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BIOMIMETIC CYCLIZATION OF HEDYCARYOL DERIVATIVES.

UNEXPECTED CYCLIZATION OF PHENYL SULFIDES WITH METHYL IODIDE

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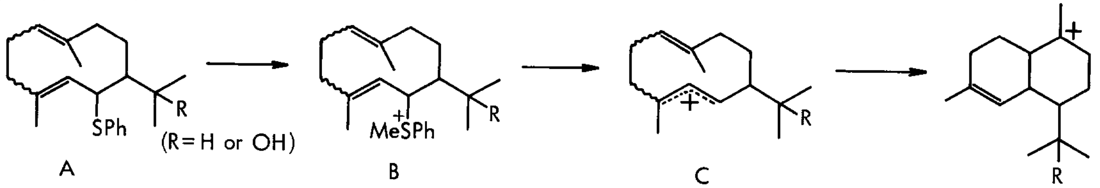
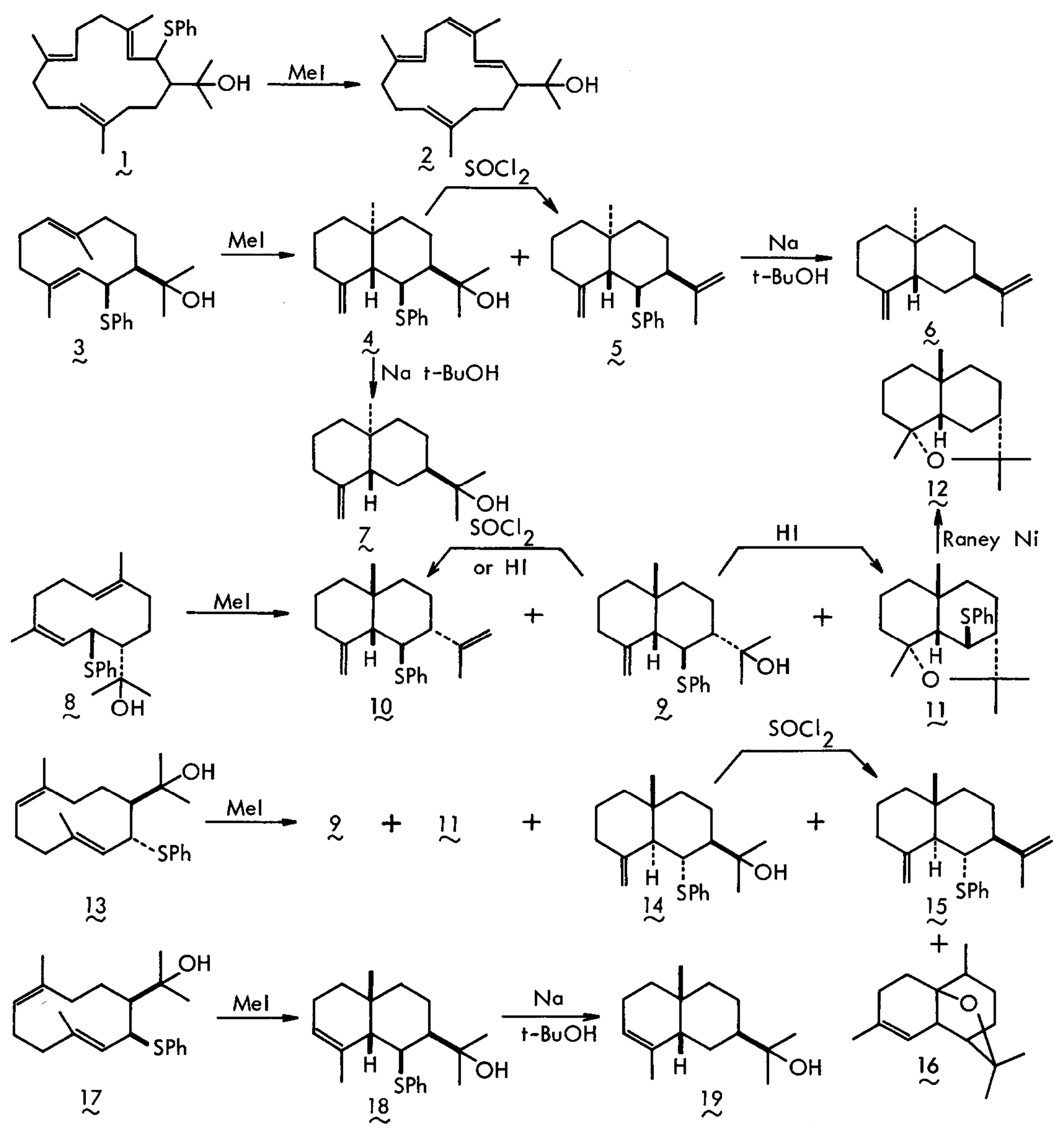
Abstract: Four isomeric hedycaryol phenyl sulfides, when reacted with MeI, yielded eudesmol derivatives with different stereochemistry from that of the acid cyclization products of the corresponding hedycaryols. New stereoisomers of α- and β-eudesmols, β-dehydroparadisiol and a defensive substance of termite were synthesized. Nephthenol phenyl sulfide yielded a 14-membered tetraene.

Recently we have achieved an effective synthesis of hedycaryol, a germacradiene, and its all possible geometrical isomers[1] and established the stereochemical course in their conversion to eudesmols and elemols[2]. Since cadinanes, another major sesquiterpene, are also derived biogenetically from germacradiene ions through the ions C[3], our effort was directed to realize such transformation[4] by generating the ions from isomeric hedycaryol phenyl sulfides A via sulfonium ions B. However, when the methylation of A was attempted, unexpected cyclization to eudesmane carbon skeleton has occurred. This paper describes the stereochemistry of the reaction and conversion of the products to natural products or their derivatives.



The reaction conditions were first elaborated using nephthenol phenyl sulfide (1); the allylic cation in the 14-membered ring diterpene carbon skeleton would not undergo cyclization but give an elimination product. Thus, 1 was treated with MeI[5] for 70 hrs at room temperature without solvent to afford the conjugated diene 2[6] in 40% yield along with methyl phenyl sulfide (75%).

The elimination reaction desired being observed, the reaction was examined next in sesquiterpene series. When E, E-hedycaryol phenyl sulfide (3) was treated under the same conditions (100 hrs), two products, 4[7] and 5[7], were formed in 38% and 30% yields, respectively. The alcohol 4 was dehydrated to 5, which in turn gave on desulfurization the dehydration product 6 of paradisiol obtained from Citrus paradisi[8], thus establishing structures of 4 and 5. Desulfurization of 4 afforded a new stereoisomer 7[7] of β-eudesmol. The reaction establishes the hitherto-unknown cis stereochemistry of PhS and -CMe_2(OH) groups in 3; the coupling constant, J_{H_6,H_7} in 4 and 5 is 6 Hz and 5 Hz, respectively.



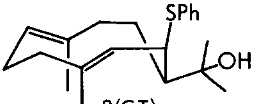
Similar treatment of the 2Z,6E-isomer **8** yielded (64 hrs) three products, **9**[7] (46%), **10**[7] (25%) and **11**[7] (16%). Dehydration of **9** afforded **10**, while its desulfurization gave the known β-dihydrooccidentalol[9]. Treatment of **9** with HI yielded **11** along with **10**. Third product **11** furnished on desulfurization the ether **12** which was identical with a defensive substance of *Amitermes evuncifer*[10].

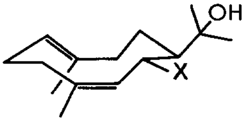
The reaction of trans-2E,6Z-hedycaryol phenyl sulfide (**13**) (6 days) afforded four eudesmane derivatives, **9** (4%), **11** (5%), **14**[7] (19%) and **15**[7] (39%), and a cadinane-type ether **16**[7] (19%). Again, the structures of **14** and **15** were determined by their interconversion and desulfurization to the mixture of α- and β-eudesmols. Spectra of **16** is consistent with the structure given, showing the presence of a sec-methyl, two tert-methyls on the carbinyl carbon, a vinyl methyl, a trisubstituted double bond, and an ether ring.

The cis-2E,6Z-hedycaryol phenyl sulfide (**17**) gave (6 days) the alcohol **18**[7] in 40% yield as an only isolable product. Its structure was deduced from the spectral analyses and the fact that the desulfurization product **19** was not identical with any known stereoisomer[11] of α-eudesmol.

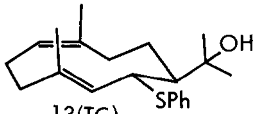
The reactions described above were likely to be induced by HI generated by the decomposition of the sulfonium salt formed initially and slowly. In fact, no reaction occurred when E,E-hedycaryol (E,E-**20**) was treated with MeI alone, but addition of geranyl phenyl sulfide induced the cyclization to eudesmols, and anhydrous HI cyclized **3** and **8** rapidly to give the mixtures of similar composition described above[12]. The rapid cyclization induced by the HI formed during the reaction must have competed with the slow formation of sulfonium ion.

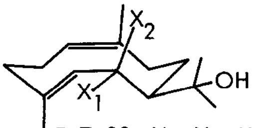
The reactions, essentially acid-catalyzed cyclization, of hedycaryol phenyl sulfides differ from those of hedycaryols (**20**) in stereochemistry. The possible reacting conformations in both reactions are depicted[13].


3(CT)


Z,E-**20**: X=H

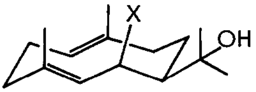
8 (CC): X=SPh


13(TC)

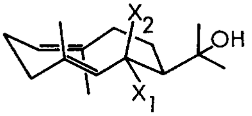

E,Z-**20**: X_1=X_2=H

13 (CC): X_1=SPh, X_2=H

17 (CC): X_1=H, X_2=SPh


E,E-**20**: X=H

3 (CC): X=SPh


13(CT) X_1=SPh, X_2=H

17(CT) X_1=H, X_2=SPh

The cyclization had occurred in all cases from a crossed conformation, which requires less activation energy[14] than parallel form. Among two crossed forms in **3**, the CC form in which E,E-**20** undergoes cyclization is not favored because of the interaction between PhS and C_3-Me. The CC form in **8** has no extra interaction, so that both **8** as well as Z,E-**20** reacted through the same CC form. **17** reacted through the CC form, one of the reacting conformations in E,Z-**20**, because the other (CT) has the same interaction as in **3** (CC). In accord with the behavior of E,Z-**20**, **13** reacted through the CT form to some extent. However, the major path was not the CC but the TC form. This difference may be attributed to the formation of **16** through the CC form, suggesting that the elimination of sulfonium ion can compete with the acid-cyclization if the latter process is not rapid enough[15]. In any case, it is interesting especially in E,E-hedycaryol series which are most frequently found in nature that stereochemical course of the reaction is completely changed by the introduction of a substituent to give another sesquiterpene carbon skeleton (paradisane).

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References and Notes

1) M. Kodama, Y. Matsuki and S. Itô, Tetrahedron Lett., 1121 (1976); M. Kodama, S. Yokoo, H. Yamada and S. Itô, ibid., 3121 (1978).

2) M. Kodama, S. Yokoo, Y. Matsuki and S. Itô, Tetrahedron Lett., 1687 (1979).

3) G.A. Cordell, *Chem. Rev.*, **76**, 425 (1976); A. Corbella, P. Gariboldi and G. Jommi, *J. Chem. Soc., Chem. Comm.*, 729 (1973).

4) For the biomimetic cyclization of germacradienes to cadinanes see: M. Niwa, M. Iguchi and S. Yamamura, *Bull. Chem. Soc. Jpn.*, **49**, 3148 (1976) and references cited therein; N.R. Deshpande, G. H. Kulkarni and G.R. Kelkar, *Indian J. Chem.*, **18B**, 25 (1979); H. Nishimura, H. Hasegawa, A. Seo, H. Nakano and J. Mizutani, *Agric. Biol. Chem.*, **43**, 2397 (1979).

5) Methyl iodide was used after being passed through alumina column.

6) M. Kodama, K. Shimada and S. Itô, *Tetrahedron Lett.*, 2763 (1977).

7) The spectra of new compounds are listed below: **4**; m/e 330 (M^+), 203, 59 (b.p.); ν 3440, 1642, 885 cm^{-1}; δ (CCl_4) 0.83 (3H, s), 1.30 (3H, s), 1.32 (3H, s), 3.59 (1H, dd, J=9, 5), 4.47 (1H, br.s), 4.87 (1H, br.s), 7.1-8.5 (5H, m). **5**; m/e 312 (M^+, b.p.), 109, 95; ν 1640, 895 cm^{-1}; δ (CCl_4) 0.83 (3H, s), 1.67 (3H, br.s), 3.47 (1H, dd, J=13, 6), 4.61 (1H, br.s), 4.83 (1H, br.s), 4.93 (2H, br.s), 7.0-7.4 (5H, m). **7**; m/e 222 (M^+), 59 (b.p.); ν 3380, 882 cm^{-1}; δ (CCl_4) 0.74 (3H, s), 1.23 (6H, s), 4.38 (1H, br.s), 4.65 (1H, br.s). **9**; m/e 330 (M^+), 312, 203, 109, 59 (b.p.); ν 3425, 1642, 890 cm^{-1}; δ (CCl_4) 0.82 (3H, s), 1.23 (3H, s), 1.29 (3H, s), 3.15 (1H, t, J=10.5), 4.25 (1H, d, J=2.5), 4.70 (1H, d, J=2.5), 4.85 (1H, m), 7.1-7.6 (5H, m). **10**; m/e 312 (M^+), 28 (b.p.); ν 1642, 886 cm^{-1}; δ (CCl_4) 0.90 (3H, s), 1.68 (3H, br.s), 1.92 (1H, br.d, J=11), 3.07 (1H, t, J=11), 4.60-4.85 (4H, m), 7.0 7.5 (5H, m). **11**; m/e 330 (M^+), 221, 109 (b.p.); ν 1155, 745, 692 cm^{-1}; δ (CCl_4) 1.19 (9H, s), 1.30 (3H, s), 2.19 (1H, br.s), 2.27 (1H, d, J=1.5), 4.22 (1H, br.s), 7.1-7.4 (5H, m). **14**; m.p. 123-124.5° (dec.); m/e 330 (M^+, b.p.), 312, 203, 59; ν 3380, 887 cm^{-1}, δ (CCl_4) 0.82 (3H, s), 1.18 (3H, s), 1.27 (3H, s), 2.99 (1H, t, J=11), 4.82 (1H, br.s), 5.14 (1H, br.s), 5.35 (1H, br.s), 7.1-7.75 (5H, m). **15**; m/e 312 (M^+, b.p.), 203; ν 885, 745, 685 cm^{-1}; δ (CCl_4), 0.75 (3H, s), 1.72 (3H, br.s), 2.79 (1H, t, J=11.5), 4.72 (3H, m), 5.00 (1H, br.s), 6.95-7.40 (5H, m). **16**; m/e 220 (M^+), 163 (b.p.); ν 1128, 805 cm^{-1}; δ (CCl_4) 0.75-0.82 (3H, m), 1.14 (3H, s), 1.28 (3H, s), 1.66 (3H, br.s), 5.22 (1H, br.s). **18**; m/e 330 (M^+), 203, 59 (b.p.); ν 3450, 745, 688 cm^{-1}; δ (CCl_4) 1.18 (3H, s), 1.24 (3H, s), 1.35 (3H, s), 1.65 (3H, br.s), 3.96 (1H, br.s), 5.43 (1H, m), 6.95-7.50 (5H, m). **19**; m/e 222 (M^+), 204, 161 (b.p.), 59; ν 3380, 810 cm^{-1}; δ (CCl_4) 1.00 (3H, s), 1.11 (6H, s), 1.64 (3H, br.s), 5.35 (1H, m).

8) H. Sulser, J.R. Scherer and K.L. Stevens, *J. Org. Chem.*, **36**, 2422 (1971).

9) β-Dihydrooccidentalol has been obtained in the acid-catalyzed cyclization of Z,E-**20** in 13% yield[2].

10) L.J. Wadhams, R. Baker and P.E. Howse, *Tetrahedron Lett.*, 1697 (1974).

11) The third stereoisomer of α-eudesmol and α-dihydrooccidentalol was obtained as a minor by-product of **7**.

12) Hedycaryol phenyl sulfides usually undergo rapid reaction with aqueous acids to give a complex mixture from which no eudesmol derivatives were obtained.

13) Although the conformation of right half of the molecules can not be defined from the products alone, other conformations with the hydroxyisopropyl projecting into the ring system can easily be eliminated from their scale models.

14) *Inter al.* W. von E. Doering and W.R. Roth, *Tetrahedron*, **18**, 67 (1962). K.J. Shea and P.B. Philips, *J. Amer. Chem. Soc.*, **100**, 654 (1978).

15) In fact, acid-catalyzed cyclization of E,Z-**20** is much slower than that of E,E- and Z,E-**20**.

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