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The Constitution and Stereochemistry of Artemisin[1,2]

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The structure of artemisin has been reinvestigated and it has been demonstrated that this sesquiterpenic lactone is 8-hydroxysantonin and not the 7-hydroxy compound as previously assumed. Its stereochemical configuration has also been established.

More than sixty years ago a new substance designated as "Artemisin" was isolated by Merck, from the last mother liquors in the technical treatment of the seed of *Artemisia maritima* L.[3] The substance was reported to have physiological effects[3] similar to those of santonin, and it has been assigned the structure of 7-hydroxysantonin chiefly as a result of the investigations of Bertolo[4] and Tettweiler, *et al.*[5] In 1950 Barton[6] discussed the stereochemistry of artemisin in terms of molecular rotation. It was concluded that its configurations at C_6, C_7,[7] C_{10} and C_{11} were all the same as those of (−)-α-santonin (I). Formula II was, therefore proposed. On the basis of the periodate oxidation of artemisinic acid, Shibata and Mitsuhashi[8] supported the previous deduction that its two hydroxyl functions were located on vicinal carbon atoms of the ring. The structure of artemisin thus has not been questioned for a long period.

We had previously synthesized[9] two racemic stereoisomers (IVa and IVb) of II by a three-step process from 3-oxoeusantona-4,6-dienic acid (IIIa) and 3-oxo-11-epieusantona-4,6-dienic acid (IIIb). Both isomers rearranged to their respective desmotropo compounds (Va and Vb) by the action of 55% sulfuric acid at 55°. Three asymmetric carbon atoms are involved in the molecules of these desmotropo compounds, so that four stereoisomers can theoretically exist in racemic forms, two with a *cis*-fused lactone and the other two with a *trans*-fused one. In the present argument, however, it is sufficient to consider only two isomers with a *cis*-lactone, since a *trans*-lactone is changed into *cis* under the rearrangement conditions employed.[6] Accordingly, assuming that artemisin possesses the structure II, either of the above phenolic compounds (Va and Vb) must be the racemate of desmotropoartemisin which is derived from the natural product. This identity would thus present confirmatory evidence for the structure of artemisin. Infrared comparison was not feasible on account of the extremely low solubility of these materials in suitable solvents however, and their diacetates were therefore compared. Bertolo reported that when desmotropoartemisin was treated with sodium acetate and acetic anhydride, a monoacetate was formed,[10a] which could be converted into the diacetate, m.p. 150°, by heating with acetyl chloride.[10b] Shibata and Mitsuhashi[8] reported the one-step preparation of the same diacetate on treatment of artemisin with acetic anhydride and sulfuric acid. Reinvestigation, however, showed that under the conditions of Bertolo desmotropoartemisin directly afforded the diacetate whose melting point was 184°. This was reconverted readily into desmotropoartemisin by alkaline hydrolysis. It was also found that the same diacetate was obtained by the rearrangement of artemisin with acetic anhydride and sulfuric acid at 90°. On the other hand, α-(5,6-dihydroxy-4,9-dimethyl-3-oxo-3,5,6,7,-8,9-hexahydro-6-naphthyl)-propionic acid lactones A (IVa) and B (IVb) rearranged to their respective phenolic diacetates (VIa and VIb) under similar conditions, and the infrared spectra of these compounds in chloroform solution were distinctly different from that of desmotropoartemisin diacetate. This fact led us to question the structure II of artemisin itself.

Examination of the experimental results of previous workers indicates that there is almost no ambiguity with regard to the following points: (1) Since dehydrogenation of hexahydroartemisin with selenium afforded 1-methyl-7-ethylnaphthalene, artemisin belongs to the eudalene group of sesquiterpenes.[5] (2) When artemisin was subjected to the dienone–phenol rearrangement, it produced the desmotropo compound.[8,10a] Therefore, its A-ring possesses the structure of a cross-conjugated dienone with an angular methyl group. Its infrared spectrum also confirms this by the characteristic absorption bands at 1661, 1631, 1616 and 834 cm.$^{-1}$.[8,11] (3) On warming with dilute alkalies artemisin affords the sodium salt of a hydroxy-acid,[13] which regenerates the original substance by acidification, demonstrating the existence of a lactone. An infrared absorption band at 1767 cm.$^{-1}$ shows that it is a saturated γ-lactone which, therefore, must be fused to the B-ring. In view of the above dehydrogenation ex-

(1) This is part XXXV of Y. Abe, "Studies on Anthelmintics."

(2) A preliminary report of this work was presented in *Proc. Japan Acad.*, **32**, 684 (1956); **33**, 153 (1957), and *Pharm. Bull. (Japan)*, **5**, 187 (1957).

(3) J. Simonsen and D. H. R. Barton, "The Terpenes," Vol. III, Cambridge University Press, Cambridge, 1951, pp. 312–320; "Encyclopaedia of Organic Chemistry," Elsevier Publishing Co., Amsterdam, 1953, 12 B, pp. 3828–3841.

(4) P. Bertolo, *Atti accad. Lincei*, [5] **32**, I, 618 (1923); *Gazz. chim. ital.*, **53**, 724 (1923).

(5) K. Tettweiler, O. Engel and E. Wedekind, *Ann.*, **492**, 105 (1932).

(6) D. H. R. Barton, *J. Org. Chem.*, **15**, 467 (1950).

(7) It was considered that the hydrogen atom at C_7 existed in the axial position in (−)-α-santonin, while in artemisin a hydroxyl group was held in the same position.

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

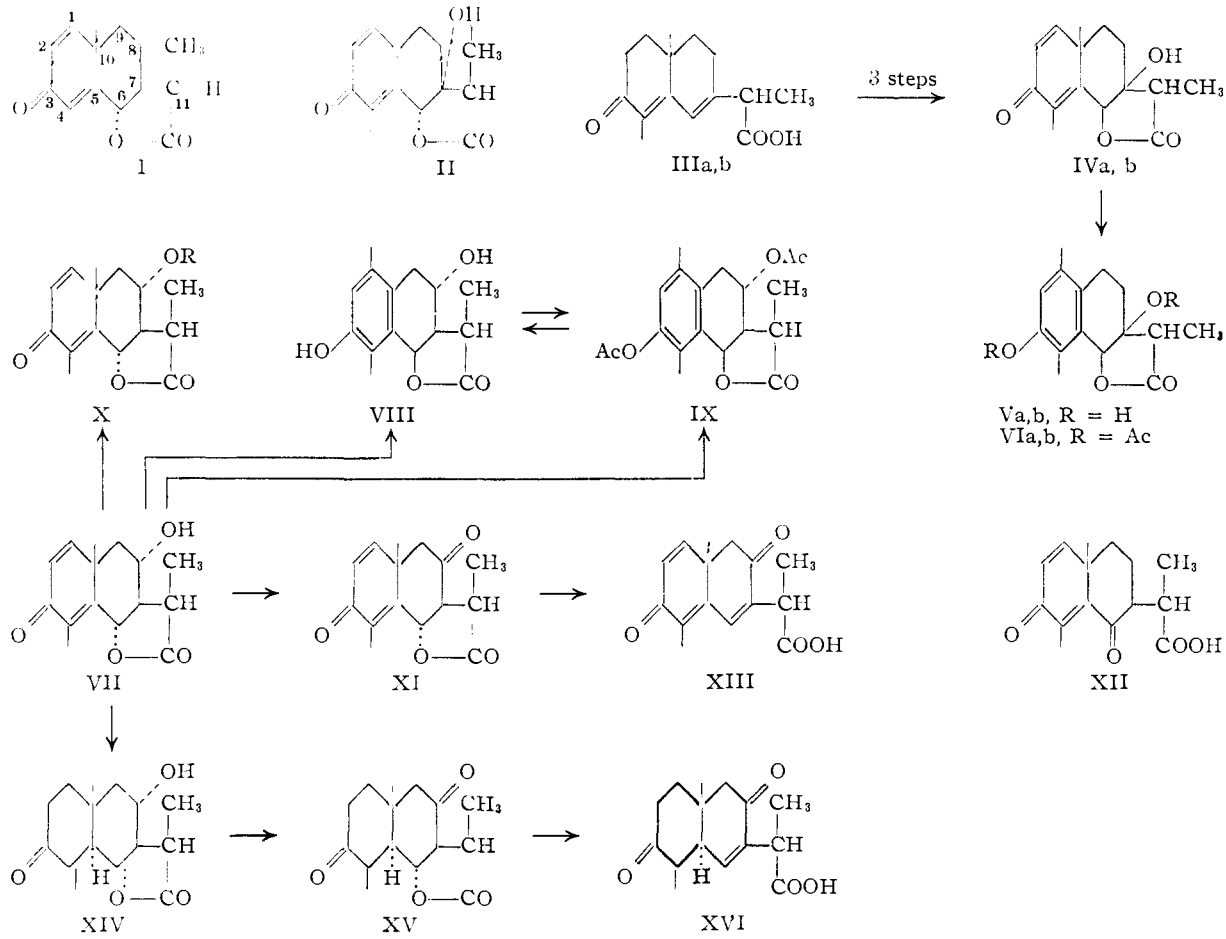
(9) M. Sumi, *ibid.*, **4**, 168 (1956).

(10) P. Bertolo, (a) *Gazz. chim. ital.*, **50**, I, 114 (1920); (b) **53**, 867 (1923).

(11) Wave numbers were checked by measurements made in this Laboratory. The last one can be associated with out-of-plane bending vibrations of the C–H bonds on the ethylenic linkage at C_1–C_2, corresponding to the G band in ketosteroids[12]; T. Kanzawa, H. Kamio, M. Sumi and M. Nishikawa, THIS JOURNAL, **80**, 3705 (1958).

(12) R. N. Jones, F. Herling and E. Katzenellenbogen, THIS JOURNAL, **77**, 651 (1955).

(13) P. Bertolo, *Atti accad. Lincei*, [5] **10**, II, 111 (1901).



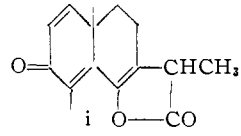
periment it is concluded that the propionic acid side-chain which constitutes the lactone ring is attached to the C_7. Accordingly, the primary objective of the present reinvestigation was the elucidation of the location and the nature of two hydroxyl groups, one free and the other lactonic.

Bertolo and Tettweiler, *et al.*, observed that artemisin was not acylated by the action of various reagents with the exception of acetyl chloride. For this reason they regarded the free hydroxyl group as tertiary.[4,5] However, we have now shown that in addition to acetyl chloride, both sodium acetate–acetic anhydride and pyridine–acetic anhydride readily react with artemisin to afford, in good yield, the acetate X (R = Ac),[14] from which artemisin is regenerated on hydrolysis with sodium carbonate. No rearrangement, therefore, occurs during the acetylation reaction. Artemisin was also found to give the tosylate X (R = Ts), the cathylate X (R = $COOC_2H_5$) and the formate[15] X (R = CHO) in high yield. Since tosyl chloride[17,18] and ethyl chlorocarbonate[18,19] do not react with tertiary alcohols, the above facts strongly suggest that the free hydroxyl group of artemisin is not tertiary as assumed previously. The nature of this hydroxyl group was further elucidated by the Kuhn–Roth oxidation of artemisin. As was already demonstrated, the latter possesses the eudalene skeleton so that if the hydroxyl group is secondary, it should contain three C-methyl groups. But if it is primary, the determination should give a lower value for C-methyl. On the basis of the formation of 2.62 equivalents of acetic acid, it has been concluded that the hydroxyl group is secondary and, accordingly, it must be held at a carbon atom of the ring system.

This was also confirmed by the pyridine–chromium trioxide oxidation of artemisin which gave a diketone XI. Although this substance reveals an infrared absorption band at 1727 cm.$^{-1}$, a

(14) For the sake of simplification correct structural formulas are employed from the beginning.

(15) When artemisin is heated in formic acid and the reaction product distilled, a substance, m.p. 182°, is produced to which the name "artemisene" and the structure i[6] has been given. The formate synthesized by us possesses m.p. 185°, very close to that of "artemisene"



and in addition, the crude oily product obtained by refluxing artemisin with formic acid afforded the formate on distillation. This observation, coupled with the report of Nishikawa, *et al.*,[16] on santonene offers doubt about the structure of "artemisene."

(16) M. Nishikawa, K. Morita and H. Hagiwara, *J. Pharm. Soc. Japan*, **75**, 1199 (1955).

(17) W. G. Dauben and P. D. Hance, THIS JOURNAL, **77**, 606 (1955).

(18) L. F. Fieser, J. E. Herz, M. W. Klohs, M. A. Romero and T. Uten, *ibid.*, **74**, 3309 (1952); L. F. Fieser and G. Ourisson, *ibid.*, **75**, 4404 (1953).

(19) C. M. Suter, "The Organic Chemistry of Sulfur," John Wiley and Sons, Inc., New York, N. Y., 1949, p. 514.

little higher than those of ordinary six-membered ring ketones, the absence of absorption in the region of 2700-2900 cm.$^{-1}$ shows[20] that the band is due to an isolated ketone grouping and not an aldehyde carbonyl. Furthermore, the newly formed carbonyl of the diketone cannot be at C_6, since it is *non-conjugated*, and the ultraviolet absorption maximum (240 mμ) is in good accordance with this view, distinctly differing from that of santenonic acid (XII, λ_{max} 250 mμ[16,21]).

The action of 0.1 *N* sodium hydroxide solution on the diketone XI readily caused the elimination of the lactonic hydroxyl function to afford a diketo-acid XIII, showing that the hydroxyl group is located at a β-position with respect to the carbonyl group,[17,22] and the ultraviolet maximum of the diketo-acid at 317 mμ indicates an additional double bond between C_5–C_7 in conjugation with the carbonyl group and the cross-conjugated dienone system between C_6–C_7. It thus follows that in this diketo-acid XIII as well as in the diketone XI the ketone grouping of the B-ring should be located at C_8 and, therefore, the lactonic hydroxyl of XI at C_6. Further evidence was provided in the tetrahydroartemisin series. Treatment of "α"-tetrahydroartemisin (XIV *vide infra*) with pyridine–chromium trioxide produced a diketone XV, which was converted into an unsaturated diketo-acid XVI by heating with dilute alkali. The α,β-unsaturated ketone system of this acid XVI was confirmed by its ultraviolet absorption maximum (239 mμ).[23] From all these experimental results, it is concluded that the free hydroxyl group of artemisin should be placed at C_8 and not at C_7 as formerly assumed. The previous placement of the lactone ring is correct. Consequently, the structure of artemisin must be 8-hydroxysantonin (VII).[24]

Attention now was directed to the elucidation of the stereochemical configuration of artemisin. Some of Barton's conclusions[6] still have validity for the new structure. It is, however, desirable that the stereochemistry of artemisin be unequivocally established.

Treatment of artemisin with acetic anhydride and sulfuric acid at 90° gave a desmotropoartemisin diacetate IX with m.p. 184° as described above. On the other hand, the action of the same reagent at room temperature produced a new desmotropo diacetate XVII, m.p. 193°, which was converted to the isomer IX by heating with this reagent at 90°. Alkaline hydrolysis of XVII afforded desmotropoartemisin (VIII) which was identical with that derived from IX. The new desmotropoartemisin diacetate possesses a positive rotation value, while the known isomer has a negative rotation. Since Cocker, *et al.*,[25] reported a closely similar observation in the santonin series, the above fact is most satisfactorily explained if the isomer with m.p. 193° (XVII) possesses a *trans*-lactone and that with m.p. 184° (IX) has a *cis*-fused one. Accordingly, the lactone ring in artemisin is expected to be *trans*-fused. This view is also supported by the molecular rotational difference[26] between two desmotropoartemisin diacetates (+577°), a value closely similar to the difference between two desmotroposantonin diacetates (+623°). Ishikawa[27] previously discovered that santonin and its homologs with *trans*-lactone fusion suffered inversion at C_6 by dimethylformamide containing hydrogen chloride to give rise to their respective epimers with a *cis*-fused lactone. Application of this procedure to artemisin (VII) resulted in the formation of a hitherto unknown stereoisomer, which readily rearranged to the desmotropoartemisin diacetate with m.p. 184° (IX, lactone, *cis*) by the action of acetic anhydride–sulfuric acid at room temperature. Therefore, this new isomer is considered to be the C_6-epimer of artemisin, having a *cis*-lactone, and the original artemisin must be a *trans*-lactone. This is in accord with Barton's conclusion.[6] As a consequence, the C_6–O and the C_7–C_{11} bonds are both equatorially oriented, as a 6–5 ring fusion cannot exist in a diaxial configuration with chair-formed cyclohexanes, in close resemblance to the santonin series.[28]

It was further expected that a more complete view on the stereochemistry of artemisin could be obtained by effecting the direct correlation of this compound with santonin whose configurations have been established.[29–32] Two transformation pathways have been selected for achieving this.

Kovács, *et al.*,[33] and Iwai, *et al.*,[34] independently obtained deoxotetrahydrosantonins by the reduction of the corresponding tetrahydrosantonins. On the other hand, Rimini, *et al.*,[35] and Tettweiler, *et al.*,[5] reported the reduction of artemisin to tetrahydroartemisins. Hence, the conversion of tetrahydroartemisin into deoxodeoxytetrahydroartemisin was first undertaken in order to compare the latter with deoxotetrahydrosantonin. Artemisin was hydrogenated in the presence of palladium-on-carbon and when the crude crystalline product was heated with 10% hydrochloric acid in alcohol, there were obtained a tetrahydro compound with m.p. 228° and a smaller amount of an isomer, m.p. 197°. These two products are regarded, respec-

(20) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954, p. 135.

(21) H. Matsumura, I. Iwai and E. Ohki, *J. Pharm. Soc. Japan*, **75**, 1043 (1955).

(22) Y. Asahina and T. Ukita, *J. Pharm. Soc. Japan*, **61**, 376 (1941); *Ber.*, **74**, 952 (1941).

(23) The alternative structure of α,β-unsaturated-γ-keto-acid, O ‖ —CC=CCOOH, is excluded since the absorption maximum of this must exist around 220 mμ. *Cf.* R. B. Woodward, *J. Japanese Chem.*, **11**, 321 (1957); *Angew. Chem.*, **69**, 50 (1957).

(24) Stereochemical configurations are still unknown at this stage.

(25) W. Cocker and T. B. H. McMurry, *J. Chem. Soc.*, 4430 (1955).

(26) W. Klyne, *J. Chem. Soc.*, 2916 (1952); 3072 (1953).

(27) H. Ishikawa, *J. Pharm. Soc. Japan*, **76**, 504 (1956).

(28) Y. Abe, T. Harukawa, H. Ishikawa, T. Miki, M. Sumi and T. Toga, (a) THIS JOURNAL, **78**, 1417 (1956); (b) **78**, 1422 (1956).

(29) Y. Abe and M. Sumi, *Chemistry & Industry*, 253 (1955); M. Sumi, *Pharm. Bull. (Japan)*, **4**, 158 (1956).

(30) E. J. Corey, THIS JOURNAL, **77**, 1044 (1955).

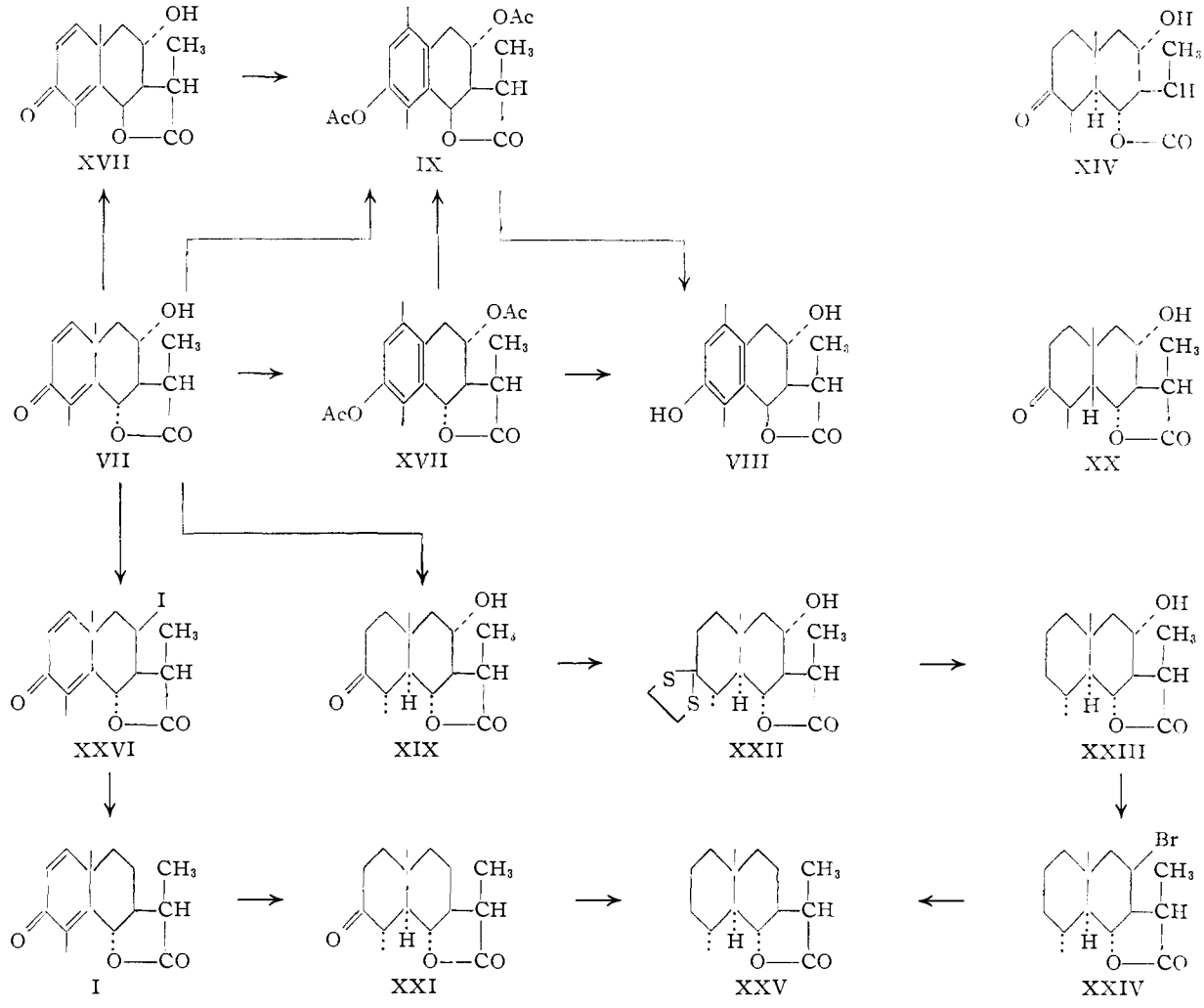
(31) H. Bruderer, D. Arigoni and O. Jeger, *Helv. Chim. Acta*, **39**, 858 (1956).

(32) Y. Abe, T. Miki, M. Sumi and T. Toga, *Chemistry & Industry*, 953 (1956).

(33) Ö. Kovács, V. Herout, M. Horák and F. Šorm, *Collection Czechoslov. Chem. Communs.*, **21**, 225 (1956).

(34) I. Iwai, E. Ohki and K. Kanzaki, *J. Pharm. Soc. Japan*, **76**, 1381 (1956).

(35) E. Rimini and T. Iona, *Gazz. chim. ital.*, **43**, 531 (1913).



tively, as the "γ"-tetrahydroartemisin (XIX)[36] and the "α"-tetrahydroartemisin (XIV)[36] isolated by the previous workers[3,32] in view of their melting points. The mother liquor of the above crystalline products was kept standing for a long time to afford a third isomer, of which the melting point proved it to be the "δ"-tetrahydroartemisin (XX).[3,33]

According to Yanagita, *et al.*,[37] treatment of the crude reduction product of (−)-α-santonin with 10% hydrochloric acid in alcohol produced the "α"-tetrahydrosantonin (XXI)[38] as a major product. Therefore, it was expected that the "γ"-tetrahydroartemisin would have the same configuration at C_4 and C_5 as this "α"-tetrahydrosantonin. After the "γ"-tetrahydroartemisin was allowed to react with ethanedithiol to give the ethylene thioketal XXII, the latter was desulfurized by Raney nickel to the "γ"-deoxotetrahydroartemisin (XXIII). By the action of phosphorus pentabromide this was converted into the oily bromo compound XXIV, which on zinc–acetic acid reduction led to a substance of m.p. 153°. That this is identical with the "α"-deoxotetrahydrosantonin prepared from the "α"-tetrahydrosantonin was established by mixed melting point determination and by the comparison of their infrared spectra and rotations. Consequently, it has been substantiated in a more direct way that (1) artemisin belongs to the same stereochemical type as (−)-α-santonin, (2) the γ-lactone of artemisin is present at the same positions as in santonins and its mode of fusion is *trans*.

Since recent investigations of Djerassi[38] on the rotatory dispersion indicated the AB *trans*-fusion and the α-configuration of 4-methyl group in the "α"-tetrahydrosantonin, the "γ" tetrahydroartemisin was shown to have the same stereochemical features, which was confirmed also by its own rotatory dispersion.[36] Therefore, it must be represented by the formula XIX.

With regard to the configuration at C_{11}, there still remains some ambiguity. Although the "α"-tetrahydrosantonin suffered no configurational change at C_{11} during the hydrochloric acid treat-

(36) That the configurations of the "α"-, the "γ"- and the "δ"-tetrahydroartemisin are represented by XIV, XIX and XX, respectively, were revealed recently by the measurement of their rotatory dispersion. It is not, however, easily understood why the "α"-isomer (4-methyl, axial) does not suffer inversion to its C_4-epimer (XIX, 4-methyl, equatorial) on heating with 10% hydrochloric acid in ethanol. Probably more drastic conditions would be needed for this inversion. The author is greatly indebted to Professor Carl Djerassi, who kindly performed the measurement of rotatory dispersion.

(37) M. Yanagita and A. Tahara, *J. Org. Chem.*, **20**, 959 (1955).

(38) Carl Djerassi, R. Riniker and B. Riniker, THIS JOURNAL, **78**, 6362 (1956).

ment,[37] it cannot be excluded that the reverse change may have occurred in the case of tetrahydroartemisins, if the latter had the opposite C_{11}-configuration. Thus, another way was explored to determine this configuration more clearly. Triphenyl phosphite methiodide[39] is a reagent which recently has become used for the replacement of a hydroxyl group with an iodine atom. Because of the mild reaction conditions, it can be employed even in the case of a relatively unstable structure such as the cross-conjugated dienone, and no inversions at other asymmetric centers are expected. By the action of this reagent on artemisin, the substitution was effected smoothly to form 8-deoxy-8-iodoartemisin (XXIX). The replacement is considered to follow the SN2 mechanism. Catalytic reduction of the iodo compound in the presence of palladium-on-carbon deactivated by pyridine then resulted in the removal of iodine without alteration of the cross-conjugated dienone system and produced a crystalline substance, m.p. 172°, whose identity with (−)-α-santonin has been fully established by direct comparison. Accordingly, the result obtained by the first pathway has now been firmly substantiated and, in addition, the C_{11}-configuration of artemisin has been proved to be identical with that of (−)-α-santonin.

The remaining unsettled problem is the configuration of the free hydroxyl group at C_8. Application of Klyne's generalization[40] on the molecular rotation is quite useful for the elucidation. The positive rotational difference between (−)-α-santonin (M_D −408°) and artemisin (M_D −221°) as well as between the latter and artemisin acetate (M_D −133°) indicates that the hydroxyl group should be assigned the α-orientation and, therefore, it is equatorial. This is in good agreement with the very easy esterification of artemisin by various reagents.

Since the absolute configuration of (−)-α-santonin has proved to be represented by I, artemisin must be formulated as VII. From the biogenetic view-point it is of great interest that a number of sesquiterpenes with similar structural features recently have been reported; for instance, temisin,[22] isotemisin,[41] ψ-santonin,[17,42] tenulin,[43] helenalin,[44] isohelenalin,[44] matricin,[45] arctiopicrin,[46] pyrethrosin,[47] etc.

Acknowledgments.—The author expresses his hearty thanks to Professor H. H. Inhoffen for a generous supply of artemisin. He appreciates the continued advice and encouragement of Professor Y. Asahina, Dr. S. Kuwada and Dr. T. Matsukawa through this work. Also he is indebted to Mr. M. Kan and his associates for performing microanalyses and to Mr. H. Kamio, Mr. T. Shima and Mr. H. Nakamachi for the determination of absorption and rotation.

(39) S. R. Landaner and H. N. Rydon, *J. Chem. Soc.*, 2224 (1953).
(40) W. Klyne and W. M. Stokes, *ibid.*, 1979 (1954).
(41) Y. Asahina and T. Ukita, *J. Pharm. Soc. Japan*, **63**, 29 (1943).
(42) N. M. Chopra, W. Cocker, B. E. Cross, J. T. Edward, D. H. Hayes and H. P. Hutchingson, *J. Chem. Soc.*, 588 (1955).
(43) D. H. R. Barton and P. de Mayo, *ibid.*, 142 (1956); B. H. Braun, W. Herz and K. Rabindran, THIS JOURNAL, **78**, 4423 (1956).
(44) G. Büchi and D. Rosenthal, *ibid.*, **78**, 3860 (1956).
(45) Z. Cékan, V. Herout and F. Šorm, *Chemistry & Industry*, 1234 (1956).
(46) M. Suchy, M. Horák, V. Herout and F. Šorm, *ibid.*, 894 (1957).
(47) D. H. R. Barton and P. de Mayo, *J. Chem. Soc.*, 150 (1957).

Experimental[48]

Desmotropoartemisin Diacetate (IX, Lactone, *cis*). (a) **From Desmotropoartemisin (VIII).**—To a solution of 200 mg. of desmotropoartemisin (VIII) in 2 ml. of acetic anhydride was added 300 mg. of fused sodium acetate. After the mixture had been heated at 95° for 1 hr., water was added to hydrolyze the acetic anhydride and the separating solid substance was recrystallized from ethanol as colorless plates, m.p. 184°, λ_{max} 273 mμ (log ε 3.04) and 280 mμ (log ε 3.07), λ_{min} 247 mμ (log ε 2.34), $[\alpha]_D$ −86.0° (*c* 0.4). *Anal.* Calcd. for $C_{19}H_{22}O_6$: C, 65.88; H, 6.40; CH_3CO, 24.84. Found: C, 66.04; H, 6.22; CH_3CO, 24.60.

(b) **From Artemisin (VII).**—To 500 mg. of artemisin dissolved in 10 ml. of acetic anhydride was added 5 drops of concentrated sulfuric acid and the solution was heated at 95° for 1 hr. After cooling, 50 ml. of water was added to decompose the acetic anhydride, and the solid separated. It was triturated with cold ethanol and filtered to afford 400 mg. of the crude product (m.p. 175–180°), which was recrystallized from ethanol as colorless plates, m.p. 184°. This showed no melting point depression on admixture with the substance obtained in (a), and the infrared spectra of the two were identical.

Hydrolysis of Desmotropoartemisin Diacetate (IX, Lactone, *cis*).—A mixture of 100 mg. of *cis*-desmotropoartemisin diacetate and 5 ml. of 0.1 *N* potassium hydroxide was heated on a water-bath for 1 hr. under stirring. After cooling, the resultant solution was acidified with dilute hydrochloric acid and the solid material obtained was recrystallized from 50% ethanol as colorless prisms (50 mg.), m.p. 240°, undepressed on admixture with an authentic sample of desmotropoartemisin. The identity was verified also by the comparison of infrared spectra.

α-(3,6-Diacetoxy-5-hydroxy-1,4-dimethyl-5,6,7,8-tetrahydronaphthyl-6)-propionic Acid Lactones. (a) **A-Isomer (VIa).**—The dienone (A-isomer, m.p. 177°, IVa, 300 mg.) was dissolved in 6 ml. of acetic anhydride and 3 drops of concentrated sulfuric acid was added. After the solution was heated at 95° for 50 minutes, it was cooled and the acetic anhydride was hydrolyzed by adding water. The solid which separated was triturated with cold ethanol. Filtration gave 150 mg. of the crude product m.p. 140–143°, which was recrystallized from ethanol as colorless prisms, m.p. 152°, λ_{max} 273 mμ (log ε 3.08) and 280 mμ (log ε 3.13), $\lambda_{min.}$ 247 mμ (log ε 2.38). *Anal.* Calcd. for $C_{19}H_{22}O_6$: C, 65.88; H, 6.40. Found: C, 66.17; H, 6.42.

(b) **B-Isomer (VIb).**—A mixture of 280 mg. of the dienone (B-isomer, m.p. 240°, IVb, 280 mg.), 4.5 ml. of acetic anhydride and 4 drops of concentrated sulfuric acid was heated and worked up in almost the same way as described in (a). There was obtained 290 mg. of the crude solid. Repeated recrystallization of the solid from ethanol and subsequently from methanol gave colorless prisms, m.p. 178°, λ_{max} 273 mμ (log ε 3.00) and 280 mμ (log ε 3.04), $\lambda_{min.}$ 247 mμ (log ε 2.19). *Anal.* Calcd. for $C_{19}H_{22}O_6$: C, 65.88; H, 6.40. Found: C, 66.03; H, 6.61.

Artemisin Acetate (X, R = $COCH_3$). (a) **By the Action of Acetic Anhydride–Sodium Acetate.**—To 500 mg. of artemisin were added 4 ml. of acetic anhydride and 500 mg. of fused sodium acetate. After the mixture was refluxed for 1 hr., the acetic anhydride was removed under reduced pressure and ether was added to the residue. The crystalline product was collected, and the filtrate was washed with aqueous sodium carbonate and water, dried and evaporated to afford another crop. Both crops were combined and recrystallized from 80% ethanol as faintly yellow prisms, m.p. 198°, yield 350 mg. (60%). Its melting point was not depressed when mixed with an authentic sample of artemisin acetate which was prepared according to Tettweiler, *et al.*[5] Their infrared spectra were also identical.

(b) **By the Action of Acetic Anhydride–Pyridine.**—A mixture of 100 mg. of artemisin, 0.75 ml. of pyridine and 0.75 ml. of acetic anhydride was kept standing overnight at

(48) All melting points are uncorrected. The ultraviolet absorption spectra were measured in ethanol with a Beckman model DK-2 spectrophotometer, and the infrared absorption spectra with a Perkin–Elmer model 21 spectrophotometer. Unless noted otherwise, the rotations were determined in ethanol.

room temperature. Addition of water to the reaction mixture resulted in the separation of crystalline product, which was recrystallized from ethanol as colorless prisms, m.p. 200°, undepressed on admixture with an authentic sample; yield 70 mg.

Hydrolysis of Artemisin Acetate (X, R = $COCH_3$).—A solution of 400 mg. of artemisin acetate in 43 ml. of 75% methanol containing 1.09 g. of potassium carbonate was refluxed for 20 minutes and then concentrated under reduced pressure to a volume of about 5 ml. The residual solution was kept standing and 220 mg. of crude product (m.p. 198–202°) was obtained by filtration. The filtrate was extracted with chloroform, which gave another crop (25 mg.). The combined crystalline material was recrystallized from ethanol as colorless plates, m.p. 202–204°, $[\alpha]^{16}D$ −80° (*c* 2.5). Its identity with artemisin was established by the mixed melting point determination and the comparison of their infrared spectra.

Artemisin Formate (X, R = CHO).—Artemisin (1.0 g.) dissolved in 5 ml. of 95% formic acid was refluxed for 2 hr. and the temperature was gradually raised to distil the formic acid. After the residue was kept at 210–220° for 10 minutes, it was cooled and *ca.* 30 ml. of ether was added. The solid was filtered (620 mg., m.p. 175–180°) and recrystallized from ethyl acetate–petroleum ether as colorless plates, m.p. 185°, $[\alpha]^{18}D$ −90° (*c* 0.4), λ_{max} 238 mμ (log ε 4.04); $\nu_{max}^{CHCl_3}$ 1786 cm.$^{-1}$ (γ-lactone), 1723 cm.$^{-1}$ (formyl), 1667 cm.$^{-1}$ (conjugated ketone), 1642, 1623 cm.$^{-1}$ (double bond), 833 cm.$^{-1}$ ($\Delta^{1,4}$-3-ketone[11]) and no hydroxyl band. *Anal.* Calcd. for $C_{16}H_{18}O_5$: C, 66.19; H, 6.26. Found: C, 66.35; H, 6.13. Distillation of the crude reaction mixture also gave the same formate.

Artemisin Tosylate (X, R = Ts).—To a solution of 500 mg. of artemisin in 6 ml. of pyridine was added 750 ml. of tosyl chloride in several portions. After the mixture was kept standing for 40 hr. at room temperature, *ca.* 40 ml. of water was added. The solid material which was precipitated was recrystallized from ethanol as colorless needles, m.p. 192°, yield 550 mg., λ_{max} 230 mμ (log ε 4.32), $[\alpha]^{23}D$ −29° (*c* 0.5). *Anal.* Calcd. for $C_{22}H_{24}O_6S$: C, 63.45; H, 5.81; S, 7.70. Found: C, 63.41; H, 5.68; S, 8.07.

Artemisin Cathylate (X, R = $COOC_2H_5$).—To a cooled solution of 500 mg. of artemisin in 6 ml. of pyridine was added 500 mg. of ethyl chlorocarbonate with shaking. The solution was kept at room temperature for 40 hr. and *ca.* 40 ml. of water was added. There was obtained 300 mg. of the crude product, m.p. 116–120°, by filtration. This was recrystallized from a small volume of methanol as colorless prisms, m.p. 118–122°, $[\alpha]^{23}D$ −30° (*c* 0.5). *Anal.* Calcd. for $C_{18}H_{22}O_6$: C, 64.65; H, 6.63. Found: C, 64.70; H, 6.60.

6α-Hydroxy-3,8-dioxoeusantona-1,4-dienic Acid Lactone (XI).—To the complex prepared from 20 ml. of pyridine and 2.0 g. of chromium trioxide was added 2.0 g. of artemisin dissolved in 20 ml. of pyridine and the mixture was allowed to stand overnight at room temperature. The reaction mixture was diluted with water and extracted with 400-ml. portions of benzene-ether (1:1) four times. The combined extract was washed with dilute hydrochloric acid and water, and concentrated to afford 1.3 g. of a crystalline material, m.p. 155–170°. Recrystallization from ethanol gave colorless plates, m.p. 178–184°. The range of m.p. was not further narrowed; λ_{max} 240 mμ (log ε 4.20); ν_{max}^{Nujol} 1789 cm.$^{-1}$ (γ-lactone), 1727 cm.$^{-1}$ (isolated ketone), 1669 cm.$^{-1}$ (conjugated ketone), 1642 and 1623 cm.$^{-1}$ (double bond), no hydroxyl band. *Anal.* Calcd. for $C_{15}H_{16}O_4$: C, 69.21; H, 6.20. Found: C, 69.23; H, 5.98.

3,8-Dioxoeusantona-1,4,6-trienic Acid (XIII).—When 500 mg. of the powdered diketone XI was added to 25 ml. of 0.1 *N* sodium hydroxide, it gradually dissolved, giving a purple color, and then the solution turned to brown. After standing at room temperature for 2 hr., the solution was acidified with dilute hydrochloric acid and extracted with ether. The ether solution was extracted with aqueous sodium carbonate, the alkaline solution acidified and extracted with ether. From this ethereal solution there was obtained 300 mg. of a crystalline product, m.p. *ca.* 150°, which was recrystallized from ethyl acetate–petroleum ether as faintly yellow plates, m.p. 150°, λ_{max} 250 mμ (log ε 3.86) and 314 mμ (log ε 4.20), $[\alpha]^{26}D$ +253° (*c* 0.5). *Anal.* Calcd. for $C_{15}H_{16}O_4$: C, 69.21; H, 6.20. Found: C, 69.45; H, 6.08.

5α-Hydroxy-3,8-dioxo-4-isoalloeusantonanic Acid Lactone[49] (XV).—To the complex prepared from 4.0 g. of chromium trioxide and 40 ml. of pyridine was added 4.0 g. of α-tetrahydroartemisin (XIV, *vide infra*) in 40 ml. of pyridine. After standing overnight at room temperature, the mixture was diluted with water and extracted with benzene–ether. The extract was washed with dilute hydrochloric acid and water, and concentrated. The residue gave a crystalline product, which was recrystallized from ethanol as colorless needles, m.p. 184°, yield 2.1 g., $[\alpha]^{34}D$ −96° (*c* 0.5); $\nu_{max}^{CHCl_3}$ 1779 cm.$^{-1}$ (γ-lactone), 1718 cm.$^{-1}$ (isolated ketone), no hydroxyl band. *Anal.* Calcd. for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.26; H, 7.42.

3,8-Dioxo-4-isoalloeusanton-6-enic Acid (XVI).—A mixture of 300 mg. of the above saturated diketone XV, 12.5 ml. of 0.1 *N* sodium hydroxide and 5 ml. of ethanol was refluxed for 1 hr. After the ethanol was removed under reduced pressure, the residual solution was acidified with dilute hydrochloric acid and extracted with ether. The ether solution was washed with aqueous sodium bicarbonate, and the washings acidified and extracted with ether again. The extracts were worked up to afford 130 mg. of the solid material, m.p. *ca.* 218°, which, on recrystallization from ethyl acetate, gave colorless prisms, m.p. 219°, λ_{max} 239 mμ (log ε 4.00), $[\alpha]^{25}D$ −29° (*c* 0.5). *Anal.* Calcd. for $C_{15}H_{20}O_4$: C, 68.16; H, 7.64. Found: C, 68.57; H, 7.64.

***trans*-Desmotropoartemisin Diacetate (XVII).**—A mixture of 200 mg. of artemisin, 4 ml. of acetic anhydride and 2 drops of concentrated sulfuric acid was kept at room temperature for 4 hr. Twenty milliliters of water was added to the solution to decompose the acetic anhydride and the solid which was precipitated was recrystallized from ethanol as colorless prisms, m.p. 193°, yield 170 mg., λ_{max} 273 mμ (log ε 2.96) and 280 mμ (log ε 2.90), $\lambda_{min.}$ 248 mμ (log ε 2.04), $[\alpha]^{26}D$ +75° (*c* 0.3). *Anal.* Calcd. for $C_{19}H_{22}O_6$: C, 65.88; H, 6.40; CH_3CO, 24.84. Found: C, 66.11; H, 6.14; CH_3CO, 24.71.

Conversion of Desmotropoartemisin Diacetate (XVII, Lactone, *trans*) into its *cis* Isomer IX.—One hundred milligrams of *trans*-desmotropoartemisin diacetate (XVII) was dissolved in 2 ml. of acetic anhydride and 2 drops of concentrated sulfuric acid. After the solution was heated at 90° for 1.5 hr., the acetic anhydride was hydrolyzed by addition of water, and the solid product was triturated with cold ethanol and filtered (80 mg.). Recrystallization from ethanol afforded 30 mg. of colorless plates, m.p. 184°, undepressed on admixture with an authentic sample of IX. The crystalline substance obtained from the mother liquors (m.p. 160–180°) possesses λ_{max} 272 mμ (log ε 3.03) and 280 mμ (log ε 3.04), proving it to be a mixture of XVII and IX.

Hydrolysis of Desmotropoartemisin Diacetate (XVII, Lactone, *trans*).—A mixture of 150 mg. of desmotropoartemisin diacetate (XVII, lactone, *trans*), 50 ml. of 0.1 *N* potassium hydroxide and 2 ml. of ethanol was heated at 90° for 1.5 hr. under stirring. The solution was concentrated to half its volume under reduced pressure. The resulting crystalline solid was filtered (70 mg., m.p. 235°) and recrystallized from dilute ethanol as colorless prisms, m.p. 241°. It showed no melting point depression when mixed with an authentic sample of desmotropoartemisin (VIII).

6β,8α-Dihydroxy-3-oxoeusantona-1,4-dienic Acid Lactone (XVIII, The C_6-Epimer of Artemisin).—Artemisin (3.0 g.) dissolved in 30 ml. of dimethylformamide containing 5% of hydrogen chloride was heated at 90° for 4 hr. After cooling, the solution was diluted with water and extracted with ether. The extract was washed with water, aqueous sodium carbonate and water again, dried and concentrated. There was obtained 1.3 g. of oily material, which resisted crystallization. This was adsorbed from 50 ml. of benzene to 50 g. of alumina and chromatographed. From benzene–ether eluates there was obtained 190 mg. of a crystalline material (m.p. *ca.* 155°) in total. Recrystallization from ethyl acetate–petroleum ether gave colorless plates, m.p. 156–157.5°, yield 120 mg., λ_{max} 245.5 mμ (log ε 4.17); $\nu_{max}^{CHCl_3}$ 3448 cm.$^{-1}$ (hydroxyl), 1770 cm.$^{-1}$ (γ-lactone), 1661 cm.$^{-1}$ (conjugated ketone), 1631 cm.$^{-1}$ (double bond) and 830 cm.$^{-1}$ ($\Delta^{1,4}$-3-ketone[49]); $[\alpha]^{20}D$ −198° (*c* 0.5). *Anal.* Calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.81; H, 6.72.

The Dienone–Phenol Rearrangement of 6β,8α-Dihydroxy-3-oxoeusantona-1,4-dienic Acid Lactone (XVIII).—A

(49) An isomer of eusantonane with the 4α-methyl group is tentatively called "4-iso" compound.

mixture of 70 mg. of XVIII, 1.4 ml. of acetic anhydride and 1 drop of concentrated sulfuric acid was allowed to stand for 4 hr. at room temperature. To this was added 10 ml. of water and the solid obtained was recrystallized from ethanol as colorless plates, m.p. 184°, yield 65 mg. Its melting point was not depressed when mixed with an authentic sample of *cis*-desmotropoartemisin diacetate (IX).

Tetrahydroartemisins.—Pure artemisin (6.5 g.) was dissolved in 130 ml. of methanol and the solution was shaken in a hydrogen atmosphere in the presence of 2.0 g. of 5% palladium-on-carbon, 1250 ml. of hydrogen being absorbed (15°, 765 mm.). After the catalyst was filtered off, the filtrate was concentrated under reduced pressure and water was added to the residue. Filtration gave 3.8 g. (m.p. *ca.* 140°) of solid material, to which was added 42 ml. of 10% hydrochloric acid and then ethanol until the solid was completely dissolved. The solution was refluxed for 45 minutes and the ethanol was subsequently removed under reduced pressure. There was obtained 1.5 g. of the crude "γ"-tetrahydroartemisin (XIX, m.p. *ca.* 220°), which was recrystallized from benzene as colorless leaflets, m.p. 228°, $[\alpha]^{14}D$ +50° (*c* 0.5). *Anal.* Calcd. for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.74; H, 8.11.

From the mother liquor of the crude "γ"-isomer was obtained 0.85 g. of the "α"-tetrahydroartemisin (XIV, m.p. *ca.* 190°). Recrystallization from ethyl acetate gave colorless prisms, m.p. 197°, $[\alpha]^{14}D$ +50° (*c* 0.5). *Anal.* Calcd. for $C_{15}H_{11}O_4$: C, 67.64; H, 8.33. Found: C, 67.45; H, 8.28. This substance melted between 195° and 220° on admixture with "γ"-tetrahydroartemisin, but their infrared spectra were distinctly different.

After the filtrate from which the crude mixture of the "γ"- and "α"-isomers had been removed was kept standing for a long period (without treating with hydrochloric acid), a third substance (0.2 g., m.p. 200–208°) was obtained. Recrystallization from ethyl acetate–petroleum ether and subsequently from benzene afforded the "δ"-tetrahydroartemisin (XX) as colorless prisms, m.p. 213°, $[\alpha]^{18}D$ 45°. *Anal.* Calcd. for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.29; H, 8.05.

When the crude reduction product, with no treatment with hydrochloric acid, was fractionally recrystallized according to the description of Tettweiler, *et al.*,[5] the isomer with m.p. 195° was isolated as a major product. Its infrared spectrum was completely identical with that of the "α"-tetrahydroartemisin described above.

"γ"-Tetrahydroartemisin Ethylene Thioketal (XXII).—A portion of the "γ"-tetrahydroartemisin (1.05 g.) was dissolved in 30 ml. of acetic acid, and 0.48 ml. of ethanedithiol and then 0.48 g. of *p*-toluenesulfonic acid in 20 ml. of acetic acid was added. After standing for 70 hr. at room temperature, the solution was poured into ice-water. The solid material was filtered and recrystallized from ethyl acetate as colorless prisms, m.p. 292°, yield 0.83 g. *Anal.* Calcd. for $C_{17}H_{26}O_3S_2$: C, 59.63; H, 7.65. Found: C, 59.67; H, 7.36.

"γ"-Deoxotetrahydroartemisin (XXIII).—A mixture of 0.85 g. of the ethylene thioketal XXII, 600 ml. of ethanol and 10 g. of Raney nickel was refluxed for 20 hr. The reaction mixture was filtered and concentrated under reduced pressure. After water was added to the residual solution, the solid material which precipitated was collected to give 0.65 g. (m.p. 230°) of the crude product. On recrystallization from ethanol there was obtained 0.45 g. of pure deoxo compound as colorless plates, m.p. 236°, $[\alpha]^{18}D$ +42°; ν_{max}^{Nujol} 3448 cm.$^{-1}$ (hydroxyl), 1751 cm.$^{-1}$ (γ-lactone), no ketonic band. *Anal.* Calcd. for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.30; H, 9.32.

"γ"-Deoxodeoxytetrahydroartemisin (XXV, "α"-Deoxotetrahydrosantonin).—After a mixture of 200 mg. of the "γ"-deoxotetrahydroartemisin and 800 mg. of phosphorus pentabromide was heated on a water-bath for 30 minutes, with exclusion of moisture, ice-water was added and the oil extracted with ether. The extract was washed with water, dried and evaporated. The residual oil was dissolved in 10 ml. of acetic acid and 1.5 g. of powdered zinc was added. The mixture was heated on a water-bath for 4 hr. under stirring and allowed to stand overnight at room temperature. After the zinc was filtered off, the filtrate was concentrated under reduced pressure and the residue extracted with ether. The ethereal solution was washed with water, aqueous sodium carbonate and water, in turn, dried and evaporated to afford 30 mg. of crude product, which was recrystallized from 94% ethanol as colorless prisms, m.p. 153°, $[\alpha]^{18}D$ +10° (*c* 1.0). Its melting point was not depressed when mixed with an authentic sample of the "α"-deoxotetrahydrosantonin, which showed $[\alpha]^{18}D$ +11° under the same conditions. Their infrared spectra were completely superimposable.

8β-Iododeoxyartemisin (XXVI).—A mixture of 1 g. of artemisin, 2 g. of triphenyl phosphite methiodide and 5 ml. of methyl iodide was refluxed for 1 hr. on a water-bath and then kept standing overnight at room temperature. After the methyl iodide was removed under reduced pressure, the residue was taken into ethyl acetate. The extract, after washing with 4% sodium hydroxide and water, was dried, and concentrated under reduced pressure to afford 580 mg. of a crystalline material, m.p. 133° dec., which was recrystallized from ethyl acetate as colorless prisms, m.p. 139° dec., yield 375 mg., $[\alpha]^{18}D$ −236° (*c* 0.5 in chloroform; λ_{max} 239 mμ (log ε 4.00)); ν_{max}^{Nujol} 1786 cm.$^{-1}$ (γ-lactone), 1662 cm.$^{-1}$ (conjugated ketone), 1631, 1613 cm.$^{-1}$ (double bonds). *Anal.* Calcd. for $C_{15}H_{17}O_3I$: C, 48.40; H, 4.60; I, 34.10. Found: C, 48.25; H, 4.33; I, 33.93.

Reduction of 8β-Iododeoxyartemisin (XXVI).—To Raney nickel catalyst (0.5 g.) suspended in 20 ml. of methanol was added 0.25 ml. of pyridine and the mixture was shaken in a stream of hydrogen for 30 minutes. Then 200 mg. of 8β-iododeoxyartemisin in 80 ml. of methanol was added and the reduction was effected in hydrogen. After absorption of hydrogen (20 ml., 16°, 770 mm.) ceased, the catalyst was filtered off and the filtrate concentrated under reduced pressure. The residue, taken up in ether, was washed with water, dilute hydrochloric acid and water, in turn. The ethereal solution was dried and evaporated to give 60 mg. of a crystalline product, m.p. 166–171°. This was recrystallized from ethanol as colorless plates, m.p. 173°, $[\alpha]^{11}D$ −169° (*c* 1.0), undepressed on admixture with (−)-α-santonin. Also their infrared spectra were completely identical.

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