998. *The Stereochemistry of Artemisin.*

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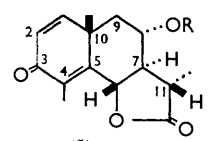
The configuration of artemisin has been confirmed as (I; R = H) by its conversion into 3β-hydroxy-5α(H),4,6,11β(H)-eudesman-6,13-olide (II).

Artemisin (I; R = H) was converted [1] by reaction with triphenyl phosphite methiodide into 8β-iodosantonin (III; R = I), which was hydrogenated over Raney nickel in pyridine–methanol, giving santonin (III; R = H). We have now shown that treatment of artemisin in hot pyridine with phosphorus oxychloride gives 8β-chlorosantonin (III; R = Cl), in which the halogen is axially disposed.

Position 8 in the santonin molecule is hindered by the axial 10-methyl group. It is also affected by strain in the lactone ring, and removal of halogen from this position is difficult. The chloro-compound is recovered when heated with sodium iodide in acetone, with pyridine or tripropylamine in benzene. Heating it with collidine affords a dark red solid which has not yet been investigated.

Reduction of 8β-chlorosantonin over palladised charcoal gave a saturated chloroketone, which, after treatment with alumina to give the stable configuration at position 4, afforded 8β-chloro-3-oxo-5α(H),4,6,11β(H)-eudesman-6,13-olide (IV). The halogen was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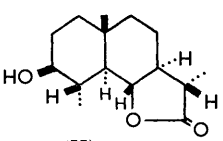
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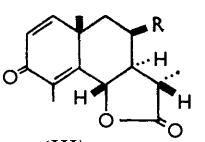
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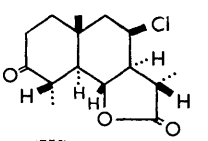
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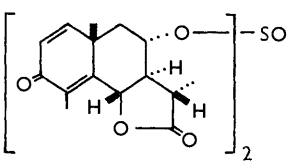
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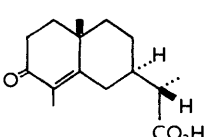
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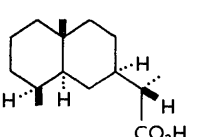
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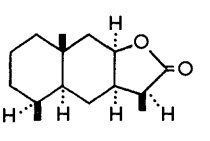
(VIII)

however, removed from this lactone (IV) by hydrogenation over Raney nickel in an autoclave, giving 3β-hydroxy-5α(H),4,6,11β(H)-eudesman-6,13-olide [2] (II). It was thus confirmed that artemisin has the same configuration as santonin at all common centres.

The following esters of artemisin (I) having good leaving groups were prepared: its

[1] Sumi, *J. Amer. Chem. Soc.*, 1958, **80**, 4869.
[2] Cocker and McMurry, *J.*, 1956, 4549 where other references are given.

methanesulphonate,[3] *m*-nitrobenzenesulphonate, *m*- and *p*-nitrobenzoates, and 3,5-dinitrobenzoate. None of these esters underwent bimolecular elimination with base at moderate temperatures. At higher temperatures the products were intractable. None of the esters underwent solvolytic elimination. Attempted replacement of the ester groups with iodine, by use of sodium iodide in acetone or diethyl ketone, failed, whilst reaction of the methanesulphonate with sodium benzyl sulphide gave a gum in which the dienone system and/or the lactone system had been attacked.

Failure to replace the methanesulphonyl group with iodine is to be contrasted with its ready hydrolysis by alkali.[3] Here, however, the initial reaction is probably hydrolysis of the lactone ring, which can relieve strain in the molecule. Failure of solvolytic elimination may be due to the lactone ring's being *trans*-fused, with consequent rigidity in ring B of the decalin system. In the ψ-santonin series, where the lactone ring is *cis*-fused and there is conformational mobility in ring B, anhydro-ψ-santonin is obtained by elimination of toluene-*p*-sulphonic acid from ψ-santonin toluene-*p*-sulphonate.[4] Reaction of artemisin with thionyl chloride in pyridine gave the 8-sulphite (V).

Artemisin formate, previously prepared[1] by vigorous methods, is conveniently obtained by treating artemisin with a mixture of formic acid and acetic anhydride at room temperature.

It is interesting to compare the lactone-carbonyl stretching frequencies of santonin and its 8-substituted derivatives. These are given in the Table and it is obvious that a large group, even when equatorial, shifts the frequency upwards. The relatively small axial chlorine atom has the same effect. Whilst electronic effects must play their part here, it seems likely that steric effects are also important.

Unsuccessful attempts were made to relate santonin to artemisin by the following route. Santonin (III; R = H) was reduced to 3-oxo-11β(H)-eudesm-4-en-13-oic acid[5] (VI), which it was intended to convert into 4,5α(H),11β(H)-eudesman-13-oic acid[6] (VII). Tetrahydroalantolactone (VIII), which has been related to artemisin,[7] was converted into 8-oxo-4,5α(H),11β(H)-eudesman-13-oic acid [the 8-oxo-derivative of (VII)],[8] which we also intended to reduce to the acid (VII). 3-Oxo-11β(H)-eudesm-4-en-13-oic acid (VI) was converted into its dithioketal but we were unable satisfactorily to desulphurise this. Its methyl ester was also only partially desulphurised. We could not form the dithioketal of 8-oxo-4,5α(H),11β(H)-eudesman-13-oic acid or its methyl ester, nor was the keto-group removed by the Clemmensen method, thus emphasising the hindrance at position 8.

One point of interest emerged from these experiments: 8β-hydroxy-4,5α(H),11β(H)-eudesman-13-oic acid was obtained as a relatively stable substance. Its methyl ester[8,9]

Derivative of santonin	C=O stretching frequency (cm.$^{-1}$)	$[M]_D$	Derivative of santonin	C=O stretching frequency (cm.$^{-1}$)	$[M]_D$
Santonin	1780	−425°[10]	8α-*m*-Nitrobenzoyloxy-	1786	+176°
Artemisin	1776	−221[11]	8α-*p*- ,, ,,	1786	+212
8α-Formyloxy-	1788	−193	8α-(3,5-Dinitrobenzoyloxy)-	1788	+157
8α-Methanesulphonyloxy	1792	−167	Sulphite (V)	1776	−204
8α-*m*-Nitrobenzenesulphonyloxy-	1788	−115	8β-Chloro	1790	−613
			8β-Iodo	1786[1]	−585[1]

[3] Barton, Levisalles, and Pinhey, *J.*, 1962, 3472.
[4] Dauben and Hance, *J. Amer. Chem. Soc.*, 1955, **77**, 606.
[5] Bruderer, Arigoni, and Jeger, *Helv. Chim. Acta*, 1956, **39**, 858; Cocker, Donnelly, Gobinsingh, McMurry, and Nisbet, *J.*, 1963, 1262.
[6] Tanabe, *Pharm. Bull.* (*Japan*), 1958, **6**, 214; Ukita and Nakazawa, *ibid.*, 1954, **2**, 239.
[7] Cocker and Nisbet, *J.*, 1963, 534.
[8] Tsuda, Tanabe, Iwai, and Funakoshi, *J. Amer. Chem. Soc.*, 1957, **79**, 5721; cf. Cocker, McMurry, and Hopkins, *J.*, 1959, 1998.
[9] Ukita and Nakazawa, *J. Amer. Chem. Soc.*, 1960, **82**, 2224.
[10] Simonsen and Barton, " The Terpenes," Cambridge Univ. Press, 1952, Vol. III, p. 250.
[11] Merck, *Merck's Jahresber.*, 1894, **3**; Elseviers' " Encyclopaedia of Organic Chemistry," Amsterdam, 1953, Vol. XII, p. 3828.

lactonised more readily than the acid. It is worth comment that the optical rotation of this acid is more negative than that of its 8-epimer.[8] 8α-Substituted santonins are also more positive in rotation than 8β-substituted santonins. Indeed, santonins substituted with large α-groups have positive molecular rotations (see Table).

Experimental

Ultraviolet spectra were measured for ethanolic solutions, infrared spectra for Nujol suspensions, and $[\alpha]_D$ for chloroform solutions, unless otherwise stated.

Purification of Artemisin.—Artemisin was Merck's 80—90% grade, which was conveniently purified as follows. It was crystallised once from ethanol; then a solution in the minimum quantity of dioxan was filtered, poured into twice its volume of water, and was extracted five times with ether (to remove santonin). The aqueous solution was evaporated under reduced pressure, giving artemisin, m. p. 200—201°, $[\alpha]_D^{20}$ −84·3° (*c* 0·38) (cf. ref. 11).

8β-*Chlorosantonin* (III; R = Cl).—Artemisin (2·0 g.) was dissolved in pyridine (30 c.c.), phosphorus oxychloride (1·6 g.) was added, and the mixture was heated on the water-bath for 30 min. After cooling, the mixture was poured into water and extracted thrice with ether, and the extracts were washed successively with 5% hydrochloric acid, 5% aqueous sodium hydrogen carbonate, and water, and evaporated. In this way the desired *chloro-compound* (1 g.) was obtained which after crystallisation from aqueous ethanol was obtained as rhombs, m. p. 159—160°, $[\alpha]_D^{20}$ −247° (*c* 0·81), $\lambda_{max.}$ 2380 Å (log ε 4·11), $\nu_{max.}$ 1790 (lactone), 1662 (C=C–C=O), 1635, 1616 (C=C), and 835 cm.$^{-1}$ ($\Delta^{1,4}$-3-ketone) (Found: C, 64·3; H, 6·1. $C_{15}H_{17}ClO_3$ requires C, 64·1; H, 6·1%).

8β-*Chloro*-3-*oxo*-5α(H),4,6,11β(H)-*eudesman*-6,13-*olide* (IV).—The preceding compound (1 g.) was hydrogenated with palladised charcoal (0·1 g.) in ethyl acetate (25 c.c.). The product, a gum, was then refluxed for 1 hr. in benzene with Merck's basic alumina (1 g.) and filtered whilst hot. The required *chloro-compound* (0·5 g.) was obtained as plates (from aqueous ethanol), m. p. 172°, $[\alpha]_D$ −45·8° (*c* 0·722), $\nu_{max.}$ 1785 (lactone), 1700 cm.$^{-1}$ (ketone) (Found: C, 62·8; H, 7·4. $C_{15}H_{21}ClO_3$ requires C, 63·3; H, 7·4%).

3β-*Hydroxy*-5α(H),4,6,11β(H)-*eudesman*-6,13-*olide* (II).—Compound (IV) (0·76 g.) in methanol (80 c.c.) was hydrogenated at 100—110°/80 atm. for 12 hr. The product (0·7 g.), a gum which became solid on trituration with ligroin, was crystallised twice from aqueous ethanol, giving the *alcohol* as needles, m. p. 170—171° undepressed on admixture with an authentic specimen,[2] $[\alpha]_D^{20}$ +55·9° (*c* 0·37) (lit.,[2] $[\alpha]_D^{15}$ +50·7°).

Esters of Artemisin.—These were prepared by treating artemisin (1 mol.) with the acid chloride (1·2 mol.) in an excess of pyridine at room temperature for 12 hr. The product was obtained either on pouring the reaction mixture into ice–water or by extraction of the aqueous mixture with chloroform.

Methanesulphonate[3] (2·2 g. from 2 g.): crystallised from methanol as rhombs, m. p. 225° (dec.), $[\alpha]_D^{20}$ −49·4 (*c* 0·39) (lit.,[3] m. p. 179—181°, $[\alpha]_D$ −56°), $\lambda_{max.}$ 2380 (log ε 4·19), $\nu_{max.}$ 1792, 1670, 1637, 1620, and 830 cm.$^{-1}$ (Found: C, 56·6; H, 6·0. Calc. for $C_{16}H_{20}O_6S$: C, 56·5; H, 5·9%).

m-*Nitrobenzenesulphonate* (0·8 g. from 0·56 g.): crystallised from ethanol as plates, m. p. 166—167° (dec.), $[\alpha]_D^{18}$ −25·9° (*c* 0·81), $\nu_{max.}$ 1788, 1668, 1634, 1618, 1540 (NO_2), and 830 cm.$^{-1}$ (Found: C, 56·6; H, 4·9. $C_{21}H_{21}NO_8S$ requires C, 56·4; H, 4·7%).

3,5-*Dinitrobenzoate* (3·85 g. from 2·4 g.): crystallised as pale yellow prisms (from ethanol), m. p. 217—218°, $[\alpha]_D^{20}$ +34·5° (*c* 0·89) $\nu_{max.}$ 1788, 1735 (ester), 1670, 1640, 1622, 1527, and 835 cm.$^{-1}$ (Found: C, 57·6; H, 4·3. $C_{22}H_{20}N_2O_9$ requires C, 57·9; H, 4·4%).

m-*Nitrobenzoate:* crystallised as colourless needles (from ether), m. p. 179—180°, $[\alpha]_D^{20}$ +42·8° (*c* 0·76), $\nu_{max.}$ 1786, 1725, 1668, 1640, 1620, 1537, and 835 cm.$^{-1}$ (Found: C, 64·1; H, 5·2. $C_{22}H_{21}NO_7$ requires C, 64·2; H, 5·15%).

p-*Nitrobenzoate:* (2·5 g. from 2·0 g.): crystallised from ethanol as pale yellow needles, m. p. 191—192°, $[\alpha]_D^{20}$ +51·6° (*c* 0·64), $\nu_{max.}$ 1786, 1725, 1670, 1640, 1622, 1527 (NO_2), and 835 cm.$^{-1}$ (Found: C, 64·6; H, 5·3%).

Sulphite (V): Artemisin (1·85 g.) in pyridine (15 c.c.) was slowly treated with a solution of thionyl chloride (1 g.) in pyridine (5 c.c.), and the mixture was set aside for 18 hr. It was

poured into water (100 c.c.) and the precipitated solid (1·7 g.) was collected, washed, and dried. Crystallisation from ethanol gave the *sulphite* as rhombs, m. p. 254°, $[\alpha]_D$ −35·8° (*c* 0·26), $\lambda_{max.}$ 2370 Å (log ε 4·36), $\nu_{max.}$ 1776, 1668, 1635, 1620, and 830 cm.$^{-1}$ (Found: C, 63·1, 62·9; H, 6·4, 6·2; S, 5·8. $C_{30}H_{34}O_9S$ requires C, 63·2; H, 6·0; S, 5·6%).

Formate: A mixture of artemisin (0·63 g.), 98—100% formic acid (1 c.c.), and acetic anhydride (1 c.c.) was set aside overnight. The mixture was poured into water, giving the required ester which crystallised from methanol as rhombs (0·43 g.), m. p. 208—210°, shrinks at 184°, $[\alpha]_D^{18}$ −66·4° (*c* 0·6) (lit.,[1] m. p. 185°, $[\alpha]_D$ −90°), $\nu_{max.}$ 1788, 1718 (formyl), 1670, 1637, 1620, and 835 cm.$^{-1}$ (Found: C, 65·9; H, 6·5. Calc. for $C_{16}H_{18}O_5$: C, 66·2; H, 6·25%).

The following illustrate the experiments carried out with a view to the elimination of the ester group. The methanesulphonate was refluxed with sodium iodide in acetone and in diethyl ketone for periods up to 48 hr. without reaction. The same ester was refluxed in dimethyl sulphoxide, dimethylformamide, pyridine, and collidine for periods up to 50 hr. without change. The *m*-nitrobenzenesulphonate was unchanged by collidine in boiling toluene for 19 hr.; with boiling dimethylformamide for 2·25 hr. it gave a glass.

Dithioketal of 3-*Oxo*-11β(H)-*eudesm*-4-*en*-13-*oic Acid* (VI).—The keto-acid [5] (1·48 g.) in a mixture of ethanedithiol (1·3 c.c.) and ether (3 c.c.) was slowly treated with boron trifluoride–ether complex (1·7 c.c.), and the mixture was set aside overnight. 5% sodium carbonate solution was added until the mixture was only weakly acid, and the product was extracted several times with ether, from which a solid (1·6 g.), m. p. 131°, was obtained. Crystallisation from aqueous ethanol gave the *dithioketal* as needles, m. p. 136°, $[\alpha]_D^{15}$ +30·8° (*c* 0·26), end-absorption at 2100 Å (log ε 3·06), $\nu_{max.}$ 1720 cm.$^{-1}$ (CO_2H) (Found: C, 62·6; H, 8·25. $C_{17}H_{26}O_2S_2$ requires C, 62·6; H, 8·0%). Its *methyl ester*, prepared in ether with diazomethane, crystallised from ethanol as needles, m. p. 75—76°, $[\alpha]_D^{20}$ +48·5° (*c* 0·33), $\nu_{max.}$ 1745 cm.$^{-1}$ (Found: C, 63·9; H, 8·5. $C_{18}H_{28}O_2S_2$ requires C, 63·5; H, 8·3%).

The dithioketal (0·5 g.) was refluxed for 18 hr. with Raney nickel (3 g.) in dioxan (15 c.c.). The solution was filtered and solvent was removed under reduced pressure, giving a glass which when rubbed with ligroin gave the dithioketal (0·14 g.), m. p. and mixed m. p. 127°. More dithioketal was extracted from the nickel by boiling dioxan.

8β-*Hydroxy*-4,5α(H),11β(H)-*eudesman*-13-*oic Acid*.—Tetrahydroalantolactone (3·7 g.) was refluxed for 4 hr. with sodium hydroxide (2 g.) in water (50 c.c.). The clear solution was cooled, 4% acetic acid was slowly added with stirring, and the precipitated solid was collected. It was crystallised from aqueous methanol (1 : 1), giving the *hydroxy-acid* (3·2 g.) as leaflets, m. p. 117°, $[\alpha]_D^{18}$ +30° (*c* 0·4), $\nu_{max.}$ 3448 (OH), 2700, and 1712 cm.$^{-1}$ (CO_2H) (Found: C, 71·0; H, 10·3. $C_{15}H_{26}O_3$ requires C, 70·8; H, 10·3%). Its methyl ester made with diazomethane crystallised from aqueous methanol as plates, m. p. 124—125°, $[\alpha]_D^{18}$ +15·3° (*c* 0·75) (lit., m. p. 122—124°, $[\alpha]_D$ +16·1°; [8] m. p. 124—127° [9]), $\nu_{max.}$ 3509 (OH), 1715 cm.$^{-1}$ (CO_2Me) (Found: C, 71·3; H, 10·4. Calc. for $C_{16}H_{28}O_3$: C, 71·6; H, 10·5%). With warm aqueous methanol it gave tetrahydroalantolactone, m. p. and mixed m. p. 143°.

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