tively rapid in all cases; it is possible that for some substituents (1–4?) the k_2 step is, in fact, rate determining. This alternative is being investigated by taking measurements of the coupling rates for 4-methoxy- and 4-methyltriphenylamine and the corresponding para-deuterated analogs. If proton loss is rate determining in these systems, then a primary isotope effect should be seen.

These mechanistic alternatives are being explored more fully, but it is felt that the radical–radical pathway is operative in these amine systems and that resonance stabilization through electron delocalization will require different substituent parameters from those for carbonium ions in some cases.

In summary, then, it appears that cation radical stabilities are fairly well predicted by existing σ^+ values in the literature, with the exception of the formyl, phenyl, and strong electron-donating substituents. Studies now in progress on the coupling rates of electrochemically generated carbazole cation radicals, as well as spectroscopic studies on several aromatic amine cation radical systems, should yield a reliable set of reactivity parameters to describe the effects of different functional groups upon cation radical stabilities.

Acknowledgments.—Financial support for this work through NSF Grant No. GP-20606 is gratefully acknowledged. Helpful discussions with Drs. R. W. Fish and R. I. Walter are also acknowledged. Special thanks are also due to Dr. R. N. Adams and Dr. D. E. Smith for their support and encouragement.

Chemistry of Santonic Acid. Oxidative and Reductive Modifications[1,2]

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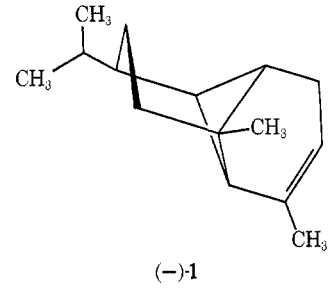
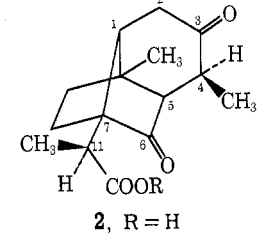
Reduction of santonic acid (**2**) with Na/Hg in aqueous base gives the previously reported "dihydrosantonic acid" which is now shown to be **4**. The C-11 epimer of **4** (*i.e.*, **6**) is similarly obtained from metasantonic acid (**5**), and is also found to be formed by epimerization of **4** during prolonged reductions of **2**. An acetoxy lactone (mp 204°) previously reported to be obtained on treatment of "dihydrosantonic acid" with acetic anhydride is shown to be **8** and was probably derived from **6** present as a contaminant in earlier preparations of **4**; a new acetoxy lactone, **7** (mp 140°), was obtained from pure **4**. An attempt to prepare "dihydrosantonide" by heating **4** in acetic acid at 145–150° gave **10**. Reduction of **2** with $NaBH_4$ gave **11**. Methyl ester **11a** gave mesylate **13a** with CH_3SO_2Cl and acetate **13b** with acetic anhydride–$HClO_4$. Mesylate **13a** on acetolysis (acetic acid, sodium acetate) gave epoxy acetoxy ester **14**, as evidenced by formation of **11** on hydrolysis. Heating either **11** with CH_3OH–H_2SO_4 or **13a** with collidine gave olefins **15** and **16a**. The presence of a dissymmetric β,γ-unsaturated ketone chromophore in **16a** gives rise to a very strong negative Cotton effect in the ORD and CD curves of **16a** which is of the magnitude observed for some other ketones of this type. Lithium–ammonia reduction of **17** yielded **18**, which gave 6β alcohol **3** on deketalization; similarly, Li–NH_3 reduction of **16** gave **19**. Reduction of **17** with $LiAlH_4$ afforded **20** and **21**. Treatment of **20** with HCl gave lactone **22**, which afforded 6α alcohol **23** on basic hydrolysis. Treatment of the mesylate of **18a** (**24**) with potassium *tert*-butoxide yielded sultone **25**, which gave **26** on hydrolysis. Deketalization of **24** afforded 3-keto mesylate **27**, which gave **28** on contact with Al_2O_3. Alkaline peroxide oxidation of **2** gave "aposantonic acid" (**29**), for which a stereostructure is proposed; a previously unreported keto lactone acid (**31**) formed by Baeyer–Villager oxidation of **2** was also obtained. Repetition of the previously reported hypobromite oxidation of **2** gave "oxysantonic acid," now formulated as **32** on the basis of analytical and spectroscopic data for several formerly reported derivatives of **32**.

The assignment of a tricyclo[4.4.0.0^{2,7}]decane structure to (−)-copaene (**1**)[3] and related naturally occurring sesquiterpenoids[4] has stimulated interest in the synthesis of this system.[5] In an attempt to achieve a synthesis of (+)-**1** *via* the route outlined in Scheme I, santonic acid (**2**)[6,7] was utilized as starting material for the preparation of suitable derivatives of **3**. Although



(−)-**1**



2, R = H
2a, R = CH_3

an example of the key 5 → 4 ring contraction step[8] has not been effected to date, the work described in this report has led to clarification of several previously reported transformations of santonic acid (**2**). These are discussed along with several additional reactions of **2** and related derivatives.

Reduction of Santonic Acid. A. Sodium Amalgam

(1) Abstracted from the Ph.D. Dissertation of D. S. Daniel, Washington University, 1970.

(2) A portion of this work has been outlined in a preliminary communication: A. G. Hortmann and D. S. Daniel, *Tetrahedron Lett.*, 2599 (1970).

(3) (a) G. Büchi, S. H. Feairheller, P. De Mayo, and R. E. Williams, *Proc. Chem. Soc.*, 214 (1963); *Tetrahedron*, **21**, 619 (1965); (b) V. H. Kapadia, B. A. Nagasampagi, V. G. Naik, and S. Dev, *Tetrahedron Lett.*, 1933 (1963); *Tetrahedron*, **21**, 607 (1965).

(4) *E.g.*, ylangene, O. Motl, V. Herout, and F. Sorm, *Tetrahedron Lett.*, 451 (1965); copadiene, V. H. Kapadia, V. G. Naik, M. S. Wadia, and S. Dev, *Tetrahedron Lett.*, 4661 (1967); mustakone, ref 3b.

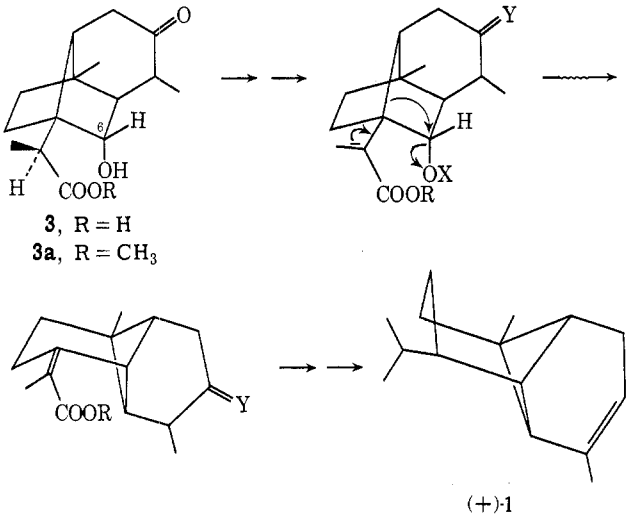
(5) A synthesis of (±)-copaene and (±)-ylangene has been described: C. H. Heathcock, R. A. Badger, and J. W. Patterson, Jr., *J. Amer. Chem. Soc.*, **89**, 4133 (1967).

(6) R. B. Woodward, F. J. Brutschy, and H. Baer, *ibid.*, **70**, 4216 (1948).

(7) For a review of santonic acid chemistry, see J. Simonsen and D. H. R. Barton, "The Terpenes," Vol. III, Cambridge University Press, New York, N. Y., 1952, pp 295–311. The stereochemistry at C-11 in santonin has since been shown to be 11*S*: J. D. M. Asher and G. A. Sim, *Proc. Chem. Soc.*, 335 (1962), and references cited therein.

(8) To our knowledge, the key ring-contraction step depicted in Scheme I has no precedent. Conceptually it may be viewed as analogous to the pinacol-type rearrangements observed for oxyanions derived from 1,2-diol monosulfonate esters. For a review, see D. Redmore and C. D. Gutsche, *Advan. Alicycl. Chem.*, **3**, 46 (1971).

SCHEME I



Reduction.—Following the suggestion[6] that "dihydrosantonic acid"[9-11] (DHS) is probably either **3** or its C-6 epimer, the reduction of santonic acid (**2**) with sodium amalgam (Na/Hg) was reinvestigated. Heating **2** under N_2 with 5% Na/Hg in 10% aqueous NaOH solution for 2 hr at reflux temperature afforded a crystalline acid in 91% yield which analyzed correctly for a dihydro derivative of **2** ($C_{15}H_{22}O_4$), could be readily reoxidized to **2** with Jones–Weedon reagent,[12] and has a broad ir absorption band at 3550–2550 cm^{-1} and ν_{max} at 3390, 3330, and 1700 cm^{-1}; the nmr spectrum of the product exhibits signals for methyl groups at δ 0.92 (s), 1.09 (d), and 1.12 (d), a quartet due to H-11 at 2.61, and a broad absorption band for three protons at 4.25–4.92. Esterification (CH_2N_2–ether) afforded "methyl dihydrosantonate" (methyl DHS) having mp 110–112° (lit.[11] mp 111–114°), ir ν_{max} 3570, 3440, and 1725 cm^{-1}, and nmr signals for C-methyl groups at δ 0.98 (s), 1.19 (d), and 1.23 (d), for H-11 at 2.76 (q), for $-OCH_3$ at 3.67 (s), and for two additional protons at 3.20 (br s). The latter two protons in the nmr spectrum of another sample of methyl DHS [which was prepared directly by treatment of methyl santonate (**2a**) with Na/Hg in absolute methanol] appeared at δ 2.92 (br s, 1 H) and 3.28 (br s, 1 H).[13]

Although the data described for DHS and methyl DHS are compatible with structures **3** and **3a** or their C-6 epimers, the disparity in chemical shift values for peaks attributable to a carbinyl proton (CHOH) in the acid (*ca.* δ 4.2–4.9) *vs.* the methyl ester (*ca.* δ 3.2–3.3) suggested that a –CHOH group was not present in either compound. Indeed, not one but *both* the protons appearing at δ 2.92 and 3.28 in methyl DHS were found to be readily exchangeable for deuterium, indicating that *two* hydroxyl groups must be present in methyl DHS, and furthermore, that both hydroxyls must be tertiary. On the basis of the data cited, DHS may therefore be assigned structure **4**.

Formation of the 1,2-cyclobutanediol moiety in **4** can be viewed as an example of an intramolecular pinacol reduction[14] of the 1,4-diketone system in **2**. Further support for structure **4** came from the observation that no significant exchange of hydrogen for deuterium occurred when DHS (**4**) was refluxed with 0.3 *M* NaOD in D_2O for 4 hr. (Similar treatment of santonic acid (**2**) led to formation of 9% **2**-d_0, 29% **2**-d_1, 36% **2**-d_2, 20% **2**-d_3 and 5% **2**-d_4 as determined by mass spectroscopic analysis.)

Treatment of metasantonic acid (**5**), the 11*R* epimer of santonic acid (**2**),[15] with Na/Hg afforded dihydrometasantonic acid, which may be formulated as **6**. Both **6** and its methyl ester **6a** exhibit spectral characteristics similar to those described for **4** and **4a** and were readily reoxidized by Jones–Weedon reagent to **5** and **5a**; furthermore, addition of acetic-d_4 to the nmr sample solution of **6a** gave rise to a new broad singlet (2 H) at δ 6.3 and disappearance of the 1 H signals due to –OH which appeared at δ 3.69 and 4.78. No reduction products of metasantonic acid (**5**) have been reported previously.[7]

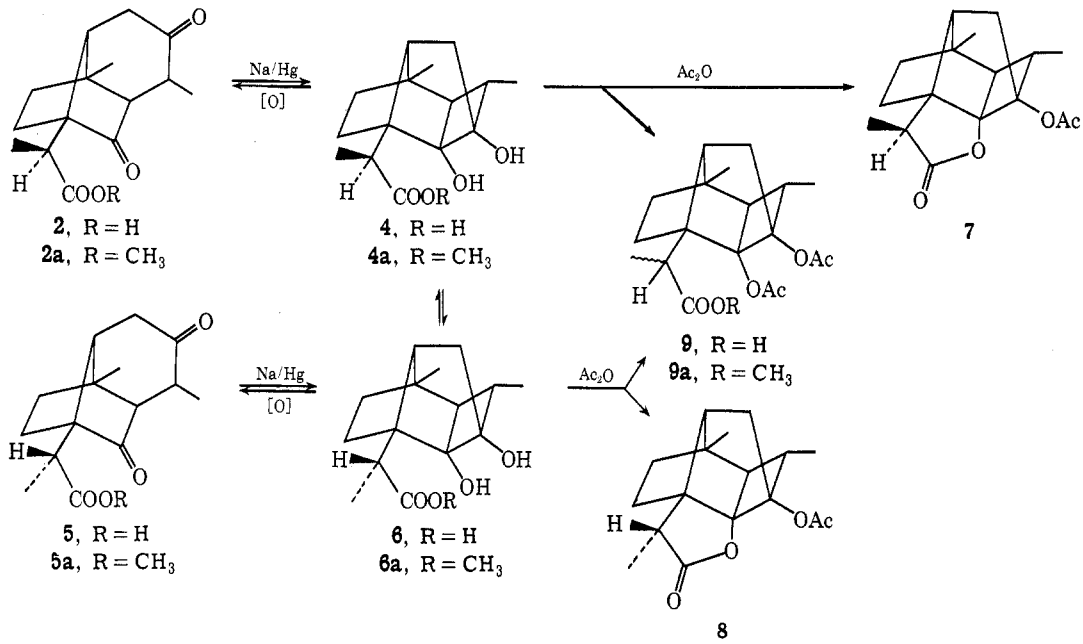
When the reduction of **2** was performed according to the procedure of Wedekind,[10] which calls for heating **2** in 10% NaOH solution at reflux in the presence of 5% sodium amalgam until H_2 liberation ceases (typically 20–48 hr), *mixtures* of **4** and **6** were obtained which contained >50% of **6** after 20 hr. In separate experiments prolonged treatment of **4** with aqueous hydroxide in the absence of reducing agent was also found to yield mixtures of **4** and **6** in which the ratios **4**:**6**[16] were found to be dependent upon the length of exposure; treatment of santonic acid (**2**) under similar conditions led to negligible amounts of metasantonic acid (**5**). Thus the formation of **6** during lengthy Na/Hg reductions of **2** occurs primarily by epimerization of **4**, possibly *via* a lactonic intermediate in which formation of an anion at C-11 would not be disfavored (as is the case for **2**) by the proximity of a carboxylate anion (Scheme II).

The likelihood that samples of "dihydrosantonic acid" used in at least some of the work reported in the earlier literature[9-11] contained substantial amounts of dihydrometasantonic acid (**6**) is indicated by the heretofore puzzling observation of Cannizzaro[9] that silver oxide oxidation of "dihydrosantonic acid" yields metasantonic acid. Repetition of this experiment using pure **4** afforded only **2** and unoxidized **4**.

In a similar vein, treatment of **4** with acetic anhydride under conditions approximating those reported by Wedekind[10] produced two acetate derivatives—an acetoxy lactone and a diacetoxy acid.[6,7,10] The acetoxy lactone (mp 140–142°) exhibits ir ν_{max} at 1780 and 1735 cm^{-1} and nmr peaks at δ 1.10 (d, 3), 1.13 (s, 3), 1.32 (d, 3), 2.04 (s, 3), 2.59 (q, 1), and 2.62 (q, 1) and may be reasonably formulated as **7**. The melting point of **7** did not agree with that of Wedekind's acetoxy lactone (mp 204°);[10] however, an acetoxy lactone obtained by treatment of dihydro*meta*santonic acid (**6**) with acetic anhydride under identical conditions had

(9) S. Cannizzaro, *Gazz. Chim. Ital.*, **6**, 341 (1876).
(10) E. Wedekind and O. Engel, *J. Prakt. Chem.*, **139**, 115 (1934).
(11) C. Harries and A. Stähler, *Chem. Ber.*, **37**, 258 (1904).
(12) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).
(13) The ester prepared from **2a** was otherwise identical spectroscopically to methyl DHS prepared from **2**.
(14) G. W. Griffin and R. B. Hager, *J. Org. Chem.*, **28**, 599 (1963). Also, *cf.* E. Wenkert and J. E. Yoder, *ibid.*, **35**, 2986 (1970); J. G. St. C. Buchanan and P. D. Woodgate, *Quart. Rev., Chem. Soc.*, **23**, 522 (1969).
(15) R. B. Woodward and P. Yates, *Chem. Ind. (London)*, 1391 (1954).
(16) The variation in the ratio of **4**:**6** with reaction time could be determined by working up aliquots of the reaction mixture, esterifying the crude mixtures of **4** and **6** obtained with CH_2N_2, and estimating the relative areas beneath the peaks due to the $-OCH_3$ group in **4a** and **6a**. A further check on the ratios of **4** to **6** was made by performing similar assays on mixtures of **2a** and **5a** obtained by oxidation of the mixtures of **4a** and **6a** after the latter had been assayed.

SCHEME II



spectral characteristics very similar to those of **7** and did correspond in melting point (204.5–206°) to that obtained from "dihydrosantonic acid" by Wedekind. Consequently, it may be concluded that Wedekind's acetoxy lactone having mp 204° is **8** and was derived from dihydrometasantonic acid, which was probably present as a contaminant in Wedekind's "dihydrosantonic acid."[17-20]

The diacetoxy acid obtained from **4** in low yield has spectral characteristics compatible with structure **9** and exhibits a melting point (235–237.5°) which is comparable with the melting point of Wedekind's diacetoxy acid (232°).[10] Similar agreement was found for the corresponding methyl ester **9a**, mp 150° (lit.[10] mp 151°). Owing to a lack of sufficient material, the diacetoxy acid obtained in very low yield by treatment of **6** with acetic anhydride was not completely purified and characterized, thus leaving the configuration of **9** at the carboxyl-bearing carbon open to question.[21]

(17) The acetoxy lactone, mp 204° (*i.e.*, **8**), had been prepared earlier[18] by treatment of "dihydrosantonic acid" with acetyl chloride. Cannizzaro also reported the formation of "dihydrosantonide," [18] $C_{15}H_{18}O_8$," mp 155–156°, upon heating "dihydrosantonic acid" with acetic acid at 140–150° in a sealed tube. "Dihydrosantonide" was also reportedly converted with acetic anhydride or acetyl chloride to the acetoxy lactone, mp 204°.[18,19] Hence "dihydrosantonide" must be the desacetyl lactone corresponding to **8** and may also be assumed to be in the meta series.

It is a matter for speculation whether "dihydrosantonide" was formed directly from metasantonic acid present in "dihydrosantonic acid," or whether epimerization at C-11 occurs during or after the formation of "dihydrosantonide" from **4**. (Acetic acid at elevated temperatures is known to catalyze epimerization at C-11 in the santonic acid and santonide series.[20])

(18) S. Cannizzaro and L. Valente, *Gazz. Chim. Ital.*, **8**, 309 (1878).

(19) See also ref 7, p 297.

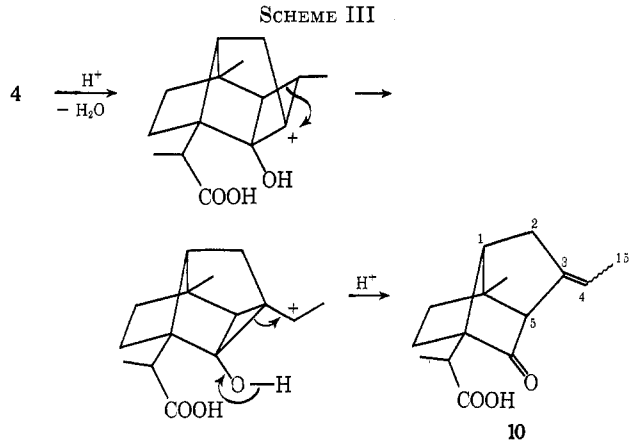
(20) R. B. Woodward and E. G. Kovach, *J. Amer. Chem. Soc.*, **72**, 1009 (1950), and references cited therein.

(21) An attempt to resolve this point by examining the product of basic hydrolysis of **9** followed by esterification (CH_2N_2–Et_2O) was unsuccessful, yielding a mixture of **4a** and **6a** in a ratio of 3:5 (nmr assay). The epimerization at C-11 observed during hydrolysis must occur at a stage prior to the actual formation of **4** since the conditions used were not sufficient (see Experimental Section) to cause isomerization of **4** to **6**.

Hydrolysis–esterification of **7** also led to a mixture of **4a** and **6a** (3:1), whereas similar treatment of **8** led to **6a** of >95% purity. [It is noteworthy that in earlier reports[10,18] hydrolyses of both "dihydrosantonide"[17] and the acetoxy lactone,[10,18] mp 204° (shown now to be in the meta series), as well as the diacetoxy acid,[10] mp 232° (*i.e.*, **9**), were claimed to afford unspecified yields of pure dihydrosantonic acid (melting point and mixture melting point determinations).[19]]

An attempt to prepare "dihydrosantonide" by heating **4** in a sealed tube with acetic acid[17,18] over a range of conditions yielded only starting DHS (**4**) and an olefinic acid to which structure **10** could be assigned on the basis of analytical and spectral data (see Experimental Section); a possible route for the formation of **10** is depicted in Scheme III. Prolonged heating ap-

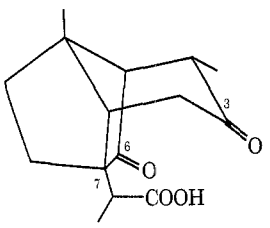
SCHEME III



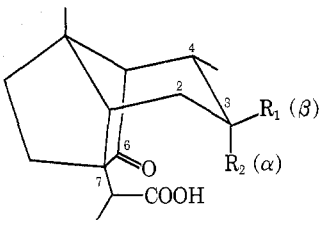
parently converted **10** to another olefinic product which was not isolated or characterized. No significant quantity of neutral material having spectral properties expected of "dihydrosantonide"[17,18] could be isolated. No attempt was made to prepare "dihydrosantonide" directly from **6** (from which it presumably originated in the earlier work[17]).

B. Sodium Borohydride Reduction.—In another approach to **3** or its C-6 epimer, santonic acid was reduced with $NaBH_4$. The dihydro derivative obtained was assigned structure **11** having hydroxyl at C-3 when it was found that the methyl ester **11a** exhibits only one strong carbonyl band at 1735 cm^{-1} (five-ring C=O and $COOCH_3$). Further confirmation of the location of the hydroxyl group followed from the observation that no significant incorporation of deuterium occurred when **11** was heated at reflux for 4 hr with 0.3 *M* NaOD in D_2O.

The hydroxyl group in **11** was assigned the α configuration on steric grounds. Models of **2** indicate that approaches of borohydride to the β face of the cyclohexane ring are less hindered than approaches to the α face, the latter being blocked by the C-6–C-7



2

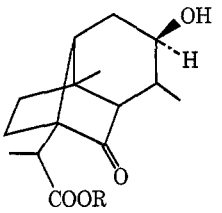


11, $R_1 = H$; $R_2 = OH$
12, $R_1 = OH$; $R_2 = H$

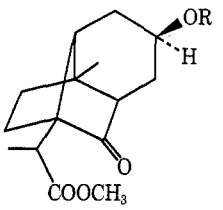
bridge carbons.[22] In addition, the observed half-width ($W_{1/2}$ = 7.5 Hz) of the nmr peak due to H-3 is in agreement with that expected for most reasonable conformations of **11** ($W_{1/2} \cong$ 6–12), and out of the range expected for H-3 in **12** ($W_{1/2} \geqq 20$) if it is assumed that the 6 ring in **12** will most likely be in a chair conformation.[23]

Several attempts were made to prepare **12** to aid in confirmation of the stereochemical assignments in the 3-OH series, as well as to open a possible route to **3** *via* base-induced hydride shift of H-3 to C-6.[24] In an initial approach, **11a** was converted into the 3α-mesylate **13a**. When subjected to acetolysis conditions, **13a** afforded not the desired 3β-acetoxy ester **12a** but the 6β-acetoxy-3α,6α-epoxy ester **14**. The structure of **14** was deduced from the following data: (a) the carbinyl proton (H-3) or **14** appears as a multiplet, $W_{1/2}$ = 7.5 Hz, at δ 4.05 suggesting that the orientation of H-3 relative to H-2, H-2′, and H-4 is similar to that in **11**; (b) hydrolysis of **14** affords **11**, and not a new alcohol (*viz.*, **12**); and (c) the acetate **14** is not identical with **13b**, which could be prepared by treatment of **11a** with acetic anhydride–$HClO_4$ and exhibits an nmr peak for its carbinyl proton at δ 4.99 (q, 1, J = 3.5 Hz).

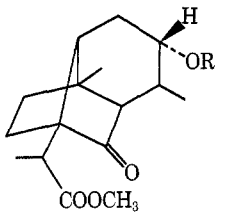
The acetoxy epoxy ester **14** presumably forms *via* formation of an intermediate C-3 carbonium ion which interacts readily with the carbonyl oxygen at C-6 to give an oxygen-bridged C-6 carbonium ion, which can react further with acetate ion to yield **14**. The formation of **14** and the nmr spectral characteristics of H-3 in **13b** and **14** conclusively support the configurational assignment at C-3 in **11**.



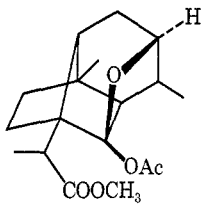
11, R = H
11a, R = CH_3



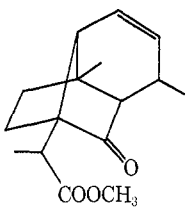
13a, R = OSO_2CH_3
b, R = $OCOCH_3$



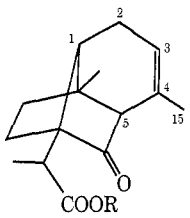
12, R = H
12a, R = $OCOCH_3$



14



15



16, R = H
16a, R = CH_3

As a second approach to **12**, hydroboration of the olefinic ester **16a** was tried. Heating either **11** with CH_3OH–H_2SO_4 or the mesylate **13a** with collidine[25] gave a crude mixture of olefins **15** and **16a** which could be separated by careful alumina chromatography and characterized spectroscopically (see Experimental Section).[26] Hydroboration of **16a** with diborane in THF[27] gave at least six compounds as determined by glpc. When treated with 9-borabicyclo[3.3.1]nonane,[28] **16a** was recovered unchanged. No additional attempts were made to prepare **12**.

C. Lithium–Ammonia Reduction.—No reduction products were observed when attempts were made to prepare **3** *via* $NaBH_4$ or Na/Hg reduction of **17**, the 3-ethylenedioxy derivative of santonic acid (**2**). The 6β-hydroxy-3-keto acid **3** was finally obtained by Li/NH_3 reduction[29] of **17** to **18** followed by acidic hydrolysis of the ketal function. Conclusive evidence

(22) Approach of borohydride to a carbonyl group is normally expected to occur by the least hindered route: H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, Menlo Park, Calif., 1972, pp 54–64.

(23) See M. Karplus, *J. Amer. Chem. Soc.*, **85**, 2870 (1963).

(24) It was felt that the juxtaposition of H-3 to the carbonyl carbon (C-6) in **12** might favor an intramolecular Cannizzaro hydride shift. See, for example, W. C. Wildman and D. T. Bailey, *ibid.*, **91**, 150 (1969), and references cited therein; D. Arigoni, *Gazz. Chim. Ital.*, **92**, 884 (1962); *Chem. Abstr.*, **58**, 7981 (1963); A. J. Birch, C. W. Holzapfel, and R. W. Rickards, *Tetrahedron, Suppl.*, **8**, 359 (1966); J. J. Dugan, P. De Mayo, M. Nisbet, and M. Anchel, *J. Amer. Chem. Soc.*, **87**, 2768 (1965). In the case of **12** → **3** it was felt that the base-induced (and presumably reversible) transformation might be effected to favor **3** by using 3 molar equiv of a base strong enough to irreversibly convert any **3** formed to its enolate anion, which could then be quenched under mild acidic conditions to obtain **3**.

(25) *Cf.* M. D. Bachi, J. W. Epstein, Y. Herzberg-Minzly, and H. J. E. Loewenthal, *J. Org. Chem.*, **34**, 126 (1969). See also G. G. Hazen and D. W. Rosenberg, *ibid.*, **29**, 1930 (1964).

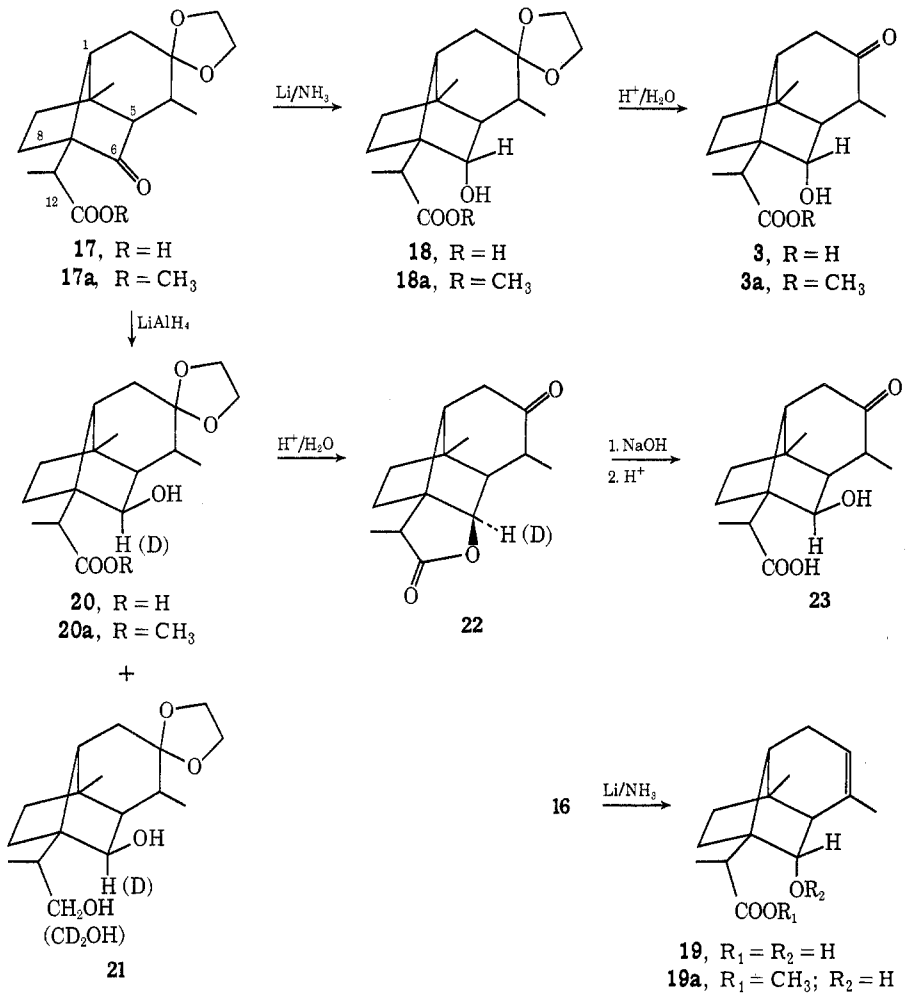
(26) The inherently dissymetric β,γ-unsaturated ketone chromophore of **16a** also gives rise, in the ORD and CD curves of **16a**, to a very strong negative Cotton effect of the order of magnitude observed for some other ketones of this type, *e.g.*, parasantonide and 3β-acetoxy-16α,17α-(17′-methylene)ethylenepregn-5-en-20-one. See A. Moscowitz, K. Mislow, M. A. W. Glass, and C. Djerassi, *J. Amer. Chem. Soc.*, **84**, 1945 (1962); P. Sunder-Plassman, P. H. Nelson, P. H. Boyle, A. Gruz, J. Iriate, P. Crabbé, J. A. Zderic, J. A. Edwards, and J. H. Fried, *J. Org. Chem.*, **34**, 3779 (1969).

(27) G. Zweifel and H. C. Brown, *Org. React.*, **13**, 1 (1963).

(28) E. F. Knights and H. C. Brown, *J. Amer. Chem. Soc.*, **90**, 5280, 5281 (1968).

(29) J. W. Huffman and J. T. Charles, *ibid.*, **90**, 6486 (1968).

SCHEME IV



for the 6β orientation of the hydroxyl group in **3** and **18** came from their nmr spectra. In each case H-6 appears as a broad singlet ($W_{1/2}$ = 3–4 Hz) indicating that $J_{6,5} \leqq 2$ Hz,[30] a value generally associated with H(exo)–H(endo) coupling of carbinyl protons in borneols.[31] See Scheme IV.

A similar Li/NH_3 reduction of **16** afforded **19**, a potentially more useful alternative to **3** as a starting material in Scheme I.

D. Lithium Aluminum Hydride Reduction.—Further support for the stereochemistry of **18** came from the observation that reduction of **17** with $LiAlH_4$ affords (in addition to diol **21**) an alcohol isomeric with **18** which could be tentatively assigned the 6α-hydroxy structure **20**. The configurational assignment at C-6 in **20** is based on the appearance of H-6 in the nmr spectrum as a doublet of doublets at δ 4.05 having $J_{6,5}$ = 5.5 Hz[31] and $J_{6,1}$ = 3.5 Hz.[32] The possibility that the reduction product might be a rearrangement product of **20** formed during the acidic work-up procedure could be eliminated when it was found that reduction of **17** with $LiAlD_4$ afforded a product which lacked a peak for the carbinyl proton at δ 4.05, but was otherise nearly identical with **20** in its nmr spectrum.

Attempts to remove the ketal function of **20** revealed that **20** was extraordinarily unreactive toward 3% HCl in boiling dioxane–H_2O, yielding only about 5–10% of the lactone **22**, along with unreacted **20**, after 16 hr. Lactone **22** and the alcohol **23** derived on hydrolysis of **22** both exhibited coupling patterns for H-6 (see Experimental Section) similar to that observed for H-6 in **20**, suggesting that **20**, **22**, and **23** probably have identical carbon skeletal structures, in spite of the vigorous acidic conditions required for the formation of **22**.[33]

Attempted Rearrangement of the Methanesulfonate of 18a.—Following Scheme I, the methanesulfonate ester **24** was prepared from **18a**. Treatment of **24** with potassium *tert*-butoxide in benzene led to the sultone **25** (2 H singlet for $-OSO_2CH_2CO-$ at δ 4.34; H-6 at δ 5.75) rather than the desired rearrangement product. Formation of **25** probably proceeds *via* generation of a sulfonyl-stabilized carbanion, which then displaces methoxide ion intramolecularly from the carbomethoxyl group. In contact with a trace of acid, **25** was deketalized to yield **26**.

In another preparation of mesylate **24**, work-up

(30) This assumes that there will be a contribution to $W_{1/2}$ of 2–4 Hz due to $J_{6,8}$ when H-6 is exo as in, *e.g.*, **3** or **18** (see examples in ref 31a–c).

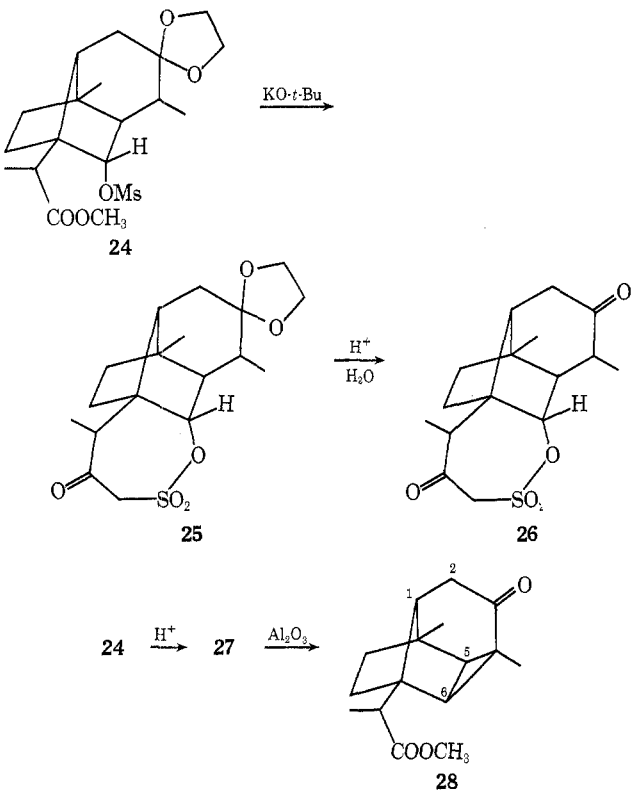
(31) Coupling constants for vicinal H(endo)–H(endo) protons in related borneols are typically in the range of about 5–10 Hz. For selected examples, see (a) H. Hikino, N. Suzuki, and T. Takemoto, *Tetrahedron Lett.*, 5069 (1967); (b) M. Kolbe and L. Westfelt, *Acta Chem. Scand.*, **21**, 585 (1967); (c) D. H. R. Barton and N. H. Werstiuk, *J. Chem. Soc. C*, 148 (1968).

(32) Coupling constants for H(2-endo)–H(7-anti) protons in norbornanes are typically 3–4 Hz: L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, Oxford, 1969, p 334.

(33) In contrast to the ease of oxidation of **18a** to **17a**, **20** and **23** were found to be inert to Jones–Weedon reagent, and to form, with stronger oxidants, mixtures of products which were not readily characterizable. Thus a direct oxidative correlation of **20** and **23** with **2** could not be made.

under acidic conditions resulted in a mixture (~1:1) of **24** and a related mesylate which was probably **27**, the 3-keto analog of **24**. Attempted chromatography of the mixture on neutral alumina afforded the cyclopropyl ketone **28** having *two* quaternary methyl groups: nmr δ 1.03 (s, 3), 1.12 (s, 3), 1.24 (d, 3), 2.68 (q, 1), 3.63 (s, 3), and the AB portion of an ABX pattern centered at 2.19 ($J_{2,2'}$ = 16.5 Hz, $J_{2,1}$ = $J_{2',1}$ = 3 Hz);[34] ir 1735 ($COOCH_3$) and 1685 cm^{-1} (cyclopropyl C=O).[35]

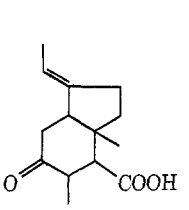
Further attempts to effect the desired rearrangement outlined in Scheme I using the tosylate (and related sulfonate esters) of **18a** and **19a** are currently in progress.



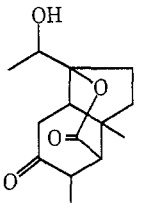
Oxidation of Santonic Acid.—The demonstrated utility of nmr spectroscopy in determination of the location and orientation of functional groups in santonic acid derivatives encouraged us to turn to a reinvestigation of the products of several previously reported oxidations of **2**.[36]

A. Alkaline Hydrogen Peroxide Oxidation.—Oxidation of **2** ($C_{15}H_{20}O_4$) with alkaline H_2O_2 was reported by Wedekind and Jäckh to yield "aposantonic acid," $C_{14}H_{20}O_3$, which on chromium oxide oxidation afforded a diketo lactone ($C_{14}H_{18}O_4$).[36] Consideration of these data led Woodward, *et al.*,[6] to propose a possible course of the oxidation which resulted in the formulation of aposantonic acid as **29**.

The proposed structure places the double bond and carboxyl group in the relationship required by the additional observation that reaction of **29** with perbenzoic acid affords a hydroxy lactone (*viz.*, **30**)[6] which (presumably) is related to the diketo lactone[36] reported earlier. To date the structures of **29** and **30** have rested entirely on analytical data and structural arguments.

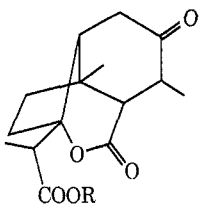


29



30

Repetition of the alkaline peroxide oxidation of **2** under conditions similar to Wedekind's[36] gave a new crystalline acid ($C_{15}H_{20}O_5$) having ir bands at 1745 (cyclopentanone C=O or γ-lactone) and 1715 cm^{-1} (COOH) and an nmr spectrum which was similar in its essential features to that of **2**. On these bases the new product was assigned structure **31**; the three alternative lactones resulting from Bayer–Villiger oxidation at either C-3 or C-6 could be rejected as possible structures since no carbinyl protons(s) appears in the δ 3.5–5.5 region of the nmr spectrum of **31**. Esterification of the remaining crude product with CH_2N_2, followed by chromatography, afforded (in addition to **31a**) a compound having analytical, ir, and nmr spectral data in accord with structure **29a** (methyl aposantonate): ir 1735, 1715, and 820 cm^{-1}; nmr δ 0.95 (d, 3), 0.99 (s, 3), 1.60 (br d, 3), 3.75 (s, 3), and 5.35 (br q).



31, R = H
31a, R = CH_3

Further examination of the nmr spectrum of **29a** revealed a trans relationship between H-2 and H-3 ($J_{2,3}$ = 12.5 Hz)[23] leading to the detailed stereostructure shown for **29a** on the basis of conformational analysis (6-ring assumed to be in chair form) and consideration of the relative stabilities of B *vs.* C under conditions conducive to epimerization at C-3 which are probably operative during the oxidation.

The lactone **31** was probably overlooked in the earlier work,[36] since even when the conditions reported were followed as closely as possible an nmr assay of the crude oxidation product showed the ratio of **2**:**29**:**31** to be 2:1:1. When the lactone **31** was treated with base for several hours, an nmr spectrum of the product showed no olefinic protons, thus ruling out the possibility that aposantonic acid (**29**) is derived from **31** by a decarboxylative β-elimination process, and suggesting that **29** probably arises from **2** by an independent (and possibly stereospecific) fragmentation process (Scheme V) similar to that proposed earlier.[6]

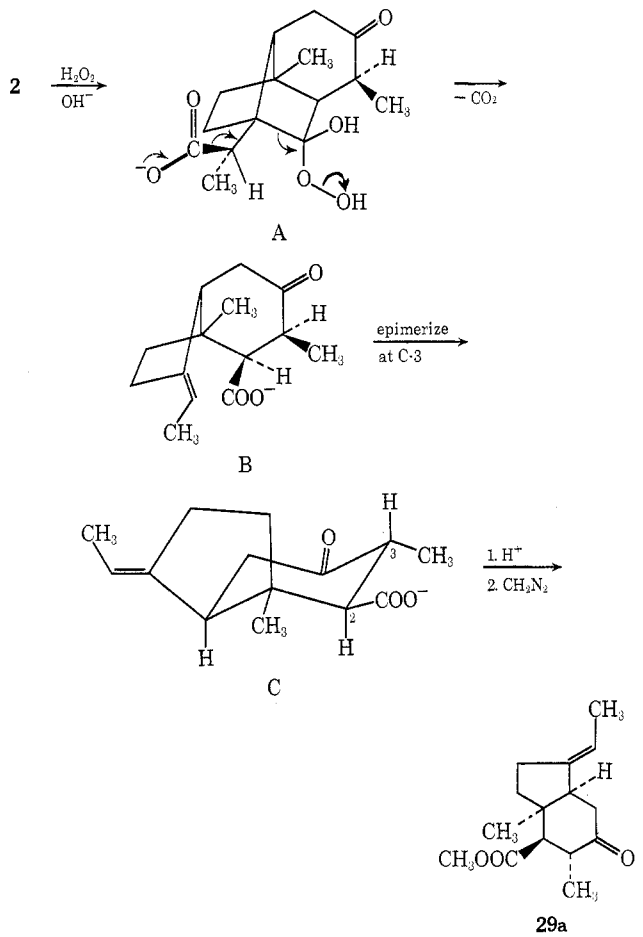
B. Potassium Hypobromite Oxidation.—Oxidation of santonic acid (**2**) with potassium hypobromite was reported[36] to give a compound referred to as "oxy-

(34) The ABX system is not H-5, H-6, and H-1, since the range for coupling observed for cis vicinal protons on cyclopropyl rings is typically 4.7–12.6 Hz. [See ref 32, p 286, and also S. A. Monti, D. J. Bucheck, and J. C. Shepard, *J. Org. Chem.*, **34**, 3080 (1969).] The resonance peaks for H-5 and H-6 in **28** apparently occur with the remaining protons in the δ 1.90–1.25 region; this seems unusual when compared with the chemical shifts observed for cyclopropyl protons located β to a carbonyl group in some other bridged systems. *Cf.* S. A. Monti, *ibid.*, **35**, 380 (1970).

(35) W. G. Dauben and R. E. Wolf, *ibid.*, **35**, 374 (1970).

(36) E. Wedekind and I. Jäckh, *J. Prakt. Chem.*, **139**, 129 (1934).

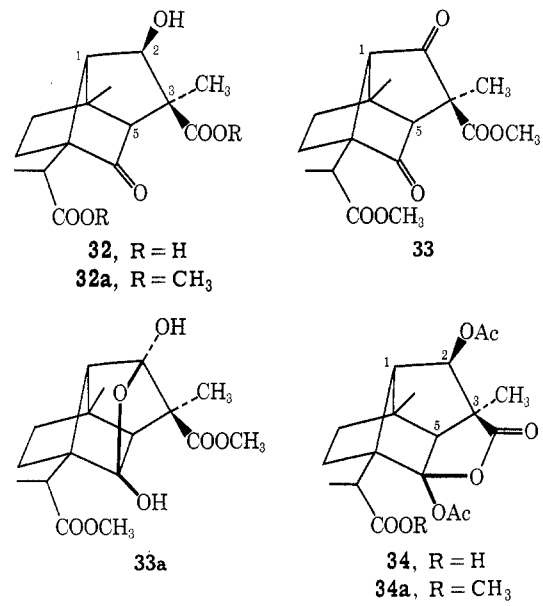
SCHEME V



santonic acid" which analyzed as a hemihydrate, $C_{15}H_{20}O_6 \cdot {}^1/_2H_2O$. Treatment of oxysantonic acid with CH_2N_2 afforded a compound ($C_{17}H_{24}O_6$) described as a methoxy monomethyl ester. Oxysantonic acid also formed a diacetoxy acid, $C_{19}H_{24}O_8$, which yielded the corresponding monomethyl ester ($C_{20}H_{26}O_8$) on treatment with CH_2N_2.

When the hypobromite oxidation of **2** was repeated, a recrystallized product having the melting point reported for oxysantonic acid was obtained in 14% yield. The acid gave a negative $FeCl_3$ test, indicating that oxysantonic acid is not an enolized α diketone, *i.e.*, 2-oxosantonic acid. Esterification with CH_2N_2 afforded a dimethyl ester (3 H singlets at δ 3.68, 3.72) having *two* quaternary C-methyl groups (3 H singlets at δ 1.33, 1.61), an unaltered $-CH(CH_3)COOR$ side chain (3 H doublet at 1.42; 1 H quartet at 3.28), and a hydrogen-bonded secondary hydroxyl function [1 H doublet for -OH at 5.08 (J = 7 Hz) which disappears on addition of acetic acid-d_4]. On these bases the gross structure **32a** could be tentatively assigned to the dimethyl ester. Additional support for structure **32a** came from the appearance of the carbinyl proton (H-2) at δ 4.49 as a doublet of doublets (J = 7, 4 Hz) which collapses to a simple doublet owing to coupling of H-2 with H-1 ($J_{2,1}$ = 4 Hz) upon exchange of the -OH proton for deuterium. Finally, H-1 appears at δ 2.54 as a doublet of doublets owing to coupling with H-2 ($J_{1,2}$ = 4 Hz) and additional long-range coupling[32] with H-5 ($J_{1,5}$ = 2.5 Hz); H-5 in turn occurs as a simple doublet ($J_{1,5}$ = 2.5 Hz) at δ 2.36.

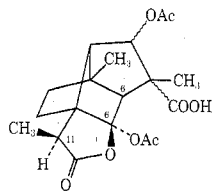
Jones-Weedon oxidation[12] of **32a** afforded **33** in which both H-1 and H-5 absorb coincidently at δ 2.72 (2 H, singlet); no signal for CHOH appears in the nmr spectrum of **33**. Compound **33** analyzed as **33**·H_2O and probably exists as the oxygen-bridged dihemiketal **33a** having one of its carbomethoxyl groups strongly hydrogen bonded [ir ν_{max} 3380, 3500–2500 (br), 1735, 1710, and 1683 cm^{-1}].



Treatment of **32** with acetic anhydride gave the diacetoxy acid obtained previously;[36] the derived methyl ester also corresponded in analysis and melting point to that reported. The diacetoxy acid exhibits ir and nmr spectral characteristics consonant with structure **34**: ν_{max} 1800, 1760, 1745, and 1710 cm^{-1}; nmr δ 1.22 (s, 3), 1.28 (d, 3), 1.48 (s, 3), 2.06 (s, 3), 2.11 (s, 3), 2.37 (dd, 1, $J_{1,2}$ = 4, $J_{1,5}$ = 2 Hz, H-1), 3.10 (d, 1, $J_{5,1}$ = 2 Hz, H-5), 3.26 (q, 1, H-11), and 5.33, (d, 1, $J_{2,1}$ = 4 Hz, H-2).[37]

The incorporation of the COOH group located at C-3 into the lactol acetate moiety of **34** establishes the configuration at C-3 of **32** and its derivatives. The configuration depicted for C-2 is based on the magnitude of the coupling interaction between H-1 and H-2 in **32a**, **34**, and **34a**. The observed coupling in each compound ($J_{1,2}$ = 4 Hz) is consistent with the

(37) The alternate structure a could be rejected for **34** on the basis of

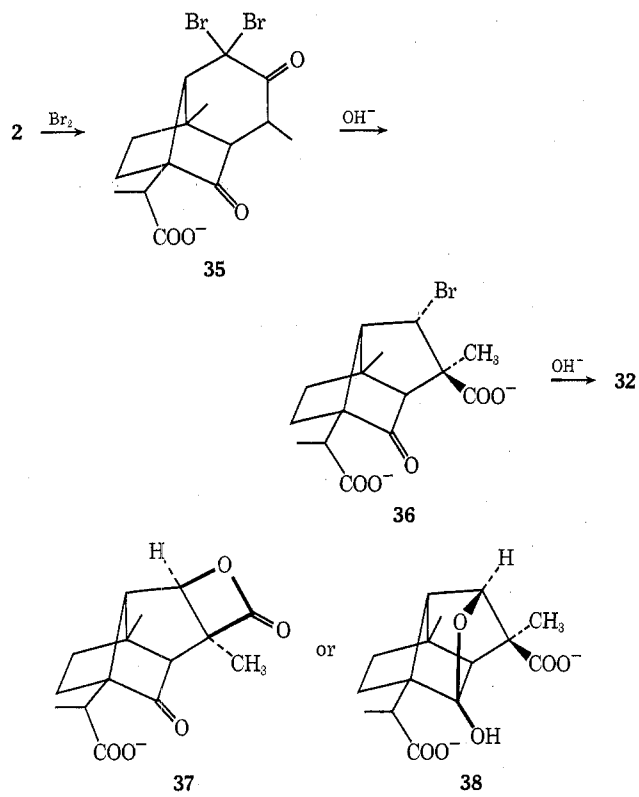


a

a comparison of the chemical shift values for H-11 in γ-lactones **7** (δ 2.62), **8** (δ 2.57), and **22** (δ 2.65) with those observed for the diacetate **34** (δ 3.26) and the diacetate methyl ester **34a** (δ 3.35). The latter values are closer to those observed (*e.g.*, δ 3.50 for **14**) for H-11 in structures having two oxygen substituents at C-6 and a freely rotating $-CH(CH_3)COOR$ side chain (which probably prefers a rotational orientation with H-11 near C-6). Although a has an additional 6-OAc which is not present in **7** and **22**, consideration of the distance of the 6-OAc group from H-11 in models of a, and its probable preferred rotational conformation (C=O oriented away from H-11) suggests that a deshielding effect due to 6-OAc of *ca.* 0.7 ppm at H-11 in a lactone such as a is improbable and would not satisfactorily explain the difference in δ values for H-11 in a *vs.* **7** or **22**.

dihedral angle of 40° found between H-1 and H-2 in Drieding models of **32**; a model of the structure epimeric to **32** at C-2 shows a dihedral angle of 85° between H-1 and H-2 corresponding to an expected coupling of $J_{1,2} \sim 0$ Hz.[23] The observation that the the 2-OH group in **32a** is hydrogen bonded is also in accord with its proposed cis orientation with respect to the 3-$COOCH_3$ group. (Hydrogen bonding of the 2-OH group with the carbonyl at C-6 is sterically impossible.)

Oxysantonic acid (**32**) probably rises *via* Favorskii rearrangement of 2,2-dibromosantonic acid (**35**) to yield **36**, followed by replacement of bromine by hydroxyl *via* propiolactone **37** or by initial attack of hydroxide at C-6 in **36** to yield an intermediate C-2–C-6 oxygen-bridged hemiketal of **32**, *i.e.*, **38**.[38]



Experimental Section[39–41]

(11*S*)-1,7-Cyclo-3,6-dioxo-4,5β-eudesman-12-oic Acid (2) (Santonic Acid).—This method is a modification of the procedure reported.[6] A solution of 100 g (0.41 mol) of α-santonin, 144 g of NaOH, and 600 ml of H_2O was heated at reflux under N_2 for 7 hr, cooled, acidified with concentrated HCl, and extracted with CH_2Cl_2. The organic phase was washed, dried, filtered, and evaporated *in vacuo*, affording 109 g of a brown gum. Trituration with ether followed by recrystallization gave 62.6 g (58%) of santonic acid (**2**): mp 173.5–179° (lit.[6] mp 170–172°); ir 1740 (C=O), 1725 (C=O), and 1710 cm^{-1} (C=O); nmr δ 1.12 (d, 3, J = 6.7 Hz, H-15), 1.37 (s, 3, H-14), 1.37 (d, 3, J = 7 Hz, H-13), 1.6–1.9 (m, 3), and 2.87 (q, 1, J = 7 Hz, H-11); nmr (DMSO-d_6) δ 0.95 (d, 3, J = 6.5 Hz), 1.22 (d, 3, J = 7 Hz), 1.32 (s, 3), and 2.74 (q, 1, J = 7 Hz).

Methyl (11*S*)-1,7-Cyclo-3,6-dioxo-4,5β-eudesman-12-oate (2a) (Methyl Santonate).—Addition of CH_2N_2 in Et_2O to a solution of **2** in Et_2O followed by concentration of the mixture gave a yellow oil which crystallized from CH_3OH–H_2O to yield **2a**: mp 66–67.5° (lit.[20] mp 86°); ir 1740, 1730, and 1715 cm^{-1}; nmr δ 1.10 (d, 3, J = 6.5 Hz, H-15), 1.31 (d, 3, J = 7 Hz, H-13), 1.38 (s, 3, H-14), 2.81 (q, 1, J = 7 Hz, H-11), and 3.65 (s, 3, $-OCH_3$).

Exchange Reaction of 2 in 0.28 *M* NaOD in D_2O.—A solution of **2** (135 mg) in 0.28 *M* NaOD was heated at reflux under N_2 for 10 hr, cooled, acidified with 0.4 ml of glacial acetic acid, and extracted with CH_2Cl_2 after dilution with 50 ml of H_2O. The organic extracts were washed with H_2O, dried, filtered, and concentrated to yield 127 mg of **2**-d_3: nmr δ 1.13 (s, 3), 1.35 (d, 3, J = 7 Hz), 1.38 (s, 3), and 2.84 (q, 1, J = 7 Hz). Overall, with the exception of the singlet at δ 1.13, loss of 2 H multiplets at 2.65 and 2.15, and appearance of a new sharp singlet at 2.15 (H-5), the spectrum of **2**-d_3 is very similar to the nmr spectrum of **2**.

Another exchange carried out under identical conditions, except for being 4 hr in duration, also showed a singlet at δ 1.13 in place of a doublet in the spectrum of **2**. Mass spectral analysis of recrystallized material indicated the presence of 9% of **2**-d_0, 29% of **2**-d_1, 36% of **2**-d_2, 20% of **2**-d_3, and 5% of **2**-d_4.

Treatment of Santonic Acid (2) with Concentrated Aqueous KOH.—A solution of 1.0 g (0.004 mol) of santonic acid (**2**) in 20 ml of 40% KOH was heated at reflux for 48 hr under N_2, acidified with concentrated HCl, and extracted with Et_2O. The ethereal layer was washed, dried, filtered, and concentrated *in vacuo* to leave 0.94 g of approximately 90% pure santonic acid (**2**) (nmr assay). Repeated recrystallization from CH_3OH–H_2O gave 0.21 g of **2**, mp 163–174°. Mixture melting point with authentic santonic acid showed no depression (mmp 158–171.5°) while a mixture melting point with metasantonic acid (**5**) was depressed (mmp 137–157°).

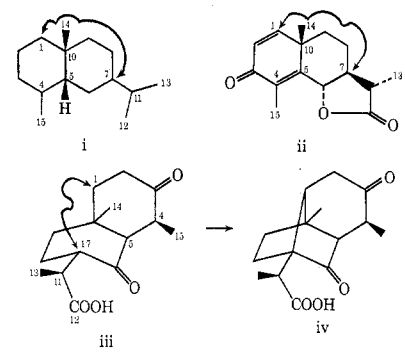
(38) The basic conditions used in the H_2O_2 and KOBr oxidations are not sufficiently strong to cause significant isomerization of **31** or **32** at C-11 to yield the corresponding 11*R* epimers (meta series). Similarly, epimerization at C-2 during the formation of aposantonic acid (**29**) is considered unlikely.

(39) Boiling points are uncorrected; melting points are uncorrected and were determined on samples in unsealed capillary tubes employing a Thomas-Hoover melting point apparatus. Infrared spectra were obtained on approximately 10% solutions in $CHCl_3$ using a Perkin-Elmer Model 457 grating spectrophotometer or a Perkin-Elmer Model 21 recording spectrophotometer. Mass spectra were determined using a Varian M-66 instrument with an ionizing potential of *ca.* 70 eV; precise mass determinations have a precision of ±0.03 amu. Nmr spectra were obtained on approximately 20–30% solutions in $CDCl_3$ (unless otherwise stated) using a Varian A-60A spectrometer; peak positions are reported in δ (parts per million) downfield from tetramethylsilane at δ 0.00 as internal standard. Complete ir and nmr spectra of most of the compounds described appear in the Ph.D. Thesis of D. S. Daniel (ref 1). Microanalyses were performed by Mikroanalytisches Laboratorium, Vienna, Austria, and Galbraith Laboratories, Inc., Knoxville, Tenn. 37921.

(40) In the normal work-up procedure, all organic extracts were washed with brine or water and dried over anhydrous magnesium sulfate. Recrystallizations, unless otherwise noted, were carried out using ethyl acetate–petroleum ether (bp 63–69°). Column chromatographic separations were carried out using Woelm alumina, neutral, activity 1; Alcoa Alumina, F-20 (basic); Fisher silica gel, Grade 923; or Davison silica gel, Grade 923. Evaporative distillations were done using a Kontes Bantamware micromolecular still, K-284500, or a noncommercial still of similar design. Short-path distillations were accomplished with a Kontes Bantamware short-path distillation apparatus, K-284800 (Kontes Glass Co., Vineland, N. J.).

(41) The compounds described are systematically named and numbered as cyclic eudesmanes where the new ring is formed between the C-1 and C-7 positions as in i. The orientation of the new bond at C-1 and C-7 is designated as α (based on the α,β-convention used in steroid systems and extended to the eudesmane structure *prior* to cyclization) and is implicit since the absolute configuration for α-santonin (ii) at C-10 is known and only one possibility exists for the orientation of the newly formed ring (iii). Trivial names from the original usage are used where applicable and no ambiguity emerges.

The nomenclature and numbering system used for the eudesmanes (i) are essentially those of W. Cocker and T. B. H. McMurry, *J. Chem. Soc.*, 4549 (1956), and further modifications in accord with the "IUPAC–IUB 1967 Revised Tentative Rules for Nomenclature of Steroids," *J. Org. Chem.*, **34**, 1517 (1969).



1,7-Cyclo-6β-hydroxy-3-oxo-4,5β-eudesman-12-oic Acid (3).—The procedure described below for the preparation of **18** by Li/NH_3 reduction of **17** was scaled down using 220 mg (0.71 mmol) of **17**. Evaporation of the NH_3 was followed by addition of dilute HCl and extraction with ether. A normal work-up followed by recrystallization afforded 140 mg (74%) of **3**: mp 186–191°; ir (Nujol) 3470 (OH), 1730 (C=O), and 1700 cm^{-1} (CO-OH); nmr (DMSO-d_6/$(CD_3)_2CO$) δ 1.03 (d, 3, J = 6.7 Hz, H-15), 1.15 (d, 3, J = 7 Hz, H-13), 1.20 (s, 3, H-14), 1.50 (s), and 3.33 (s, 1, $W_{1/2}$ = 3 Hz, CHOH).

Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33. Found: C, 67.34; H, 8.15.

(11*S*)1,7:3α,6α-Biscyclo-3β,6β-dihydroxy-4,5β-eudesman-12-oic Acid (4) (Dihydrosantonic Acid). Method A.—To a solution of 300 mg (1.14 mmol) of santonic acid (**2**) in 10 ml of 2% NaOH was added 3.21 g of 5% sodium amalgam.[42] The mixture was heated at reflux under N_2. The temperature was monitored during the course of the reaction. The duration of the reaction was 350 min (*i.e.*, until the activity of the amalgam had ceased—no hydrogen evolution). The temperature climbed from 25 to 91° during the first 15 min, then from 91 to 101° over the next 25 min, and remained at 101°. The mixture was cooled, decanted from the mercury, washed with CH_2Cl_2, acidified with concentrated HCl, and extracted with Et_2O. The organic layer was washed, dried, filtered, and evaporated *in vacuo* to afford 304 mg of partially crystalline material which contained **4** and **6** in a ratio of *ca.* 20:1 as determined by nmr assay (see Table I) of the methyl esters **4a** and **6a** (276 mg) formed by

TABLE I

SODIUM AMALGAM REDUCTION OF SANTONIC ACID (2)

Time, hr	Ratio of diol esters (4a/6a)	Ratio of oxidized esters (2a/5a)
2.5	~10	~10
5	3.5	3.7
10	2.1	1.8
20	0.8	0.9
5.8[a]	~20	~20

[a] Conditions used in method A for the preparation of **4**; the concentration of NaOH at the outset was 2% instead of 10%.

treatment of the crude product with CH_2N_2 in Et_2O. As a further check of purity, the ester mixture was dissolved in 5 ml of acetone at 0–5° and treated with 1 ml of Jones-Weedon reagent.[12] The mixture was stirred for 15 min; isopropyl alcohol, H_2O, and NaCl were added, and the solution saturated in NaCl was extracted with ether. The organic layer was washed, dried, filtered, and concentrated *in vacuo* to afford 238 mg of methyl santonate (**5a**) in greater than 95% purity as estimated by nmr analysis.

Method B.—To a solution of 5.0 g (0.019 mol) of santonic acid (**2**) in 150 ml of 10% aqueous NaOH was added 40.0 g of 5% sodium amalgam. The mixture was heated at reflux under N_2 for 2 hr, cooled, decanted from the mercury, washed with CH_2Cl_2, acidified with concentrated HCl, filtered, washed, and air dried, yielding 4.59 g (91%) of dihydrosantonic acid (**4**): mp 170.8–182.5° (lit.[10] mp 190–192°); ir (Nujol mull) 3390 (OH), 3330 (OH), and 1700 cm^{-1} (C=O); nmr (DMSO-d_6) δ 0.92 (s, 3, H-14), 1.09 (d, 3, J = 7 Hz, H-13 or H-15), 1.12 (d, 3, J = 6.8 Hz, H-15 or H-13), 2.61 (q, 1, J = 7 Hz, H-11), and 4.25–4.92 (broad band, OH).

Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33. Found: C, 67.48; H, 8.32.

Reduction of Santonic Acid (2) with Na/Hg over Varying Lengths of Time.—The procedure followed was that of method A except that 4.0 g of 5% sodium amalgam and 0.3 g of **2** were heated at reflux with 10 ml of 10% aqueous NaOH under N_2 for varying lengths of time. The mixture was processed as in method A for the preparation of **4** by forming the diol methyl esters and oxidizing the diols (Jones–Weedon reagent). Determination of the ratio of products at each stage was accomplished by integration of the areas of the OCH_3 peaks (diol esters, δ 3.65 for **4a**, 3.70 for **6a**; diketo esters, δ 3.62 for **2a**, 3.67 for **5a**) in the expanded nmr spectra (See Table I.)

(42) W. R. Brasen and C. R. Hauser, "Organic Syntheses," Collect. Vol. IV, N. Rabjohn, Ed., Wiley, New York, N. Y., 1963, p 509.

Jones–Weedon Oxidation of 4 to 2.—To a solution of 72 mg (0.27 mmol) of **4** in 5 ml of acetone at 0° was added 0.4 ml of Jones–Weedon reagent.[12] After a few minutes of stirring, the excess chromic acid was destroyed with methanol. The solution was saturated with NaCl and extracted with Et_2O. The ethereal layer was washed, filtered, and evaporated *in vacuo* to give 55 mg (77%) of crystalline material having an nmr spectrum identical with that of authentic **2**.

Silver Oxide Oxidation of 4.—To a solution of 1.0 g of **4** in 1.5 ml of 10% NaOH under N_2 was added 4 ml of 20% $AgNO_3$ and 20 ml of H_2O. The mixture was brought to pH 10 with 4 ml of saturated Na_2CO_3 solution, heated at reflux for 10 min (*i.e.*, until the mirror which had formed disappeared and a solid conglomerated at the bottom of the flask), cooled, and filtered, yielding 850 mg of gray metallic solid. The yellow filtrate was cooled, acidified by dropwise addition of concentrated HNO_3, and extracted with Et_2O. The Et_2O extracts were washed, dried, filtered, and evaporated *in vacuo* to leave 1.05 g of oily solid which was treated with CH_2N_2. The nmr spectrum of the esterified product indicated the presence of methyl santonate (**2a**) and methyl dihydrosantonate (**4a**) in a ratio of 1.6:1. No compounds of the metasantonic acid series were evident in the nmr spectrum.

When the reaction was carried out according to the procedure of Cannizzaro,[9] *i.e.*, heated at reflux for 1 hr, only polymeric material and an oil with an uninterpretable nmr spectrum was obtained.

Methyl (11*S*)-1,7;3α,6α-Biscyclo-3β,6β-dihydroxy-4,5β-eudesman-12-oate (4a) (Methyl Dihydrosantonate). Method A.—Diazomethane in Et_2O was added to the Et_2O extract of **4** (500 mg, 1.9 mmol) prepared by method A, affording 464 mg (88%) of crude **4a**. Several recrystallizations afforded 128 mg of pure **4a**: mp 110.4–112° (lit.[11] mp 111–114°); ir 3570 (OH), 3440 (OH), and 1725 cm^{-1} (C=O); nmr δ 0.98 (s, 3, H-14), 1.19 (d, 3, J = 7 Hz, H-13 or H-15), 1.23 (d, 3, J = 7 Hz, H-15 or H-13), 2.76 (q, 1, J = 7 Hz, H-11), 3.67 (s, 3, $-OCH_3$), and 3.20 (s, 2, OH).

Method B.—Following the procedure outlined by Harries and Stähler,[11] an ice-cooled solution of 1.0 g (0.0036 mol) of methyl santonate (**2a**) in 25 ml of absolute CH_3OH under N_2 was treated with 30 g of 3% Na/Hg. The mixture was stirred for 7 hr with gradual warming to room temperature, filtered, and concentrated *in vacuo*. The residue was dissolved in ether and the ether solution was washed, dried, filtered, and evaporated *in vacuo*, yielding 0.84 g (83%) of crude material which gave 0.39 g (39%) of recrystallized **4a**, mp 107–111° (lit.[11] mp 111–114°); the nmr spectrum was identical with that of **4a** prepared by method A except that two broad 1 H singlets for OH appeared at δ 2.92 and 3.28 in lieu of the 2 H signal at δ 3.20. Shaking the nmr sample with 1 drop of D_2O resulted in a decrease in the total area for the signals at δ 2.92 and 3.28. Exposure to a trace of hydrochloric acid shifted the signals to δ 3.07 and 3.45, respectively.

(11*R*)-1,7-Cyclo-3,6-dioxo-4,5β-eudesman-12-oic Acid (5) (Metasantonic Acid).—A mixture of 4.73 g (0.019 mol) of β-santonin and 60 ml of 17% NaOH under N_2 was heated at reflux for 4 hr, cooled, acidified with HCl, and extracted with Et_2O. The extracts were washed, dried, filtered, and evaporated *in vacuo* to leave 5.68 g of oil which crystallized from ethyl acetate to yield 2.38 g (45%) of metasantonic acid (**5**): mp 165–169° (lit.[9] mp 164–167° dec); ir 1740, 1725, and 1710 cm^{-1}; nmr δ 1.13 (d, 3, J = 6.8 Hz, H-15 or H-13), 1.15 (d, 3, J = 7.4 Hz, H-13 or H-15), 1.40 (s, 3, H-14), and 2.78 (q, 1, J = 7 Hz, H-11).

(11*R*)-1,7;3α,6α-Biscyclo-3β,6β-dihydroxy-4,5β-eudesman-12-oic Acid (6) (Dihydrometasantonic Acid).—A solution of 1.0 g (0.004 mol) of metasantonic acid (**5**) in 30 ml of 10% NaOH was heated at reflux under N_2 with 11.15 g of 5% sodium amalgam for 2 hr. A normal work-up procedure afforded 1.06 g of dihydrometasantonic acid (**6**) as white crystals: mp 163.5–177°; ir (Nujol mull) 3470 (OH), 3260 (OH), and 1687 cm^{-1} (acid C=O); nmr (DMSO-d_6) δ 0.94 (s, 3, H-14), 0.97 (d, 3, J = 6.8 Hz), 1.08 (d, 3, J = 6.5 Hz), 1.96 (q, 1, J = 7 Hz, H-4), and 2.60 (q, 1, J = 7 Hz, H-11).

Methyl (11*R*)-1,7;3α,6α-Biscyclo-3β,6β-dihydroxy-4,5β-eudesman-12-oate (6a) (Methyl Dihydrometasantonate).—A solution of CH_2N_2 in Et_2O was added to 946 mg (3.6 mmol) of dihydrometasantonic acid (**6**) in ether. Concentration of the solution left 1.06 g of an oil which was evaporatively distilled (twice) and the fractions boiling at 106° (0.1 mm) to 112° (0.08 mm) (bath temperature) were collected to afford 866 mg (87%) of methyl dihydrometasantonate (**6a**): ir 3560 (OH), 3360 (OH), 1740 (C=O), and 1700 cm^{-1} (C=O); nmr δ 1.01 (s, 3, H-14), 1.10 (d, 3, J = 7 Hz, H-15 or H-13), 1.17 (d, 3, J = 7 Hz, H-13 or H-15),

2.09 (q, 1, J = 7 Hz, H-4), 2.78 (q, 1, J = 7 Hz, H-11), 3.26 (s, 1, OH), 3.69 (s, 3, $-OCH_3$), and 4.78 (s, 1, OH). When 1 drop of acetic acid-d_4 was added the 1 H peak at δ 3.26 disappeared and a 2 H peak was found at δ 4.8; upon addition of a second drop, the 2 H peak at 4.8 ppm disappeared and a broad 2 H singlet appeared at 6.3 ppm.

Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.55; H, 8.63. Found: C, 67.30, 67.25; H, 8.18, 7.99.

Oxidation of 6 to 5. Method A. Jones-Weedon Oxidation.—A solution of 500 mg (1.8 mmol) of **6** in acetone was oxidized as described for dihydrosantonic acid (**2**) to yield 164 mg (35%) of pure metasantonic acid (**5**), mp 147–165° dec. A mixture melting point with santonic acid was depressed (mmp 137–156°), but with metasantonic acid was not depressed (mmp 152.5–164.5°).

Method B. *N*-Bromoacetamide Oxidation.[43]—To a solution of 500 mg (1.8 mmol) of dihydrometasantonic acid (**6**) in 0.5 ml of H_2O and 8 ml of acetone was added 660 mg of *N*-bromoacetamide under N_2 with cooling in an ice bath. The solution was stirred in the dark for 12 hr. The bromine formed was destroyed with 0.1 *N* sodium thiosulfate and the solution was diluted with saturated NaCl solution and extracted with ether. The extracts were washed, dried, filtered, and concentrated *in vacuo* to leave 540 mg of oil which was recrystallized from ethyl acetate to yield 170 mg (36%) of metasantonic acid (**5**) as white crystals, mp 157–168°. A mixture melting point with an authentic sample of metasantonic acid was not depressed (mmp 155–165°).

Oxidation of 6a to 5a.—A solution of 720 mg (2.6 mmol) of methyl dihydrometasantonate (**6a**) in acetone was treated with Jones-Weedon reagent[12] as described for the oxidation of **4** to **2**. The crude product (670 mg, 62%), after recrystallization from methanol, afforded 175 mg of pure **5a**: mp 101–102.8° (lit.[7] mp 101.5–102.5°); ir 1735, 1725, and 1710 cm^{-1}; nmr (CCl_4) δ 1.08 (d, 3, J = 7.2 Hz, H-13), 1.04 (d, 3, J = 6.5 Hz, H-15), 1.38 (s, 3, H-14), 2.64 (q, 1, J = 7.0 Hz, H-11), and 3.58 (s, 3, $-OCH_3$).

Formation of 7 and 9 by Treatment of Dihydrosantonic Acid (4) with Acetic Anhydride.—By analogy with the procedure described by Wedekind and Engel,[10] a mixture of 2.0 g (0.008 mol) of **4** and 27 ml of acetic anhydride was heated at reflux under N_2 for 1 hr, cooled, poured into ice water, and extracted with methylene chloride. The organic layer was evaporated *in vacuo;* the residual solid was dissolved in ether and the solution was washed with saturated $NaHCO_3$ (three 30-ml portions) and brine, dried, filtered, and evaporated *in vacuo* to leave 2.09 g of solid. Several recrystallizations yielded 0.71 g (31%) of **(11*S*)-1,7;3α,6α-biscyclo-3β-acetoxy-4,5β-eudesmane 12,6β-lactone** (**7**) as white crystals: mp 140–141.8°; ir 1780 (lactone C=O) and 1735 cm^{-1} (acetate C=O); nmr δ 1.10 (d, 3, J = 7 Hz, H-15), 1.13 (s, 3, H-14), 1.32 (d, 3, J = 7.8 Hz, H-13), 2.04 (s, 3, $-OCOCH_3$), 2.59 (q, 1, J = 7 Hz, H-4), and 2.62 (q, 1, J = 7.8 Hz, H-11).

Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.31; H, 7.64. Found: C, 70.48; H, 7.53.

Treatment of the mother liquor, dissolved in ether, with sodium bicarbonate (as above), followed by concentration of the ethereal layer and crystallization yielded another 0.76 g of acetoxy lactone **7**.

The combined aqueous layers were acidified with concentrated HCl and extracted with Et_2O. The organic extracts were washed, dried, filtered, and evaporated *in vacuo* to leave 200 mg of solid. Two recrystallizations afforded 35 mg of **1,7;3α,6α-biscyclo-3β,6β-diacetoxy-4,5β-eudesman-12-oic acid** (**9**) (**diacetoxydihydrosantonate**): mp 235–237.5° (lit.[10] mp 232°); ir 1735 (acetate C=O) and 1705 cm^{-1} (acid C=O); nmr δ 0.98 (d, 3, J = 7 Hz, H-15), 1.05 (s, 3, H-14), 1.18 (d, 3, J = 7 Hz, H-13), 2.08 (s, 3, $-OCOCH_3$), 2.12 (s, 3, $-OCOCH_3$), 2.76 (q, 1, J = 7 Hz, H-11), and 1.67 (br s).

Anal. Calcd for $C_{19}H_{26}O_6 \cdot {}^1/_2H_2O$: C, 63.51; H, 7.52. Found: C, 63.82; H, 7.43.

Methyl 1,7;3α,6α-Biscyclo-3β,6β-diacetoxy-4,5β-eudesman-12-oate (**9a**).—The diacetoxy acid **9** (14.2 mg) was treated with CH_2N_2–Et_2O. Concentration of the solution yielded 8.9 mg (62%) of methyl diacetoxydihydrosantonate (**9a**): mp 150° (lit.[10] mp 151°); nmr (microcavity tube) δ 0.98 (d, J = 7 Hz), 1.05 (s, H-14), 1.15 (d, J = 7 Hz), 2.09 (s, unresolved, but separated into two peaks when the nmr sweep width was expanded, two $-OCOCH_3$), 2.70 (q, J = 7 Hz, H-11), and 3.65 (s, $-OCH_3$).

(43) E. P. Oliveto, H. L. Herzog, M. A. Jevnik, H. E. Jorgensen, and E. B. Hershberg, *J. Amer. Chem. Soc.*, **75**, 3651 (1953).

Hydrolysis of 7.—A mixture of 100 mg of **7** in 1 ml of dioxane and 2 ml of 10% NaOH under N_2 was heated at reflux for 2 hr, cooled, acidified with concentrated HCl, and extracted with ether. The product was esterified (CH_2N_2), yielding 165 mg of oil which consisted of a mixture of **4a** and **6a** in a ratio of 3:1 (nmr assay).

Hydrolysis of 9.—A mixture of 50 mg of **9** and 2 ml of 10% NaOH under N_2 was heated at reflux for 2 hr, cooled, acidified by dropwise addition of concentrated HCl, and extracted with ether. Treatment with CH_2N_2 and concentration *in vacuo* gave 40 mg of oil which consisted of a mixture of **4a** and **6a** in a ratio of 3:5 (nmr assay).

(11*R*)-1,7;3α,6α-Biscyclo-3β-acetoxy-4,5β-eudesmane 12,6β-Lactone (**8**).—A solution of 131 mg (0.79 mmol) of dihydrometasantonic acid (**6**) and 3 ml of acetic anhydride was heated at reflux for 5.25 hr, cooled, and extracted with methylene chloride. The organic extract was washed, dried, filtered, and evaporated *in vacuo* to leave 129 mg of solid. The solid was dissolved in ether, washed with saturated $NaHCO_3$ and NaCl solutions, dried, filtered, and evaporated *in vacuo* to afford 113 mg (49%) of the acetoxy lactone. Several recrystallizations yielded 70 mg of pure **8**: mp 204.5–206° (lit.[10] mp 204°); ir 1780 (C=O) and 1735 cm^{-1} (C=O); nmr δ 1.08 (d, 3, J = 7 Hz, H-15 or H-13), 1.17 (d, 3, J = 7 Hz, H-13 or H-15), 1.19 (s, 3, H-14), 2.02 (s, 3, $-OCOCH_3$), and 2.57 (two overlapping q, 2, J = 7 Hz, H-11 and H-4).

Hydrolysis of 8.—A solution of 44 mg (0.15 mmol) of acetoxy lactone **8** in 1 ml of dioxane and 1 ml of 10% NaOH was heated at reflux for 1 hr under N_2, cooled, acidified with HCl, and extracted with ether. The extracts were washed, dried, filtered, and treated with CH_2N_2 to give an oil which contained >95% methyl dihydrometasantonate (**6a**) (nmr assay).

1,7-Cyclo-3-ethylidene-6-oxo-*A*-5β-noreudesman-12-oic Acid (**10**).—Dihydrosantonic acid (**4**) was prepared in the usual manner from 5.0 g (0.019 mol) of santonic acid (**2**), then dissolved in 30 ml of glacial acetic acid, sealed in a glass tube, and heated at 145–150° for 4 hr. The contents of the tube were dissolved in methylene chloride and washed successively with H_2O, $NaHCO_3$ (saturated), and H_2O, dried, filtered, and evaporated *in vacuo* to leave 1.33 g of semisolid material which gave 0.52 g of yellow solid on recrystallization. Several additional recrystallizations afforded analytically pure **10**: mp 144.2–146.5°; ir 3400–2910, 1725, 1705, and 835 cm^{-1}; mass spectrum (70 eV) m/e (rel intensity) 248 (89.4), 230 (39.3), 202 (47.1), 175 (62.5), 147 (100), 146 (89.4), 55 (32.2) 43 (32), 41 (63.2), and 18 (36.9); nmr[44] δ 1.06 (s, 3, H-14), 1.43 (d, 3, J = 7 Hz, H-13), 1.75 (dt, 3, $J_{15,4}$ = 7, $J_{15,2}$ = $J_{15,2'}$ = 2 Hz,[45] H-15), 2.06 (apparent q, 1, $J_{1,5}$ = $J_{1,2}$ = $J_{1,2'}$ = 2 Hz, H-1), 2.45 (apparent q), probably a sextet, or possibly two overlapping quintets (*i.e.*, high-intensity central signals) of AB pattern where $\nu_1 - \nu_{2'} \cong 2$ Hz with $J_{2,15}$ = 2, $J_{2',15}$ = 2, $J_{2,1}$ = 2, $J_{2',1}$ = 2 Hz, H-2, H-2′), 2.91 (q, 1, J = 7 Hz, H-11), 3.16 (d, 1, $J_{1,5}$ = 2 Hz, H-5), and 5.46 (apparent qtd, 1, $J_{4,15}$ = 7, $J_{4,2}$ = 2, $J_{4,2'}$ = 2, $J_{4,x}$ = 1 Hz, H-4).

Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.42; H, 8.11.

An nmr spectrum of the mother liquor from recrystallization (of the 1.33 g of semisolid) indicated a 2:1 ratio of **10** to a new olefinic compound (br m at 5.05 ppm) which was not investigated further. (In another experiment run for 20 hr at 160° the crude product was found to consist almost entirely of the same olefin.)

The $NaHCO_3$ wash solution was acidified and extracted to afford 3.09 g of oil which consisted of **10** and **4** in a 4:3 ratio (nmr assay). Trituration with $CHCl_3$ left 1.02 g of **4**; the soluble material was nearly entirely **10** (nmr assay) but could be crystallized only with difficulty.

1,7-Cyclo-3α-hydroxy-6-oxo-4,5β-eudesman-12-oic Acid (**11**).—A solution of 2.0 g (0.008 mol) of santonic acid (**2**) in 28 ml of anhydrous isopropyl alcohol containing 1.55 g of $NaBH_4$ was stirred at room temperature and under N_2 for 17 hr.

The reaction mixture was acidified with dilute HCl and extracted with ether. The ether extracts were washed, dried, filtered, and evaporated *in vacuo* to leave 2.55 g of oil. Crystal-

(44) The nmr spectrum was run at 100 Mz on a Varian HA-100 spectrometer; all couplings cited were confirmed by spin-decoupling experiments.

(45) The coupling of $J_{15,2}$ = 2 Hz is an example of homoallylic coupling. See, for instance, $J_{6,12}$ = 1.8 Hz observed for γ-metasantonin, A. G. Hortmann, D. S. Daniel, and J. Schaefer, *J. Org. Chem.*, **33**, 3988 (1968); $J_{2,9} \cong$ 1 Hz in methyl isokhusenate, G. A. Neville and I. C. Nigam, *Tetrahedron Lett.*, 837 (1969).

lization afforded 1.15 g (55%) of **11**: mp 86–113°; ir 3600, 3300–2800, 1705, and 1460 cm^{-1}; nmr δ 1.02 (d, 3, J = 7 Hz, H-15), 1.04 (s, 3, H-14), 1.28 (d, 3, J = 7 Hz, H-13), 3.37 (q, 1, J = 7 Hz, H-11), 4.05 (br m, 1, $W_{1/2}$ = 7.5 Hz, CHOH), and 1.35–2.33 (m, 9).

An analytical sample was prepared by recrystallization from ethanol–water, mp 93–108.4°. Drying *in vacuo* [40° (0.4 mm) over P_2O_5] changed the melting point to 140–144.5°.

Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33. Calcd for $C_{15}H_{22}O_4 \cdot {}^1/_4H_2O$: C, 66.5; H, 8.2. Found: C, 66.62; H, 8.01.

Treatment of **11** with CH_2N_2 in ether afforded the methyl ester **11a**: mp 93.3–94.5°; ir 3610, 3450, and 1735 cm^{-1}; nmr δ 1.03 (d, 3, J = 6.5 Hz, H-15), 1.03 (s, 3, H-14), 1.25 (d, 3, J = 7 Hz, H-13), 2.06 (q, 1, J = 6.5 Hz, H-4), 3.42 (q, 1, J = 7 Hz, H-11), 3.63 (s, 3, $-OCH_3$), 4.04 (br m, 1, J = 3.5 Hz, $W_{1/2}$ = 7.8 Hz, CHOH), and 1.35–2.35 (m, 7).

Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.55; H, 8.63. Found: C, 68.64; H, 8.59.

Methyl 1,7-Cyclo-3α-methanesulfonyloxy-6-oxo-4,5β-eudesman-12-oate (13a).—To a cold solution of 3.37 g (0.001 mol) of **11a** in 40 ml of anhydrous pyridine was added 10 ml of methanesulfonyl chloride. The mixture was kept at 10° for 24 hr, poured into ice water, and extracted with ether. The extracts were washed with 10% HCl and brine, dried, filtered, and evaporated *in vacuo* to leave 5.9 g of oil. Chromatography on alumina (80 g, neutral, 1.5 × 45 cm) using benzene as eluent yielded 3.08 g (72%) of mesylate **13a**: ir 1730, 1355, 1180, and 1155 cm^{-1}; nmr (CCl_4) δ 1.07 (s, 3, H-14), 1.10 (d, 3, J = 7 Hz, H-15), 1.22 (d, 3, J = 7 Hz, H-13), 1.43 (br s), 2.48 [t (dd), 1, $J_{1,5}$ = 2, $J_{4,5}$ = 2 Hz, H-5); 3.04 (s, 3, $-OSO_2CH_3$), 3.37 (q, 1, J = 7 Hz, H-11), 3.57 (s, 3, $-OCH_3$), 3.91 (br m, 1, CHOR), and 1.3–2.4 (m, 8).

Further elution of the column with chloroform yielded 1.13 g of starting hydroxy ester **11a**.

Methyl 3α-Acetoxy-1,7-cyclo-6-oxo-4,5β-eudesman-12-oate (13b).—A solution of 350 mg (1.3 mmol) of **11a** in 15 ml of acetic anhydride containing 50 μl of 70% $HClO_4$ was stirred in an ice bath for 13 hr, added to ice water, and extracted with ether. The extracts were washed successively with NaCl, $NaHCO_3$, 10% NaOH, and saturated NaCl solutions, dried, filtered, and evaporated *in vacuo* to yield 424 mg of brown oil. The oil was passed through 10 g of alumina (neutral, 1 × 14 cm): fraction 1 (benzene, 75 ml), 239 mg of acetate *via* nmr (*vide infra*); fraction 2 (chloroform, 50 ml), 98 mg of acetate **13b** and at least two other compounds that were not identified. The first fraction was evaporatively distilled (twice) to afford 208 mg (52%) of acetate **13b**: bp 84° (bath temperature) (0.09 mm); ir 1785 (shoulder) and 1735 cm^{-1}; nmr (CCl_4) δ 0.92 (d, 3, J = 7 Hz, H-15), 1.11 (s, 3, H-14), 1.38 (d, 3, J = 7 Hz, H-13), 1.94 (s, 3, $-OCOCH_3$), 3.09 (q, 1, J = 7 Hz, H-11), 3.59 (s, 3, $-OCH_3$), and 4.99 (br q, 1, J = 3.5 Hz, CHOR).

Anal. Calcd for $C_{18}H_{26}O_5$: C, 67.48; H, 7.55. Found: C, 67.45; H, 8.23.

Hydrolysis of 13b.—A solution of 169 mg of **13b** in 8 ml of 40% ethanol containing 6% NaOH was heated at reflux under N_2 for 3 hr. Work-up afforded **11** in >80% yield.

Methyl 6β-Acetoxy-1,7-cyclo-3α,6α-epoxy-4,5β-eudesman-12-oate (14).—A mixture of 3.08 g (0.009 mol) of mesylate **13a**, 50 ml of glacial acetic acid, and 4.0 g of anhydrous sodium acetate was heated at reflux under N_2 for 2 hr, cooled, diluted with H_2O, and extracted with CH_2Cl_2. The organic extract was washed, dried, filtered, and evaporated *in vacuo* to yield 2.53 g (91%) of oil. Crystallization afforded 1.95 g (70%) of **14**: mp 79.6–83.6°; ir 1760, 1730, and 1100 cm^{-1}; nmr δ 1.08 (s, 3, H-14), 1.10 (d, 3, J = 7 Hz, H-15 or H-13), 1.27 (d, 3, J = 7 Hz, H-13 or H-15), 2.05 (s, 3, $-OCOCH_3$), 2.63 (dd, 1, $J \cong 3$, $J \sim 1.5$ Hz, H-5), 3.50 (q, 1, J = 7 Hz, H-11), 3.65 (s, 3, $-OCH_3$), and 4.05 (br m, 1, $W_{1/2}$ = 7.3 Hz, H-3). An analytical sample had mp 79.5–81°.

Anal. Calcd for $C_{18}H_{26}O_5$: C, 67.06; H, 8.13. Found: C, 67.06; H, 8.08.

Hydrolysis of 14.—A mixture of 1.53 g of **14** and 1.94 g of NaOH in THF–H_2O (3:2) was heated at reflux under N_2 for 6 hr and cooled. Extraction with ether afforded 1.35 g of neutral oil which was identical (nmr) with methyl ester **11a**. The basic aqueous solution was acidified and extracted with ether to yield 0.16 g of oil which was identical in its nmr spectrum with hydroxy acid **11**.

Dehydration of 11a. Method A.—A solution of 26.4 g (0.1 mol) of santonic acid (**2**) was reduced with $NaBH_4$ as described above. A solution of the crude alcohol **11a** in CH_3OH (350 ml) containing 0.5 ml of concentrated H_2SO_4 was refluxed for 2.5 hr and worked up as usual to afford, after esterification (CH_2N_2) and distillation at reduced pressure, 18.5 g of oil, bp 90–144° (0.15–0.22 mm). Chromatography on alumina (Alcoa F-20) yielded 14.3 g of a mixture of two olefins (5:1 ratio) and 3.37 g (13%) of recrystallized **11a**. The olefin mixture was rechromatographed four times on large alumina columns. Fractions containing the olefin eluted first were combined (650 mg) and distilled twice to afford 505 mg of **methyl 1,7-cyclo-6-oxo-4,5β-eudesm-2-en-12-oate (15)**: bp 64–70° (bath temperature) (0.11 mm); ir 1735, 1640, and 670 cm^{-1}; nmr δ 1.08 (d, 3, J = 7 Hz, H-15), 1.09 (s, 3, H-14), 1.50–2.7 (m, 7), 1.33 (d, 3, J = 7 Hz, H-13), 2.88 (q, 1, J = 7 Hz, H-11), 3.67 (s, 3, $-OCH_3$), 5.50 (ddd, 1, $J_{3,2}$ = 10, $J_{3,4}$ = 2, $J_{3,1}$ = 1 Hz, C=CH), and 5.75 (ddd, 1, $J_{2,3}$ = 10, $J_{2,1}$ = 5.25, $J_{2,4}$ = 2 Hz, CH=C). An analytical sample of **15** was prepared by glpc (6-ft column, 1% SE-30 on Anakrom AS).

Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.25; H, 8.22.

The fractions containing the olefin eluted last from the columns were combined (7.4 g) and distilled to afford 4.49 g of **methyl 1,7-cyclo-6-oxo-5β-eudesm-3-en-12-oate (16a)**: bp 62–72° (0.06 mm); ir (film) 1735, 1670, and 815 cm^{-1}; nmr (CCl_4) δ 0.97 (s, 3, H-14), 1.33 (d, 3, J = 7 Hz, H-13), 1.70 (dt, 3, $J_{15,3}$ = 1.2, $J_{15,2}$ = $J_{15,2'}$ = 2.3 Hz, H-15), 2.17 (m, 3), 2.97 (q, 1, J = 7 Hz, H-11), 3.58 (s, 3, $-OCH_3$), and 5.33 (br s, 1, $W_{1/2}$ = 8 Hz, C=CH, H-3); ORD[46] (*c* 0.62, cyclohexane) $[\alpha]_{228}$ 0°, $[\alpha]_{287}$ +40,300°, $[\alpha]_{245}$ +35,800°, $[\alpha]_{273}$ +53,600°, $[\alpha]_{298}$ 0°, $[\alpha]_{314}$ −42,300°, $[\alpha]_{328}$ −20,900°, $[\alpha]_{350}$ = −8200°; CD[46] (*c* 0.62, cyclohexane) $[\theta]_{216}$ 0°, $[\theta]_{223.5}$ +42,700°, $[\theta]_{242}$ +6,100°, $[\theta]_{254}$ 0°, $[\theta]_{295}$ −70,100°, $[\theta]_{328}$ −1600°.

Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45; mol wt, 262.157. Found: C, 73.10; H, 8.27; mol wt, 262.193 (mass spectrum).

Method B.[25]—A solution of 200 mg of **11a**, 20 ml of anhydrous dimethylformamide, and 5 ml of collidine was cooled under N_2 and 2 ml of methanesulfonyl chloride was added. The mixture was stirred at room temperature (23°) for 12 hr and heated at 90–100° for 2 hr, cooled, poured into ice water, and extracted with ether. The extracts were washed with 20% HCl and brine, dried, filtered, and evaporated *in vacuo* to afford 218 mg of brown oil. The nmr spectrum indicated the presence of three compounds, *viz.*, **11a** (<5%), **15** (<5%), and **16a** (>90%).

Hydrolysis of 16a.—A mixture of 711 mg of **16a**, 10 ml of dioxane, and 20 ml of 10% NaOH was heated at reflux under N_2 for 2 hr. A normal work-up procedure afforded 678 mg of product which upon crystallization from ethyl acetate gave **1,7-cyclo-6-oxo-5β-eudesm-3-en-12-oic acid (16)** as white rods: mp 181.6–183°; nmr δ 0.84 (s, 3, H-14), 1.26 (d, 3, J = 7 Hz, H-13), 1.78 (dt, 3, $J_{15,3}$ = 1.2, $J_{15,2}$ = $J_{15,2'}$ = 2.3 Hz, H-15), 2.93 (q, 1, J = 7 Hz, H-11), 5.44 (br s, 1, $W_{1/2}$ = 7.5 Hz, H-3, C=CH), and 10.83 (s, 1, OH).

Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.49; H, 8.10.

Attempted Hydroboration of Methyl 1,7-Cyclo-6-oxo-5β-eudesm-3-en-12-oate (16a). Method A.[26]—To a cold (salt–ice bath) solution of 512 mg (1.9 mmol) of **16a** in 10 ml of anhydrous THF under N_2 was added 4 ml of 1.0 *M* borane in THF over 10 min; the solution was stirred at room temperature for 12 hr, H_2O was added dropwise until foaming ceased, and 5 ml of 10% NaOH and 5 ml of 30% H_2O_2 were added. After stirring for 1 hr at room temperature, the solution was extracted with ether. The extracts were washed, dried, filtered, and evaporated *in vacuo*, yielding 452 mg of oil: nmr (CCl_4) δ 1.12 (d, $J \sim 7$ Hz), 1.19 (s), 1.29 (s), 1.68 (br s), 2.59 (q, J = 7 Hz), 4.12 (dd, J = 7, 1.5 Hz), 4.34 (dd, J = 7, 1 Hz), 5.28 (br s), and 5.50 (br s). The ratio of the last four signals was about 5:4.5:1.3:0.5. Vpc analysis (6-ft column, 1% SE-30/Anakrom AS) indicated at least six compounds.

Method B.—The procedure of Knight and Brown[27] was followed in preparing 9-borabicyclo[3.3.1]nonane. A solution of 200 mg (0.76 mmol) of **16a** in 1 ml of THF was added by means of a syringe to the solution of 9-borabicyclo[3.3.1]nonane. The resulting reaction mixture was stirred at room temperature for 20 hr; H_2O was added followed by 1 ml of 10% NaOH and 1 ml of

(46) The ORD and CD curves were measured using a Durrum-Jasco Model J-20 spectropolarimeter.

30% H_2O_2. The resulting basic solution was warmed for 10 min and extracted with ether. The extracts were washed with 10% HCl and brine, dried, filtered, and evaporated *in vacuo* to afford 435 mg of oil; the nmr spectrum showed mainly **16a** and *ca.* 20% of 1,5-cyclooctadiene.

1,7-Cyclo-3-ethylenedioxy-6-oxo-4,5β-eudesman-12-oic Acid (17).—In a boiling flask equipped with a Dean–Stark trap, 52.8 g (0.2 mol) of santonic acid (**2**), 1.0 g of *p*-toluenesulfonic acid, and 100 ml of ethylene glycol in 1.05 l. of benzene were heated at reflux for 10 hr. The benzene was removed *in vacuo*, and 60 g of KOH, 300 ml of methanol, and 150 ml of H_2O were added. The solution was heated at reflux for 1 hr, cooled, evaporated *in vacuo*, acidified with dilute acetic acid, and extracted with CH_2Cl_2. The combined extracts were washed, dried, filtered, and evaporated *in vacuo*, affording 69.5 g of solid. Recrystallization yielded 51.7 g (83%) of santonic acid ketal (**17**): mp 146–149.6°; ir 1740 and 1705 cm^{-1}; nmr δ 0.99 (d, 3, J = 6.5 Hz, H-15), 1.22 (s, 3, H-14), 1.49 (d, 3, J = 7 Hz, H-13), 1.3–2.6 (complex m, 8), 3.33 (q, 1, J = 7 Hz, H-11), and 3.98 (m, 4, $-OCH_2CH_2O-$).

Anal. Calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.84. Found: C, 66.26; H, 7.86.

A solution of 100 mg (0.33 mmol) of **17** in 5 ml of acetone, 2 ml of water, and 5 drops of concentrated H_2SO_4 was heated at reflux under N_2 for 1 hr, cooled, and concentrated *in vacuo*, affording 70 mg (82%) of crude material having an nmr spectrum identical with that of authentic **2**. Recrystallization gave **2**, mp 165–177°, mmp 168–174° with authentic **2**.

Methyl 1,7-Cyclo-3-ethylenedioxy-6-oxo-4,5β-eudesman-12-oate (17a).—A solution of 1.60 g (0.005 mol) of **17** in ether was treated with CH_2N_2. Distillation afforded 1.3 g (78%) of **17a**: bp 172–185° (1.3 mm); ir 1740 (shoulder) and 1725 cm^{-1}; nmr δ 0.87 (d, 3, J = 7 Hz, H-15), 1.17 (s, 3, H-14), 1.34 (d, 3, J = 7 Hz, H-13), 3.17 (q, 1, J = 7 Hz, H-11), 3.62 (s, 3, $-OCH_3$), and 3.93 (m, 4, $-OCH_2CH_2O-$).

1,7-Cyclo-3-ethylenedioxy-6β-hydroxy-4,5β-eudesman-12-oic Acid (18).—Following a procedure analogous to that of Huffman and Charles,[29] a solution of 2.24 g (0.007 mol) of **17** in 40 ml of anhydrous THF was added to 500 ml of distilled liquid NH_3 in a flask equipped with a Dry Ice–acetone condenser; NH_4Cl (57 g) was then added. This was followed by addition of 6.4 g of Li wire in small pieces over 20 min at −60°. The mixture was stirred for 1 hr and warmed to room temperature. After evaporation of most of the NH_3 and addition of water, glacial acetic acid was added dropwise to the cooled mixture until the pH was 6. Extraction with CH_2Cl_2 followed by a normal work-up procedure afforded 2.45 g of white solid. Recrystallization gave 1.85 g (82%) of the hydroxy acid **18**: mp 198–201°; ir (Nujol) 3455 (OH), 3500–2600 (br, OH), and 1740 cm^{-1}; nmr (DMSO-d_6) δ 0.83 (d, 3, J = 6.5 Hz, H-15), 0.99 (s, 3, H-14), 1.08 (d, 3, J = 7 Hz, H-13), 1.32 (s), 2.78 (q, 1, J = 7 Hz, H-11), 3.82 (m, 4, $-OCH_2CH_2O-$), 4.26 (br s, 1, $W_{1/2}$ = 3 Hz, CHOH), and 11.69 (br s, 1, OH).

Anal. Calcd for $C_{17}H_{26}O_5$: C, 65.78; H, 8.44. Found: C, 65.81; H, 8.36.

The nmr spectrum of the mother liquor (333 mg) indicated a 7:3 ratio of unreduced **17** to 6β-hydroxy acid **18**. No 6α-hydroxy acid **20** was discernible.

Methyl 1,7-Cyclo-3-ethylenedioxy-6β-hydroxy-4,5β-eudesman-12-oate (18a).—Diazomethane in ether was added to a solution of 3.74 g (0.012 mol) of once-recrystallized acid **18**. Evaporation *in vacuo* gave an oil which was chromatographed on alumina (neutral) to remove small amounts of **17a**. The fractions containing **18a** were combined and a portion (0.21 g) was distilled using a sublimation apparatus to obtain an analytical sample: bp 80–82° (bath temperature) (0.10 mm); ir 3630, 3480, and 1725 cm^{-1} (C=O); nmr δ 0.90 (d, 3, J = 7 Hz, H-15), 1.05 (s, 3, H-14), 1.23 (d, 3, J = 7 Hz, H-13), 1.95 (s, 1, OH), 3.00 (q, 1, J = 7 Hz, H-11), 3.63 (s, 3, $-OCH_3$), 3.92 (m, 4, $-OCH_2CH_2O-$), and 4.48 (s, 1, $W_{1/2}$ = 4 Hz, CHOH).

Anal. Calcd for $C_{18}H_{28}O_5$: C, 66.64; H, 8.70. Found: C, 66.45; H, 8.51.

Oxidation of 18a to 17a.—To a cooled (ice bath) solution of 87 mg (0.27 mmol) of **18a** in 10 ml of acetone (distilled from chromic trioxide), 0.25 ml of Jones–Weedon reagent[12] was added dropwise over 10 min until a red color persisted. The mixture was stirred for 35 min. Methanol and H_2O were added and the mixture was extracted with ether. The extracts were washed with brine, dried, filtered, and evaporated *in vacuo* to afford 80 mg (92%) of **17a**: nmr δ 0.95 (d, 3), 1.00 (s, 3), 1.42 (d, 3), 3.28 (q, 1), 3.65 (s, 3), and 3.95 (m, 4).

1,7-Cyclo-6β-hydroxy-5β-eudesm-3-en-12-oic Acid (19).—A solution of 2.24 g (0.009 mol) of **16** in 30 ml of anhydrous THF was added to 500 ml of distilled liquid NH_3 in a flask cooled with a Dry Ice–acetone bath and fitted with a Dry Ice–acetone condenser. Ammonium chloride (53 g) was added,[29] followed (during 25 min) by 5.70 g of Li wire cut in small pieces. The cold mixture was stirred until the blue color had disappeared, and then warmed to room temperature. After evaporation of the NH_3, the mixture was cooled, treated with water, acidified with glacial acetic acid to pH 6, and extracted with CH_2Cl_2. A normal work-up afforded 2.99 g of yellowish oil which, after several recrystallizations, afforded 1.01 g (45%) of **19**: mp 126.5–128.5°; nmr δ 0.94 (s, 3, H-14), 1.22 (d, 3, J = 7 Hz, H-13), 1.52 (apparent br s), 1.71 (apparent br d, 3, J = 1.5 Hz, H-15), 2.77 (q, 1, J = 7 Hz, H-11), 3.73 (br s, 1, $W_{1/2}$ = 2.5 Hz, CHOH), 5.12 (br s, 1, $W_{1/2}$ = 6 Hz, CH=C, H-3), and 7.48 (s, 2, OH).

Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.98; H, 8.92.

Methyl 1,7-Cyclo-6β-hydroxy-5β-eudesm-3-en-12-oate (19a).—A solution of **19** in ether was treated with CH_2N_2. Several distillations using an evaporative still gave **19a**: bp 82–84° (bath temperature) (0.12 mm); ir 3630, 3510, 1730, and 805 cm^{-1}; nmr δ 0.93 (s, 3, H-14), 1.21 (d, 3, J = 7 Hz, H-13), 1.47 (br peak, 4, $W_{1/2}$ = 3.3 Hz), 1.71 (dt, 3, $J_{15,2}$ = 2.3, $J_{15,3}$ = 1.5 Hz, H-15), 2.46 (s, 1, OH), 2.78 (q, 1, J = 7 Hz, H-11), 3.64 (s, 3, $-OCH_3$), 3.73 (s, 1, $W_{1/2}$ = 2 Hz, CHOH), and 5.10 (br s, 1, $W_{1/2}$ = 7.5 Hz, CH=C, H-3).

A sample for elemental analysis was prepared by glpc (10.5-ft column, 2% SE-30 on Anakrom 60/70 ABS).

Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.29; H, 9.17.

Preparation of 20, 21, and 22 by Lithium Aluminum Hydride Reduction of 17.—A solution of 24.0 g (0.08 mol) of **17** in 225 ml of anhydrous THF was added dropwise during 2 hr to a mixture of 5.0 g of $LiAlH_4$ in 200 ml of anhydrous THF at −1 to −5° and under N_2. The mixture was stirred at 0° for 3 hr. Wet ether and aqueous $NaHCO_3$ solution were added dropwise and in succession at 0° and the resulting mixture was stirred for 1 hr, diluted further with H_2O, and extracted with ether. The organic layer was worked up as usual by washing with brine, drying, filtering, and evaporating *in vacuo* to yield 4.96 g of gummy tan solid. The solid was slurried in saturated Na_2CO_3 solution for 30 min. Extraction with ether and work-up as before afforded 2.40 g of solid. Recrystallization gave **1,7-cyclo-3-ethylenedioxy-4,5β-eudesmane 6α,12-diol (21)** as white prisms: mp 108.8–110.4°; ir 3610 and 3420 cm^{-1}; nmr δ 0.90 (d, 3, J = 6.7 Hz), 0.93 (d, 3, J = 6.7 Hz), 1.12 (s, 3, H-14), 1.21 (s), 1.72 (br d, 1, $J_{5,6}$ = 4.5 Hz, H-5), 2.78 (br s, 2, -OH), 3.51 (d, 1, $J_{12,12'}$ = 11.0, $J_{12,11}$ = 0 Hz, H-12), and 3.71 [dd (partially obscured), 1, $J_{12',12}$ = 11.0, $J_{12',11} \sim 5$ Hz, H-12'], 3.76 (s, 4, $-OCH_2CH_2O-$), and 4.04 (dd, 1, $J_{6,5}$ = 4.5, $J_{6,1}$ = 3 Hz, CHOH).

Anal. Calcd for $C_{17}H_{28}O_4$: C, 68.89; H, 9.52. Found: C, 68.98; H, 9.33.

The diol **21** was also obtained in high yield by $LiAlH_4$ reduction of the hydroxy acid **20**.

The combined basic aqueous layers containing the acidic product after removal of **21** were cooled, acidified by addition of HCl, saturated with NaCl, and extracted with ether. The extracts were combined, washed, dried, filtered, and evaporated *in vacuo*, leaving 23.3 g of oil. The oil was dissolved in ethyl acetate, and petroleum ether (bp 30–60°) was added. Upon cooling to 0°, crystals were deposited. Filtration yielded 0.87 g of starting ketal **17** (nmr), mp 134–140°. The filtrate was concentrated, taken up in ether, washed with Na_2CO_3 and saturated NaCl solutions, dried, filtered, and evaporated *in vacuo* to leave 167 mg of diol **21** (nmr). The basic wash solutions were acidified and extracted as before to recover the bulk of the oily product (*ca.* 22 g). The oil was dissolved in 220 ml of dioxane. Hydrochloric acid (10%, 110 ml) was added and the resulting mixture was heated at reflux for 3 hr, cooled, saturated with NaCl, and extracted with ether. The extracts were washed with $NaHCO_3$ and saturated NaCl solutions, dried, filtered, and evaporated *in vacuo*, affording 20.8 g of oil. The oil was stirred with aqueous Na_2CO_3 for 2 hr and extracted with ether. The ether layer was processed as before to yield 0.45 g of solid which afforded **1,7-cyclo-3-oxo-4,5β-eudesmane 12,6α-lactone (22)** upon recrystallization: mp 173–175.5°; ir 1780 (C=O) and 1715 cm^{-1} (C=O); nmr δ 1.21 (d, 3, J = 7 Hz), 1.23 (d, 3, J = 7 Hz), 1.28 (s, 3, H-14), 2.65 (q, 1, J = 7 Hz, H-11), and 4.35 (dd, 1, $J_{6,5}$ = 7, $J_{6,1}$ = 2 Hz, CHO-).

Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.46; H, 7.91.

The aqueous bicarbonate layer remaining after removal of **22** was cooled to 0° and acidified by dropwise addition of HCl. Extraction with ether was followed by a normal brine wash. Drying, filtration, and concentration gave an oil which crystallized to yield 17.1 g (71%) of **1,7-cyclo-3-ethylenedioxy-6α-hydroxy-4,5β-eudesman-12-oic acid (20)** as white prisms: mp 112–116.5°; ir 3590, 3440, and 1705 cm^{-1}; nmr[44] δ 0.90 (d, 3, $J_{15,4}$ = 6.7 Hz, H-15), 1.13 (s, 3, H-14), 1.16 (d, 3, $J_{13,11}$ = 7 Hz, H-13), 1.78 [m, 2 (appears as br d, J = 5 Hz, at 60 MHz), H-1 and H-5], 2.13 (q, 1, $J_{4,15}$ = 6.7 Hz, H-4), AB parts of an ABX pattern centered at 1.51 (dd, 1, $J_{2,2'}$ = 13, $J_{2,1}$ = 2.5 Hz, H-2), and 2.29 (dd, 1, $J_{2',2}$ = 13, $J_{2',1}$ = 2.5 Hz, H-2'), 3.27 (q, 1, $J_{11,13}$ = 7 Hz, H-11), 3.78 (m, 4, $-OCH_2CH_2O-$), 4.05 (dd, 1, $J_{6,5}$ = 5.5, $J_{6,1}$ = 3.5 Hz, CHOH), and 6.94 (br s, 2, OH). An analytical sample of **20** had mp 117.9–118.5°.

Anal. Calcd for $C_{17}H_{26}O_5$: C, 65.78; H, 8.44. Found: C, 65.69; H, 8.61.

The mother liquors afforded another 0.78 g of **20**.

Preparation of 22 by Treatment of 20 with HCl.—A mixture of 1.00 g (0.003 mol) of **20**, 10 ml of 10% HCl, and 20 ml of dioxane was heated at reflux under N_2. After 16 hr, a 20-ml aliquot was added to 10% NaOH solution. The solution was extracted with ether and the extracts were washed, dried, filtered, and evaporated *in vacuo* to afford 0.028 g of lactone **22** (nmr). The basic solution was cooled, acidified with HCl, extracted with ether, and worked up in the normal manner to leave 0.507 g of the starting acid **20** (nmr). The nmr spectrum was poorly resolved and at least 20% of other material could have gone undetected. After heating for 84 hr, the remaining mixture was worked up as for the aliquot to afford 0.067 g of lactone **22** and 0.238 g of acid **20**.

The acidic material (0.507 g) obtained from work-up of the aliquot was subjected to further acid treatment for 50 hr and worked up as before to yield 0.523 g of material containing lactone **22** and acid **20** in a ratio of ~2:3 by nmr assay.

Preparation of 20-*6β-d*$_1$ and 21-*6β,12,12-d*$_3$.—Ketal **17** (2.0 g, 0.007 mol) was reduced with 0.52 g of $LiAlD_4$ as described above for the preparation of **20**, **21**, and **22**, yielding 0.18 g of neutral diol, **21-*6β,12,12-d*$_3$**: mp 105–106.5°; nmr δ 0.88 (d, 3, J = 6.5 Hz, H-15), 0.93 (d, 3, J = 6.8 Hz, H-13), 1.12 (s, 3, H-14), 1.71 (br s, 1, $W_{1/2}$ = 2.5 Hz), 2.32 (q, 1, J = 7 Hz), 2.37 (q, 1, J = 7 Hz), and 3.78 (s, 4, $-OCH_2CH_2O-$). An additional 0.21 g of crystals were obtained from the mother liquor on evaporation and cooling.

Further processing as described for the $LiAlH_4$ reduction afforded trace amounts of lactone **22-*d*$_3$** followed by 0.87 g of **20-*6β-d*$_1$**: mp 111–112.9°; nmr δ 0.90 (d, 3, J = 6.5 Hz, H-15), 1.12 (s, 3, H-14), 1.14 (d, 3, J = 6.5 Hz, H-13), 1.77 (s, 2), 3.22 (q, 1, J = 6.7 Hz, H-11), and 3.75 (s, 4, $-OCH_2CH_2O-$). Another 0.76 g of crystals (mp 112–115°) was obtained from the mother liquor after concentrating and cooling.

Attempted Oxidation of 20 to 17.—A solution of 1.00 g of **20** in 20 ml of anhydrous DMF containing 1.00 g of anhydrous CrO_3[47] was treated with 100 λ of concentrated H_2SO_4 and stirred at room temperature for 5 days. The reaction was quenched by adding methanol to destroy the excess oxidant. The mixture was diluted with $NaHCO_3$ solution and extracted with ether. The extracts were washed, dried, filtered, and evaporated *in vacuo* to yield 246 mg of oil, whose nmr spectrum showed that the ratio of the area for CHOH to the area of $-OCH_2CH_2O-$ was 1:1 and the ratio of area for lactonic CHO– to CHOH was 1:4.

The aqueous layer was acidified with HCl and extracted with ether. The ether layer was worked up as above to obtain 880 mg of oil. An nmr spectrum of the oil was not readily interpreted; however, integration indicated that the areas for the lactonic CHO–, CHOH, and $-OCH_2CH_2O-$ protons were in a ratio of 1:3:8. Also, a signal at δ 1.28 could be assigned to H-14 of the lactone **22** and a signal at 1.12 assigned to a methyl group of the acid **20**.

Methyl 1,7-Cyclo-3-ethylenedioxy-6α-hydroxy-4,5β-eudesman-12-oate (20a).—A solution of **20** in ether was treated with CH_2N_2–Et_2O concentrated *in vacuo* to leave the methyl ester **20a**: bp 120–140° (bath temperature) (0.1 mm); ir 3413 and 1705 cm^{-1} (d); nmr δ 0.90 (d, 3, J = 6.5 Hz, H-15), 1.12 (s, 3, H-14), 1.30 (d, 3, J = 7 Hz, H-13), 1.78 (dd, 1, $J_{5,6}$ = 5.5, $J_{5,1}$ = 2, $J_{5,4}$ = 0 Hz, H-5), 2.11 (q, 1, J = 6.5 Hz, H-4), 3.10 (s, 1, OH), 3.25 (q, 1, J = 7 Hz, H-11), 3.67 (s, 3, $-OCH_3$), 3.75 (s, 4, $-OCH_2CH_2O-$), and 4.02 (dd, 1, $J_{6,5}$ = 5.5, $J_{6,1}$ = 2.5 Hz, CHOH). An analytical sample was prepared by distilling an aliquot twice using an evaporative still and collecting the fraction boiling at 140–143° (bath temperature) (0.1 mm).

Anal. Calcd for $C_{18}H_{28}O_5$: C, 66.64; H, 8.70. Found: C, 66.60; H, 8.61.

Attempted Oxidation of 20a to 17a.—To an ice-cooled solution of 258 mg of **20a** in 10 ml of anhydrous DMF was added 120 mg of CrO_3.[47] The mixture was stirred until dissolution was complete (30 min). Three drops of concentrated H_2SO_4 was added. The solution was stirred at room temperature for 7 hr, treated with aqueous $NaHSO_3$, and extracted with ether. The extracts were washed, dried, filtered, and evaporated *in vacuo* to yield 210 mg of oil; the nmr spectrum had the usual peaks for **20a** plus C-methyl peaks for a related compound in minor amount. However, the ratio of the peaks at δ 3.63 (s, $-OCH_3$), 3.73 (s, $-OCH_2-CH_2O-$), and 3.98 (dd, J = 5.5, J = 2.5 Hz, CHOH) was 2:2:1.

Attempted Ketalization of 22.—A mixture of 243 mg of the lactone **22**, 20 ml of benzene, 10 ml of ethylene glycol, and 9.81 mg of *p*-toluenesulfonic acid was heated at reflux for 48 hr using a Dean–Stark trap to collect water formed. The benzene was distilled and 10 ml of 20% KOH and 20 ml of methanol were added. The resulting solution was heated at reflux under N_2 for 1 hr, cooled, acidified with acetic acid, and extracted with CH_2-Cl_2. The organic phase was washed, dried, filtered, and evaporated *in vacuo* to afford 238 mg of oily solid. Recrystallization from ethyl acetate yielded 96 mg of white crystals, mp 169.5–174.5°. The product was identical with **23** in its nmr spectrum (see below). The mother liquor gave a poorly defined nmr spectrum in which **20** could not be clearly identified.

1,7-Cyclo-6α-hydroxy-3-oxo-4,5β-eudesman-12-oic Acid (23).—A mixture of 315 mg (1.3 mmol) of lactone **22** and 5 ml of 10% NaOH was warmed to 57° over 3 hr under N_2 until the solid had dissolved; the solution was cooled, acidified by dropwise addition of HCl, and extracted with ether. The extracts were washed, dried, filtered, and evaporated *in vacuo*, leaving 354 mg of solid. Recrystallization afforded 213 mg (63%) of **23**: mp 181–183.5°; ir (Nujol) 3320 (OH) and 1705 cm^{-1} (C=O); nmr (DMSO-d_6) δ 0.80 (d, 3, J = 6.7 Hz, H-15), 1.00 (d, 3, J = 7 Hz, H-13), 1.07 (s, 3, H-14), 1.15–2.2 (m, 8), 3.11 (q, 1, J = 7 Hz, H-11), 3.60 (dd, 1, $J_{6,5}$ = 5.5, $J_{6,1}$ = 2.5 Hz, CHOH), and 6.0 (br s, OH).

Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33. Found: C, 67.49; H, 8.21.

Methyl 1,7-Cyclo-3-ethylenedioxy-6β-methanesulfonyloxy-4,-5β-eudesman-12-oate (24).—To an ice-cooled solution of 336 mg (1.04 mmol) of **18a** in 7 ml of anhydrous pyridine was added 1 ml of methanesulfonyl chloride. The mixture was kept at 10° for 38 hr, and then treated with ice water and extracted with CH_2Cl_2. The extracts were washed with H_2O, dilute acetic acid (10%), and saturated $NaHCO_3$ solution, dried, filtered, and evaporated *in vacuo* to leave 366 mg (88%) of **24**: nmr δ 1.00 (d, 3, J = 7 Hz, H-15), 1.09 (s, 3, H-14), 1.22 (d, 3, J = 7 Hz, H-13), 2.99 (s, 3, $-OSO_2CH_3$), 3.13 (q, 1, J = 7 Hz, H-11), 3.63 (s, 3, $-OCH_3$), 3.94 (m, 4, $-OCH_2CH_2O-$), and 5.53 (s, 1, H-6).

Methyl 1,7-Cyclo-3-ethylenedioxy-6α-methanesulfonyloxy-4,-5β-eudesman-12-oate (C-6 Epimer of 24).—To a solution of 1.05 g (0.003 mol) of **20a** in 20 ml of anhydrous pyridine at 0° under N_2 was added 0.5 ml of methanesulfonyl chloride. The mixture was stirred for 45 min (formation of a precipitate occurred), poured into cold 10% HCl, and extracted with ether. The extracts were washed with dilute HCl and brine, filtered, and evaporated *in vacuo* to leave a solid which upon recrystallization afforded 1.09 g (81%) of the C-6 epimer of **24**: mp 122–123°; ir 1730 (C=O), and 1360 and 1178 cm^{-1} ($-SO_2O-$); nmr δ 0.88 (d, 3, J = 6.5 Hz, H-15), 1.10 (s, 3, H-14), 1.13 (d, 3, J = 7 Hz, H-13), 1.77 (dd, 1, $J_{5,6}$ = 5.5, $J_{5,1}$ = 2 Hz, H-5), 2.10 (q, 1, J = 6.5 Hz, H-4), 3.04 (s, 3, $-SO_2CH_3$), 3.22 (q, 1, J = 7 Hz, H-11), 3.63 (s, 3, $-OCH_3$), 3.93 (8 lines, 3, –CHO– and A_2 of A_2B_2 for $-OCH_2CH_2O-$), and 4.32 (8 lines, 2, B_2 of A_2B_2 for $-OCH_2CH_2O-$).

Anal. Calcd for $C_{19}H_{30}O_7S$: C, 56.71; H, 7.51; S, 7.51. Found: C, 56.61; H, 7.48; S, 7.65.

1,7-Cyclo-3-ethylenedioxy-13-oxo-4,5β-13-homoeudesmane 13a,6β-Sultone (25).—A solution of 256 mg (0.64 mmol) of **24** in 10 ml of dry benzene was added to 380 mg of potassium *tert*-butoxide (Ventron, powder) in 10 ml of dry benzene. The mixture was heated at reflux under N_2 for 1 hr, cooled, poured into ice water, and extracted with ether. The extracts were washed, dried, filtered, and evaporated *in vacuo* to afford 134 mg (57%) of sultone **25**: ir 1715, 1370, and 1160 cm^{-1}; nmr δ 0.95 (d, 3, J = 6.5 Hz), 1.06 (d, 3, J = 7 Hz), 1.14 (s, 3, H-14), 1.59 (br s,

(47) G. Snatzke, *Chem. Ber.*, **94**, 729 (1961).

$W_{1/2}$ = 6.5 Hz), 2.35 (qd, 1, $J_{4,15}$ = 7, $J_{4,5}$ = 2 Hz, H-4), 3.29 (q, 1, J = 7 Hz, H-11), 3.97 (m, 4, $-OCH_2CH_2O-$), 4.34 (s, 2, H-13a), and 5.75 (s, 1, H-6). A sample for elemental analysis, mp 130.5–132° dec, was prepared by recrystallization from ethanol.

Anal. Calcd for $C_{18}H_{26}O_6S$: C, 58.37; H, 7.08; S, 8.63. Found: C, 58.42; H, 6.78; S, 9.52, 8.68.

A new crystalline material formed when the sultone **25** was left at room temperature in the presence of a trace of acid. Recrystallization from methanol afforded 3-oxo sultone **26**: mp 137–141° dec; ir 1715, 1370, and 1165 cm^{-1}; nmr δ 1.14 (d, J = 7 Hz), 1.20 (d, 3, J = 6.5 Hz), 1.27 (s, 3, H-14), 2.76 (dq, 1, $J_{4,15}$ = 7, $J_{4,5}$ = 2.5 Hz, H-4), 3.18 (q, 1, J = 7 Hz, H-11), 4.31 (s, 2, H-13a), and 4.56 (br, 1, $W_{1/2}$ = 3 Hz, CHO–).

Anal. Calcd for $C_{16}H_{22}O_5S$: C, 58.88; H, 6.79; S, 9.81. Found: C, 59.06; H, 7.04; S, 9.51.

Methyl 1,7;4,6α-Biscyclo-3-oxo-5β-eudesman-12-oate (28).—Mesylate **24** was prepared as described using 207 mg (0.64 mmol) of the ester **18a**. In the work-up procedure the ethereal solution was washed with 10% HCl instead of acetic acid as described above. An nmr spectrum of the oil obtained (228 mg) indicated that partial loss of the ketal function had occurred resulting in formation of two mesylates, *viz.*, **24** and **27**, in a ratio of *ca.* 1:1. The oil was chromatographed on 9 g of alumina to afford, after distillation, 104 mg of **28**: bp 72–75° (bath temperature) (0.10 mm); ir 1735, 1685, 1465, 1380, 875, and 855 cm^{-1}; nmr δ 1.03 (s, 3, H-15), 1.12 (s, 3, H-14), 1.24 (d, 3, J = 7 Hz, H-13), 2.14 (dd, A of ABX, 1, $J_{2,2'}$ = 16.5, $J_{2,1}$ = 3.0 Hz), 2.25 (dd, B of ABX, 1, $J_{2',2}$ = 16.5, $J_{2',1}$ = 3.0 Hz), 2.68 (q, 1, J = 7 Hz, H-11), and 3.63 (s, 3, $-OCH_3$); in benzene the doublet at 2.14 ppm was shifted to 2.07 ppm. The outer low-intensity doublets (J = 3 Hz) of the AB portion of the ABX system were partially obscured by other resonance peaks.

Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.67; H, 8.52.

Alkaline Peroxide Oxidation of Santonic Acid (2).—To a cooled solution of 3.00 g (0.012 mol) of **2** in 15 ml of 10% NaOH was added 20 ml of 15% H_2O_2. The solution was left at 10° for 38 hr, acidified by dropwise addition of 4 *N* HCl (15 ml), and extracted with ether. The extracts were washed, dried, filtered, and evaporated *in vacuo*, yielding 3.88 g of solid. Recrystallization from benzene and four times from ethyl acetate afforded 229 mg of **1,7-cyclo-*B*-homo-6a-oxa-3,6-dioxo-4,5β-eudesman-12-oic acid (31)**: mp 181–183° dec; ir 1745 and 1715 cm^{-1}; nmr δ 1.08 (d, J = 6.5 Hz, H-15), 1.35 (d, J = 7 Hz, H-13), 1.44 (s, 3, H-14), 3.04 (q, 1, J = 7 Hz, H-11), and 9.63 ppm (s, 1.3, –COOH).

Anal. Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.23; H, 7.05.

The mother liquors were combined, treated with CH_2N_2–Et_2O, and evaporated *in vacuo* to give 2.06 g of oil. The oil was chromatographed on neutral alumina. Rechromatography on silica gel of the fractions eluted from alumina with petroleum ether and CCl_4 afforded, on elution with $CHCl_3$ (following elution with CCl_4 and benzene), 0.134 g of **29a** (see below) and 1.21 g of a mixture of **31a** and **29a** in a ratio of ~12:1. Distillation of the 0.134-g fraction afforded 0.124 g of **methyl 1β,3α-dimethyl-7-ethylidene-4-oxo-5β-bicyclo[4.3.0]octane-2-carboxylate (29a) (methyl aposantonate)**: bp 62–72° (bath temperature) (0.06 mm); mp 71–73°; ir 1735, 1715, and 820 cm^{-1}; nmr δ 0.95 (d, 3, J = 6.0 Hz, 3-CH_3), 0.99 (s, 3, 1-CH_3), 1.60 (dt, 3, J = 7, 1.5 Hz, C=CHCH_3), 2.51 [d, 1, $J_{2,3}$ = 12.5 Hz, H-2 (upfield half of doublet partially obscured)], 2.92 (dq, 1, $J_{3,2}$ = 12.5, J_{3,CH_3} = 6 Hz), 3.75 (s, 3, $-OCH_3$), and 5.35 (br q, 1, J = 7 Hz, C=C**H**-CH_3).

Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.92; H, 8.76.

Two distillations of the 1.21-g mixture followed by glpc separation afforded 67 mg of the lactone ester **31a**: mp 111.8–127°; nmr δ 1.06 (d, 3, J = 6.75 Hz, H-15), 1.30 (d, 3, J = 7 Hz, H-13), 1.43 (s, H-14), 3.00 (q, 1, J = 7 Hz), and 3.70 (s, 3 $-OCH_3$). An analytical sample was prepared by glpc (6-ft column, 1% SE-30 on Anakrom AS).

Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 64.99; H, 7.40.

The reaction was repeated following as closely as possible the procedure given by Wedekind and Jäckh.[36] Santonic acid (**2**, 3.00 g) in 50 ml of 2% KOH in the cold was treated with 40 ml of 15% H_2O_2 for 24 hr. The resulting solution was acidified with 10% HCl, saturated with NaCl, and extracted with ether. The extracts were washed with brine, dried, filtered, and evaporated *in vacuo* to afford 2.91 g of oil; the nmr spectrum indicated santonic acid (**2**), olefin **29**, and lactone **31** in a ratio of 2:1:1.

Treatment of Santonic Acid (2) with Potassium Hypobromite.—By analogy with the procedure of Wedekind and Jäckh,[36] a solution of 10 ml of Br_2 in 600 ml of 5% KOH was added to a solution of 10.0 g (0.04 mol) of **2** in 200 ml of 5% KOH at room temperature. Within 30 min solid formed. After 24 hr, the mixture was filtered to yield 100 mg of carbon tetrabromide, mp 90–92°. The filtrate, after 13 days, was cooled and acidified with HCl. Sodium bisulfite and NaCl were added and the mixture was extracted with ether. The extracts were washed, dried, filtered, and evaporated *in vacuo* to afford 9.9 g of white solid. A solution of 3.47 g of the solid in ethyl acetate was diluted with petroleum ether until the solution became cloudy. The solution was warmed gently on the hot plate until a slight amount of brown oil began to form; upon cooling, crystals began to form. Filtration gave 0.46 g (14%) of **2(3 → 4β)*abeo*-1,7-cyclo-2α-hydroxy-6-oxo-5β-eudesmane-3,12-dioic acid (32) (oxysantonic acid)**: mp 211–213° (sealed tube) (lit.[36] mp 215° dec); ir (Nujol mull) 3600–2600, and a broad absorption band at 1786–1690 having peaks (shoulders) at 1768, 1745, 1735, and 1718 cm^{-1}. A second crop of crystals yielded another 0.12 g of the diacid.

Anal. Calcd for $C_{15}H_{20}O_6$: C, 60.80; H, 6.80. Calcd for $C_{15}H_{20}O_6 \cdot {}^1/_4H_2O$: C, 59.8; H, 6.7. Found: C, 59.77, 59.62; H, 6.87, 6.81.

Dimethyl 2-(3 → 4β)*abeo*-1,7-Cyclo-2α-hydroxy-6-oxo-5β-eudesmane-3,12-dioate (32a).—A solution of 0.211 g (0.71 mmol) of **32** in ether was treated with CH_2N_2 to yield 0.230 g (100%) of the dimethyl ester **32a**: nmr δ 1.33 (s, 3, H-14), 1.42 (d, 3, J = 7 Hz, H-13), 1.61 (s, 3, H-15), 2.36 (d, 1, $J_{5,1}$ = 2.5 Hz, H-5), 2.54 (dd, 1, $J_{1,2}$ = 4, $J_{1,5}$ = 2.5 Hz, H-1), 3.28 (q, 1, J = 7 Hz, H-11), 3.68 (s, 3, $-OCH_3$), 3.72 (s, 3, $-OCH_3$), 4.49 (dd, 1, $J_{2,OH}$ = 7, $J_{2,1}$ = 4 Hz, H-2), and 5.08 (d, 1, $J_{OH,2}$ = 7 Hz, OH). The signal at δ 5.08 disappeared upon addition of one drop of acetic acid-d_4; the doublet of doublets at δ 4.49 became a doublet ($J_{2,1}$ = 4 Hz) and a broad absorption band appeared at δ 9.47.

Dimethyl 2(3 → 4β)*abeo*-1,7-Cyclo-2,6-dioxo-5β-eudesmane-3,12-dioate (33).—To a cold solution of 84 mg (0.26 mmol) of **32a** in 5 ml of acetone was added 0.5 ml of Jones–Weedon reagent.[12] After the solution was stirred for 24 min, excess oxidant was destroyed with methanol, H_2O was added, and the solution was extracted with ether. The extracts were washed with brine, dried, filtered, and evaporated *in vacuo* to leave 61 mg (73%) of yellow oil. The oil was passed through silica gel using chloroform as eluent. Concentration of the eluate *in vacuo* gave dihemiketal **33a**: ir (Nujol) 3500–2500 (br band with max at 3380), 1735, 1710, and 1683 cm^{-1}; nmr δ 1.35 (s, 3, H-14), 1.39 (d, 3, J = 7 Hz, H-13), 1.58 (s, 3, H-15), 2.72 (s, 2, H-1 and H-5), 3.07 (q, 1, J = 7 Hz, H-11), 3.66 (s, 3, $-OCH_3$), and 3.72 (s, 3, $-OCH_3$). An analytical sample was prepared by recrystallization from CH_3OH–H_2O, mp 207–211°.

Anal. Calcd for $C_{17}H_{22}O_6$: C, 63.34; H, 6.88. Calcd for $C_{17}H_{22}O_6 \cdot H_2O$: C, 59.99; H, 7.11. Found: C, 60.19, 60.20; H, 7.38, 7.16.

2(3 → 4β)*abeo*-1,7-Cyclo-4α,6α-carbonyloxy-2α,6-diacetoxy-5β-eudesman-12-oic Acid (34).—A solution of 529 mg of **32** in 5 ml of pyridine and 2.5 ml of acetic anhydride was stirred at room temperature for 62 hr, diluted with ice water, and extracted with ether. The extracts were washed with dilute HCl and brine, dried, filtered, and evaporated *in vacuo* to leave 600 mg of oil. Crystallization from benzene–petroleum ether followed by ethyl acetate–petroleum ether afforded 129 mg of the diacetoxy acid **34**: mp 194.5–196° (lit.[36] mp 192° dec); ir 1800, 1760, 1745, and 1710 cm^{-1}; nmr δ 1.22 (s, 3, H-14), 1.28 (d, 3, J = 7 Hz, H-13), 1.48 (s, 3, H-15), 2.06 (s, 3, $-OCOCH_3$), 2.11 (s, 3, $-OCOCH_3$), 2.37 (dd, 1, $J_{1,2}$ = 4, $J_{1,5}$ = 2 Hz, H-1), 3.10 (d, 1, $J_{5,1}$ = 2 Hz, H-5), 3.26 (q, 1, J = 7 Hz, H-11), and 5.33 (d, 1, $J_{2,1}$ = 4 Hz, H-2).

Anal. Calcd for $C_{19}H_{24}O_8$: C, 59.97; H, 6.36. Found: C, 60.14; H, 6.32.

Methyl 2(3 → 4β)*abeo*-1,7-Cyclo-4α,6α-carbonyloxy-2α,6β-diacetoxy-5β-eudesman-12-oate (34a).—A solution of 208 mg of the diacetoxy acid **34** in ether was treated with CH_2N_2 to afford 204 mg of diacetoxy ester **34a**: mp 139.5–140.8° (lit.[36] mp 142°); nmr δ 1.22 (s, 3, H-14), 1.22 (d, 3, J = 7 Hz, H-13), 1.43 (s, 3, H-15), 2.02 (s, 3, $-OCOCH_3$), 2.08 (s, 3, $-OCOCH_3$), 2.18 (dd, 1, $J_{1,2}$ = 4 Hz, $J_{1,5}$ = 2.5 Hz, H-1), 3.03 (d, 1, $J_{5,1}$ = 2.5 Hz, H-5), 3.35 (q, 1, J = 7 Hz, H-11), 3.93 (s, 3, $-OCH_3$), and 5.17 (d, 1, $J_{2,1}$ = 4 Hz, H-2).

Anal. Calcd for $C_{20}H_{26}O_8$: C, 60.90; H, 6.64. Found: C, 60.98; H, 6.68.

Registry No.—**2**, 510-35-0; **3**, 36492-45-2; **4**, 29598-38-7; **5**, 34167-05-0; **6**, 29598-40-1; **6a**, 29598-41-2; **7**, 36539-92-1; **9**, 36492-47-4; **10**, 36492-48-5; **11**, 36492-50-9; **11a**, 36492-49-6; **13a**, 36492-51-0; **13b**, 36563-78-7; **14**, 36492-52-1; **15**, 36492-53-2; **16**, 36492-54-3; **16a**, 36492-55-4; **17**, 36492-56-5; **17a**, 36492-57-6; **18**, 36492-58-7; **18a**, 36492-59-8; **19**, 36492-60-1; **19a**, 36492-61-2; **20**, 36492-62-3; **20-6β-d_1**, 36492-63-4; **20a**, 36492-64-5; **21**, 36492-65-6; **21-6β-12,12-d_3**, 36492-66-7; **22**, 36492-67-8; **23**, 36492-68-9; **24**, 36492-69-0; **24** C-6 epimer, 36492-70-3; **25**, 36492-71-4; **26**, 36492-72-5; **28**, 36492-73-6; **29a**, 36492-74-7; **31**, 36492-75-8; **31a**, 36492-76-9; **32**, 36492-77-0; **32a**, 36492-78-1; **33**, 36492-79-2; **34**, 36492-80-5; **34a**, 36594-88-4.

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Notes

Synthesis of Diterpenoid Acids. XII.[1] Preparation of a Lactone Related to *cis*-Dehydrodeisopropylabietic Acid

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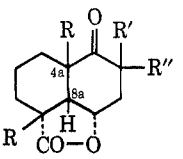
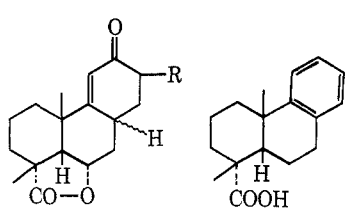
We have described the preparation of the bicyclic cis keto lactone **1a** as an intermediate in the synthesis of diterpenoid acids.[2] In the present work we have added an aromatic ring C in the hope that it would then be possible to epimerize the bridgehead hydrogen,[1,3] and thus obtain diterpenoid acids related to abietic acid.

The Robinson–Mannich annelation failed with **1a**. However, the hydroxymethylene compound **1b** reacted with trimethyl-3-oxobutylammonium iodide in the presence of base to give the diketo aldehydo lactone **1c**, which, after prolonged treatment with sodium ethoxide, underwent an aldol cyclization to form **2a**. Apparently the formation of the third ring is hindered by the presence of the lactone, since the cyclization went more smoothly in the presence of aqueous base; in the work-up of this reaction the lactone was reclosed by heating the crude product in benzene with *p*-toluenesulfonic acid.[4]

We also prepared **2a** from **1a** by an approach similar to that used by Dutta in his synthesis of *cis*-dehydrodeisopropylabietic acid (**3**).[3] Compound **1a** was converted in poor yield to the Mannich base **1d**, whose

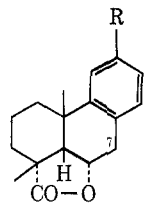


1a, R = CH_3; R′ = R″ = H
b, R = CH_3; R′R″ = C(OH)H
c, R = CH_3; R′ = CHO; R″ = $CH_2CH_2C(=O)CH_3$
d, R = CH_3, R′ = $CH_2N(CH_3)_2$; R″ = H
e, R = CH_3; R′ = $CH_2N^+(CH_3)_3I^-$; R″ = H
f, R = CH_3; R′R″ = CH_2
g, R = H; R′R″ = $CHSC_4H_9$

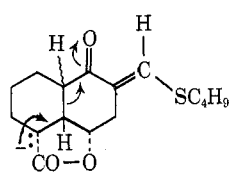


2a, R = H
b, R = $COOC_2H_5$

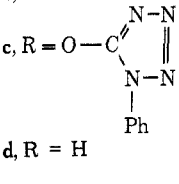
3



4a, R = OCH_2Ph
b, R = OH



5



c, R = O—C(=N—N(Ph)—N=)
d, R = H

methiodide **1e** condensed with acetoacetic ester to give crude **2b**. By carrying out the Mannich reaction of **1a** in refluxing isoamyl alcohol we obtained the methylene derivative **1f**, which condensed with acetoacetic ester to give **2b** and **2a** in poor yields. The structures of compounds **1b–f**, **2a**, and **2b** are based on spectral and analytical data.

The preparation of **2a** *via* the formyl derivative **1b** is more satisfactory than the one *via* the methylene derivative **1f** and was the one normally used. However, the product from both routes melted over a range of 5°. The nmr spectra showed that the main product

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