Kinetics and Mechanism of the Acid-induced Rearrangements of α-Santonin,† 6-*epi*-α-Santonin, and Related Compounds

Anthony J. Waring
Department of Chemistry, University of Birmingham, P.O. Box 363, Birmingham B15 2TT

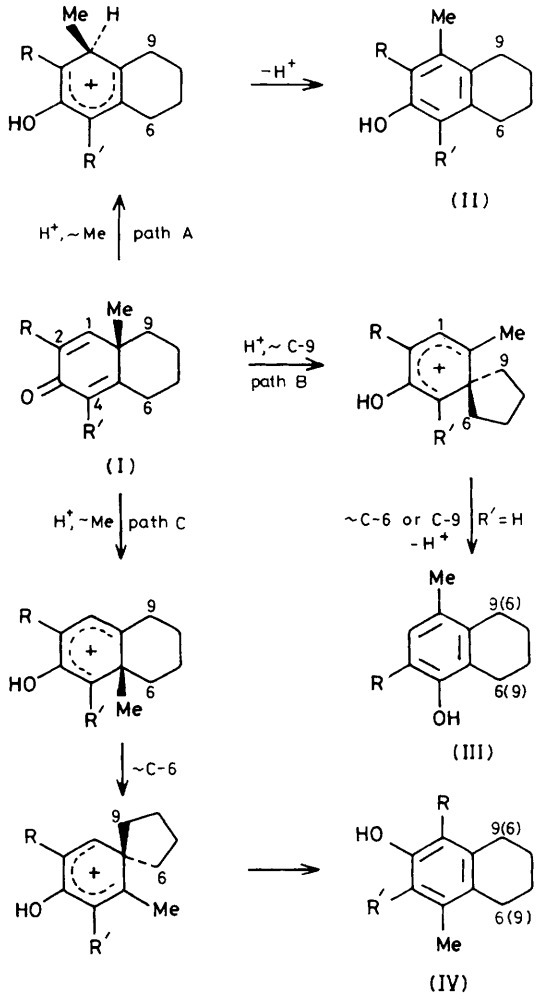
The well known rearrangements of α-santonin (2) to α-desmotroposantonin (3) in aqueous sulphuric acid, and to its acetate in acetic anhydride, have been reinvestigated. No evidence was found for the formation of isomeric products apart from the known β-desmotroposantonin (4). Kinetic and basicity measurements, allied to the use of acidity functions, allow the conclusion that, in >45% H_2SO_4, α-santonin (2) rearranges slowly to *trans*-desmotroposantonin, which rapidly epimerises to (3). In more dilute acid there is evidence of a change in mechanism. The cation of 6-*epi*-α-santonin (5) rearranges about 1 000 times faster than those of α-santonin and a number of analogues, including the lactone-free analogue (6). This is attributed to a favourable interaction between the lactone ring of (5) and the dienone ring over which it can be closely folded.

We recently gave evidence regarding the existence and rates of three reaction paths in the acid-induced dienone–phenol rearrangement of fused bicyclic cyclohexadienones of type (I) (see Scheme 1).[1,2] As part of our study we showed that compound (1; R′ = H), for which path B is blocked by the 4-methyl group, reacts by paths A and C. The complex path C makes up *ca.* 16% of the reaction in 50% aqueous sulphuric acid at 100 °C, 8% in 79% H_2SO_4 at 25 °C, and 30% in acetic anhydride–H_2SO_4 at 20 °C. The same substitution pattern as in (1) is found on the dienone ring of (−)-α-santonin (2), its stereoisomer 6-*epi*-α-santonin (5), and the analogue (6), which are the subjects of the present paper.

It has been known for nearly a hundred years that (−)-α-santonin (hereafter referred to as α-santonin) rearranges in aqueous sulphuric acid under mild conditions to give (−)-α-desmotroposantonin (3), and that further isomerisation to (+)-β-desmotroposantonin (4) takes place upon more vigorous treatment.‡[3,4] The formation of (3) involves, amongst other things, a dienone–phenol rearrangement by path A, but we know of no reports of path C operating here. This intrigued us, particularly because dienones of type (I; R = R′ = H) which bear a $^-CH_2CO_2H$ group at C-7 have been reported to react *via* paths A, B, and C, whereas the compounds (I; R = H, R′ = Me) having a $^-CH_2CO_2H$ group at C-7 appeared to follow path A.[6] No clear explanation of this variation in behaviour was available.

We have examined the products of rearrangement of α-santonin, to try to detect the operation of path C, and have studied the basicity of α-santonin and the kinetics of its rearrangement in aqueous sulphuric acid. Comparison with 6-*epi*-α-santonin (5), and with (6), which lacks the lactone ring but retains the 7-substituent, allows the mechanism of the conversion of α-santonin into α-desmotroposantonin to be clarified. We also discuss further questions which arose when we found 6-*epi*-α-santonin to rearrange much faster than does α-santonin.

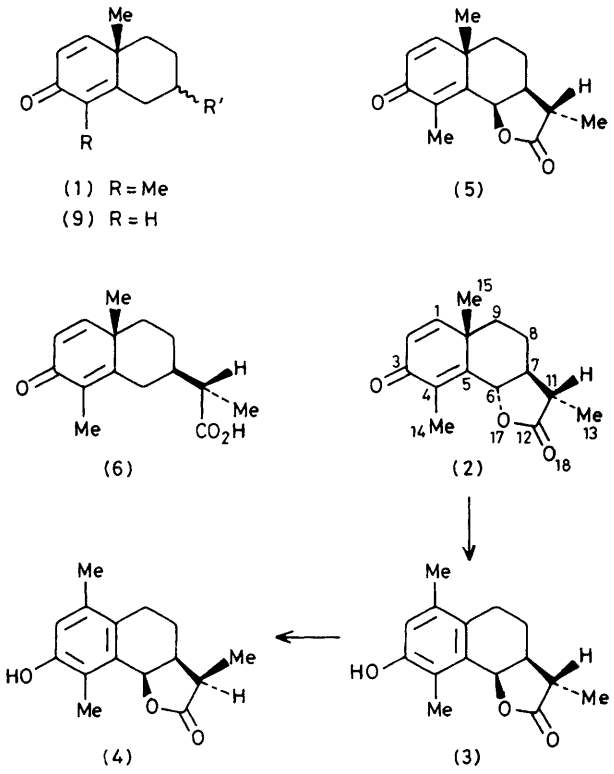
Product Studies.—Authentic samples of (−)-α-desmotroposantonin and its acetate, and of (+)-β-desmotroposantonin, were made from α-santonin under well established conditions. Our ^1H and ^{13}C n.m.r. data recorded on the crude (−)-α-desmotroposantonin acetate, obtained by rearranging α-santonin in acetic anhydride and a trace of sulphuric acid, with no purification, agree with published spectra. No trace of other isomeric products was evident (*cf.* ref. 1). The spectra of authentic α- and β-desmotroposantonin were recorded in [$^2H_6$]dimethyl sulphoxide and, for the α-isomer, in deuteriochloroform: the β-isomer is insufficiently soluble in this solvent. Preparative rearrangements of α-santonin under the



Scheme 1.

† (11*S*)-3-Oxoeudesma-1,4-dien-12,6α-olactone.

‡ The apparent stereochemical inversion at C-11 proceeds by inversion at C-6 and C-7 (see later).[5] The stereochemistry of α-santonin, which had been subject to doubt previously, was firmly established in 1962.



commonly used conditions (50% H_2SO_4 at 25 °C) gave crude products the ^1H and ^{13}C n.m.r. spectra of which showed no peaks other than those due to α-desmotroposantonin and, at longer reaction times, a trace of the β-isomer. Samples analysed by ^1H n.m.r. spectroscopy after partial reaction were used to give some kinetic information (see later): they showed no trace (<2%) of compounds other than α-santonin and α-desmotroposantonin. Similar rearrangement of 6-*epi*-α-santonin in aqueous H_2SO_4 for 6 half-lives gave only α-desmotroposantonin, small amounts of the β-isomer (4), and unchanged starting material.

The rearrangement of (−)-3-oxoeusantona-1,4-dienic acid (6) * in *ca.* 67% sulphuric acid at 35—70 °C gave mainly a product which is assigned the structure (7; R = $CHMeCO_2H$) on the basis of the very close correspondence of its ^1H and ^{13}C n.m.r. spectra with those of (7; R = H) which we examined critically before.[1] A minor phenolic product, which makes up about 10% of the total, has not yet been positively identified. Rearrangements were also carried out on the pure cyclohexylamine salt of the acid (6), but in more dilute acid at 25 °C. Samples were worked up and examined by ^1H n.m.r. spectroscopy at intervals. This allowed rate constants to be calculated for the reaction (6) ⟶ (7; R = $CHMeCO_2H$), which corroborated the rate constants measured using u.v. spectroscopy, and showed that the products were the same as produced from (6) at higher temperature and acidity.

Kinetic Studies.—The rates of rearrangement of α-santonin were measured in aqueous H_2SO_4 of various concentrations at 25 °C and other temperatures. The reactions could be followed using u.v. and ^1H n.m.r. spectroscopy, but because of the very low solubility of α-santonin the u.v. method was mostly used. At low acidities the rearrangements are very slow, and the appearance of slight colour during the many weeks required for complete reaction cast some doubt on the reliability of the u.v.-derived rate constants. Monitoring by ^1H n.m.r. of reaction mixtures isolated at intervals lacked this problem, but not all the santonin and desmotroposantonin remained in solution so these results are of value only in a broadly confirmatory sense. Similar n.m.r. measurements on samples isolated from reaction in deuteriosulphuric acid–deuterium oxide allowed the extent and sites of deuterium incorporation into recovered α-santonin and desmotroposantonin to be determined. Similar kinetic measurements were made on 6-*epi*-α-santonin (5) and its analogue (6). The observed rate constants for pseudo-first-order reaction, k_{obs}, are given in Tables 1—3. They are related to the rate constants, k_1, for reaction of the cation of the dienone by [7] equation (i), where the protonation equilibrium is described by equation (ii). At high acidities, where all three dienones are essentially completely protonated, k_1 is identical with k_{obs}. At lower acidities, where [S]/[SH$^+$] is significant, equations (ii) and (iii) have to be used (see the next section).[8,9]

Qualitatively, both α-santonin (2) and the lactone-free analogue (6) rearrange slowly at all acidities. The plots of log k_{obs} against H_0 for (2) and (6) are parallel and very close to one another at ' high acidities ' (>45% H_2SO_4) and also very close to that for the reaction of the simpler analogue (1; R′ = H) ⟶ (7; R = H) by path A. The order of rates is (1; R′ = H) > (6) > α-santonin, with a factor of two between (1; R′ = H) and (2). An approximate equality of

Table 1. Kinetics for rearrangement of (−)-α-santonin (2) in aqueous sulphuric acid at 25 °C and other temperatures; u.v. measurements at 250, 268, and 310 nm

Wt. % acid	Temp. (°C)	$-H_0$	$-\log_{10}(k_{obs}/s^{-1})$	$-\log_{10}(k_1/s^{-1})$ [a]
26.5	25.0	1.50	6.46 ± 0.16	4.75 ± 0.15
26.6	25.0	1.50	6.43 ± 0.07	4.7 ± 0.2
33.4	25.0	1.95	6.30 ± 0.04	5.0 ± 0.15
37.6	25.0	2.25	6.20 ± 0.05	5.2 ± 0.1
40.1	25.0	2.43	6.08 ± 0.11	5.24 ± 0.15
40.7	25.0	2.48	6.25 ± 0.05	5.4 ± 0.1
42.8	25.0	2.67	6.15 ± 0.08	5.5 ± 0.1
43.8	25.0	2.76	6.20 ± 0.07	5.61 ± 0.09
47.7	25.0	3.10	6.15 ± 0.03	5.78 ± 0.05
51.9	25.0	3.47	5.96 ± 0.03	5.75 ± 0.03
55.6	25.0	3.86	5.6 ± 0.1	5.5 ± 0.1
57.7	25.0	4.10	5.66 ± 0.02	5.60 ± 0.02
60.8	25.0	4.47	5.46 ± 0.03	5.43 ± 0.03
61.6	25.0	4.58	5.48 ± 0.01	5.46 ± 0.01
64.2	25.0	4.94	5.35 ± 0.02	5.34 ± 0.02
66.0	25.0	5.20	5.26 ± 0.01	5.26 ± 0.01
69.3	25.0	5.73	5.20 ± 0.01	5.20 ± 0.01
69.4	25.0	5.74	5.15 ± 0.01	5.15 ± 0.01
71.4	25.0	6.06	5.05 ± 0.01	5.05 ± 0.01
73.6	25.0	6.40	4.96 ± 0.02	4.96 ± 0.02
74.0	22.4		5.20 ± 0.01	
69.4	25.2	5.74	5.15 ± 0.02	5.15 ± 0.02
74.0	25.2	6.47	5.00 ± 0.01	5.00 ± 0.01
69.4	29.7		4.90 ± 0.01	
74.0	29.7		4.73 ± 0.01	
74.0	34.7		4.45 ± 0.01	
69.4	40.3		4.29 ± 0.01	
74.0	40.3		4.12 ± 0.01	
42.8 [b]	25.0	2.67	6.74 ± 0.12	
47.8 [b]	25.0	3.10	6.22 ± 0.05	
c	25.0	3.25	6.11	

[a] Values of k_{obs} are modified using equations (i) and (ii) and the parameters quoted in Table 6 where protonation is incomplete. [b] Values by ^1H n.m.r. spectroscopy: minimum rates owing to incomplete solubility (see text). [c] Value by ^1H n.m.r. spectroscopy in 7.0M-D_2SO_4/D_2O: minimum rate (see footnote *b*).

* (11*S*)-3-Oxoeudesma-1,4-dien-12-oic acid.

Table 2. Kinetics for rearrangement of (−)-6-*epi*-α-santonin (5) in aqueous sulphuric acid at 25 °C and other temperatures; u.v. measurements at 250, 268, and 310 nm

Wt. % acid	Temp. (°C)	$-H_0$	$-\log_{10}(k_{obs}/s^{-1})$	$-\log_{10}(k_1/s^{-1})$ [a]
24.0	25.0	1.34	5.46 ± 0.02	3.68 ± 0.01
26.5	25.0	1.50	5.18 ± 0.06	3.56 ± 0.01
36.7	25.0	1.98	4.569 ± 0.006	3.38 ± 0.03
39.2	25.0	2.36	4.114 ± 0.004	3.25 ± 0.05
40.5	25.0	2.47	4.027 ± 0.005	3.25 ± 0.05
42.8	25.0	2.67	3.796 ± 0.003	3.17 ± 0.05
44.2	25.0	2.80	3.699 ± 0.002	3.17 ± 0.05
47.3	25.0	3.06	3.42 ± 0.03	3.05 ± 0.05
51.2	25.0	3.41	3.074 ± 0.001	2.86 ± 0.04
55.6	25.0	3.86	2.708 ± 0.002	2.62 ± 0.02
55.8	25.0	3.88	2.68 ± 0.01	2.59 ± 0.03
57.0	25.0	4.01	2.61 ± 0.01	2.54 ± 0.02
61.6	25.0	4.58	2.27 ± 0.02	2.25 ± 0.02
66.0	25.0	5.20	2.055 ± 0.013	2.05 ± 0.01
69.4	25.0	5.74	1.89 ± 0.03	1.89 ± 0.03
74.0	25.0	6.47	1.70 ± 0.08	1.70 ± 0.08
74.0	25.0	6.47	1.61 ± 0.02	1.61 ± 0.02
74.0	17.8		2.051 ± 0.005	
47.3	30.0		3.132 ± 0.009	
55.8	30.0		2.452 ± 0.005	
74.0	30.0		1.480 ± 0.004	
47.3	35.0		2.90 ± 0.04	
55.8	35.0		2.267 ± 0.002	
74.0	35.0		1.299 ± 0.005	

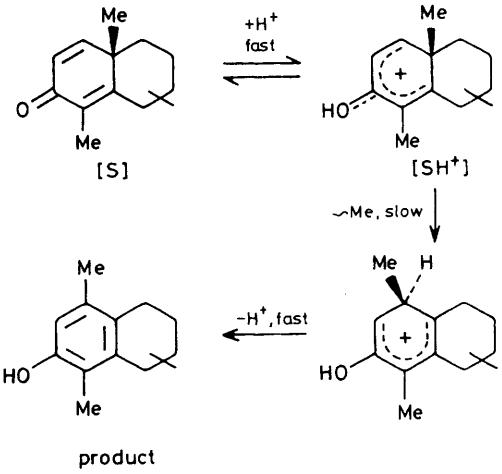
[a] Values of k_{obs} are modified using equations (i) and (ii), with the u.v.-derived parameters shown in Table 6, where protonation is incomplete. When the basicity parameters were calculated from kinetic data only, using the KINBASIC program, the standard deviation between $\log_{10}k_1$ (calculated) and $\log_{10}k_1$ (observed) was 0.068.

Table 3. Kinetics for rearrangement of (−)-3-oxoeusantona-1,4-dienic acid (6) in aqueous sulphuric acid at 25 °C and other temperatures; u.v. measurements at 250, 268, and 310 nm

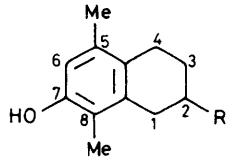
Wt. % acid	Temp. (°C)	$-H_0$	$-\log_{10}(k_{obs}/s^{-1})$	$-\log_{10}(k_1/s^{-1})$ [a]
36.7	25.0	2.18	6.54 ± 0.13 [b]	6.28 ± 0.20
43.8	25.0	2.76	5.73 ± 0.02	5.66 ± 0.02
46.4	25.0	2.99	5.62 ± 0.02	5.58 ± 0.02
50.0	25.0	3.30	5.51 ± 0.02	5.49 ± 0.02
51.9	25.0	3.47	5.49 ± 0.02	5.45 ± 0.02
57.7	25.0	4.10	5.29 ± 0.01	5.28 ± 0.02
64.2	25.0	4.94	5.13 ± 0.01	5.12 ± 0.02
69.3	25.0	5.73	4.95 ± 0.02	4.95 ± 0.02
73.6	25.0	6.40	4.84 ± 0.02	4.84 ± 0.02
69.4	22.4		5.19 ± 0.03	5.19 ± 0.03
74.0	22.4		5.19 ± 0.03	5.19 ± 0.03
69.3	25.2	5.73	4.96 ± 0.01	4.96 ± 0.01
74.0	25.2	6.47	4.85 ± 0.01	4.85 ± 0.01
69.4	34.7		4.45 ± 0.03	
74.0	34.7		4.31 ± 0.01	
51.9	44.0		4.31 ± 0.01	
69.4	44.0		3.95 ± 0.03	
74.0	44.0		3.80 ± 0.01	

[a] See text. Values of k_{obs} are modified using equations (i) and (ii) and the parameters quoted in Table 6 when protonation is incomplete. [b] Values by ^{1}H n.m.r. spectroscopy: minimum values owing to incomplete solubility.

rates extends to other analogues such as (I; R = Me, R′ = H),[2] to (I; R = R′ = H) and its *trans*-6-methyl derivative, and to androsta-1,4-diene-3,17-dione.[9] The appropriate values of the parameters c and $\log k_{1,0}$ [see equation (iv)] are



Scheme 2.



(7)

in Table 4. At 'lower' acidities (<45% H_2SO_4) the value of $\log k_{obs}$ for (6) starts to fall steeply, as expected when protonation becomes more incomplete and k_{obs} deviates strongly from k_1 [see equation (i)]. Calculated values of $\log k_1$ [from equations (i) and (ii)] correlate with equation (iv), giving the

$$\text{d[stoicheiometric substrate]/d}t = -k_{obs}[\text{stoicheiometric substrate}]$$

$$\therefore \text{d}[S + SH^+]/\text{d}t = -k_{obs}[S + SH^+] = -k_1[SH^+]$$

$$\therefore k_1 = k_{obs}\{1 + [S]/[SH^+]\} \quad \text{(i)}$$

$$\log [SH^+]/[S] = m_0[(H_0)_{\frac{1}{2}} - H_0] = pK - m_0H_0 \quad \text{(ii)}$$

$$= \log (\varepsilon - \varepsilon_S)/(\varepsilon_{SH^+} - \varepsilon) \quad \text{(iii)}$$

$$\log k_1 = \log k_{1,0} + cH_0 \quad \text{(iv)}$$

parameters shown in Table 4. However, α-santonin behaves differently. As the acidity is lowered, its rate (k_{obs}) does not fall as strongly as expected. Below about 50% H_2SO_4 k_{obs} levels out, and the calculated value of k_1 increases steeply. Similarly, the Bunnett and Olsen plot [10] [equation (v)] shows strong curvature.* At 'high' acidity the value of the slope parameter, φ, is about −0.26, and at 'low' acidity it is *ca.* +0.86. This behaviour indicates a change of mechanism, which will be discussed later.

The most notable feature of 6-*epi*-α-santonin is that it rearranges, by simple methyl migration by path A, about 1 000

* The corrections made to k_{obs} to give k_1, according to equations (i) and (ii), use the basicity parameters established for α-santonin (see later) which represent the protonation of the cyclohexadienone ring.

Table 4. Kinetic relationships for rearrangements in aqueous sulphuric acid at 25 °C

Compound	$-c$ [a]	$-\log_{10}(k_{1,0}/s^{-1})$ [a]	φ [b]	$-\log_{10}(k_{1,0}/s^{-1})$ [b]
(2)	0.24 ± 0.01 [c]	6.54 ± 0.07 *,[c]	−0.27 ± 0.01 [c]	6.39 ± 0.06 *,[c]
	−0.64 ± 0.04 [d]	3.78 ± 0.08 [d]	+0.86 ± 0.07 [d]	3.84 ± 0.11 [d]
(5)	0.40 [e]	4.16 *,[e]	−0.44 ± 0.01 [e]	3.92 ± 0.03 *,[e]
	0.40 ± 0.01 [f]	4.21 ± 0.03 *,[f]	−0.46 ± 0.01 [f]	4.02 ± 0.03 *,[f]
(6)	0.21 ± 0.01	6.18 ± 0.02 *	−0.23 ± 0.01	6.04 ± 0.02 *
(I; R = R′ = H) [g]	0.12	6.5 ± 0.1 [h]	−0.12	6.39 [h]
	0.12	6.6 ± 0.1 [i]	−0.12	6.5 [i]
trans-6-methyl-	0.25	7.1 ± 0.1 [h]	−0.27	6.91 [h]
(I; R = R′ = H) [g]	0.25	7.3 ± 0.1 [i]	−0.27	7.1 [i]
(1; R′ = H) [j]	0.18 ± 0.01	5.84 ± 0.04 [h]	−0.19 ± 0.01	5.69 ± 0.04 [h]
	0.18 ± 0.01	5.87 ± 0.04 [i]	−0.19 ± 0.01	5.72 ± 0.04 [i]
(I, R = Me, R′ = H) [j]	0.05 ± 0.03	5.8 ± 0.2 [h]	−0.06 ± 0.03	5.8 ± 0.2 [h]
	0.05 ± 0.03	6.5 ± 0.2 [i]	−0.06 ± 0.03	6.5 ± 0.2 [i]

* Correlation coefficient, r, >0.99.

[a] Values in equation (iv). [b] Values in equation (v). [c] At high acidity (>46% H_2SO_4). [d] At low acidity (<46% H_2SO_4) using basicity data estimated for the lactone ring (see text). [e] Values from the kinetic curve-fitting program, KINBASIC. [f] Values using the basicity data reported in Table 6, derived from u.v. spectra. [g] From ref. 9. [h] Correlation of total rate. [i] Correlates the part of the rate assigned to path A only. Calculated from data in refs. 1 and 2.

Table 5. Activation parameters for rearrangements in aqueous H_2SO_4 at 25—45 °C

Compound	% H_2SO_4	$\Delta H^{\ddagger}$/kJ mol^{-1}	$\Delta S^{\ddagger}$/J mol^{-1} K^{-1} [a]	$T\Delta S^{\ddagger}$/kJ mol^{-1} [a]
(2)	69.4	99 ± 2	−11 ± 7	−3.2 ± 2.2
	74.0	103 ± 2	+6 ± 4	+1.9 ± 1.2
(5)	47.3	83.3 ± 6.2	−30 ± 20	−9.1 ± 6.1
	55.8	72.5 ± 3.9	−53 ± 13	−15.9 ± 3.9
	74.0	73.2 ± 8.4	−31 ± 7	−9.4 ± 2.3
(6)	51.9	109 ± 1.0	+3.3 ± 3.3	+1.0 ± 1.0
	69.4	99 ± 3	−8 ± 10	−2.6 ± 3.1
	74.0	99.2 ± 0.8	−5.5 ± 2.5	−1.6 ± 0.7
trans-6-methyl-				
(I; R = R′ = H) [b]	67.6	108 ± 4.2	−4.0 ± 4.0	−1.2 ± 1.2

[a] Calculated at 25 °C. [b] Values from ref. 9, or calculated from data given there.

times faster than does α-santonin. This will be discussed later. The kinetic parameters for the cation were derived using the treatment described in ref. 7, in which the values of log k_{obs} are fitted to a combination of equations (i), (ii), and (iv) using an iterative computer program (KINBASIC). The pattern of overall variation of rate with acidity agrees closely with that found for other cyclohexadienones which rearrange by an *A*-1 process.[7]

The rate constants for (2), (5), and (6) were also correlated with acidity using Bunnett and Olsen's equation [equation (v)],[10] giving the parameters shown in Table 4. Activation

$$\log k_1 = \log k_{1,0} + \varphi(H_0 + \log [H_2SO_4]_{stoich}) \quad (v)$$

parameters, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, were derived using standard methods,[11] and are given in Table 5 for a common acidity in which all three dienones are essentially completely protonated. These values are discussed later.

Basicity Measurements.—Because α-santonin (2) and the other dienones (5) and (6) are incompletely protonated in many of the acids used, we investigated their protonation equilibria. Conventional plots [8] against the Hammett acidity function, H_0, of the u.v. absorbance at suitable wavelengths were used (for details, see Experimental section). The low solubility of α-santonin in aqueous solution presented significant practical difficulties which were greatly reduced by also using the *ratios* of u.v. absorbance data at different wavelengths: this technique is discussed elsewhere.[12] The results, summarised in Table 6, suggest that α-santonin is close to a Hammett base, with pK −(3.1 ± 0.1). The analogue (6), which lacks the lactone ring, is significantly more basic: it is essentially a Hammett base with pK −(2.0 ± 0.1). This compares well with the analogue (I; R = Me, R′ = H), which is a Hammett base with pK −(2.18 ± 0.11),[2] and with other bicyclic and steroidal dienones.[9] With 6-*epi*-α-santonin (5) there is more of a problem. Because it rearranges very rapidly at high acidities, the plots of u.v. absorbance against acidity could not be extended far enough to allow reliable corrections for medium effects.[8] Moreover, any heat of mixing will affect the extrapolation of the kinetic line to the time of mixing and give a low absorbance value. The use of absorbance ratios may reduce, but not eliminate, the latter errors. However, the plots for 6-*epi*-α-santonin of molar absorbance, ε, at three wavelengths, and their ratios against acidity, are identical with those for α-santonin, and we believe the protonation equilibria and pK values are also identical. The values given in Table 6 assume this.*

An independent estimate of 6-*epi*-α-santonin's protonation behaviour is given by analysing [7] the variation with acidity of the rate constant, k_{obs}. This is made possible by our fortunate ability to measure rates over a range of acidity representing very little up to virtually complete protonation. The derived

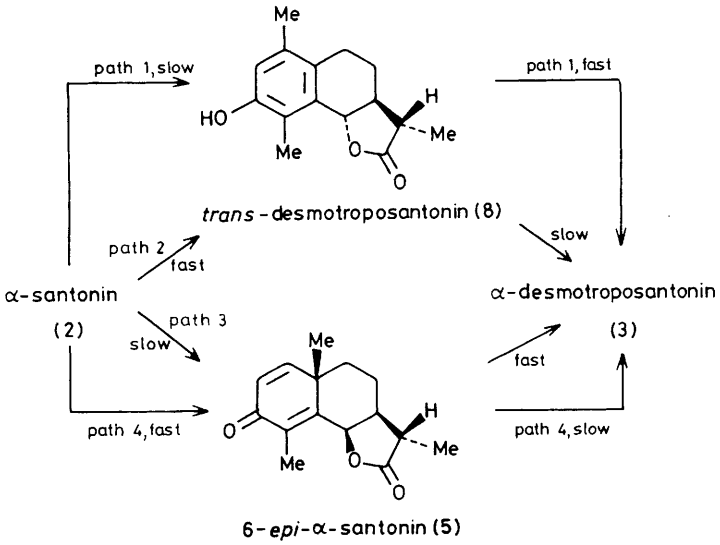
* Use of the raw absorbance data suggests that $(H_0)_{\frac{1}{2}}$ is −3.95 ± 0.10, and m_0 = 0.54 ± 0.02. Allowance for a modest medium effect, as for α-santonin, changes $(H_0)_{\frac{1}{2}}$ little, but m_0 and therefore the pK value quite drastically.

Table 6. Basicity measurements in aqueous sulphuric acid at 25.0 °C

Compound	λ/nm [a]	$-(H_0)_{\frac{1}{2}}$ [b,c]	m_0 [c]	$-pK$ [d]
(2)	250,* 268, 310	3.24 ± 0.1	0.95 ± 0.05	3.1 ± 0.1
(5)	250,* 268, 310	3.2 ± 0.1	0.95 ± 0.05	3.1 ± 0.1
	Kinetics †	3.36 ± 0.1	0.88 ± 0.03	3.0 ± 0.1
(6)	250,* 268, 310	2.23 ± 0.3	0.9 ± 0.1	1.96 ± 0.12
(I; R = Me, R′ = H) [e]		2.18 ± 0.11	1.02 ± 0.10	2.18 ± 0.11
(I; R = R′ = H) [f]		2.14 ± 0.06	0.77 ± 0.04	1.7 ± 0.1
6-methyl-(I; R = R′ = H) [f]		1.95 ± 0.12	1.02 ± 0.04	2.0 ± 0.2

[a] Wavelengths used for the measurements. [b] Half-protonation acidity on the Hammett acidity function, H_0, using the scale of C. D. Johnson, A. R. Katritzky and S. A. Shapiro, *J. Am. Chem. Soc.*, 1969, **91**, 6654. [c] Values in equation (ii). [d] Estimate of thermodynamic pK, taken to be m_0 $(H_0)_{\frac{1}{2}}$: see equation (ii). [e] Values from ref. 2. [f] Values from ref. 9.

* Moderately strong medium effect at this wavelength. † Calculated from rate constants; see text.



Scheme 3.

pK value (−2.95 ± 0.10) is in excellent agreement with that given above, and strongly supports our conclusions there, and the view that the monocation of the dienone function is the kinetically active species, as shown in the kinetic scheme (Scheme 2).

Discussion.—The conversion of α-santonin into α-desmotroposantonin requires a dienone–phenol rearrangement in ring *A*, and a stereochemical isomerisation of the lactone ring at C-6 (see Scheme 3). Path 1 assumes a rate-determining dienone–phenol rearrangement to an abnormal stereoisomer, *trans*-α-desmotroposantonin (8), then fast epimerisation at C-6. Path 2 goes *via* the same intermediate, but by a fast rearrangement followed by slow epimerisation. In paths 3 and 4 the stereochemical change to 6-*epi*-α-santonin is assumed to occur first, and the dienone–phenol rearrangement follows.* At all acidities, path 4 is excluded, because *epi*-santonin rearranges much faster than does santonin. Path 2 is also excluded because it would lead to an accumulation of *trans*-desmotroposantonin which would be seen easily by ^{1}H n.m.r. spectroscopy of samples quenched after partial reaction. This was not observed. The progress of the reaction was followed using the integration of vinylic *vs.* phenolic aromatic protons, and of *trans- vs. cis*-coupled signals due to 6-H: there was no discrepancy between these. Furthermore, the rate measured by u.v. spectroscopy, which is based on the loss of the characteristic strong dienone absorption, would be significantly greater than that measured using ^{1}H n.m.r. spectroscopy. Again, this is not found.

Paths 1 and 3, both of which assume a slow step followed by a fast one, are more difficult to distinguish. Path 3 could be consistent with the relative rearrangement rates found for α-santonin and *epi*-santonin. Path 1 is also chemically reasonable. The literature contains a capricious [13] preparation of *trans*-α-desmotroposantonin acetate,[14] and it was found that an attempt to release *trans*-α-desmotroposantonin from its sodium salt resulted in immediate epimerisation at C-6.[14] We believe path 1 to apply at high acidities ($H_0 < -3$; >46% H_2SO_4) for two overwhelming reasons. First, the very close similarity in rates for α-santonin, its lactone-free analogue (6), and the simpler analogue (1; R′ = H), and the close parallelism of their plots of log k_{obs} or log k_1 against acidity, indicate that the reactions all involve the same rate-determining step, which is the *A*-1 migration of a methyl group in a dienone–phenol rearrangement. This conclusion is supported by the close similarity of the activation parameters for α-santonin, for (6), and for the methyl migration (by path A) in the *trans*-6-methyl derivatives of (I; R = R′ = H) [9] (see Table 5).

At low acidities the form of plots of log k_1 against acidity for α-santonin, and the value of the Bunnett and Olsen par-

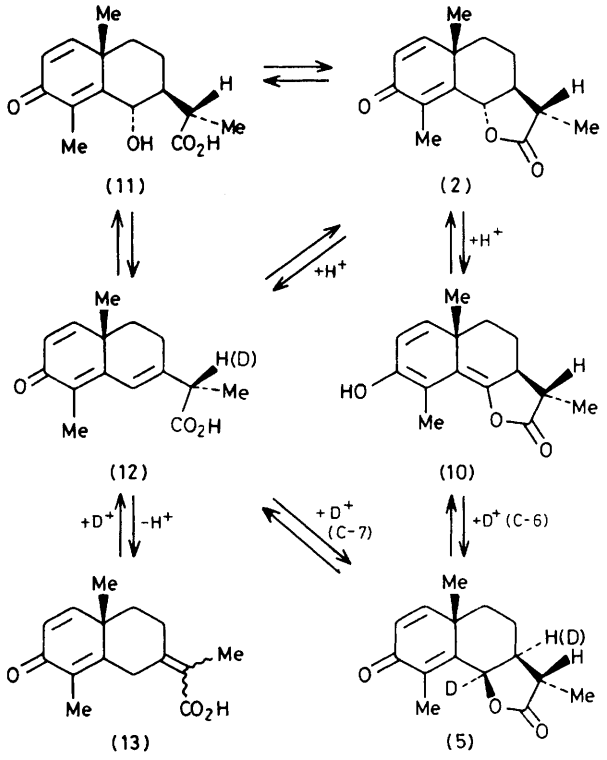
* Path 4 is known to apply under the conditions used to prepare 6-*epi*-α-santonin from α-santonin, using anhydrous HCl in dimethylformamide (see Experimental section).

ameter φ indicate the intrusion of a different mechanism having water as a nucleophile. However, to gain useful φ values we must correct k_{obs} to k_1 using a basicity equilibrium appropriate to the part of the molecule which is now protonated to give the reactive species. If we assume that the lactone ring is protonated in about the same manner as many other ester groups, we can take a pK value close to that of α-santonin and a value of m_0 [see equation (ii)] around 0.6, as was done by Yates [15] and Lee [16] and their co-workers. This gives a rough line at low acidities with φ about 0.3, again implying [10] a rate-determining attack by water on a protonated species. It seems most probable that the rate-determining reaction is the lactone epimerisation at C-6, followed by the more rapid rearrangement of the 6-*epi*-α-santonin, as shown in path 3 of Scheme 3. Further studies of this reaction are in progress.

We now consider the reasons for α-santonin and 6-*epi*-α-santonin not showing reaction by path C of Scheme 1, and for the analogue (6) showing not more than 10% of this path. The studies of Hirakura and his co-workers are relevant here. It was found [6] that (9; R′ = *cis*-CH_2CO_2H) rearranged predominantly by path A in 50% sulphuric acid, along with a trace of path B. Its stereoisomer (9; R′ = *trans*-CH_2CO_2H) rearranged mainly by paths C (40% of isolated yield) and A 24%), with a trace of path B. In contrast, similar rearrangement of (1; R′ = *cis*- or *trans*-CH_2CO_2H) gave a single product, assumed to arise *via* path A. To summarise the position, in (9), when the 4- and 7-group are H, paths A, B, and C occur.[1,2,6,17] A 4-methyl group suppresses path B, and leaves paths A and C. Our previous kinetic measurements [2] showed that introducing the 4-methyl group accelerates path A by at least 12 times, but does not affect the rate of path C. If we consider Hirakura's compound (9; R′ = *cis*-CH_2CO_2H) which has a high ratio of path A to path C, and introduce a 4-methyl group to give (1; R′ = *cis*-CH_2CO_2H), the A/C ratio should increase considerably, making path C insignificant. This is the result found for α-santonin and its analogues.

Steric arguments reinforce the previous discussion about the difficulty of reaction by path C. The first step of this path moves the angular methyl group from C-10 to C-5. If ring *B* is chair-like (see later) the new 5-methyl and *cis* group at C-7 will be diaxial, leading to strain. If ring *B* becomes boat-like, the 5-methyl and 8β-H are forced together. Then in the second step of path C, the C-7 group is forced close to the 5-methyl which is, in turn, buttressed by the 4-methyl and 3-hydroxy groups. Thus, the *cis* 7-group and the 4-methyl group both work to slow path C relative to path A. If we consider α-santonin to react with its lactone ring intact, the first intermediate in path C could not have a chair-like ring *B*, which would require the lactone to be fused in a *trans*-diaxial fashion. If ring *B* were boat-like it would still have considerable strain, but in the second (spiran) intermediate the lactone would have to be *trans*-fused onto a cyclopentane ring which would render path C impractical. We will discuss shortly the fact that in 6-*epi*-α-santonin path A is strongly accelerated so that reaction at a normal rate by path C would be unnoticed. The reasons we will advance for this acceleration will possibly be absent in the first migration step of path C, and certainly in the second and third.

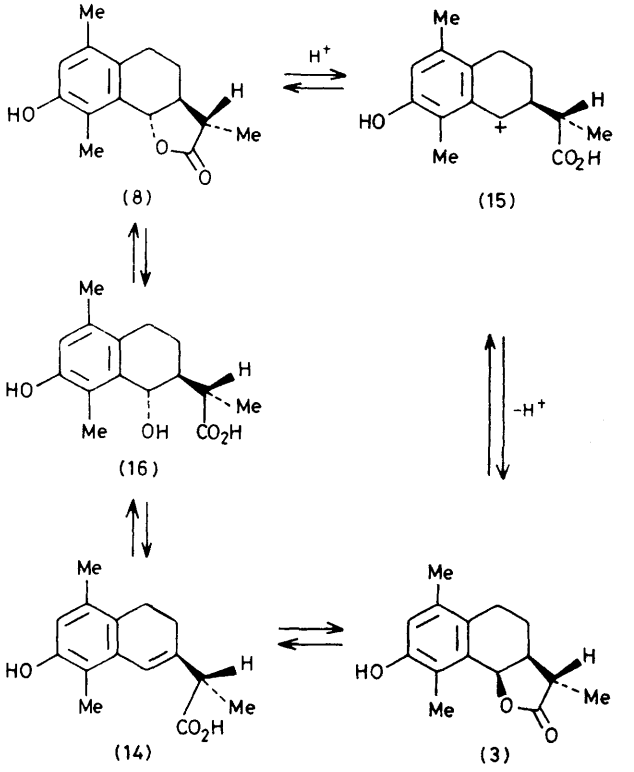
Our results throw some light on other questions implicit in the transformation of α-santonin into α-desmotroposantonin. We rearranged α-santonin in *ca.* 50% by weight D_2SO_4–D_2O at 25 °C and measured the rate and positions of deuterium incorporation by ^1H and ^{13}C n.m.r. spectroscopy, for direct comparison with the results in H_2SO_4. Samples were taken at intervals up to 45 days. Recovered α-santonin appeared not to have incorporated deuterium. The α-desmotroposantonin product retained at least 80% of 6-H, and 7-H also seems to be largely untouched. The 2-proton is 60—65%



replaced by deuterium, but there is no detectable deuterium at 11-H nor in the 13-, 14-, or 15-methyl group. We conclude that, under these conditions, α-santonin does not to any great extent afford α-desmotroposantonin by the route (2) ⟶ (10) ⟶ (5) ⟶ (3). It is, however, possible that this could be a minor path.* Similarly, if α-santonin were to be hydrolysed to (11) we must assume that dehydration to (12) is slower than relactonisation: for if (12) were to be formed during the reaction there would be deuterium incorporation at C-7 of the desmotroposantonin ultimately produced. Similar arguments exclude the formation of (13). It does, however, seem possible that the hydroxy acid (11) could rearrange, by a dienone–phenol reaction, followed by rapid conversion into α-desmotroposantonin as discussed later. In any case, if α-santonin undergoes the dienone–phenol reaction in this way, the equatorial 6-hydroxy group must be without significant effect on the rate, and if it reacts with the lactone ring closed this cannot affect the rate much either.

We now turn to the isomerisation of *trans*- to *cis*-α-desmotroposantonin, which is required to be fast in path 1 of Scheme 3. It is clear from the deuterium incorporation experiments that dihydroartemisic acid (14) cannot be an intermediate because the α-desmotroposantonin formed from it would have a 7-deuterium label. However, (14) has been shown to be the intermediate between α- and β-desmotroposantonin,[5] so it can be formed somewhat more slowly than the reactions we have studied. A model system allows some clarification. The lactone ring of α-santonin could be protonated, with production of the benzylic cation (15) by an $A_{Al}1$ reaction, or water might attack the β-face at C-6 to give

* McMurry and his co-workers (personal communication) have also rearranged α-santonin in deuteriated acids. The position and extent of incorporation of deuterium into α-desmotroposantonin and related products allowed the conclusion that rearrangement in deuteriosulphuric acid in D_2O or acetic anhydride favours path 1 or 2 of Scheme 3.



an $A_{Al}2$ reaction. Acyl–oxygen cleavages will not, themselves, produce the required product unless, for example the alcohol (16) subsequently reacts with cleavage of the C-6,O bond. The acetates of a number of benzylic alcohols have been hydrolysed in aqueous sulphuric acid,[15] the closest analogue to desmotroposantonin being 4-methoxybenzyl acetate.* This is hydrolysed more than 300 times faster than 6-*epi*-α-santonin rearranges to α-desmotroposantonin. Both $A_{Ac}2$ and $A_{Al}1$ mechanisms were observed for the various benzyl acetates, with the latter becoming more important at higher acidities and with better benzylic-cation-stabilising substituents. The 4-methoxybenzyl acetate was hydrolysed at least 90% by the $A_{Al}1$ process in the strongest acid used (35% H_2SO_4).[15] Thus we believe that an $A_{Al}1$ stereochemical inversion of *trans*- to *cis*-α-desmotroposantonin, (8) ⟶ (3), *via* the cation (15), should occur much faster than any rearrangement we have observed.

Finally, we will consider the rapidity of 6-*epi*-α-santonin's rearrangement by path A, as compared with α-santonin and the bicyclic and steroidal analogues which lack the β-*cis*-fused lactone ring. The form of the plots of rate *vs.* acidity shows that the mechanism involves fast, reversible protonation of the dienone carbonyl group, followed by a rate-determining unimolecular (*A*-1) rearrangement, and that the rapidity is due to this cation's high intrinsic reactivity. The constant φ in the Bunnett and Olsen type of correlation (Table 4) can be multiplied [10] by 4.5 to suggest that the cation sheds 2.0 molecules of water on passing to the transition state, whereas those of α-santonin and the other analogues listed shed 1.0 molecule of water. The activation parameters (Table 5), all measured at about the same acidity, which achieves essentially complete protonation, show that 6-*epi*-α-santonin's cation reacts faster because $\Delta H^{\ddagger}$ is lower by about 30 kJ mol^{-1} than for the other compounds, although there is a partially compensating more negative entropy of activation which makes its value of $T\Delta S^{\ddagger}$ more negative by about 10 kJ mol^{-1}. When an allowance [18] is made for *epi*-santonin's loss of an extra molecule of water ($T\Delta S^{\ddagger}$ *ca.* 6 kJ mol^{-1}) the lowering of $\Delta H^{\ddagger}$ may be associated with a decrease in $T\Delta S^{\ddagger}$ of about 16 kJ mol^{-1}. The lactone ring, which must be responsible for the acceleration, is strongly folded over ring *B* of *epi*-santonin. Ring *B* is quite flexible and is believed to exist in a chair-like form with the 6-oxygen pseudo-axially attached, although a boat-form is readily adopted.[13] The cation formed by methyl migration from C-10 to C-1 can be stabilised by overlap of the π-system with either the lone pair electrons from O-17 of the lactone ring or from O-17 and the 18-oxygen atoms of a hydrated lactone. To maximise these stabilising interactions, the lactone ring can fold quite close to ring *A*, with ring *B* in a boat conformation. This high degree of ordering is no doubt responsible for the negative contribution to the entropy of activation. We assume that the transition state resembles the cation formed by methyl migration, which is of higher energy than the dienone-cation (being analogous to a *meta*-protonated phenol as opposed to a *para*-protonated one).[19,20] The lactone ring should thus reduce the activation energy in any case, but it is also better able to interact with the positions of high positive charge density in the rearranged cation (at C-4 and C-10) than in the starting cation (at C-5). In contrast, the α-santonin molecule is held rigidly and rather flat, with a planar cyclohexadienone ring fused to a chair-like ring *B*. The lactone ring has atoms C-6, O-17, C-12, O-16, and C-11 coplanar, with C-7 below the plane.[21] The oxygen attachment at C-6 to O-17 is close to equatorial, with strong delocalisation of one lone pair from O-17 into a π-orbital (over O-17, C-12, and O-18) nearly perpendicular to ring *A*. The remaining lone pair on O-17 is in the plane of rings *A* and *B*, and directed away from them so that no conjugative stabilisation of charge on ring *A* is possible, either in the dienone-cation or the cation produced by the methyl shift of path *A*. Similarly, the stabilisation provided by a hydrated lactone ring is very slight. It is interesting that the base-weakening effect of the lactone group of α-santonin and 6-*epi*-α-santonin (see Table 6) is independent of the stereochemistry. This implies that the axial 6-oxygen (O-17) of *epi*-santonin does not significantly stabilise the dienone-cation relative to the free dienone.

* Desmotroposantonin has $\Sigma\sigma^{+} = -0.71$ for the substituents on the aryl ring; the 4-methoxy group has $\sigma^{+} = -0.78$. We assume that the ability to stabilise a benzylic cation is most important (see the following discussion).

Experimental

^{1}H N.m.r. spectra were recorded at 100 MHz with a Varian XL 100 instrument, and ^{13}C n.m.r. spectra at 15.03 MHz with a JEOL-FX60, both with and without proton decoupling, in deuteriochloroform with tetramethylsilane as internal standard. U.v. spectra were measured with a Pye–Unicam SP8-100 instrument fitted with a thermostatted cell block connected to a Pye–Unicam water circulator, with monitoring of the cell temperature. U.v. data for the dienones and their cations are in Table 7. For most u.v. kinetics and basicity measurements, data were recorded at three or four preselected wavelengths and were printed out by an interfaced Hewlett–Packard HP-97S electronic calculator which also made baseline corrections. Rate constants were calculated for the pseudo-first-order reactions using Swinbourne's graphical method,[22] and a non-weighted least-squares program, or/and programs based on Wiberg's,[23] but written for the HP-97S or, in BASIC, for a CBM 4032 computer. All methods gave the same results. For calculations of basicity parameters the methods described in ref. 8 were used when medium effects were apparent. When the latter were negligible, or could not be estimated (for 6-*epi*-α-santonin) we used a program written

Table 7. U.v. spectra of compounds and their cations

Compound	Form	Acid (wt. %) [a]	$\lambda_{max.}$/nm	$\varepsilon_{max.}$/dm^3 mol^{-1} cm^{-1}
(2)	Neutral	H_2O	244	1.34×10^4
	Cation	69.4 (H_0 − 5.74)	267	1.18×10^4
			313	6.77×10^3
		73.6 (H_0 − 6.40)	268	1.06×10^4
			314	6.19×10^3
(5)	Neutral	H_2O	250	1.46×10^4
		6.8 (H_0 − 0.01)	250	1.54×10^4
	Cation [b]	64.2 (H_0 − 4.94)	270	$(1.10 \pm 0.05) \times 10^4$
			310 ± 1	$(4.0 \pm 0.5) \times 10^3$
(6) [c]		H_2O	246	9.74×10^3
			272sh	6.09×10^3
	Neutral	6.8 (H_0 − 0.01)	255	7.63×10^3
	Cation	73.6 (H_0 − 6.40)	268	9.53×10^3
			318	6.13×10^3
			364sh	1.02×10^3

[a] In water or aqueous sulphuric acid at 25 °C. [b] Fast rearrangement: spectrum regenerated by extrapolation to the time of mixing: ε values are likely to be too small. [c] Using the purified cyclohexylamine salt: the spectrum in water is for reference only.

for the HP-97S calculator which allowed iteration of $(H_0)_{\frac{1}{2}}$, m_0, and ε_{BH^+}, with ε_B being accurately known. This program minimises the sum of squares of deviations of the experimental points from those calculated by equations (ii) and (iii), using a first-order Newton–Raphson technique (see ref. 24 for the general principles). For the reasons given earlier, absorbance (ε) values at selected wavelengths, or their ratios,[12] were used: the results from both methods were similar, but the ratios allowed greater precision.

(−)-α-Santonin, m.p. 172—174 °C (lit.,[4] 171—172 °C) had δ ($CDCl_3$) 6.748 (1 H, d, *J* 9.8 Hz, 1-H), 6.208 (1 H, d, *J* 9.8 Hz, 2-H), 4.860 (1 H, d, *J* 9.5 Hz, of q, *J* 1.5 Hz, axial 6-H), 2.100 (3 H, d, *J* 1.5 Hz, 14-H_3), 2.47 (1 H, d, *J* 11 Hz, of q, *J* 7 Hz, 11-H), 1.355 (3 H, s, 15-H_3), 1.260 (3 H, d, *J* 7.1 Hz, 13-H_3), and complex, 2.0—1.4 (5 H, 7-H and 8- and 9-H_2). This agrees closely with the reported spectrum.[25] The ^{13}C n.m.r. spectrum agrees excellently with the published data.[26] However, since these were reported for C_6D_6 solution, we give our values: δ ($CDCl_3$) 186.21 [C(3)O], 177.70 (lactone C=O, 12-C), 155.22 (C-1), 151.45 (C-5), 128.32 (C-4), 125.66 (C-2), 81.35 (C-6), 55.54 (C-7), 41.45 (C-10), 40.87 (C-11), 37.81 (C-9), 25.08 (angular Me), 22.93 (C-8), 12.47 (13-Me), and 10.85 (14-Me).

(−)-6-*epi*-α-Santonin, prepared using the developed procedure [27] based on that in ref. 28, had m.p. 104—107 °C (from ethyl acetate; lit.,[27] m.p. 103—104 °C; lit.,[28] 105 °C; lit.,[29] 102—105 °C). The ^1H n.m.r. spectrum, δ 6.74 (1 H, d, *J* 10 Hz, 1-H), 6.20 (1 H, d, *J* 10 Hz, 2-H), 5.54 (1 H, d, *J* 4.5 Hz, equatorial 6-H), 2.55 (1 H, q, *J* 8 Hz, 11-H), 2.04 (3 H, s, 14-H_3), 1.38 (3 H, d, *J* 8 Hz, 13-H_3), 1.28 (3 H, s, 15-H_3), and 2.3—1.5 (5 H, complex, 7-H and 8- and 9-H_2), agrees closely with those reported [25,27] and allows very clear distinction from α-santonin. The ^{13}C n.m.r. spectrum agrees closely with the published data: [26] δ ($CDCl_3$) 186.01 [C(3)O], 179.51 (lactone C=O, C-12), 157.30 (C-1), 148.53 (C-5), 137.48 (C-4), 125.85 (C-2), 76.21 (C-6), 43.79 and 43.40 (C-7 and -11), 39.18 (C-10), 34.43 (C-9), 24.82 (angular Me), 23.00 (C-8), 14.68 (13-Me), and 10.98 (14-Me).

(−)-3-*Oxoeusantona*-1,4-*dienic Acid* (6).—Reduction of (−)-6-*epi*-α-santonin [27,28] with zinc dust gave compound (6) as an oil, which was sometimes used as such for preparative rearrangements; δ 8.20 (1 H, br, CO_2H), 6.71 (1 H, d, *J* 9 Hz, 1-H), 6.20 (1 H, d, *J* 9 Hz, 2-H), 1.90 (3 H, d, *J* 1.5 Hz, 14-H_3), 1.25 (3 H, d, *J* 7 Hz, 13-H_3), and 1.22 (3 H, s, 15-H_3), in good agreement with the published values.[27] The ^{13}C n.m.r. spectrum had δ 186.86 (dienone carbonyl, C-3), 180.81 (CO_2H), 159.84 (dienone, C-5), 157.04 (dienone, C-1), 129.43 (dienone, C-4), 126.05 (C-2), 44.77 (*C*HMe, C-11), 41.91 (C-7), 40.41 (angular C-10), 37.62 (9-CH_2), 31.97 (8-CH_2), 23.98 (6-CH_2), 23.32 (15-Me), 14.10 (13-Me), and 10.46 (14-Me). These values are consistent with those for analogous compounds.

Cyclohexylamine Salt of the Acid (6).—Prepared as in ref. 27, but recrystallised from ethyl acetate, the salt had m.p. 123—125 °C (lit.,[27] 122—124 °C) (Found: C, 72.8; H, 9.7; N, 4.3. Calc. for $C_{21}H_{33}NO_3$: C, 72.6; H, 9.6; N, 4.0%), δ 6.73 (1 H, d, *J* 10 Hz, 1-H), 6.20 (1 H, d, *J* 10 Hz, 2-H), 6.4—6.0 (3 H, br, solvent- and temperature-dependent, NH_3^+), 1.88 (3 H, s, 14-H_3), 1.21 (3 H, s, 15-H_3), and 1.10 (3 H, d, *J* 7 Hz, 13-H_3).

Preparative Rearrangements of α-Santonin.—(a) *In acetic anhydride.* To (−)-α-santonin (200 mg) in acetic anhydride (5 cm^3) was added conc. H_2SO_4 (1 small drop). After 6 h at 25 °C, water (15 cm^3) was added: the mixture was extracted with dichloromethane (4 × 20 cm^3) and the extracts were washed once with water (5 cm^3), dried ($MgSO_4$), and evaporated. The ^1H n.m.r spectrum of this crude oil showed all the expected peaks for (−)-α-desmotroposantonin acetate, and agreed fully with the quoted spectrum (±0.04 p.p.m.).[25] A very small peak at δ 1.28, assumed to be half a methyl doublet, is assigned to a trace of the β-isomer. The ^{13}C n.m.r. spectrum agreed fully (±0.15 p.p.m.) with that published for (−)-α-desmotroposantonin acetate,[26] and showed no additional signals. The data for $CDCl_3$ solution are: δ 179.25 (lactone C=O, C-12), 169.52 (acetate C=O), 147.49 (C-3), 134.82 (C-5), 134.04 (C-10), 131.31 (C-1), 129.04 (C-4), 123.84 (C-2), 75.43 (C-6), 41.65 (C-7), 40.41, (C-11), 23.98 (C-8), 23.39 (C-9), 20.73 (1-Me), 19.49 (acetate Me), 14.42 (C-13), and 12.08 (C-14).

(b) *In 50% sulphuric acid at* 100 °C. Reaction of (−)-α-santonin for 30 min followed by dilution with water and extraction and work-up as in (a) gave a white solid, m.p. >240 °C (decomp.) [lit.,[4] m.p. for (+)-β-desmotroposantonin, 260 °C with rapid heating]. The material was too insoluble to give a ^1H n.m.r. spectrum in $CDCl_3$. In CD_3SOCD_3 it had δ 8.96 (1 H, s, OH), 6.66 (1 H, s, 2-H), 5.35 (1 H, d, *J* 4.2 Hz, 6-H, *cis*-coupled), 3.10 (1 H, d of q, *J* 6.5—7 Hz, 11-H), 2.8—2.2 (3 H, complex, 7-H and 9-H_2), 2.12 (6 H, s, 1- and 4-Me), 1.6—2.0 (2 H, complex, 8-H_2), and 1.09 (3 H, d, *J* 7 Hz,

13-H_3). No peaks attributable to products other than β-desmotroposantonin were observed (below 2%).

(c) *In* ca. 50% *sulphuric acid at* 25 °C. To samples of α-santonin (30—80 mg each) aq. H_2SO_4 (47.8% by wt., 3.0 or 4.0 cm^3) was added and the tubes were sealed, then placed for a few minutes in a small ultrasonic cleaning bath containing cold water (to aid dissolution). They were kept at 25 °C for various times, and occasionally returned to the ultrasonic bath. Separate work-up by dilution with water (5 or 6 cm^3) and extraction, *etc.*, as in (a) gave crude samples which were examined by ^1H and ^{13}C n.m.r. spectroscopy. In each case the recoveries were virtually quantitative and the only peaks present were due to α-santonin and α-desmotroposantonin. Other compounds (particularly 6-*epi*-α-santonin) or additional peaks were absent at the 2% level. Integration of the ^1H n.m.r. spectrum (vinyl/phenyl, and *trans*/*cis*-fused lactone 6-H peaks, and the methyl peaks) was used to give approximate kinetic data (see Table 1). Examples of the results are: at 192 h, 32 ± 2% reacted; 260 h, 47 ± 4%; 548 h, 63 ± 3%. In another acid (42.8%, H_0 − 2.67), 18 ± 1% had reacted in 432 h. A similar sample which was briefly heated to 100 °C contained both α-desmotroposantonin (soluble in $CDCl_3$, ^1H n.m.r. as in a pure sample) and β-desmotroposantonin (insoluble in $CDCl_3$). The mixture had δ (CD_3SOCD_3) for the α-desmotroposantonin, 8.99 (1 H, OH), 6.68 (1 H, s, 2-H), 5.60 (1 H, d, *J* 6.0 Hz, 6-H, *cis*-coupled), 3.38 (1 H, br, 11-H), 2.12 (3 H, s, aryl-Me), 2.08 (3 H, s, aryl-Me), 1.26 (3 H, d, *J* 7.1 Hz, 13-H_3), and 2.2—2.8 (br). All the peaks quoted above for the β-isomer were also present in the spectrum of the mixture (α : β ratio *ca.* 4 : 3). The samples of α-desmotroposantonin had δ ($CDCl_3$) 6.65 (1 H, s, 2-H), 5.60 (1 H, d, *J* 5.5—6 Hz, 6-H, *cis*-coupled), 2.24 (3 H, s, 1-Me), 2.14 (3 H, s, 4-Me), 1.37 (3 H, d, *J* 7 Hz, 13-H_3), and 2.4—2.7 and 1.7—2.0 (br, complex, 7-, 8-, 9-, and 11-H): this is very similar to the spectrum of the acetate. No other peaks were evident. The ^{13}C n.m.r. spectrum has δ ($CDCl_3$) 179.68 (lactone C=O, C-12), 152.10 (C-3), 134.50 (C-5), 130.92 (C-1), 128.13 (C-10), 122.54 (C-4), 117.73 (C-2), 75.95 (C-6), 41.91 (C-7), 40.48 (C-11), 23.65 (C-8 and -9), 19.49 (1-Me), 14.49 (C-13), and 11.43 (C-14). The assignments for the aryl ring atoms 1, 4, 5, and 10 are linked to those of the acetate using tabulated shift parameters [30] on peaks of similar relative intensities.

(d) *In* 50% *deuteriated sulphuric acid.* Deuteriosulphuric acid and D_2O were mixed to give a density corresponding [31] to 7.0M, $D_0 = H_0 = -3.25$. A sample of α-santonin (19.2 mg) in the acid (0.7 cm^3), and a trace of $Me_4N^+Cl^-$ as internal standard, was sealed in an n.m.r. tube, subjected to brief ultrasonic mixing, and kept at 25 °C with occasional shaking. The ^1H n.m.r. spectrum was recorded after 1 h, and 1, 4, 11, 44, and 45 days. As reaction proceeded the product came out of solution. Integration suggested that the α-santonin which remained in solution was not incorporating deuterium, and that the product was too insoluble to give detectable spectral peaks even at high scale expansion. After 45 days the mixture was worked up by the addition of D_2O (1.5 cm^3) and extraction with $CDCl_3$ (4 × 1.5 cm^3); the extracts were washed with D_2O (1.0 cm^3), dried ($CaSO_4$), and evaporated. The ^1H n.m.r. spectrum showed <5% of santonin to remain, and the product to be α-desmotroposantonin. The peaks due to 13-, 14-, and 15-H_3 showed no deuterium incorporation; 11-H and 7-H are not exchanged because the visible multiplets to which they couple (13-H_3, and 6-H) showed no collapse. However, 60—65% of 2-H had been replaced by deuterium, and some of 6-H (14 ± 5%) had been also. The ^{13}C n.m.r. spectrum was consistent with this result.

Preparative Rearrangement of (−)-6-epi-α-*Santonin.*—The *epi*-santonin (89.0 mg) in 50% aq. H_2SO_4 (8.0 cm^3) was shaken and kept for 120 min at 25 °C (>6 half-lives). Work-up by the addition of water (10 cm^3), extraction with chloroform (5 × 10 cm^3), and then as for α-santonin (earlier), gave a quantitative recovery of a white solid. The ^1H and ^{13}C n.m.r. spectra ($CDCl_3$) showed all the peaks and intensities found for (−)-α-desmotroposantonin, and a small amount of unchanged *epi*-α-santonin. A trace of insoluble white solid (<5% of the total) may have been (+)-β-desmotroposantonin, but this was clearly absent in the spectra.

Preparative Rearrangements of (−)-3-*Oxoeusantona*-1,4-*dienic Acid* (6) *and its Cyclohexylamine Salt.*—(a) *The acid* (6). The crude acid (6) (180 mg, containing a trace of acetic acid as the only impurity shown in the ^1H n.m.r. spectrum) and aq. sulphuric acid (5 cm^3; 76% w/w) was heated to 70 °C over 6 h. After the usual work-up ($CHCl_3$), evaporation gave mainly 2-(1,2,3,4-tetrahydro-7-hydroxy-5,8-dimethylnaphthalen-2-yl-propionic acid (7; R = $CHMeCO_2H$) (112 mg, 62%) as a pale yellow solid (Found: *m*/*z* 248.138. Calc. for $C_{15}H_{20}O_3$: *M*, 248.141). A little material was insoluble in chloroform. The ^1H n.m.r. spectrum ($CDCl_3$) had δ 6.64 (0.1 H, s, aryl H), 6.46 (0.9 H, s, aryl H), 2.91—2.37 (4 H, br, 1- and 4-H_2), 2.13 (3 H, s, aryl Me), 2.06 (3 H, s, aryl Me), 1.78 (<1 H, d, *J* 7 Hz, unassigned), 1.26 (3 H, d, *J* 7 Hz, side-chain CH*Me*), 1.26 (small s), a broad low, complex around δ 1.2, and a broad hydroxy peak removed by D_2O. The spectrum is virtually identical with that given by the products of later rearrangements. The ^{13}C n.m.r. spectrum showed δ ($CDCl_3$) 181.85 (CO_2H), 151.00 (C-7), 135.73 (angular C-8a), 134.24 (quaternary C-5), 127.09 (quaternary C-4a), 119.29 (quaternary C-8, *ortho* to OH), 114.42 (aromatic C-6, *ortho* to OH), 44.25 (C-2), 36.97 (side-chain CH), 32.03 (probably C-1), 29.69 (minor isomer impurity?), 26.64 (probably C-3), 25.53 (probably C-4), 19.43 (5-Me), 15.20 (side-chain Me), and 10.78 (8-Me).

(b) *On the salt of* (6). Samples of the cyclohexylamine salt of acid (6) (22—30 mg) were dissolved in aquous sulphuric acid (3.0 cm^3; 36.7% w/w) and kept at 25 °C for periods of 14, 29, and 70 days. Work-up using $CHCl_3$ and evaporation in the usual way gave recoveries of 85—100% of products whose ^1H n.m.r. spectra were recorded. These showed the starting acid (6) to diminish, and the appearance of two new products. The rate of reaction was calculated as given in Table 3 for the formation of the major product, using the vinylic and aryl proton peaks, and the methyl peak integrations. The spectrum assigned to the two products was virtually identical with that given by the rearrangement product from (6) itself under more vigorous conditions, with small chemical shift differences (<0.05 p.p.m.) due, we believe, to the presence of unchanged starting material. The ratio of products is about 10 : 1.

Acknowledgements

Professor T. B. H. McMurry, and Macfarlan Smith Ltd. are thanked for samples of 6-*epi*-α-santonin and of santonin used in the early stages of this study.

References

1 A. J. Waring, J. H. Zaidi, and J. W. Pilkington, *J. Chem. Soc., Perkin Trans. 1*, 1981, 1454.
2 A. J. Waring, J. H. Zaidi, and J. W. Pilkington, *J. Chem. Soc., Perkin Trans. 2*, 1981, 935.
3 A. Andreocci and P. Bertolo, *Ber.*, 1898, **31**, 3131.
4 The early literature is summarised by J. Simonsen and D. H. R. Barton, ' The Terpenes,' vol. III, Cambridge University Press, Cambridge, 2nd edn., 1952.
5 A. J. N. Bolt, M. S. Carson, W. Cocker, L. O. Hopkins, T. B. H.

McMurry, M. A. Nisbet, and S. J. Shaw, *J. Chem. Soc. C*, 1967, 261.
6 M. Hirakura, M. Yanagita, and S. Inayama, *J. Org. Chem.*, 1961, **26**, 3061.
7 A. J. Waring, *J. Chem. Soc., Perkin Trans. 2*, 1979, 1029.
8 K. L. Cook and A. J. Waring, *J. Chem. Soc., Perkin Trans. 2*, 1973, 84.
9 M. J. Hughes and A. J. Waring, *J. Chem. Soc., Perkin Trans. 2*, 1974, 1043.
10 J. F. Bunnett and F. P. Olsen, *Can. J. Chem.*, 1966, **44**, 1899.
11 J. F. Bunnett, in ' Investigation of Rates and Mechanisms of Reactions,' vol. VI of ' Techniques of Chemistry,' ed. A. Weissberger, 1974, 3rd edn., ch. IV.
12 A. J. Waring, *Anal. Chim. Acta*, 1983, **153**, 213.
13 C. R. Narayanan and N. K. Venkatasubramanian, *J. Org. Chem.*, 1968, **33**, 3156.
14 W. Cocker and T. B. H. McMurry, *J. Chem. Soc.*, 1955, 4430.
15 R. A. McClelland, T. A. Modro, M. F. Goldman, and K. Yates, *J. Am. Chem. Soc.*, 1975, **97**, 5223.
16 D. G. Lee and M. H. Sadar, *J. Am. Chem. Soc.*, 1974, **96**, 2862.
17 P. J. Kropp, *Tetrahedron Lett.*, 1963, 1671.
18 L. L. Shaleger and F. A. Long, *Adv. Phys. Org. Chem.*, 1963, **1**, 1.
19 D. M. Brouwer, E. L. Mackor, and C. MacLean, in ' Carbonium Ions,' eds. G. A. Olah and P. von R. Schleyer, Wiley, New York, 1970, vol. 2, ch. 20.
20 K. L. Cook, M. J. Hughes, and A. J. Waring, *J. Chem. Soc., Perkin Trans. 2*, 1972, 1506 and references therein.
21 J. D. M. Asher and G. A. Sim, *J. Chem. Soc.*, 1965, 6041.
22 E. S. Swinbourne, *J. Chem. Soc.*, 1960, 2371.
23 K. B. Wiberg, in ' Investigation of Rates and Mechanisms of Reactions,' vol. VI of ' Techniques of Chemistry,' ed. A. Weissberger, 1974, 3rd edn., ch. XIII.
24 K. J. Johnson, ' Numerical Methods in Chemistry,' Dekker, New York and Basel, 1980, particularly ch. 5.
25 J. T. Pinhey and S. Sternhell, *Austr. J. Chem.*, 1965, **18**, 543.
26 G. P. Moss, P. S. Pregosin, and E. W. Randall, *J. Chem. Soc., Perkin Trans. 1*, 1974, 1525.
27 E. Piers and K. F. Cheng, *Can. J. Chem.*, 1968, **46**, 377.
28 H. Ishikawa, *J. Pharm. Soc. Jpn.*, 1956, **76**, 504 (*Chem. Abstr.*, 1957, **51**, 303d).
29 M. Nakazaki and K. Naemura, *Bull. Chem. Soc. Jpn.*, 1964, **37**, 1842.
30 E. Pretsch, J. Seibl, W. Simon, T. Clerc, ' Tabellen zur Strukturaufklärung organischer Verbindungen mit spektroskopischen Methoden,' Springer-Verlag, Berlin, Heidelberg and New York, 2nd edn., 1981.
31 J. H. Freeman and C. E. C. Richards, Report of British Atomic Energy Research Establishment, AERE GP/R, 1958, 2479; E. Högfeld and J. Bigeleisen, *J. Am. Chem. Soc.*, 1960, **82**, 15; J. Sierra, M. Ojena, and P. A. H. Wyatt, *J. Chem. Soc. B*, 1970, 1570.

Received 5th May 1983; *Paper* 3/721