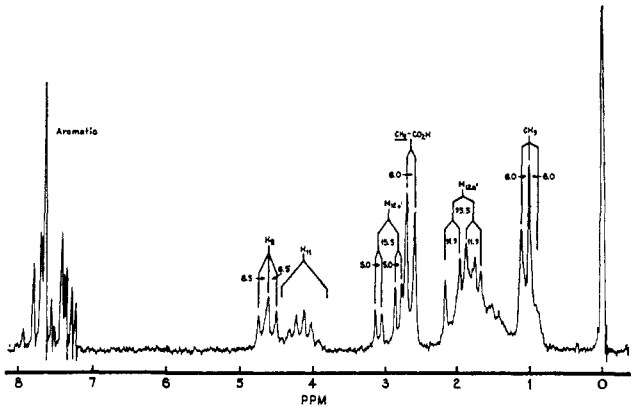


Figure 1. Nmr spectrum of frenolicin.

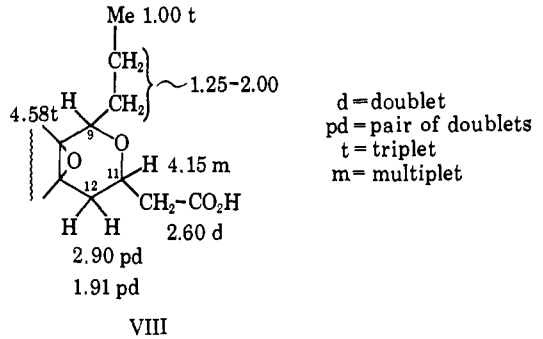
ν_{max}^{KBr} 1740, 1660 (sh), 1640, and 1614 cm^{-1}. As expected of a quinone, the yellow color of neutral solutions and the purple color in base were discharged with dithionite. Deoxyfrenolicin was also obtained by treatment of frenolicin with potassium iodide in refluxing acetic acid.[6]

The nmr spectrum of frenolicin (Figure 1) exhibits a primary C-methyl group with a three-proton triplet at δ 1.00 (J = 6.0 cps). This evidence, in conjunction with the loss of propyl (M − 43) as the strongest fragmentation ion in the mass spectra of frenolicin, O-methylfrenolicin methyl ester (IV), and deoxyfrenolicin methyl ester (VII), indicates the presence of the *n*-propyl grouping in frenolicin. The sharp two-proton doublet at 2.60 (J = 6.0 cps) in the nmr spectrum of frenolicin is assigned to two equivalent methylene protons deshielded by the carboxyl group and coupled with a tertiary proton, *i.e.*, $>CHCH_2COOH$.

A one-proton symmetrical triplet at δ 4.58 (J = 6.5 cps) implies the presence of a $-CH_2CHO-$ grouping. A pair of doublets at δ 2.90 (J = 5.0 and 15.5 cps) is attributed to the A portion of an ABX system where the A and B protons are nonequivalent geminal hydrogen atoms. The higher field signal of the B proton at δ 1.91 also appears as a pair of doublets (J = 11.3 and 15.5 cps). The X proton of the set was located by spin decoupling as a multiplet at δ 4.15. The latter proton was also shown to be coupled to the δ 2.60 methylene adjacent to the carboxyl group, establishing the grouping $-CH_2CH(CH_2COOH)O-$.

It remained to assemble the components that have been detailed above. To satisfy the molecular formula, the two fragments with unspecified oxygen atoms must be joined through an ether bridge, and a methylene group of the propyl side chain must be included in these fragments. An assembly of these portions with the established 1,4-naphthoquinone oxide system in a manner consistent with all foregoing data led to the partial structure VIII. This structure was further substantiated by the spin decoupling of the C-9 proton signal (δ 4.58, triplet to singlet) from an upfield methylene group at *ca.* δ 1.9, which must be part of the *n*-propyl side chain.

The only remaining structural feature to be clarified was the position of the phenolic hydroxyl group. Acylation or methylation of this group changes the nmr signal of the C-9 proton in frenolicin from a symmetrical triplet to a pair of doublets (δ 4.58, J = 3.0 and 10.0 cps) with no effect on the signal of the C-12 protons. This effect is apparently without analogy and is most likely related to the difference in magnetic anisotropy between the chelated carbonyl group of frenolicin and the nonchelated carbonyl of the derivatives. Confirmation of the nonequivalence of the methylene protons adjacent to the C-9 asymmetric carbon in O-methylfrenolicin methyl ester was obtained by spin-decoupling experiments which showed the C-9 proton signal to be collapsed to a doublet by irradiation at either of two different δ values in the methylene region (δ 1.62 and 2.12). On this basis the phenolic group was assigned to C-8 rather than to C-5.



VIII

Consideration of the coupling constants for the C-12 and C-11 protons in frenolicin ($J_{12,11}^{e'a}$ = 5.0 cps, $J_{12,11}^{a'a}$ = 11.3 cps) showed the C-11 proton to be axial.[7] Comparison of the coupling constants of the C-9, C-11, and C-12 protons in the nmr spectrum of deoxyfrenolicin methyl ester ($J_{12,12}^{gem}$ = 19.0, $J_{12,11}^{a'a}$ = 10.0, $J_{12,11}^{e'a}$ = 3.5, $J_{9,12}^{a'e'}$ = 2.0, $J_{9,12}^{e'e'}$ < 1 cps) with the analogous protons in isoeleutherin[5] confirmed the assignment at C-11 and showed the C-9 proton to be pseudo-equatorial. Thus the relative stereochemistry at C-9 and C-11 is as shown in I.

(6) S. Bodforss, *Ber.*, **49**, 2801 (1916).

(7) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959); H. Conroy, *Advan. Org. Chem.*, **2**, 311 (1960); C. N. Banwell and N. Sheppard, *Discussions Faraday Soc.*, **34**, 115 (1962).

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The Total Synthesis of (±)-Copaene and (±)-8-Isocopaene

Sir:

The tricyclic sesquiterpene copaene has been reported as a constituent of numerous essential oils,[1] although the structure of this material was in doubt for many years. Several structures containing a cyclopropane ring were proposed, criticized, and rejected before the correct formulation (**15**) was simultaneously ascertained by two groups of workers.[2] Since that time an unsuccessful

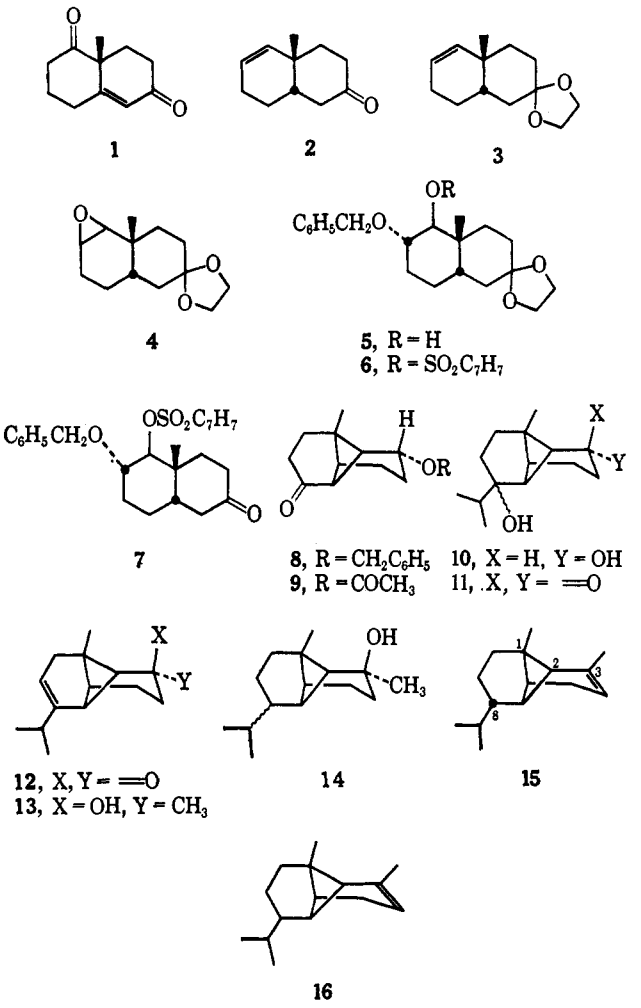
(1) See *inter alia* (a) Schimmel and Co., Berichte Schimmel, April 1914, p 48; (b) G. G. Henderson, W. M'Nab, and J. M. Robertson, *J. Chem. Soc.*, 3077 (1926); (c) L. H. Briggs and W. I. Taylor, *ibid.*, 1338 (1947); (d) L. H. Briggs and M. D. Sutherland, *J. Org. Chem.*, **13**, 1 (1948); (e) F. Vonasek, V. Herout, and F. Sorm, *Collection Czech. Chem. Commun.*, **25**, 919 (1960); (f) L. Westfelt, *Acta Chem. Scand.*, **18**, 572 (1964); (g) F. M. Couchman, A. R. Pinder, and N. H. Bromham, *Tetrahedron*, **20**, 2037 (1964).

(2) (a) P. DeMayo, R. E. Williams, G. Büchi, and S. H. Feairheller, *Tetrahedron*, **21**, 619 (1965); (b) V. H. Kapadia, B. A. Nagasampagi, V. G. Naik, and S. Dev, *ibid.*, **21**, 607 (1965).

attempt at the synthesis of copaene has appeared.[3] We now wish to report the total synthesis of racemic copaene in a rational 17-stage route which confirms the previous structure assignment[2] and additionally provides an authentic specimen of the C-8 stereoisomer.[4,5]

The starting point for our synthesis was the readily available diketone **1**,[11] which was converted into the *cis*-fused octalone **2** by the method reported earlier.[6] Ketalization of octalone **2** furnished in quantitative yield the unsaturated ketal **3**, mp 35° (*Anal.* Found: C, 74.97; H, 9.90),[12] which was converted, with *meta*-chloroperbenzoic acid in chloroform, into the oxide **4**, mp 42–43.5° (*Anal.* Found: C, 69.55; H, 8.72), in 90% yield. When this epoxide was treated with a solution of 1 *N* sodium benzylate in benzyl alcohol at 200°, there was obtained in 70% yield the ether **5**, mp 79–80° (*Anal.* Found: C, 71.99; H, 8.33). Compound **5** was further transformed by the conventional method into its *p*-toluenesulfonate ester **6**, mp 145–146° (*Anal.* Found: C, 66.58; H, 6.92), which was subsequently deketalized with sulfuric acid in aqueous acetone to afford the keto tosylate **7**, mp 103–104° (*Anal.* Found: C, 67.62; H, 6.70).

We were now ready to transform our decalin precurser into the requisite tricyclic skeleton of copaene. The method previously developed by us for this purpose (cyclization with methyl sulfinyl carbanion in dimethyl sulfoxide)[6] served admirably, affording the tricyclic keto ether **8** [oil (*Anal.* Found: C, 79.68; H, 8.00); 2,4-dinitrophenylhydrazone, mp 211–213° (*Anal.* Found: N, 12.69)] in nearly quantitative yield. Compound **8** was then debenzylated, in 55% yield, using 1 *N* hydrogen bromide in glacial acetic acid, to obtain the crystalline keto acetate **9**, mp 66–67° (*Anal.* Found: C, 69.99; H, 7.97), whose nmr spectrum confirmed that the tricyclo[4.4.0.0^{2,7}]decane skeleton was still intact.[13] Alkylation of **9** with isopropyllithium yielded the oily diol **10** as a mixture of the C-8 epimers. This material was oxidized by the method of Jones[14] to the mixture of ketols **11** which was, in turn, directly dehydrated with phosphorus oxychloride in



pyridine to obtain the tricyclic unsaturated ketone **12** [liquid (*Anal.* Found: C, 82.13; H, 10.03); 2,4-dinitrophenylhydrazone, mp 182–184° (*Anal.* Found: N, 14.35)] in an over-all yield of 17% for the three steps.

Ketone **12** reacted with methyllithium in ether to yield the carbinol **13** [viscid oil (*Anal.* Found: C, 81.69; H, 10.81)] which was reduced by hydrogen in the presence of palladized carbon to obtain the mixture of stereoisomeric saturated alcohols **14** [viscid oil (*Anal.* Found: C, 80.86; H, 11.96)] in a ratio of 50:50.[15] When the stereoisomeric mixture **14** was dehydrated with phosphorus oxychloride in pyridine, there was obtained a mixture of (±)-copaene (**15**) and (±)-8-isocopaene (**16**) which was separated by preparative gas chromatography.[16] The synthetic copaene had infrared, nmr, and mass spectra which were identical with those of natural (−)-copaene from copaiba oil, ylang-

(3) M. Brown, *Chem. Commun.*, 340 (1965).

(4) At least two numbering systems have been used for the copaene ring system.[2b,6a] We propose to retain the numbering system of the parent tricyclo[4.4.0.0^{2,7}]decane skeleton, with the bridgehead carbon which bears the methyl group being C-1.[6] Groups attached to carbons 3–5 are designated as *syn* or *anti* relative to C-1, while groups attached to carbons 8–10 are designated as *syn* or *anti* relative to C-2. The correct name for copaene is thus 1,3-dimethyl-8-*anti*-isopropyltricyclo-[4.4.0.0^{2,7}]dec-3-ene.

(5) This structure has been assigned[7] to the sesquiterpene ylangene, first isolated from ylang-ylang oil[8] and later from other sources.[9] However, it has recently been demonstrated that commercial ylang-ylang oil contains copaene but not its stereoisomer.[10] Until this ambiguity is clarified, then, we shall refer to our synthetic material only as (±)-8-isocopaene or by its correct name, 1,3-dimethyl-8-*syn*-isopropyltricyclo[4.4.0.0^{2,7}]dec-3-ene.[4]

(6) C. H. Heathcock, *Tetrahedron Letters*, 2043 (1966).

(7) (a) O. Molt, V. Herout and F. Sorm, *ibid.*, 451 (1965); (b) G. L. K. Hunter and W. B. Brodgen, Jr., *J. Org. Chem.*, **29**, 982 (1964); **30**, 4394 (1965).

(8) V. Herout and D. I. Dimitrov, *Chem. Listy*, **46**, 432 (1952).

(9) (a) M. Holub, V. Herout, and F. Sorm, *Collection Czech. Chem. Commun.*, **24**, 3730 (1959); (b) O. Motl, V Herout, and F. Sorm, *ibid.*, **25**, 1656 (1960); (c) O. Motl, V. G. Bucharov, V. Herout, and F. Sorm, *Chem. Ind.* (London), 1759 (1963).

(10) R. Teranishi, private communication.

(11) (a) P. Wieland and K. Miescher, *Helv. Chim. Acta.*, **33**, 2215 (1950); (b) S. Ramachandran and M. S. Newman, *Org. Syn.*, **41**, 38 (1961).

(12) All compounds reported were characterized by their infrared, nuclear magnetic resonance, and, where feasible, mass spectra. In no case were the spectra incompatible with the assigned structure.

(13) The spectrum of **9** shows a one-proton singlet at τ 7.31, an absorption which we have found to be characteristic for 1-methyltricyclo[4.4.0.0^{2,7}]decan-8-ones.[6]

(14) K. Bowden, I. M. Heilbron, E. R. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

(15) We shall discuss more fully the stereochemistry of hydrogenation of **13** as well as that of **12** in our complete report of this work.

(16) Preliminary purification was effected on a 100 ft × 0.25 in. Carbowax column, with the final purification being done on a 1000 ft × 0.03 in. capillary column. The purification was accomplished by Dr. Roy Teranishi of the Western Regional Laboratories of the USDA in Albany, Calif., who has developed the technique for the isolation and identification of sesquiterpenes from essential oils. We gratefully acknowledge Dr. Teranishi's assistance.

ylang oil, and a chloranthus oil.[2a] The analogous spectra of (±)-8-isocopaene (**16**) were quite similar to those of copaene, but contained significant differences.[17]

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(17) NOTE ADDED IN PROOF. Compound 16 has now been shown, by direct comparison, to be identical with a sample of ylangene from *Schizandva chinensis* (Turcz.) Baill.[9c] We wish to thank Dr. Herout for supplying the sample.

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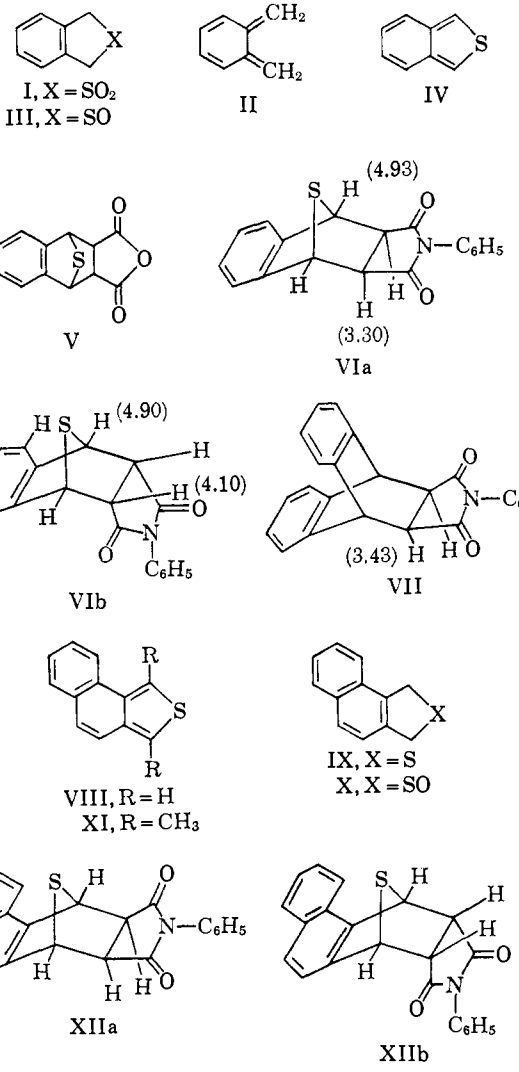
A Novel Synthesis of Isothianaphthenes

Sir:

The thermal decomposition of 1,3-dihydrobenzo[*c*]-thiophene 2,2-dioxide (I) is a convenient and simple method for the generation of the unstable *o*-quinodimethane (II), sulfur dioxide being extruded in the process.[1] We have now studied the thermal decomposition of 1,3-dihydrobenzo[*c*]thiophene 2-oxide (III).[2,3] Contrary to our original expectation, III gave no evidence of decomposition into sulfur monoxide and *o*-quinodimethane, but underwent dehydration under remarkably mild conditions to give benzo[*c*]thiophene (IV, "isothianaphthene"). Thus, when a 1:2 mixture of III and neutral alumina was heated under 20-mm pressure at 100–125° in a sublimer, IV condensed on the cold finger in 94% yield as a white crystalline crust, mp 47–56° (mp 53–55° after resublimation; lit.[4] mp 50–51°). The spectral properties of IV prepared in this way were in agreement with those previously described,[4] and the compound reacted with maleic anhydride to give the expected adduct V, mp 148–152° (lit.[4] mp 153–154°).

Adduct V could be prepared directly (25% yield) from sulfoxide III (without isolation of IV) by refluxing a mixture of III and maleic anhydride in acetic anhydride solution. Similarly, dehydration of III with acetic anhydride in the presence of N-phenylmaleimide gave a mixture of stereoisomeric adducts (86% total yield) which was separated, by fractional crystallization, into the *exo* isomer, mp 203–204° (VIa), and the *endo* isomer, mp 236–239° (VIb). Structures VIa and VIb were distinguished on the basis of their nmr spectra.[5]



The nmr spectrum of VIa shows the two protons α to the imide carbonyls at δ 3.30, a position similar to that (3.43) of the corresponding protons of the N-phenylmaleimide–anthracene adduct (VII);[6] molecular models indicate no shielding of these protons in VIa and VII. Other features of the nmr spectrum of VIa include the bridgehead protons at δ 4.93 and a broad band of nine aromatic protons in the δ 7.0–7.5 region. The nmr spectrum of the *endo* isomer VIb shows, in addition to the bridgehead protons at δ 4.90 and seven aromatic protons in the δ 7.0–7.5 region, two aromatic protons at δ 6.43; the appearance of the latter two protons at an unusually high-field position is the result of shielding by the carbonyls of the imide system. Also, the protons α to the imide carbonyls in VIb appear at δ 4.10, indicating a strong deshielding of these protons by the sulfide bridge.

The generality of our method to the synthesis of higher benzologs of IV is exemplified by the synthesis of the previously unreported naphtho[1,2-*c*]thiophene (VIII). Thus, oxidation of 1,3-dihydronaphtho[1,2-*c*]thiophene

(1) M. P. Cava and A. A. Deana, *J. Am. Chem. Soc.*, 81, 4266 (1959).
(2) S. F. Birch, R. A. Dean, and E. V. Whitehead, *J. Inst. Petrol.*, 40, 76 (1954).
(3) The structure of III is confirmed by an infrared band at 1035 cm^{-1}, characteristic of sulfoxides, and by its nmr spectrum, which is in agreement with that previously reported (R. F. Watson and J. F. Eastham, *J. Am. Chem. Soc.*, 87, 664 (1965)). In addition, oxidation of III with peracetic acid gives sulfone I.
(4) R. Meyer, H. Kleinert, S. Richter, and K. Gewald, *J. Prakt. Chem.*, 20, 244 (1963).
(5) All melting points are uncorrected. Satisfactory analyses were obtained for all new compounds reported. Nmr spectra were determined in $CDCl_3$; ultraviolet spectra were determined in methanol.
(6) M. P. Cava and R. H. Schlessinger, *Tetrahedron*, 21, 3073 (1965).