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TERPENES—V[1]

REINVESTIGATION OF A SYNTHESIS OF THUJANE

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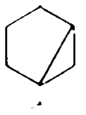
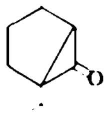
Abstract— The reaction of 2,4-dibromomenthone with zinc and alcohols has been reinvestigated using the newer techniques, such as, gas chromatography, NMR and mass spectroscopy. The product of this reaction is not the cyclopropanone derivative "keto-thujane" as reported in the old literature; instead a mixture of menthone, isomenthone, 2-alkoxy- and 4-alkoxy-menthones (major constituent) and *p*-menthene-3-ones is formed. The Clemmensen reduction of this mixture led only to menthanes and menthenes instead of the cyclopropane derivative, thujane, reported previously. Analogous products were obtained from the reaction of 1,3-dibromocarvomenthone with zinc and methanol.

Guha and Nath[2] reported a synthesis of thujane (I), a bicyclic terpene containing the cyclopropane ring *via* an intermediate "keto-thujane" to which they assigned the cyclopropanone structure II. In view of the current interest in cyclopropanones, we decided to repeat the reaction of 2,4-dibromomenthone (VI) with zinc and ethanol and the subsequent Clemmensen reduction as described.[2] Had the compound II been formed by the reaction of zinc on VI, it should have been converted by alcohol to the cyclopentanecarboxylic acid esters III and IV. If one of the final products from the Clemmensen reduction was indeed thujane, perhaps a cyclopropyl ketone, such as V, could represent the "keto-thujane" of Guha and Nath. We planned to take advantage of the characteristic NMR spectra of cyclopropyl compounds in reexamining the intermediates and final products of these workers. It has been established that cyclopropyl protons resonate at very high field.[3]



I



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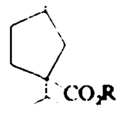

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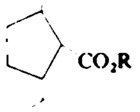

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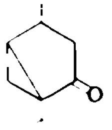
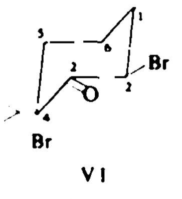


V



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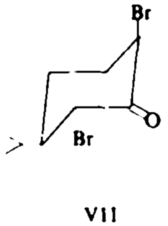

VII

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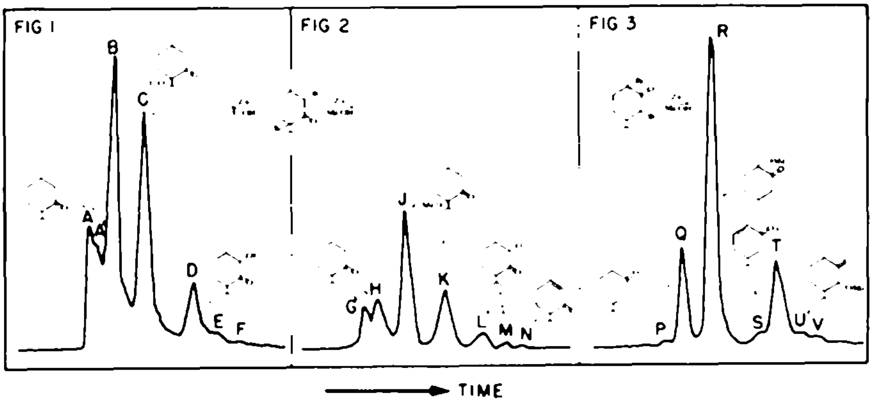
[1] Abstracted from the Ph.D. thesis of M.S.T., Stevens Institute of Technology, 1966. Part IV: A. K. Bose, S. Harrison and L. Farber, *J. Org. Chem.*, **28**, 1223 (1963).

[2] P. C. Guha and B. Nath, *Ber. Dtsch. Chim. Ges.* **70**, 931 (1937).

[3] For example, see G. Ohloff, G. Uhde, A. F. Thomas and E. sz. Kováts, *Tetrahedron* **22**, 309 (1966).

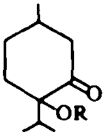
2,4-Dibromomenthone (VI) was allowed to react with zinc powder in absolute ethanol under the conditions described previously.[2] VPC of the reaction mixture indicated the presence of several compounds with similar retention time (Fig. 1). This was in contrast to the previous report that essentially two fractions (within a 25° boiling range) were obtained.

The components of the reaction mixture were individually collected in glass capillary tubing from the eluent of a gas chromatograph. The first two fractions (peaks A and A′) were identified as menthone and isomenthone, respectively by the comparison of their IR spectra with those of authentic samples. The IR spectra of B, C and D are very similar, showing strong carbonyl stretching band absorption at $5\cdot80\ \mu$, and medium strength C—O stretching bands in the 8–9 μ region, suggestive of an ether. The mass spectra of these compounds display the same molecular ion peak at *m/e* 198. The fragmentation patterns of B and C are practically identical. Both B and C exhibit a small peak at *m/e* 170 (M—CO) and a strong peak at *m/e* 154 (M-44). Since the debromination reaction was carried out in absolute ethanol, the M-44 peak strongly suggests the loss of a [C_2H_4O] fragment. For both B and C, the base peak which appears at *m/e* 127 corresponds to a loss of 43 mass units (C_3H_7) from *m/e* 170. The mass spectral fragmentation together with the IR data lead to the conclusion that B and C are configurationally isomeric ethoxymenthones.

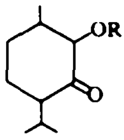


Compound D exhibits a molecular ion peak at *m/e* 198 as do compounds B and C. However, the fragmentation pattern is different. The *m/e* 170 (M−CO) peak is much stronger in compound D and the base peak occurs at *m/e* 99. A strong peak at M-44 indicates the loss of [C_2H_4O]. Thus, it appears from the mass spectra and IR data that compound D is a positional isomer of B and C. The NMR spectra of compounds B, C and D were complicated because the methylene protons of the ethyl group resonate in the same region as the ring protons vicinal to the carbonyl and ethoxy functions. We decided to study the debromination reaction of 2,4-dibromomenthone with zinc and anhydrous methanol since the NMR spectra of methoxy compounds would be easier to interpret.

VPC of the reaction products of 2,4-dibromomenthone with zinc and methanol (Fig. 2) was very similar to that obtained with zinc and ethanol. From a study of the IR and mass spectral data we concluded that peaks G and H (Fig. 2) corresponded to menthone and isomenthone, respectively while peaks J, K, L and M represented the four isomeric α-methoxy-*p*-menthane-3-ones. The last peak in this series, namely N, appears on the basis of spectral data to correspond to Δ^1-*p*-menthene-3-one. Since the NMR spectra of J and K do not show any low field methine protons, these two compounds must be assigned the isomeric-4-methoxy-3-menthone structures (VIII). Compounds L and M must be 2-methoxy-3-menthones (IX) as their NMR spectra display the appropriate signal for the methine proton at C-2.



VIII



IX

Our VPC and NMR analyses of the products from the reaction of 2,4-dibromomenthone with zinc and an alcohol show that II, III, IV and V were present in insignificant amounts only, if at all. In an earlier study before many of the new physical methods were available, Dauben *et al.*[4] had concluded that an ethoxymenthone, most likely VIII (R=Et), was the "keto-thujane" of Guha and Nath.

We have also studied the reaction of 1,3-dibromocarvomenthone (VII) with zinc and methanol. The gas chromatogram of the reaction mixture showed three prominent peaks and several minor peaks (Fig. 3). In addition to carvomenthone (Q), two methoxycarvomenthones are produced, R and T, which are configurational isomers as indicated by their mass spectral fragmentation patterns. Neither compound R nor T exhibit a methine type proton in the NMR spectrum. The singlet methyl peak at τ 8·93 for R and τ 8·87 for T indicates that the MeO group is located at C_1. The IR spectrum of U showed it to be a saturated ketone—it must therefore be a 3-methoxy-*p*-menthane-2-one. The peak S corresponds to Δ^6-*p*-menthene-2-one because it shows an olefinic proton signal at τ 3·67 and carbonyl absorption at 5·98 μ. The peak V was not characterized for lack of adequate material.

Thus, the reaction of 1,3-dibromocarvomenthone with zinc and methanol proceeds in a manner analogous to that of the reaction of 2,4-dibromomenthone with zinc and methyl or ethyl alcohol. In each case the major product is a *tert*-alkoxy derivative composed of nearly equal quantities of both geometrical isomers (menthyl- and isomenthyl-). It is unlikely that the *tert*-ethers could arise from a Grignard type derivative, such as X, involving the *tert*-bromine atom, because such an intermediate would be nucleophilic. Thus, in a somewhat similar case, the intermediate XI has been postulated in the reaction between an α-bromoester, zinc and a nitrile.[5]

A mechanism for explaining the formation of the observed products from dibromomenthone of known conformation VI[6] is suggested in Chart I. Debromination of VI with zinc could produce the mono-bromo intermediates XII and XIII. The The S_N1 mechanism conceived for the subsequent course of the reaction would lead to a preponderance of the *tert*-carbonium ion XV over the sec-carbonium ion

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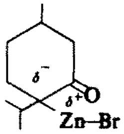
[4] W. G. Dauben, A. C. Albrecht, E. Hoerger and H. Takimoto, *J. Org. Chem.* **23**, 457 (1958).

[5] H. B. Kagan and Y-H Suen, *Bull. Soc. Chim. Fr.* 1819 (1966).

[6] J. A. Wunderlich and W. N. Lipscomb, *Tetrahedron* **11**, 219 (1960).

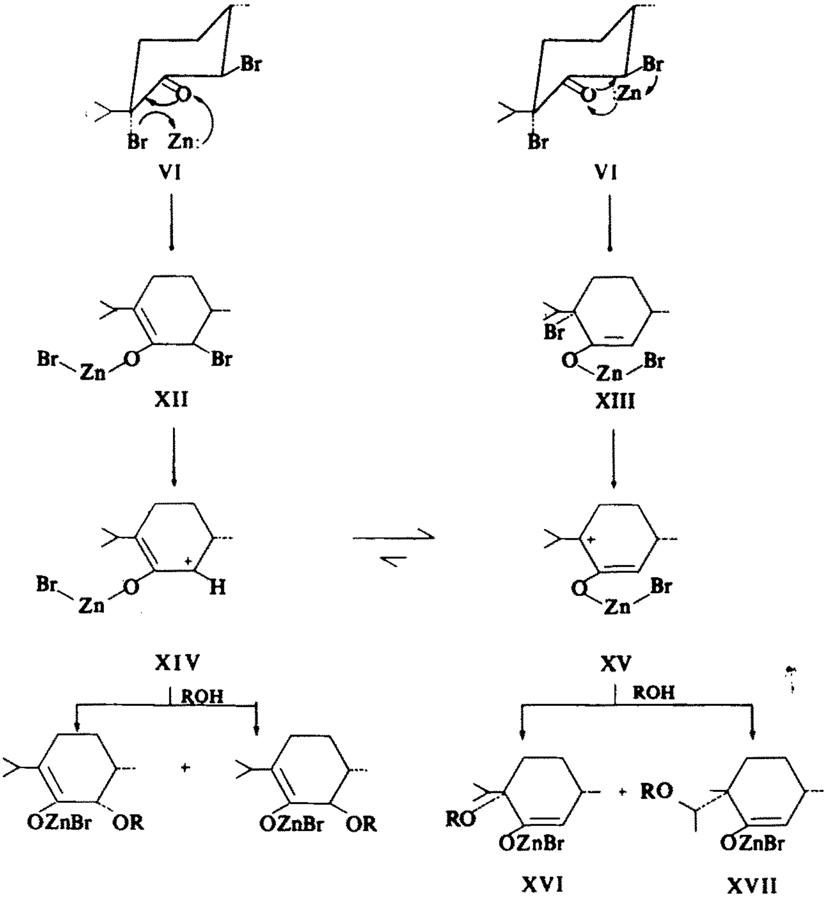


X

XI

XIV and account for the nearly equal formation of the menthone and isomenthone derivatives corresponding to XVI and XVII as the major products of the reaction.

Guha and Nath[2] believed that they had obtained thujane from the Clemmensen reduction of their "keto-thujane" intermediate. We have carried out the Clemmensen reduction of the mixture of ethoxymenthones corresponding to Guha's "keto-thujane" and found that only menthenes and menthanes are formed. No cyclopropyl proton resonance was observed in the τ 9·0–9·5 region of the NMR spectrum of the reduction products.



EXPERIMENTAL

The NMR spectra were obtained with a Varian DP-60 spectrometer operating at 56·4 Mc or a Varian A-60A spectrometer operating at 60 Mc. TMS served as the internal standard. Singlet peaks are designated by *s*, doublet by *d*, and complex or multiplet peaks by *m*.

The mass spectra were recorded on a Consolidated Electrodynamics Corporation mass spectrometer Model No. 21-103C using an all-glass inlet system, heated at 145°. The temp of the source was 250°. The ionizing energy was maintained at 70 eV and the ionizing current at 10·2 μa. All liquid samples were introduced into the mass spectrometer with 0·5–2·0 microliter capillary dippers through a fritted glass-based gallium well. The samples were expanded from the gallium well into a 3 litre ballast bulb connected to a gold leak of the mass spectrometer. The pressure in the analyzer region was maintained at approximately 10^{-7} mm. The samples for mass spectrometric and IR determinations were collected by inserting a chilled, unsealed capillary into the exit tube of a gas chromatograph, thereby causing the effluent vapors to condense on the inner walls of the capillary. A Perkin–Elmer Infra-cord Model 137B spectrophotometer was used for IR measurements.

The analytical VPC was carried out on an F & M gas chromatograph Model 720, equipped with a 6 ft Carbowax 20M column. For collecting larger samples a Wilkens "Auto-Prep-Model A700" preparative gas chromatograph was used.

M.ps were observed on a Fisher–Johns m.p. apparatus and were uncorrected.

Reaction of 2,4-*dibromomenthone with zinc and ethanol*

2,4-Dibromomenthone[2] was allowed to react with powdered Zn and EtOH according to the procedure of Guha[2] and as repeated by Dauben.[4] After the reaction mixture was worked up, the solvent was removed and 1 μl sample of the product was injected into a gas chromatograph equipped with a 6 ft Carbowax 20M column. A chromatogram exhibiting essentially 7 peaks was obtained. The 7 peaks were labeled A, A′, B, C, D, E and F as indicated in Fig. 1. A larger sample (25–30 μl) was injected into a preparative gas chromatograph and the peaks A through D were individually collected in capillary tubing chilled in dry ice.

Peak A (menthone): IR (neat): 5·84 μ; mass spectrum, significant *m/e* values: 154 (M^+), 139, 112 (base), 97, 83, 70, 69.

Peak A′ (isomenthone): IR (neat): 5·86 μ; mass spectrum, significant *m/e* values: 154 (M^+), 139, 112 (base), 97, 83, 70, 69.

Peak B (4-ethoxymenthone): IR (neat): 5·82 μ, 9·33 μ. Mass spectrum, significant *m/e* values: 198 (M^+), 154, 127 (base), 99, 81, 71, 69; NMR (CCl_4): complex spectrum.

Peak C (4-ethoxymenthone): IR (neat): 5·82 μ, 8·96 μ, 9·26 μ; mass spectrum, significant *m/e* values: 198 (M^+), 154, 127 (base), 99, 81, 71, 69; NMR (CCl_4): complex spectrum.

Peak D (2-ethoxymenthone): IR (neat): 5·80 μ; 8·71 μ, 9·45 μ; mass spectrum, significant *m/e* values: 198 (M^+), 170, 154, 112, 99, 85, 82, 71; NMR (CCl_4): complex spectrum.

Reaction of 2,4-*dibromomenthone with zinc and methanol.*

2,4-Dibromomenthone was allowed to react with Zn and MeOH (reagent grade) in the same manner as with EtOH according to previous workers.[2, 4] The solvent-free product gave a chromatogram exhibiting 7 peaks as indicated in Fig. 2, labeled G, H, J, K, L, M and N. The compounds represented by the various peaks were collected individually in chilled capillary tubes from the gas chromatograph effluent. Samples collected in this manner were used for IR and mass spectral studies. Where larger samples were desired, preparative VPC was used.

Peak G and Peak H (menthone and isomenthone): characterized as described previously.

Peak J (4-methoxy-*p*-methane-3-one): IR (neat): 5·85 μ, 9·34 μ; mass spectrum, significant *m/e* values: 184 (M^+), 141, 140, 127, 113 (base), 100, 99, 85, 81; NMR (CCl_4) τ: 7·00 (*s*, 3H), 9·14 (*s*, 4·5H), 9·27 (*s*, 4·5H).

Peak K (4-methoxy-*p*-methane-3-one): IR (neat): 5·84 μ, 9·12 μ; mass spectrum, significant *m/e* values: 184 (M^+), 141, 140, 127, 113 (base), 100, 99, 85, 81; NMR (CCl_4) τ: 6·92 (*s*, 3H), 8·98 (*s*, 1½H), 9·07 (*s*, 3H), 9·18 (*s*, 3H), 9·28 (*s*, 1½H).

Peak L (2-methoxy-*p*-menthane-3-one): IR (neat): 5·81 μ, 8·68 μ; mass spectrum, significant *m/e* values: 184 (M^+), 156, 141, 113, 109, 99, 98 (base), 85, 82, 72, 71; NMR (CCl_4) τ: 6·34 (*d*, 1H, J = 3·8 c/s), 6·68 (*s*, 3H).

Peak M (2-methoxy-*p*-menthane-3-one): IR (neat): 5·80 μ, 8·85 μ; NMR (CCl_4) τ: 6·65 (*s*, 3H), 8·86 (*d*, 1H, J = 9·9 c/s).

Peak N (Δ-*p*-menthen-2-one): IR (CCl_4, 0·1 mm cell): 5·98 μ, 6·1 μ; NMR (CCl_4) τ: 8·74 (*s*, 3H).

Carvomenthone

Carvomenthone was prepared by catalytic hydrogenation of carvone with 5% Pd C catalyst. In a typical procedure, 6·0 g (0·4 m) of carvone (K. and K. Laboratories, Inc.) was mixed with 89 g of 95% EtOH to which was added 1·4 g 5% Pd C catalyst. The carvone was hydrogenated at an initial pressure of ca. 50 lb/in^2 for ca. 2½ hr during which time 26·5 lb/in^2 of H_2 reacted with the carvone. The hydrogenated soln was filtered, and the EtOH removed via a rotary evaporator. The product was injected into a gas chromatograph and exhibited one major peak on a 6 ft Carbowax 20M column. IR (neat): 5·85 μ.

Preparation of 1,3-*dibromocarvomenthone*

1,3-Dibromocarvomenthone was prepared by allowing carvomenthone to react with bromine in $CHCl_3$ soln according to the procedure used for the preparation of 2,4-dibromomenthone. The typical yield of 1,3-dibromocarvomenthone after crystallization from MeOH was 50–60%, m.p. 78–79·5° (lit[7], m.p. 80–81°). IR ($CHCl_3$ mull on NaCl plates): 5·78 μ; NMR (CCl_4) τ: 4·66 (*d*, 1H, *J* = 11·5 c/s), 8·11 (*s*, 3H); ORD: 328 mμ (trough), 285 mμ (intersection of abscissa).

Reaction of 1,3-*dibromocarvomenthone with zinc and methanol*

1,3-Dibromocarvomenthone was allowed to react with powdered Zn and MeOH in the manner[2,4] described for 2,4-dibromomenthone, Zn and EtOH. After the usual work up, the products were injected into a gas chromatograph with a 6 ft Carbowax 20 M column. The resulting chromatogram exhibited essentially 7 peaks representative of compounds labeled P, Q, R, S, T, U and V. The individual peaks were collected in chilled capillary tubes for IR and mass spectral studies. Preparative VPC was used for collecting peaks to be examined by NMR.

Peak P: not examined but presumed to be isocarvomenthone.

Peak Q (carvomenthone): IR (neat): 5·84 μ (spectrum identical with that of carvomenthone prepared by the reduction of carvone).

Peak R (1-methoxy-*p*-menthane-2-one): IR (neat): 5·83 μ, 9·21 μ; mass spectrum, significant *m/e* values: 184 (M^+), 141, 140, 113, 85 (base), 81, 72; NMR (CCl_4) τ: 7·02 (*s*, 3H), 8·93 (*s*, 3H), 9·12 (median, *d*, 6H).

Peak S (Δ^6-*p*-menthen-2-one): IR (neat): 5·98 μ; NMR (CCl_4) τ: 3·67 (*m*, 1H), 8·38 (*d*, 3H), 9·11 (*d*, 6H).

Peak T (1-methoxy-*p*-menthane-2-one): IR (neat): 5·81 μ, 9·21 μ; mass spectrum, significant *m/e* values: 184 (M^+), 141, 140, 113, 85 (base), 81, 72; NMR (CCl_4) τ: 6·96 (*s*, 3H), 8·87 (*s*, 3H), 9·12 (median, *m*, 6H).

Peak U (3-methoxy-*p*-menthane-2-one): IR (neat): 5·80 μ, 8·72 μ.

Peak V: not examined but presumed to be a configurational isomer of peak U.

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[7] O. Wallach, *Liebig's Ann.* **414**, 350 (1918).