1	Run 2	Run 1	Run 2
c-C_3H_5COOH†	120 500	102 300		
c-$C_3H_5NH_2$‡	25 900	23 300	21.5	22.8

*Determined by a liquid scintillation counter, with appropriate corrections for quenching.
†Assayed as *N*-phenylcyclopropanecarboxamide.
‡Assayed as *N*-cyclopropylbenzamide.

most of the products given in Table 1. However, the possibility that some of these products might also have been derived from concerted displacements involving the nucleophiles and the alkoxybromocarbene, ROCBr, could not be excluded. Moreover, as the **1**-OH was converted to **2**-OH and **3**-OH, these rearranged alcohols likely could themselves undergo deoxidation reactions and contribute to the overall product distribution. Since *c*-$C_3H_5CH_2O^-$ would be the most abundant nucleophile present in the reaction mixture, it is not surprising that, aside from the recovered **1**-OH, the product obtained in the highest yield was dicyclopropylcarbinyl ether (**1**-O**1**) (Table 1).

It is of interest to note that CH_2Br_2 was found among the reaction products (Table 1). The formation of this compound could be attributed to hydride abstraction by dibromocarbene; for example, a process involving *c*-$C_3H_5CH_2O^-$ would give rise to cyclopropanecarboxaldehyde, eqs. 2*a* and *b*. Similarly, if cyclobutoxide were

[2*a*] $$c\text{-}C_3H_5CH_2O^- + CBr_2 \rightarrow c\text{-}C_3H_5CHO + CHBr_2^-$$

[2*b*] $$CHBr_2^- + H_2O \text{ or } ROH \rightarrow CH_2Br_2 + HO^- \text{ or } RO^-$$

involved, cyclobutanone would be produced. Actually, both cyclopropanecarboxaldehyde and cyclobutanone were detected among the products in the present study. Starer (10) has also noted the formation of CH_2Br_2 and CH_3CH_2CHO in the deoxidation of 1-propoxide and has suggested the possibility of hydride abstraction.

From Table 2, it is seen that, unlike the reported absence of isotopic scrambling in the gaseous 1,3-butadiene product (1), the **1**-OH-x-^{14}C recovered from the deoxidation with **1**-OH-α-^{14}C under the present conditions showed about 22% rearrangement of the ^{14}C-label from C-α to the cyclopropyl group, presumably to the C-2 and -3 methylene carbons of the ring. A thorough study of the stereochemistry of such cyclopropylcarbinyl to cyclopropylcarbinyl rearrangements has recently been reported by Wiberg and Szeimies (11). From the present work it is seen that as in the deamination of **1**-NH_2-α-^{14}C (6), the three methylene carbons in the recovered **1**-OH-x-^{14}C have not attained complete equivalence. Some of the excess ^{14}C at C-α undoubtedly was due to unreacted **1**-OH-α-^{14}C. Another possibility that might have contributed to more ^{14}C at C-α would be a concerted displacement by OH^- on *c*-C_3H_5-$^{14}CH_2OCBr$ to produce unrearranged **1**-OH-α-^{14}C. Thus the present ^{14}C-scrambling results once again suggest that both deoxidation and deamination reactions may involve similar, though not necessarily identical, rearrangement processes; such a conclusion was also arrived at in a comparison of the deoxidation and deamination reactions with the 1-^{14}C-1-propyl system (12).[2]

Experimental

*Preparation of Cyclopropylcarbinyl, Cyclobutyl, and Allylcarbinyl Bromides (**1**-Br, **2**-Br, and **3**-Br)*

Compounds **1**-Br and **2**-Br were prepared by the reaction of triphenylphosphine with the corresponding alcohol and carbon tetrabromide in anhydrous ether (13–15). The yields obtained for **1**-Br and **2**-Br, both boiling within the range of 109–113° (lit. (9) b.p. of a 2:1 mixture of **1**-Br and **2**-Br, 110.5–112.0°), were 90 and 50%, respectively. Initially v.p.c. analysis of the **1**-Br

[2]For a recent review on "free carbonium ions" generated from the decomposition of diazonium ions, deoxidation and anodic oxidation of carboxylic acids, see Keating and Skell (17).

using an Aerograph 200 chromatograph with flame ionization detector with a 25 ft 1/8 in. copper column packed with 25% β,β′-oxidipropionitrile on 60/80 mesh Chromatosorb P, AW, operating at a column temperature of 85° and N_2 carrier gas flow rate of 35 ml/min, showed the appearance of varying amounts of **2**-Br and **3**-Br. (The above v.p.c. column operated under the conditions described will be referred to as the analytical column.) However, it was later found that the use of a 10 ft 1/8 in. stainless steel column packed with 25% FFAP indicated that both the **1**-Br and **2**-Br obtained in these preparations were essentially pure (less than 2% impurities), suggesting that the **1**-Br could undergo some rearrangement, presumably on the copper walls of the column, during v.p.c. analysis with the analytical column.

Compound **3**-Br was prepared by the reaction of **3**-OH with PBr_3 in CH_2Cl_2 as described by Roberts and Mazur (9) for the reaction of **1**-OH with PBr_3. Fractionation gave a 60% yield of crude product, b.p. 102–110°, the v.p.c. analysis of which (FFAP stainless steel column) showed the presence of about 10% impurities. The final purification was effected by preparative v.p.c. using a Model 15 Pye chromatograph with a 15 ft 3/8 in. copper column packed with 25% β,β′-oxidipropionitrile on 60/80 mesh Chromosorb P, AW, operating at a column temperature of 90° and N_2 carrier gas flow rate of 75 ml/min. (This column operated under the conditions described will be referred to as the preparative column.) The b.p. of the purified **3**-Br was 97° at 717 mm (literature (9), b.p. 99–100°). The n.m.r. spectra of **1**-Br, **2**-Br, and **3**-Br are shown in Fig. 1.

Preparation of Dicyclopropylcarbinyl, Cyclobutyl Cyclopropylcarbinyl, and Allylcarbinyl Cyclopropylcarbinyl Ethers (1–O1, 1–O2 and 1–O3)

These ethers were prepared by the reaction of **1**-Br with the corresponding sodium alkoxide, **1**-ONa, **2**-ONa, or **3**-ONa. In the preparation of **1-O1**, 5.0 g (0.07 mole) of **1**-OH in 100 ml of anhydrous ether was stirred with an equivalent amount of Na to give the alkoxide and then 9.4 g (0.07 mole) of **1**-Br was added. After the mixture was refluxed for 5 h, apparently a fair amount of unreacted material was still present. In an attempt to raise the reaction temperature, 40 ml of acetone was introduced and the reaction mixture was refluxed for a further 5 h. More ether was then added and the resulting material was washed with water and dried over $MgSO_4$. Fractional distillation gave 4.1 g of crude product, b.p. 140–150°, the v.p.c. analysis of which showed the presence of about 20% impurities. Pure **1-O1**, b.p. 148–149°, was obtained after separation by v.p.c. using the preparative column.

Both preparations of **1-O2** and **1-O3** were then carried out simultaneously and in these cases the acetone was introduced at the beginning of the reaction. The use of acetone as a means of raising the reaction temperature turned out to be an error, and the major product obtained in these reactions was mesityl oxide from the condensation of acetone. However, in each preparation, a small fraction, b.p. 138–148°, (1–2 g) was obtained and it contained the desired ether. Pure **1-O2** or **1-O3** was separated from these crude fractions by v.p.c. using the preparative column. The n.m.r. spectra of **1-O1**, **1-O2** and **1-O3** are shown in Fig. 1.

Deoxidation with 1-OH

The reaction was carried out under conditions similar to those used by Lee and Hahn (5). Compound **1**-OH (2.0 g, 0.028 mole) was refluxed for 1 h on an oil bath with a concentrated KOH solution (15 g KOH in 6.0 ml H_2O). This mixture was cooled to about 100° and 3.53 or 7.06 g (0.014 or 0.028 mole) of $CHBr_3$ was added in one batch. After the initial vigorous reaction had subsided, the mixture was refluxed for 1 h. Water (60 ml) was then added and the resulting material was continuously extracted with ether for 24 h. The extract was dried over $MgSO_4$, concentrated, and subjected to v.p.c. analysis using the analytical column.

In order to identify the minor components, the products from six runs as described above were combined and then separated by v.p.c., using the preparative column, into various fractions, each containing one or more components. The n.m.r. spectra of each of these fractions were examined and each fraction was also analyzed by the analytical column, with identifications made by peak enhancement using known compounds. As it turned out with the analytical column, cyclobutanone (Aldrich) and cyclopropanecarboxaldehyde (prepared by reaction of *c*-C_3H_5CN with $LiAlH_4$ (16)) have the same retention time as cyclobutyl cyclopropylcarbinyl ether (**1-O2**). However, with a 25 ft 1/8 in. column packed with 20% bis-2-(2-methoxyethoxy)ethyl ether on 60/80 mesh firebrick, these three products were resolved into their individual components.

Deoxidation with 1-OH-α-^{14}C

Compound **1**-OH-α-^{14}C was prepared as described by Mazur *et al.* (6) and it was subjected to deoxidation using an equivalent amount of $CHBr_3$ as in the deoxidation with **1**-OH. The resulting **1**-OH-x-^{14}C was recovered from the reaction mixture with the aid of inactive **1**-OH as carrier. After purification by preparative v.p.c. it was degraded by oxidation to cyclopropanecarboxylic acid, followed by conversion to cyclopropylamine via the Schmidt reaction as previously described (6).

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Synthesis of vitamin K_1 analogs. A new class of vitamin K_1 antagonists

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The synthesis of two analogs of vitamin K_1, namely, 2-chloro (**2**) and 2-bromo (**3**) analogs, is described. The separation of *cis* and *trans* isomers of both these compounds on preparative t.l.c. is reported along with the spectral data.

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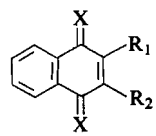
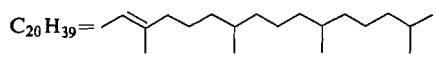
With the object of synthesizing vitamin K_1, **1**, analogs of potential biological interest, and of investigating the influence of substituents in position 2 of the naphthoquinone nucleus on biological activity, the synthesis of 2-chloro and 2-bromo analogs of vitamin K_1 was undertaken. These two analogs of vitamin K_1 were found to constitute a new class of vitamin K_1 antagonists, the chloro analog having been shown to be the most active one (1–3). In this communication, we now report the synthesis and characterization of these two analogs of vitamin K_1, namely, 2-chloro-3-phytyl-1,4-naphthoquinone (**2**) and 2-bromo-3-phytyl-1,4-naphthoquinone (**3**).

The synthesis was carried out essentially according to the published procedures (4–8) with some modifications. We have used activated manganese dioxide as the oxidizing agent in the final oxidation step, *i.e.*, in the oxidation of 2-halo-3-phytyl-1,4-naphthohydroquinone to 2-halo-3-phytyl-1,4-naphthoquinone (*vide* Experimental). We were also able to separate the *cis* and *trans* isomers (9, 10) of both the synthetic chloro and bromo analogs by means of t.l.c. on silica gel. Both the isomers of the chloro and bromo analogs were further characterized by n.m.r. spectroscopy (11).



1 X = O; R_1 = CH_3; R_2 = $C_{20}H_{39}$
2 X = O; R_1 = Cl; R_2 = $C_{20}H_{39}$
3 X = O; R_1 = Br; R_2 = $C_{20}H_{39}$



Experimental

Experiments were carried out in the dark and under nitrogen. The i.r. spectra were recorded on a Perkin–Elmer model 257 spectrophotometer. The u.v. spectra were taken in ethanol on a Beckman DB-G recording spectrophotometer. The n.m.r. spectra were recorded on Varian A-60 spectrometer with tetramethylsilane as an

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