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# Formation of a Novel Norcamphor upon Treatment of 2-Hydroxy-4-isopentyl-4-methylcyclopentanone with Acid

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Treatment of 2-hydroxy-4-isopentyl-4-methylcyclopentanone (1) with polyphosphoric acid or 85% phosphoric acid can lead to 1-isopropyl-4-methylnorcamphor (2), as well as the previously reported 1,4,4-trimethylbicyclo[3.2.1]-octan-6-one (3). An alternative preparation of 2 from 4-methylnorcamphor (4) is described, and formation of 2 from 1 is rationalized in terms of intermediates 14–18. The series of rearrangements suggested includes a 1,5-hydride shift, an intramolecular Prins reaction, and a pinacol rearrangement.

In this report we describe the acid-catalyzed dehydration and rearrangement of acyloin 1 to 1-isopropyl-4-methylnorcamphor (2). Some years ago we observed that treatment of 1 with polyphosphoric acid first at room temperature and then overnight at 100 °C led to 58% of 3 as the only volatile product.[1] In repeating this preparation we have confirmed the earlier observation but also found that treatment of 1 with polyphosphoric acid at room temperature only or at 100 °C for a shorter time yields 2 as well as 3. Both ketones are also formed from 1 in hot 85% phosphoric acid. Separate experiments have shown that 2 is destroyed much faster than 3 by hot acid and that the ketones are not interconvertible under the reaction conditions. Below we give evidence supporting structure 2, report an independent synthesis of this ketone, and comment on the mechanism of this exceptional transformation.

This new compound is isomeric with ketone 3, has an odor reminiscent of menthone, and has spectroscopic characteristics consistent with its formulation as an isopropyl- and methyl-substituted norcamphor. These included ir carbonyl absorption at 1744 $cm^{-1}$, a $^1H$ NMR spectrum containing a singlet methyl signal as well as absorption attributable to an isopropyl substituent with magnetically nonequivalent methyl groups, and a $^{13}C$ NMR spectrum compatible with the published spectra of methylnorcamphors,[2,3] particularly that of 4-methylnorcamphor (4).[3] There have been extensive investigations of the photochemistry of norcamphors,[4] and on previous occasions we have found that ultraviolet irradiation provided a convenient and informative degradation of novel bridged-ring ketones.[5] For these reasons we sought definitive structural information in photolysis of the new compound.

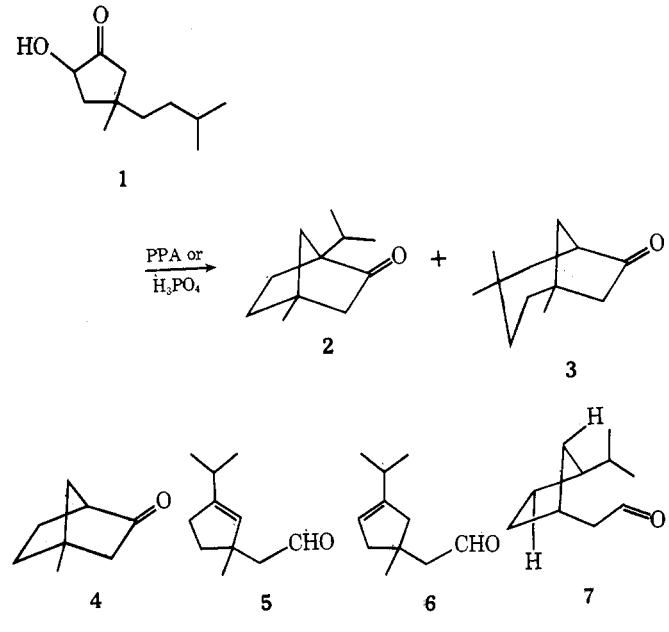
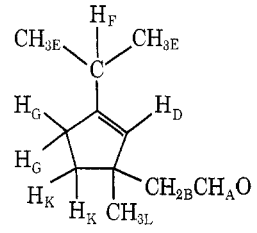
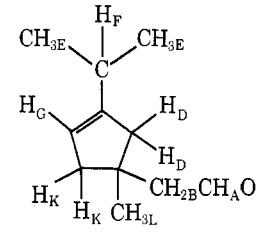


Table I. NMR Spectra of Aldehydes 5 and 6



5

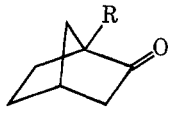


6

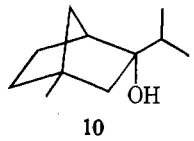
| Signal, δ | |
|---|---|
| Major isomer | Minor isomer |
| 1.02 (d, $J$ = 7 Hz, 6 H, $H_E$) | 0.98 (d, $J$ = 6 Hz, 6 H, $H_E$) |
| 1.15 (s, 3 H, $H_L$) | 1.15 (s, 3 H, $H_L$) |
| 1.43–1.94 (m, 2 H, $H_K$) | |
| 2.00–2.57 (m, $H_F$, $H_G$) } 5 H | 1.83–2.57 (m, $H_D$, $H_F$, $H_K$) } 7 H |
| 2.29 (d, $J$ = 1.5 Hz, $H_B$) } | 2.32 (d, $J$ = 1.5 Hz, $H_B$) } |
| 5.17 (m, 1 H, $H_D$) | 5.13 (m, 1 H, $H_G$) |
| 9.67 (t, $J$ = 1.5 Hz, 1 H, $H_A$) | 9.68 (t, $J$ = 1.5 Hz, 1 H, $H_A$) |

Photochemical isomerization in benzene–methanol (λ >2800 Å) led to two products in the ratio 2:1. From spectroscopic evidence, particularly the NMR data presented in Table I, these appeared to be the unsaturated aldehydes **5** and **6**. The two aldehydes may be readily distinguished from each other since 6 has five allylic hydrogens while compound **5** has only three. One of the spectra then should have an upfield signal for the two nonallylic hydrogens. The unique signal at 1.43–1.94 ppm in the spectrum of the major photoproduct thus indicates that this is **5**. These aldehydes are accounted for most simply as products of two alternative transfers of hydrogen possible from biradical **7**, the intermediate expected on photochemical α-cleavage of ketone **2**.[6]

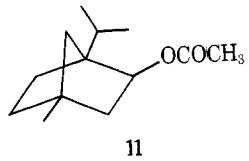
We verified these assignments of structure to **2**, **5**, and **6** by independent synthesis of **2** from 4-methylnorcamphor (**4**).[3] Treatment of **4** with isopropylmagnesium bromide gave a crude tertiary alcohol **10**, which underwent rearrangement in acetic acid containing *p*-toluenesulfonic acid to form **11**. This



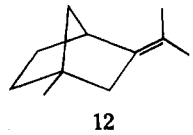
**8**, R = H
**9**, R = $CH_3$
**13**, R = $CH(CH_3)_2$



**10**



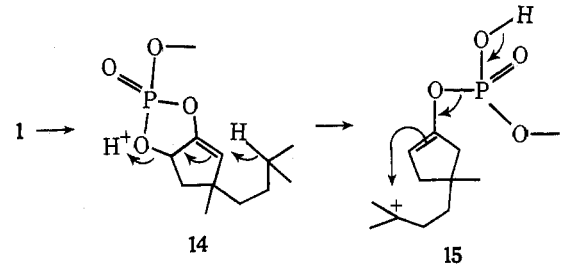
**11**



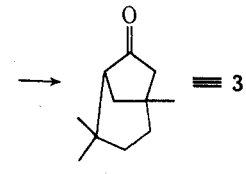
**12**

Wagner–Meerwein rearrangement has been used frequently for preparation of other 1-substituted 2-norbornyl alcohols and esters.[7,8] In the present case rearrangement competes with a large amount of simple dehydration, which yields **12**. Conversion of **11** to the corresponding alcohol using lithium aluminum hydride and subsequent oxidation then gave authentic **2**, identical in all respects with the ketone obtained from acyloin **1**. It was convenient to work out conditions for the conversion of **4** into **2** using norcamphor (**8**) as a model, and this led to 1-isopropylnorcamphor (**13**).

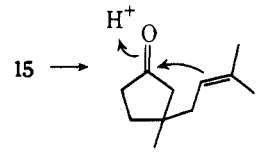
The unanticipated formation of **2** from **1** can be explained by the following series of rearrangements. Hydride transfer from side chain to ring in the protonated enol of **1** or related enol phosphate **14** leads to carbonium ion **15**. We have previously suggested this hydride shift and the subsequent cyclization of **15** as shown in accounting for formation of **3**.[1] If, instead of this cyclization, **15** undergoes ketonization and proton loss, the product is unsaturated cyclopentanone **16**. This could then undergo ring closure to **17** in an intramolecular Prins reaction. Hydride shift, or the equivalent deprotonation–reprotonation, gives the tertiary 2-norbornyl ion **18**,



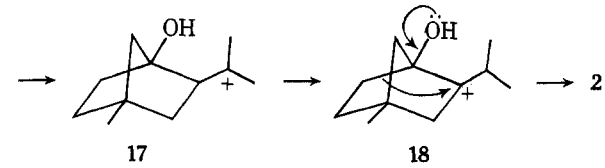
**14** **15**



**3**



**16**



**17** **18**

from which a simple pinacol rearrangement furnishes the required substituted norcamphor **2**.

While the combined yield of **2** and **3** at 100 °C is ~60% in both cases, the ratio of **2** to **3** is ~1:4 in polyphosphoric acid but rises to ~3:4 in 85% phosphoric acid. In terms of the mechanistic scheme outlined above this ratio depends on the fate of **15**. It is reasonable that the conversion of **15** to **16** would be favored by the availability of water in the reaction medium, and this effect would suffice to account for our observation.

The acyloin **1** thus undergoes transformations in which the originally unactivated isopentyl side chain becomes involved

in cyclizations leading both to a bicyclo[3.2.1]octan-6-one (3) and to a bicyclo[2.2.1]heptan-2-one (2) on exposure to phosphoric or polyphosphoric acid. While good precedents exist for the suggested individual steps,[9] the overall transformation of 1 into 2 and 3 remains unusual and noteworthy.

## Experimental Section

**Materials and Equipment.** These have been previously described.[5] The VPC columns used in the present work were A, 25% QF-1, 25 ft × 0.25 in.; B, 25% DEGS, 15 ft × 0.25 in.; C, 25% QF-1, 10 ft × 0.25 in. The $^{13}C$ spectrum was obtained in $C_6D_6$ at 22.63 MHz on a Bruker HX-90 spectrometer modified for pulse operation with broad band proton decoupling and benzene as internal reference.

**Formation of 1-Isopropyl-4-methylnorcamphor (2) from Acyloin 1.** A mixture of polyphosphoric acid (9.0 g) and acyloin 1 (111 mg) were mixed thoroughly with a spatula and allowed to stand at room temperature for 7 h. The mixture was dissolved in water and the products were extracted into ether which was washed with aqueous $NaHCO_3$ and brine and dried over $MgSO_4$. Removal of solvent and bulb-to-bulb distillation (140 °C, 8 mm) gave 83.4 mg of a colorless oil (83%). Analytical VPC on column A indicated the presence of three compounds in the ratio of 3:12:1. Preparative VPC on column A yielded **2:** ir 2948 (s), 2860 (m), 1744 (s), 1468 (w), 1450 (m), 1405 (w), 1382 (w), 1377 (w), 1366 (w), 1322 (w), 1178 (w) $cm^{-1}$; $^1H$ NMR (220 MHz) $\delta$ 0.907 (d, $J$ = 7 Hz, 3 H), 0.939 (d, $J$ = 7 Hz, 3 H), 1.24 (s, 3 H), 1.27–1.70 (m, 5 H), 1.70–2.05 (m, 4 H); $^{13}C$ NMR $\delta$ 215.7, 63.2, 52.7, 44.9, 40.8, 35.3, 28.3, 27.3, 21.1, 19.4, 18.8; mass spectrum $m/e$ 166.1351 ($M^+$, calcd for $C_{11}H_{18}O$, 166.1357).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.92. Found: C, 79.34; H, 10.86.

The second and third components were identified as **3**[1] and the simple dehydration product 4-isopentyl-4-methylcyclopent-2-enone[1] by comparison of ir and NMR spectra with those of authentic samples.

Treatment of the acyloin (148 mg) with 85% phosphoric acid for 1 h at 100 °C gave a 63% yield of the same three compounds in the ratio of 6:8:1.

**Photolysis of 4-Methyl-1-isopropylnorcamphor (2).** A104-mg sample of **2** in 50 ml of benzene containing 1.5 ml of methanol was degassed for 25 min with $N_2$ and then irradiated through Pyrex for 6 h. Usual workup[5] and preparative VPC on column B gave, in order of elution, 3-isopropyl-1-methylcyclopent-2-en-1-acetaldehyde (**5**) and 3-isopropyl-1-methylcyclopent-3-en-1-acetaldehyde (**6**) in the ratio 2:1. Characterization data are given in Table I and below. For **5:** ir 2955 (s), 2860 (m), 2720 (w), 1725 (s), 1645 (w), 1460 (m), 840 $cm^{-1}$ (w); mass spectrum $m/e$ 151.1126 [$(M - CH_3)^+$, calcd for $C_{10}H_{15}O$, 151.1123], 123.1155 [$(M - C_2H_3O)^+$, calcd for $C_9H_{15}$, 123.1174].

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.92. Found: C, 79.51; H, 10.83.

Characterization data for **6:** ir 2955 (s), 2925 (m), 2860 (m), 2835 (m), 2725 (w), 1725 (s), 1638 (w), 1455 $cm^{-1}$ (w); mass spectrum $m/e$ 151.1105 [$(M - CH_3)^+$, calcd for $C_{10}H_{15}O$, 151.1123], 123.1138 [$(M - C_2H_3O)^+$, calcd for $C_9H_{15}$, 123.1174].

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.92. Found: C, 79.58; H, 10.97.

**Synthesis of 1-Isopropyl-4-methylnorcamphor (2) from 4-Methylnorcamphor (4).** A 429-mg sample of **4**[3] (mp 47.5–49 °C) was treated with isopropylmagnesium bromide in refluxing ether in the usual manner and worked up by pouring into cold aqueous $NH_4Cl$ followed by ether extraction. The crude product alcohol **10** showed ir absorption at 3610 (w), 3470 (br w), 2940 (s), 2860 (s), 1455 (m), and 1470 $cm^{-1}$ (m), and NMR (60 MHz) absorption at $\delta$ 0.87 (d, $J$ = 6 Hz) and 1.06 (s). This material was treated directly with 7.5 ml of acetic acid containing 10 drops of acetic anhydride and 300 mg of $p$-toluenesulfonic acid at 40 °C for 3 days.[8] After cooling the mixture was treated with ice and aqueous $NaHCO_3$, and the products were extracted into ether–pentane. The organic extracts were washed with water, aqueous $NaHCO_3$, and brine and then dried. Removal of solvent and bulb-to-bulb distillation yielded a volatile product mixture which from analysis on column B was largely **12** and **11** in the approximate ratio 7:1. Preparative VPC gave samples of each which were characterized as follows. For **11:** ir 2950 (s), 2860 (m), 1730 (s), 1453 (w), 1370 (w), 1265 (m), 1240 (s), 1020 $cm^{-1}$ (m); NMR $\delta$ 0.3–1.50 with d, $J$ = 6.5 Hz, at 0.77 and 0.88, and s at 1.10 (m, 16 H), 1.50–2.23 with s at 1.96 (m, 5 H), 4.65 (m, 1 H). For **12:** ir 2945 (s), 2920 (s), 2860 (s), 2830 (w), 1455 $cm^{-1}$ (m); NMR $\delta$ 0.83–1.72 with s at 1.17, 1.47, and 1.58 (m, 15 ), 1.82 (br, 2 H), 2.77 (br, 1 H).

Anal. Calcd for $C_{11}H_{18}$: C, 87.92; H, 12.08. Found: C, 88.01; H, 12.21.

A 15-mg sample of acetate **12** was reduced with $LiAlH_4$ in 25 ml of ether first at 0 °C and then at room temperature. After destruction of excess hydride with saturated aqueous $Na_2SO_4$ the ether solution was dried over $Na_2SO_4$. The solvent was removed and the remaining crude 1-isopropyl-4-methyl-2-norbornanol was oxidized in 5 ml of acetone with 5 drops of Jones reagent[10] at 10–15 °C for 45 min. Excess reagent was destroyed with 2-propanol, and the reaction mixture was worked up with water and pentane. After removal of pentane the product was purified on column B (essentially one peak) to give 8.8 mg of 1-isopropyl-4-methylnorcamphor (**2**). Retention time as well as ir and NMR spectra of this sample were virtually identical with those of **2** described above.

**Synthesis of 1-Isopropylnorcamphor (13) from Norcamphor (8).** The sequence of reactions described for conversion of **4** into **2** was initially developed using norcamphor (**8**). This led through the analogous intermediate alcohols and ester and yielded 1-isopropylnorcamphor (**13**). An analytical sample was obtained from column B: ir 2900 (s), 2865 (m), 1745 (s), 1470 (w), 1455 (w), 1408 (w), 1380 (w), 1365 (w), 1292 $cm^{-1}$ (w); NMR $\delta$ 0.91 and 0.94 (2 d, $J_1 = J_2$ = 7 Hz, 6 H), 1.13–2.33 (m, 9 H), 2.50 (br, 1 H); mass spectrum $m/e$ 152.1201 ($M^+$, calcd for $C_{10}H_{16}O$, 152.1200).

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**Registry No.**—**1**, 33315-86-5; **2**, 59247-54-0; **4**, 49664-72-4; **5**, 59247-55-1; **6**, 59247-56-2; **8**, 497-38-1; **10**, 59247-57-3; **11**, 59247-58-4; **12**, 59247-59-5; **13**, 59247-60-8; isopropyl bromide, 75-26-3; 1-isopropyl-4-methyl-2-norbornanol, 59247-61-9.

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(5) For earlier examples, see S. Wolff and W. C. Agosta, *J. Org. Chem.*, **38**, 1694 (1973); W. C. Agosta and S. Wolff, *J. Am. Chem. Soc.*, **98**, 4182 (1976); and ref. 1.
(6) It is significant that both **5** and **6** are formed on irradiation of **2**, since photolysis of norcamphor (**8**) and 1-methylnorcamphor (**9**) yields in each case *only* the $\Delta^2$ aldehyde corresponding to **5**, which results from hydrogen transfer from C(7). (For details and references, see ref 4.) We are currently investigating whether the transfer of hydrogen from both C(6) and C(7) in **7** is attributable to the bulky isopropyl group at C(1) or the methyl substituent at C(4).
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