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Stereochemical Studies of Monoterpene Compounds. XII.[1] The Acid-Catalyzed Rearrangements of 2*α*-Bromo-10*β*-pinan-3-one

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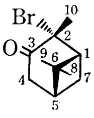
In connection with the bromination of 3-acetoxy-pin-2-ene (II), the acid-catalyzed rearrangement of 2α-bromo-10β-pinan-3-one (I) was investigated under several conditions. The bromoketone (I) was thus found to yield (+)-6-*endo*-bromocamphor (III), (−)-α-carvone (V), (−)-8-hydroxycarvotanacetone (VI), carvacrol (VII), (+)-dihydro-β-campholenolactone (VIII), and (+)-campholenic acid (IX). It also became clear that the bromocamphor (III) and the (V), (VI), and (VII) products are directly formed from the bromoketone (I), whereas the γ-lactone (VIII) is obtained *via* α-campholenic acid (IX) from the bromocamphor (III). The mechanistic implications of the rearrangements are discussed.

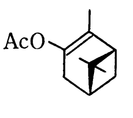
Because 2α-bormo-10β-pinan-3-one (I) was necessary in the course of our study of the stereochemistry of the oxygenated pinane system, the bromination of 3-acetoxy-pin-2-ene (II) was carried out by following the method in the literature,[3] but the literature has reported the formation of only the bromoketone (I). In contrast with the results reported in the literature, however, we found the method to result in the formation of not only the bromoketone (I), but also an isomeric bromoketone, 6-*endo*-bromocamphor (III). We now wish to report on the results of the bromination of II and, further, to deal with the acid-catalyzed rearrangement of the bromoketone (I) and the mechanistic implications of the reaction.

Results and Discussion

Under exactly the same conditions as in the literature,[3] the treatment of a carbon tetrachloride solution of (−)-3-acetoxy-pin-2-ene (II) with bromine in the presence of anhydrous sodium carbonate gave an oily reaction mixture, which was composed of (−)-2α-bromo-10β-pinan-3-one (I) (84% yield) and (+)-6-*endo*-bromocamphor (III) (5.0%), accompanied by unchanged enol-acetate (II) (4.0%). The bromocamphor (III) was confirmed by comparing its spectral data with those reported for 6-*endo*-bromocamphor[4] and by converting it into (+)-camphor (IV) on debromination.



I



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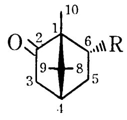
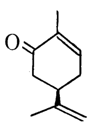


III : R = Br
IV : R = H



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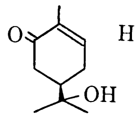

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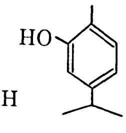

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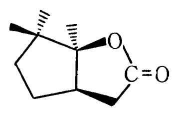
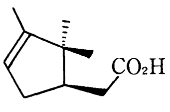
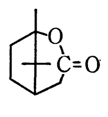


VIII



IX



X

In order to clarify the mechanism of the formation of the bromocamphor (III), the bromoketone (I) was subjected to acid treatments under various conditions. In the literature,[3] the treatment of the bromoketone (I) with 10% acetic acid under reflux for 3 hr has been reported to give only an intractable oil. The re-examination of this reaction clarified that the product consisted of (−)-carvone (V), (−)-8-hydroxycarvotanacetone (VI), carvacrol (VII), and (+)-dihydro-β-campholenolactone (VIII), accompanied by a trace of the bromocamphor (III). On the other hand, the bromoketone (I) was converted into the bromocamphor (III) in a 55% yield on treatment with 10% acetic acid at 50°C for 5 hr. The reaction of the bromoketone (I) with dilute hydrobromic acid at 50°C for 5 hr yielded also the bromocamphor (III) in a

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[1] Paper XI of this series: T. Suga, T. Hirata, and T. Matsuura, *J. Chem. Soc.*, *C*, submitted for publication.

[2] To whom all inquiries regarding to this paper should be addressed.

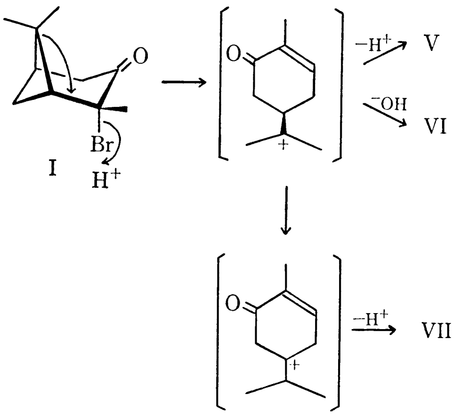
[3] M. P. Hartshorn and A. F. A. Wallis, *Tetrahedron*, **21**, 273 (1965).

[4] M. P. Hartshorn and A. F. A. Wallis, *J. Chem. Soc.*, **1964**, 5254.

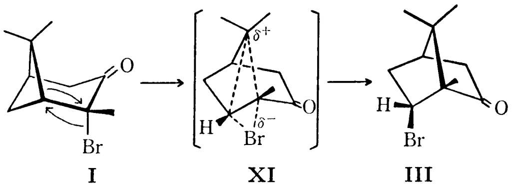
34% yield, along with the same kinds of products as above. These results show the ready conversion of the bromoketone (I) into the bromocamphor (III) by the acid-catalyzed reaction. Thus, the formation of the bromocamphor (III) in the bromination of the enol-acetate (II) is clearly due to the acid (probably hydrobromic acid)-catalyzed rearrangement of the bromoketone (I) initially produced.

The heating of the bromocamphor (III) with 10% acetic acid afforded only dihydro-β-campholenolactone (VIII). This shows the bromocamphor (III) to be connected only with the formation of the γ-lactone (VIII), not with that of such products as (V), (VI), and (VII). Moreover, the milder reaction of the bromocamphor (III) with aqueous acetic acid indicated the formation of (+)-α-campholenic acid (IX), along with the γ-lactone (VIII) and 1,2-campholide (X). The acid (IX) is expected as an intermediate in the formation of the lactone (VIII). The formation of the acid (IX) was also proved in the reaction of the bromoketone (I) with aqueous hydrobromic acid.

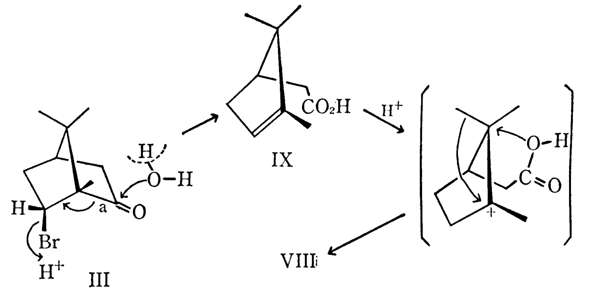
The formation of the products from the bromoketone (I) is best explained by the following three pathways: (a) the alteration of the bicyclo[3.1.1]skeleton to the monocyclic system, (b) the intramolecular rearrangement to the bicyclo[2.2.1]skeleton, and (c) lactonization involving the Wagner-Meerwein rearrangement. The formation of the (V), (VI), and (VII) products can be explained by the (a) pathway and can be explained as initiated by the detachment of the *t*-bromine atom from the bromoketone (I) with the acid, followed by the opening of the bridge to form the carbonium ion, as is shown in Scheme I. The intramolecular rearrangement in the (b) pathway is supported by the ready conversion of the bromoketone (I) into the bromocamphor (III) even under such conditions as in the absence of bromine. The mutual exchange between the *gem*-dimethyl brigde and the bromine atom in the bromoketone (I), followed by intramolecular rearrangement through a transition state (XI), results in the formation of a more stable compound, the bromocamphor (III), as is shown in Scheme II. The transition state (XI) is not so absurd because of the analogy to the transition state in the diaxial-diequatorial rearrangement proposed by Grob[5] and Barton.[6] Finally, the formation of dihydro-β-campholenolactone (VIII) from the bromocamphor (III) can be explained by the same mechanism as the rearrangement of 2-hydroxypinocamphone with anhydrous oxalic acid, which was reported recently by us.[7] The migration of the bromine atom and the (a) bond affords the acid (IX) as an intermediate product. It suffers protonation on an ethylenic bond, the 1,2-shift of a methyl group of the *gem*-dimethyl group, and then the lactonization of the carboxyl group, thus yielding the γ-lactone (VIII) (Scheme III).



Scheme I



Scheme II



Scheme III

Experimental

The IR spectra were recorded with a Hitachi EPI-S Infrared Spectrophotometer. The NMR spectra were measured with a Hitachi Perkin-Elmer R-20 high-resolution spectrometer, using tetramethylsilane as the internal standard. The mass-spectral analyses were performed by a Hitachi mass-spectrometer, Model RMS-4, ionizing at the order of 80 eV. Vapour-phase chromatographic analyses were made using a Hitachi Perkin-Elmer F6-D gas chromatograph with attached a column packed with 20% PEG-6000 on Celite.

3-Acetoxy-pin-2-ene (II). Following the method in the literature,[3] the treatment of isopinocamphone ($[\alpha]^{25}_{D}$ −11.1°) with acetic anhydride in the presence of perchloric acid, followed by purification on a silica gel column, afforded II in a 76% yield: $[\alpha]^{25}_{D}$ −35.0° (*c* 0.29, MeOH), lit[3] $[\alpha]^{25}_{D}+36°$ (*c* 1.00), derived from (+)-isopinocamphone; $\nu^{liq.}_{max}$ 1760 cm^{-1} (enol-acetate); NMR (CCl_4) δ 0.98 (s, C_9-3H), 1.30 (s, C_8-3H), 1.55 (t, $J=1.5$ Hz, $C_{10}-3H$), and 2.09 ppm (s,OAc).

Bromination of 3-Acetoxy-pin-2-ene (II). To a stirred suspension of 1.08 g of II and 1.00 g of anhydrous sodium carbonate in 5 m*l* of carbon tetrachloride, we added 0.94 g of bromine in 4 m*l* of carbon tetrachloride over a 5-min period at 0°C. After stirring for an additional 5 min, the reaction mixture was isolated by ether to give 1.13 g of an

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[5] C. A. Grob and S. Winstein, *Helv. Chim. Acta*, **35**, 782 (1952).

[6] D. H. Barton and J. F. King, *J. Chem. Soc.*, **1958**, 4398.

[7] T. Suga, T. Hirata, M. Noda, and T. Matsuura, *Experientia*, **26**, 1192 (1970).

oily product, which was then subjected to column chromatography on silica gel with a mixture of ethyl acetate and *n*-hexane to obtain 0.94 g of I, 0.06 g of III, and 0.05 g of unchanged II. The (I) and (III) products were identified on the basis of the following physical properties and the chemical reaction.

The Bromoketone (I): $[\alpha]^{25}_{D}$ −101.8° (*c* 1.18, MeOH); $\nu^{liq.}_{max}$ 1722 (C=O), lit[3] 1726 cm^{-1}, and 1376 and 1393 cm^{-1} (*gem*-dimethyl); λ^{MeOH}_{max} 313 nm (ε 135.3), lit[3] 312.5 nm (ε 130). The C–9, C–8, and C–10 methyl proton signals appeared at δ 0.91, 1.41, and 1.93 ppm in a 10% carbon tetrachloride solution, at δ 0.49, 0.93, and 1.88 ppm in a 10% benzene solution, and at δ 0.73, 1.19, and 1.93 ppm in a 10% pyridine solution, respectively, as singlets.

The Bromocamphor (III): mp 132—133°C, lit[4] mp 133—134°C; $[\alpha]^{25}_{D}+36.6°$ (*c* 0.63, MeOH), lit[4] $[\alpha]^{25}_{D}+44°$ (*c* 1.04); $\nu^{CCl_4}_{max}$ 1751 (C=O), lit[4] 1757 cm^{-1}, and 1381 and 1396 cm^{-1} (*gem*-dimethyl); λ^{MeOH}_{max} 291 nm (ε 40.8); NMR (CCl_4) δ 0.90 (s, C_8– and C_{10}-3H), 0.98 (s, C_9-3H), and 4.11 ppm (d.d, J=9.5 and 3.5 Hz, C_6-H); mass spectrum *m/e* (rel. intensity) 232 and 230 (M$^+$; 4) 217 and 215 (2), 190 and 188 (1), 175 and 173 (13), 151 (66), 135 and 133 (4), 109 (100), 94 (13).

The Debromination of 50 mg of III was carried out in 0.4 m*l* of 70% acetic acid with the addition of 50 mg of zinc powder under reflux over a 1-hr period. Ether extraction of the filtrate freed from the zinc powder afforded 31 mg of (+)-camphor (IV): $[\alpha]^{25}_{D}+30.1°$ (*c* 0.19, MeOH); $\nu^{KBr}_{C=O}$ 1743 cm^{-1}.

Rearrangement of 2α-Bromo-10β-pinan-3-one (I). A) With Hydrobromic Acid: A stirred suspension of 800 mg of the bromoketone (I) in 40 m*l* of 10% hydrobromic acid was heated at 50°C for 5 hr. The reaction product was treated with a 5% sodium carbonate solution, and then it was extracted with ether. The neutral reaction mixture obtained from the ether layer was subjected to column chromatography on silica gel with a mixture of ethyl acetate and *n*-hexane; we thus obtained 153 mg of (+)-6-*endo*-bromocamphor (III), 14 mg of (−)-carvone (V), 158 mg (−)-8- hydroxycarvotanacetone (VI), 24 mg of carvacrol (VII), and 90 mg of (+)-dihydro-β-campholenolactone (VIII). The aqueous layer, after it had been acidified with dilute hydrochloric acid, was extracted with ether to yield 25 mg (+)-α-campholenic acid (IX). Each component was confirmed by comparing its spectra and physical properties with those of an authentic sample[8] and/or by preparing their crystalline derivatives, as is shown below.

(+)-Bromocamphor (III): mp 132—133°C; $[\alpha]^{25}_{D}+37.0°$ (*c* 0.63, MeOH); ν^{KBr}_{max} 1752 cm^{-1} (C=O).

(−)-Carvone (V): $[\alpha]^{25}_{D}-45.0°$ (*c* 0.15, MeOH); $\nu^{liq.}_{max}$ 1677 (α,β-unsaturated C=O) and 3063 cm^{-1} (*endo*- methylene); λ^{MeOH}_{max} 236 nm (ε 6900); the 2,4-dinitrophenylhydrazone, mp 187—188°C.

(−)-8-Hydroxycarvotanacetone (VI): $[\alpha]^{25}_{D}-40.5°$ (*c* 0.15, MeOH); $\nu^{liq.}_{max}$ 1660 (α,β-unsaturated C=O) and 3400 cm^{-1} (OH); λ^{MeOH}_{max} 235 nm (ε 9100); NMR (CCl_4)δ 1.18 (s, C_9- and C_{10}-3H), 1.72 (b.s, C_7-3H), and 6.66 ppm (b.s, C_6-H); the semicarbazone, mp 178—179°C.

Carvacrol (VII): $\nu^{liq.}_{max}$ 1619 and 1584 (aromatic C=C), 1370 and 1385 (isopropyl), and 3400 cm^{-1} (OH); λ^{MeOH}_{max} 277 nm (ε 2150).

(+)-Dihydro-β-campholenolactone (VIII): mp 30°C; $[\alpha]^{25}_{D}$ +22.8° (*c* 0.15, EtOH); ν^{KBr}_{max} 1775 cm^{-1} (C=O); NMR (CCl_4)δ 0.90, 1.08, and 1.26 ppm (s, 3H, respectively).

(+)-α-Campholenic Acid (IX): $[\alpha]^{25}_{D}+5.3°$ (*c* 0.10, MeOH); $\nu^{liq.}_{max}$ 1710 (COOH), 1370 and 1392 cm^{-1} (*gem*-dimethyl); NMR (CCl_4)δ 0.78 (s, 3H), 0.99 (s, 3H), 1.58 (b.s, 3H), and 5.17 ppm (b.s, 1H).

B) Under Other Conditions: The reactions were carried out under various conditions, as is shown below. The bracketed figures in the heading show the experimental number in Table 1. (1) A solution of the bromoketone (I) (100 mg) in carbon tetrachloride (5 m*l*) was maintained at 50°C for 5 hr. (2) The bromoketone (300 mg) was stirred into a suspension of bromine (300 mg) and anhydrous sodium carbonate (300 mg) in carbon tetrachloride (15 m*l*) at 50°C over a 5-hr period. (3) The bromoketone (100 mg) was heated in 10% acetic acid-carbon tetrachloride (5 m*l*) at 50°C for 5 hr. (4) A suspension of the bromoketone (100 mg) in 10% aqueous acetic acid (5 m*l*) was stirred at 50°C for 5 hr. (5) The bromoketone (100 mg) was refluxed in 10% aqueous acetic acid (5 m*l*) for 3 hr. (6) A suspension of the bromoketone (100 mg) in 5% hydrobromic acid (5 m*l*) was stirred at 50°C for 5 hr. (7) The bromoketone (100 mg) was maintained in a mixture of 5% hydrobromic acid (5 m*l*) and methanol (10 m*l*) at 50°C for 5 hr. (8) The bromoketone (100 mg) was heated in the stirred suspension of 10% hydrobromic acid (2.5 m*l*) and 10% aqueous acetic acid (2.5 m*l*) at 50°C for 5 hr.

After the reaction, the whole reaction mixture were extracted with ether. The ether solution was washed with a sodium bicarbonate solution, and then water, after which it was dried over anhydrous sodium sulfate. The removal of the solvent from the solution gave a reaction mixture, which was subjected to preparative thin-layer chromatography on silica gel with a mixture of ethyl acetate and *n*-hexane (3:7 by volume) in order to separate the components. Each component was confirmed by comparing its spectra and physical properties with those of an authentic sample. The results of these reactions are summarized in Table 1.

TABLE 1. REARRANGEMENTS OF BROMOKETONE (I) UNDER VARIOUS CONDITIONS

Expt. No.	Yield of products (%)					
	III	V	VI	VII	VIII	I (unchanged)
1	trace[a]	—	—	—	—	95
2	2.3	—	—	—	—	94
3	7.6	—	—	—	—	87
4	55	12	21	trace[a]	trace[a]	—
5	trace[a]	3.0	17	41	13	—
6	30	8.0	11	trace[a]	trace[a]	13
7	22	9.5	6.1	trace[a]	5.6	22
8	30	5.1	32	1.0	3.2	—

a) These were only detected by gas chromatographic and thin-layer chromatographic analyses.

Rearrangements of (+)-6-endo-Bromocamphor (III). A) Under Reflux for 3 hr: The bromocamphor (III) (50 mg), dissolved in 10% acetic acid (2.5 m*l*) was stirred under reflux for 3 hr. The reaction mixture was extracted by ether to obtain a reaction product (36 mg). Gas-chromatographic analysis showed the product to consist of 93% of the γ-lactone (VIII) and 1.6% of the unchanged bromocamphor (III). The product was subjected to preparative thin-layer chromatography with silica gel with 30% ethyl acetate - *n*-hexane in order to isolate the lactone (VIII) (32 mg): mp 30—31°C; $[\alpha]^{25}_{D}+29.8°$ (*c* 0.24, EtOH); ν^{KBr}_{max} 1775 cm^{-1} (γ-lactone).

B) Under Milder Conditions: A suspension of III in

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[8] T. Hirata, T. Suga, and T. Matsuura, This Bulletin, **43**, 2588 (1970).

10% acetic acid was stirred at 105°C for 2 hr in the same manner as above. The ether solution of the reaction mixture was then treated with a 5% sodium carbonate solution in order to isolate (+)-α-campholenic acid (IX) (16%): $[\alpha]_D^{25}$ 5.0° (*c* 0.15, MeOH); $\nu_{max}^{liq.}$ 1710 cm^{-1} (COOH). The neutral reaction mixture freed from the acid was composed of (+)-γ-lactone (VIII) (55%), 1,2-campholide (X) (1.5%), and the unchanged bromocamphor (III) (4.5%). The δ-lactone (X) was only detected by gas-chromatographic and thin-layer chromatographic analyses.