Sesquiterpenoid Lactones of *Artemisia* Species. I. *Artemisia princeps* Pamp.

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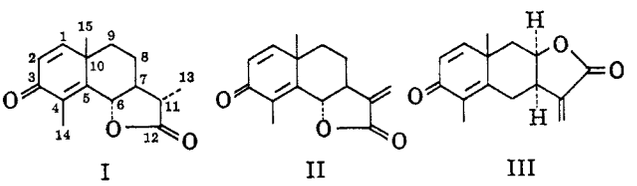
The structure of a sesquiterpenoid lactone from *Artemisia princeps* Pamp. has been shown to be III. Intraspecific variation in chemical composition has been observed in this species of *Artemisia*.

The large and taxonomically difficult genus *Artemisia* (*Compositae*, tribe *Anthemideae*) consists of somewhat over 200 species[1] which are commonly divided into the sections *Abrotanum*, *Absinthium*, *Dracunculus*, and *Seriphidium*,[2] primarily on the basis of floral morphology.

Chemical investigations of *Artemisia* were motivated in early years primarily by the use of *Artemisia absinthium* as a bitter tonic and by the presence in a number of species of the medicinally important compound santonin (I), and in recent years by an interest in a large group of sesquiterpenoid compounds, most of them lactones, that are widely distributed in the *Compositae*, and are, with one or two exceptions[3] found only in this plant family. Although some 50 species of *Artemisia* have been examined with respect to their sesquiterpenoid lactone constituents, about half of these were studied primarily as sources of santonin. One of the most interesting, and potentially most fruitful aspects of the chemistry of this genus derives from the indication from the scanty information available that there may exist relationships between chemical constitution and section or subgenus classification. Santonin is found only in a limited number of the members of the section *Seriphidium* and not in all species in this section. The section *Dracunculus* has not yet been found to contain sesquiterpenoid lactones; those species that have been studied have been found to contain coumarins. Although naphthalenoid sesquiterpenes are typical of the section *Seriphidium*, several examples of this structural type are found in members of the section *Abrotanum*, and guaianolides are found in both *Seriphidium* and *Abrotanum* species, as well as in the section *Absinthium*. The question naturally arises, in view of the few but striking regularities of this kind, whether chemical criteria based upon the nature of the sesquiterpenoid constituents might be of taxonomic value and useful in disclosing phylogenetic relationships.

As part of a study of the sesquiterpenoid constituents of plants of the *Compositae* family, an examination of *Artemisia princeps* Pamp., section *Abrotanum*, was undertaken. *A. princeps* Pamp. is a common perennial which is widely distributed in Japan.[4] The specimen used for this study was collected in northern Honshu. The dried leaves and small stems were crushed and extracted exhaustively with methylene chloride and, after the usual procedure (see Experimental Section), yielded an oily concentrate that showed a multiplicity of spots on a thin layer chromatogram. Chromatography of the mixture of alumina afforded a small yield (about 0.1%) of a crystalline compound, "yomogin,"[5] whose composition was found to be $C_{15}H_{16}O_3$.

The almost complete identity of the infrared spectra of yomogin and santonin in the carbonyl region (1600–1800 cm^{-1}) suggested that yomogin contains the dienone system present in santonin and artemisin. The lactone carbonyl absorption of yomogin was found to be at 1768 cm^{-1}, in contrast to the 1785 cm^{-1} found for santonin and 1776–1788 cm^{-1} reported[6,7] for artemisin and a number of its derivatives. The ultraviolet absorption maximum of yomogin was 238 mμ (log ϵ 4.09), in close accord with that reported for santonin[8,9] and artemisin.[6,7] While the ultraviolet spectrum of santonin falls to a low value of extinction at wavelengths below 238 mμ, that of yomogin falls to a minimum at a high ϵ value at 220 mμ and then rises to high extinction values from 220 to 200 mμ. This fact, along with the low frequency (1768 cm^{-1}) of the lactone carbonyl absorption (and the nmr spectrum), shows that yomogin contains the α-methylene γ-lactone grouping which is commonly found in many sesquiterpenoid lactones of the *Compositae*. These observations, coupled with the composition $C_{15}H_{16}O_3$ can be accommodated (except for the indicated stereochemistry) in the structures II and III. An alternative guaianolide-based dienone structure, such as that found in such related compounds, known in *Artemisia*, as matricarin and deacetoxymatricarin, is excluded, not only because of the nearly complete correspondence between the infrared and ultraviolet spectra of yomogin and santonin, but also because the matricarin chromophore shows an ultraviolet absorp-



I II III

(1) The number of species depends upon the taxonomic treatment and upon the designation of species, subspecies, and varieties by individual authors: for example, (a) H. M. Hall and F. E. Clements, "The Phylogenetic Method in Taxonomy," Carnegie Institution of Washington, D. C., 1923; (b) G. H. Ward, *Contr. Dudley Herbarium*, **4**, 155 (1953); (c) P. Poljakov, *Flora USSR*, **26**, 425 (1961).

(2) Poljakov[1c] combines both *Abrotanum* and *Absinthium* into the subgenus *Artemisia*, and designates the other two sections as subgenera. This grouping was earlier made by A. Gray, "Synoptical Flora of North America," Vol. 1, Part 2, Smithsonian Institution, Washington, D. C., 1884, p 369.

(3) Parthenolide is reported to occur both in *Chrysanthemum parthenium* L. (*Compositae*) and in *Michelia champaca* (*Magnoliaceae*): T. R. Govindachari, B. S. Joshi, and V. N. Kamat, *Tetrahedron Letters*, 3927 (1964). Laserolide, reported to be a guaianolide, is found in *Laser trilobum* (*Umbelliferae*): M. Holub, D. P. Popa, V. Herout, and F. Šorm, *Collection Czech. Chem. Commun.*, **29**, 938 (1964).

(4) Recent examination of a number of specimens of this species, collected in several locations in Japan, has shown that considerable intraspecific variation occurs in what is regarded as a single taxon. This is described below and is the subject of continuing study.

(5) The vernacular name for *Artemisia* in Japan is "yomogi."

(6) A. J. N. Bolt, W. Cocker, and T. B. H. McMurry, *J. Chem. Soc.*, 5235 (1960).

(7) Y. Sumi, *J. Am. Chem. Soc.*, **80**, 4869 (1958).

(8) S. Shibata and H. Mitsuhashi, *Pharm. Bull.* (Tokyo), **1**, 75 (1953).

(9) D. H. R. Barton, J. E. D. Levisalles, and J. T. Pinhey, *J. Chem. Soc.*, 3472 (1962).

tion maximum at 255 mμ, and because of nmr data to be described below.

The nmr spectrum (at 60 Mc) of yomogin confirms the presence of the cyclohexadienone A ring and of the α-methylene γ-lactone shown in II and III. In addition, it provides evidence for structure III. In the nmr spectrum of santonin, the AB system of the protons at C-1 and C-2 is found as a pair of doublets centered at 6.18 and 6.65 ppm (J = 10 cps). Other expected features of the santonin spectrum that are seen are the C-4 methyl group as a 3-H singlet at 2.12, a 3-H singlet for the C-10 methyl group at 1.3, and a 3-H doublet for the C-13 methyl group of the lactone ring at 1.24 ppm (J = 7 cps). The C-6 methine proton of the santonin lactone ring is found as a 1-H doublet centered at 4.92 ppm (J = 8 cps). This accords with the stereochemistry of the lactone ring of santonin (C-6α, C-7β), and the low-field position of the C-6 proton is consistent with its allylic character.

Yomogin shows the C-1/C-2 (AB) system as a pair of doublets almost identical in appearance and position with those of santonin (6.16 and 6.77 ppm, J = 10 cps), and in addition shows a pair of signals at 5.72 and 6.20 ppm (each 1-H) slightly coupled (J = 1.5 cps), probably with the proton at C-7. These are characteristic of the α-methylene grouping of the lactone ring, and agree with the signals shown by this grouping in many of the α-methylene lactones of related sesquiterpenoid lactones. The methyl groups of yomogin appear as sharp 3-H singlets at 1.32 and 1.95 ppm; the C-13 methyl group of santonin (doublet at 1.24 ppm) is absent. All of these data point unequivocally to the structure II or III, and the choice between these can be made upon several grounds, one of which is a consideration of the nature of the signal for the C-6 methine proton. This proton appears in the spectrum of santonin as a 1-H doublet at 4.92 ppm, but in yomogin it is found at 4.48 ppm as a multiplet. The position of this proton signal in yomogin, as compared with that in santonin, shows that it is not allylically disposed, and the nature of its coupling pattern indicates its position at C-8 (as in III) rather than at C-6 (as in II). Were yomogin to have the structure II, the methine proton of the lactone would be expected to show the coupling pattern found in santonin (with a *trans*-fused lactone), or the even more distinctive doublet found in such *cis*-fused lactones as those in ambrosin and coronopilin.[10,11]

An additional observation that clearly disposes of II and points to the correctness of the gross structure III is the following. In the nmr spectrum of santonin, no protons are found at lower fields than the allylic ones (of CH_3) at 2.12 ppm (except for the methine proton at C-6 and the two vinyl protons at C-1 and C-2). All of the protons of the remainder of the ring system of santonin are at higher fields than that of the C-4 methyl group. Yomogin, however, shows a total of four protons downfield from the C-4 methyl group, which is found at 1.95 ppm (in addition to those of the methine proton at C-8 and the four vinyl protons in the 6-ppm region). In structure III there are three allylic protons (two at C-6, one at C-7) in addition to those of the methyl group at C-4. The fourth proton in this integration region is one of those at C-9, deshielded by the lactone ring and moved into the region of around 2.5 ppm (Table I).

TABLE I

Proton position	Ppm	J	Cps
1	6.87	$J_{1,3}$	10
2	6.23		10
CH_3(4)	1.97	$J_{A\,Me}$	1.2
(A) 6(ax)	2.30	J_{AB}	12
(B) 6(eq)	3.07	J_{AD}	12
(D) 7	3.12	J_{BD}	7
(E) 8	4.52	J_{DE}	6–7
(F) 9(ax)	1.73	J_{EF}	5
(G) 9(eq)	2.45	J_{EG}	3
CH_3(10)	1.30	J_{FG}	15.25
$=CH_2$	5.75	J	1.5
	6.25		1.5

The above interpretation of the 63-Mc spectrum has been confirmed and the stereochemistry established as that shown in III, by a nmr spectrum measured at 230 Mc.[12] In Table I are given the values (in ppm) of the shifts for all of the protons in the molecule, and the coupling constants (J, cps) for those indicated.

The *cis*-fused structure of the C-7/C-8 lactone has been assigned in asperilin,[11] ivasperin,[13] and pinnatifidin[14] (although the force of these observations in providing analogy in support of III is lessened by the observations that *trans*-fused lactones of related gross structures are also reported in other *Compositae* lactones, and that the compounds cited above are found in tribes of the *Compositae* other than the *Anthemideae*). It is also to be noted that the C-8 methine proton of the correspondingly constituted lactone of ivasperin[13] is found at 4.59 ppm (its coupling pattern is obscured by the superposition of another proton, and was not analyzed). The corresponding proton of asperilin[13] is found at 4.50 ppm. Both of these are very similar in position to that of the C-8 proton in yomogin (4.48 ppm).

The presence of the naphthalenoid compound yomogin in *A. princeps* (*Abrotanum*) is not a unique occurrence of this ring system in this section. Vulgarin[15] (tauremisin),[16] present in *Artemisia vulgaris* L. (*Abrotanum*), is also naphthalenoid, and it is an interesting fact that this compound is also reported to occur in *Artemisia taurica* Willd.[14] and *Artemisia Szowitziana* Grossh.,[1c] both members of the section *Seriphidium*.

A further observation, still of a qualitative nature, that is noteworthy in connection with the question of the chemotaxonomic significance of these compounds, is the following. Five leaf samples of *A. princeps*,

(10) M. Suchý, V. Herout, and F. Šorm, *Collection Czech. Chem. Commun.*, **28**, 2257 (1963).

(11) The spectra of these lactones have been measured in this laboratory; both show well-defined 1-H doublets at 4.82 ppm, J = 9 (ambrosin), and 5.02, J = 8 (coronopilin).

(12) We are grateful to Dr. N. S. Bhacca of Varian Associates for carrying out this measurement and for his calculations of the coupling constants given in the table. It will be noted that there are some small but trivial discrepancies between the chemical shifts measured on the A-60 and the 230-Mc instrument.

(13) W. Herz and N. Viswanathan, *J. Org. Chem.*, **29**, 1022 (1964).

(14) W. Herz, R. B. Mitra, K. Rabindran, and N. Viswanathan, *ibid.*, **27**, 4041 (1962).

(15) T. A. Geissman and G. A. Ellestad, *ibid.*, **27**, 1855 (1962).

(16) K. S. Rybalko and L. Dolejs, *Collection Czech. Chem. Commun.*, **26**, 2909 (1961).

collected in Japan,[17] were assayed by thin layer chromatography (tlc) of crude extracts, prepared by chloroform extraction of the plants and ethanol–water extraction of the residues of the chloroform extracts. Only one of the five contained yomogin in significant amount. It was possibly present in trace amount in one other specimen, completely lacking in three. Of the four lacking yomogin, the thin layer chromatograms of two were nearly identical, the other two being similar to each other but differing in detail from the first pair. Further investigation of this intraspecific chemical diversity is planned.

These observations suggest that chemical constitution may not be a reliable criterion upon which to draw conclusions as to taxonomic status and that "chemical races," such as are known to exist in other tribes of the *Compositae*,[18] may be encountered within a given taxon. It is believed, however, that the chemotaxonomic value of the sesquiterpenoid constituents of the *Artemisia* can be assessed only after more information has been accumulated.

A minor constituent of *A. princeps* was also isolated in this work. By manipulation of column fractions other than those containing yomogin, there was isolated a small amount of 7-methoxycoumarin (herniarin). The presence of coumarins in the *Anthemideae* has been known since the isolation of 7-methoxycoumarin from *Matricaria chamomilla* L. in 1914,[19] and since that time scopoletin has been isolated from *Artemisia abrotanum*,[20] and both 6,7-dimethoxycoumarin (scoparone) and 7-methoxycoumarin have been found in several species of *Artemisia* of the section *Dracunculus*.[21–24]

Experimental Section

Extraction of Plant Material.—The "yomogi" (*A. princeps* Pamp.) used was a collection made in the fall of 1964 in northern Honshu, Japan. The air-dried plants were stripped of leaves and small stems and this material (3.8 kg) was extracted with methylene chloride by allowing it to stand for several days covered with the solvent. Evaporation of the solvent yielded a thick green-black tar. This was dissolved in 200 ml of hot ethanol, and to the solution was added 500 ml of hot water, with shaking. The aqueous layer was separated from a black, tarry deposit (the latter was re-extracted, again in the same way) and filtered with the aid of Celite and a little Norit. The cloudy yellow filtrate, now free of tar and chlorophyll, was extracted with chloroform (five 100-ml portions); the chloroform solution, after drying over sodium sulfate, was evaporated *in vacuo*. The residual viscous yellow-brown syrup (41 g) did not yield a crystalline product upon manipulation in the usual ways. An infrared spectrum of the crude oil showed well-defined peaks at 3450 (OH), 1775 (γ-lactone), and 1655 (C=C) cm^{-1}. A thin layer chromatogram showed that the oil was a mixture of many components.

Chromatography.—The crude oily product was soluble in about 100 ml of benzene, but further dilution with benzene caused the separation of a considerable quantity of a gummy material. Benzene was added to a total volume of 250 ml and the clear yellow supernatant solution that formed on standing was decanted. The gummy residue was soluble in 10 ml of chloroform, and dilution of this solution with 100 ml of benzene led again to the formation of a gummy precipitate and a clear supernatant solution.

The combined clear solutions (about 350 ml) were added to a column of alumina (Woelm, neutral, II, 4 × 30 cm) prepared in benzene, and the column was eluted successively with benzene, benzene–ether, ether, and ether–ethanol. After 450 ml of benzene, the succeeding three 50-ml fractions yielded oily residues (upon removal of the solvent) that crystallized spontaneously when ether was added. No other fraction gave any crystalline product. In a larger run, carried out substantially as described here, a 14-kg sample of dried yomogi gave 1.09 g of pure, crystalline product (0.08%).[25]

Yomogin.—The crystalline product obtained from the column eluates was recrystallized from ethyl acetate, from which it formed crisp white needles, mp 201–202°. It gave no color with alcoholic alkali, in contrast with santonin and artemisin, both of which turn deep pink on heating with this reagent. The mixture melting point of yomogin with artemisin (mp 201–202°) was about 160–180°.

Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.78; H, 6.56. Found: C, 74.07; H, 6.56.

Yomogin was optically active: $[\alpha]^{20}D$ −88° (*c* 0.11, $CHCl_3$). It gave a single well-defined spot on thin layer chromatography; with benzene–acetone (4:1) on silica gel G the R_f was almost identical with that of santonin.

The infrared spectrum of yomogin was nearly identical with that of santonin in the carbonyl double-bond region. The following peaks had nearly the same relative intensities: yomogin, 1615, 1633, 1665, 1768; and santonin, 1618, 1638, 1667, 1785 cm^{-1} ($CHCl_3$).

Yomogin showed a maximum absorption in the ultraviolet at 238 mμ (log ϵ 4.09), which is almost identical with that of santonin and of several derivatives of artemisin.[6,7] The ultraviolet curve fell to a minimum at about 220 mμ, then rose sharply between 215 and 200 mμ, a behavior characteristic of the α-methylene γ-lactone grouping.

The nmr spectra of yomogin and santonin, described above, were measured in deuteriochloroform solution.

Extraction of *Artemisia princeps* Pamp. (Tokyo).—A collection of young plants of *A. princeps* growing on the campus grounds of Tokyo University (1000 g, dry) was extracted as described above. Careful chromatography on alumina yielded a series of fractions, the R_f on tlc of which showed the expected progression from high to low R_f as the eluent was varied from benzene to methylene chloride. Those fractions showing (by tlc) components in the range characteristic of yomogin were carefully examined and rechromatographed. All efforts to obtain crystalline material failed, and the chromatographic evidence indicated that yomogin was not present. The conclusion that yomogin was absent from this plant sample was reinforced by the fact that, in three separate experiments using the yomogin-containing sample, crystalline yomogin was obtained with ease in every case.

Later experiments (small scale, tlc) with various specimens of *A. princeps* from different sources confirmed the findings that there exist morphologically indistinguishable races, in some of which yomogin is present, in others absent.

Isolation of 7-Methoxycoumarin.—The column fractions other than those from which yomogin was isolated were combined and treated as follows. The total oily material was partitioned between hexane and 60% ethanol, and the ethanol layer washed further with fresh hexane, then extracted with benzene and then with ether. Thin layer chromatograms of the hexane layer indicated that it contained only high R_f, fatty materials; it was discarded. The benzene and ether extracts were combined, evaporated, and chromatographed on alumina. None of the fractions (benzene–ether) yielded crystalline material, and the middle series of fractions showing similar tlc patterns were treated with acetic anhydride–pyridine in the hope that an acetyl derivative might be obtained. The crude oil recovered from the acetylation reaction was chromatographed on alumina (benzene–hexane to benzene–ether). A middle fraction, eluted with benzene, crystallized upon removal of the solvent. The compound proved

(17) The author is grateful to Professor S. Shibata for securing these specimens. The specimens were not morphologically distinguishable (Professor H. Hara, Botany Department, Tokyo University, Japan) and were all identified as members of a single taxon.

(18) For example, see H. E. Miller, H. B. Kagan, W. Renold, and T. J. Mabry, *Tetrahedron Letters*, 3397 (1965).

(19) F. B. Bowers and A. Browning, *J. Chem. Soc.*, **105**, 2280 (1914).

(20) P. Schmersah, *Naturwissenschaften*, **52**, 498 (1965).

(21) E. Steinegger and A. Brantschen, *Sci. Pharm.*, **27**, 184 (1959).

(22) T. A. Geissman and S. Murayama, unpublished observation of the presence of herniarin and scoparone in *Artemisia dracunculus* L.

(23) K. Imai and N. Sampei, *Ann. Rept. Takamine Lab.*, **4**, 54 (1952).

(24) A. N. Ban'kovskaya and A. I. Ban'kovskii, *Tr. Vses. Nauchno-Issled. Inst. Lekarstv. i Aromat. Rast.*, 177 (1959).

(25) The author is grateful to Professor J. Shoji of Showa University, Tokyo, for carrying out this large-scale extraction.

to be 7-methoxycoumarin. It had mp 116–117° [lit. (for 7-methoxycoumarin) mp 115–116°[19] and 117–118°[26]].

Anal. Calcd for $C_{10}H_8O_3$: C, 68.18; H, 4.55. Found: C, 67.83; H, 4.47.

The ultraviolet spectrum (λ_{max} 322 mμ, λ_{min} 259 mμ) was nearly identical with that of umbelliferone, and an infrared spectrum of the compound was identical with that of an authentic sample of 7-methoxycoumarin.[27]

(26) B. B. Dey, R. H. R. Rao, and T. R. Seshadri, *J. Indian Chem. Soc.*, **11**, 743 (1934).

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(27) Grateful acknowledgment is made to Mr. M. A. Irwin, who prepared the specimen of herniarin and measured its infrared spectrum.

Experiments Directed toward the Total Synthesis of Terpenes. VII. The Synthesis of (±)-8β-Carbomethoxy-13-oxopodocarpanone, a Degradation Product of Phyllocladene[1]

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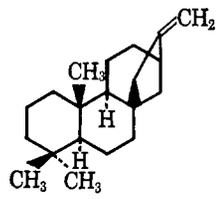
The synthesis of (±)-8β-carbomethoxy-13-oxopodocarpanone (**23**) *via* the Claisen rearrangement of the vinyl ether of 13α-hydroxypodocarp-8(14)-ene (**18**) is discussed.

The bridged bicyclic C/D ring structure is common to several members of the tetracyclic diterpenes. This structural unit, in the form of a substituted bicyclo[3.2.1]octane system, is present in phyllocladene **1**,[5] kaurene **2**,[6] and hibaene **3**.[7] Oxygenated variants of the same bicyclo[3.2.1]octane system can be found in steviol **4**,[8] gibberellic acid **5**,[9] and the alkaloid garryine **6**,[10] while the oxygenated bicyclo[2.2.2]octane system is present in the alkaloid atisine **7**.[11] The wide distribution of this structural feature made a scheme of general utility for the synthesis of such bridged bicyclic systems appear quite useful to ultimate total synthesis efforts in this area. The structural simplicity of the phyllocladene **1** system appeared to offer the logical substrate on which to practice and initial efforts were launched in this direction.

Inspection of the phyllocladene molecule **1** reveals the presence of the familiar *trans-anti-trans*-perhydrophenanthrene system (boldface in structure **1**) that is so prevalent among the diterpenes. The presence of this ring system suggested that formation of the bridged



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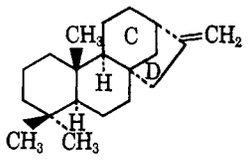

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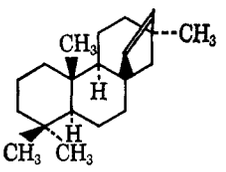

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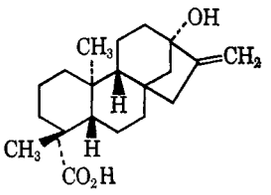

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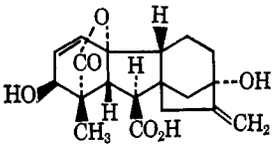

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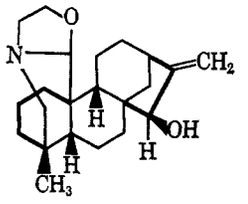

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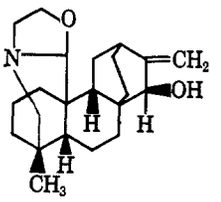

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component of the structure **8** might be accomplished through a generalized intermediate such as that represented by structure **9**. The concept involves introduction of a functionalized carbon atom, C–X, at C_8 of the perhydrophenanthrene nucleus, and the retention of sufficient functionality, Y, in ring C to allow ultimate closure of the carbon bridge to C_{13}. The exact type of

(1) A preliminary report of this work appeared in *Tetrahedron Letters*, **No. 17**, 1 (1960).

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(4) Public Health Service Research Fellow, National Heart Institute, 1958–1960.

(5) P. K. Grant and R. Hodges, *Tetrahedron*, **8**, 261 (1960); L. H. Briggs, B. F. Cain, B. R. Davis, and J. K. Wilmhurst, *Tetrahedron Letters*, **No. 8**, 8 (1959).

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