321. *Sesquiterpenes. Part II.*[1] *The Double-bond Derivatives of Santonin.*

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The many reported double-bond derivatives of santonin, from chlorination, epoxidation, and subsequent changes, have been re-examined and stereochemical structures assigned to them by physical methods and conformational analysis. Several unexpected and novel rearrangements in the series have been uncovered and are discussed.

IN connexion with studies on the rearrangements of decalin to perhydroazulenes, we required certain derivatives of santonin having a substitution in the 1-position * and so were led to examine the various derivatives of the double bonds of santonin. It soon appeared that, although much evidence on these derivatives exists,[4] previous investigators had disregarded the complexity of the problem. Thus there are *a priori* sixteen possible vicinal chlorohydrins of santonin: eight from each double bond, four with chlorine α and four with chlorine β to the 3-ketone group. There are forty possible dihydrochlorohydrins, and, further, because of the extensive substitution both boat and chair forms of ring A for each of the forty must be considered. Three chlorohydrins of santonin and their corresponding saturated dihydro-derivatives have been reported, as well as two santonin dichlorides and two epoxides.[4]

At the outset of our work, it seemed clear from the interrelations in the literature that

* Steroid numbering and the αβ-convention of steroids are used. However, Greek letters used to designate the different epoxides and chlorohydrins by the original authors are retained; fortuitously they indicate configuration correctly (see below). The Greek letter designations of the tetrahydrosantonins are those apparently in current common use,[2,3] α- and γ-tetrahydrosantonin being *trans*-decalins with an equatorial and an axial 4-methyl group, respectively, and β- and δ-tetrahydrosantonin *cis*-decalins with an equatorial and an axial 4-methyl group, respectively.

[1] Part I, *Tetrahedron*, 1959, **7**, 82.
[2] Banerji, Barton, and Cookson, *J.*, 1957, 5041.
[3] Djerassi, "Optical Rotatory Dispersion," McGraw-Hill, New York, 1960, *e.g.*, p. 80.
[4] For a review see Simonsen and Barton, "The Terpenes," Vol. III, Cambridge Univ. Press, 1952, pp. 249 *et seq.*, where the formulæ on pp. 276—278 summarize previous formulations, although the need for revision was appreciated (cf. p. 277).

all these known compounds were formed by reaction at the 1,2-double bond, as formulated.[4] We were led, however, to question this by a report [5] that the α-epoxide showed olefinic hydrogen in the nuclear magnetic resonance spectrum. A definitive conclusion, then, as to the position of the remaining double bond and hence of the substituents was imperative and depended first on possession of the model mono-olefins, dihydrosantonin A (V) ($\Delta^{4,5}$) which was known,[2] and dihydrosantonin B (III) ($\Delta^{1,2}$). The latter was made by conversion of α-tetrahydrosantonin (I) of known *trans*-decalin stereochemistry [6] into the 2-bromo-compound (II; X = Br), which was then dehydrobrominated with collidine. These conversions and others discussed below are represented on the accompanying chart and show the stereochemical assignments made in this work.

The so-called α-epoxide (the major epoxidation product of santonin) and its two related chlorohydrins can now be shown to be formed by reaction at the 4,5-double bond as follows. The ultraviolet spectra (see Table 1) of dihydrosantonin A (245 mμ, calc.[7]

TABLE 1.

Spectra of santonin and its derivatives.

Formula	Compound	Ultraviolet *	Infrared *			
VI	Santonin	240 (4·12); 260 (3·93)s	1780	1665	1635	1615
V	Dihydrosantonin A	245 (4·19)	1780	1667	1622	
III	Dihydrosantonin B	227 (4·03)	1775	1675		
I	α-Tetrahydrosantonin	—	1770	1710		
	γ-Tetrahydrosantonin	—	1772	1705		
Cf. II	2α-Chloro-α-tetrahydrosantonin	—	1775	1732		
Cf. II	2α-Bromo-α-tetrahydrosantonin	—	1770	1727		
XVI	2-Chlorosantonin	251 (4·19)	1785	1655	1620	
IX	Santonin chlorohydrin	229 (3·94)	1780	1688		
X	Santonin α-epoxide	223(3·95)	1780	1685		
XI	Santonin α-isochlorohydrin	235 (3·88)	1775	1679		
XIII	Dihydrosantonin chlorohydrin	—	1780	1730		
XIV	Dihydrosantonin α-epoxide	—	1775	1700		
XV	Dihydrosantonin α-isochlorohydrin	297 (1·54)	1773	1717		
VII	Santonin dichloride	251 (4·10)	1780	1694	1625	
XII	Dihydrosantonin dichloride	—	1770	1727		
XVII	2α-Chlorodihydrosantonin A	248 (4·16)	1780	1690	1625	

* Ultraviolet spectra in 95% ethanol recorded as $\lambda_{max.}$ in mμ (log ε); infrared spectra in chloroform, all peaks in the double-bond region recorded in $cm.^{-1}$.

254 mμ) and B (227 mμ, calc. 227 mμ) show clearly the differences in substitution on the olefinic bonds, while the spectra of the chlorohydrin (229 mμ), α-epoxide (223 mμ), and α-isochlorohydrin (235 mμ) attest the presence in these compounds of the 1,2-double bond, as in dihydrosantonin B. The nuclear magnetic resonance spectra confirm this, for santonin, dihydrosantonin B, and the epoxide show a pair of doublets ($J_{AB} \sim 10$ c.p.s.) in the 3—4 τ region (see Table 2) owing to the pair of *cis*-olefinic hydrogen atoms which are mutually split.[8] Tetrahydrosantonin, dihydrosantonin A, and the dihydroepoxide show no absorption in this region. Further, the peak for a methyl group attached to a double bond appears at 7·9—8·1 τ in santonin, monochlorosantonin, and dihydrosantonin A, but is shifted to 8·44 in the epoxide and dihydroepoxide, where the methyl is attached to a carbon bearing the epoxide, and to 8·63 in the saturated tetrahydrosantonin and in dihydrosantonin B. Further, the chlorohydrins are unaffected by chromic acid, which supports their formulation as tertiary, not secondary, alcohols. Finally, the α-dihydroepoxide was made from dihydrosantonin A and found to be identical with that made by

[5] G. Buchi, personal communication.

[6] Djerassi, Riniker, and Riniker, *J. Amer. Chem. Soc.*, 1956, **78**, 6362; Yanagita and Futaki, *J. Org. Chem.*, 1956, **21**, 949; Yanagita and Ogura, *ibid.*, 1957, **22**, 1092; Cocker and McMurry, *J.*, 1956, 4549.

[7] Dorfman, *Chem. Rev.*, 1953, **53**, 47.

[8] Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon, London, 1959, Chapters 4 and 6.

TABLE 2.

Proton magnetic resonance spectra.*

Formula	Compound						
VI	Santonin	3·13	3·38	3·75	4·01	7·93	8·67
V	Dihydrosantonin A	—	—	—	—	8·12	8·63
III	Dihydrosantonin B	3·14	3·39	4·02	4·27	8·62	8·87
I	α-Tetrahydrosantonin	—	—	—	—	8·63	8·90
X	Santonin α-epoxide	3·84	4·11	4·35	4·61	8·42	8·82
XIV	Dihydrosantonin α-epoxide	—	—	—	—	8·45	8·88
VII	Santonin dichloride	5·23	5·51	5·77	6·05	7·97	8·74
XVI	2-Chlorosantonin	3·36	—	—	—	8·00	8·66
XVII	2α-Chlorodihydrosantonin A *	—	—	—	—	7·90	8·74

* Values of relevant peaks in τ-units; spectra in $CDCl_3$ at 40 mc.; the spectrum of 2α-chlorodihydrosantonin A was too weak, owing to low solubility, to afford the expected triplet at 5—6 τ. The first four peaks shown are in each case a pair of doublets of total relative intensity of about unity, whereas the last two peaks are usually in relative intensity ratio of about 3 : 6.

catalytic hydrogenation of the olefin in santonin α-epoxide.[9] The conclusion that these derivatives arise by attack on the 4,5-double bond is therefore inescapable.

The chlorohydrins of santonin especially require clarification because of their unusual chemistry. The chlorohydrin (IX) is formed as the sole product in good yield by stirring a suspension of santonin (VI) in chlorine-water for some days. It is in turn converted into the α-epoxide (X) by warm aqueous alkali hydroxide (but not by cold pyridine). The α-epoxide yields a different product, the α-isochlorohydrin (XI), on dissolution in hydrochloric acid, and this is immediately reconverted into the α-epoxide by cold pyridine. The major product of treatment of the α-epoxide with hydrochloric acid is, however, santonin dichloride (VII), which is also produced by chlorinating santonin in chloroform. The same interconversions were reported [4,9] to occur in the dihydro-series, each dihydrocompound being made by hydrogenation of the parent.

The existence of two chlorohydrins related to the one epoxide will be considered first. The evidence for chlorine α to the 3-ketone group in each compound is provided by their negative periodate tests [10] and the typical equatorial α-chloro-ketone shift [11] in the infrared spectrum of 2α-chloro-α-tetrahydrosantonin (cf. II) as well as in that of the dihydrochlorohydrin (XIII) (see Table 1; the shifts are 22 and 20 $cm.^{-1}$, respectively, to lower wavelength from α-tetrahydrosantonin). The dihydro-α-isochlorohydrin (XV), however, shows only a slight shift (7 $cm.^{-1}$) but, alone among the saturated derivatives, shows the shift of the *R*-band in the ultraviolet region typical of axial α-chloro-ketones.[12] The unsaturated α-isochlorohydrin itself shows a shift in the main absorption band 8 mμ from that of dihydrosantonin B, 6 mμ from that of the chlorohydrin, typical of the behaviour of αβ-unsaturated α′-halogeno-ketones.[13] Also the infrared spectra of various authentic equatorial αβ-unsaturated α′-halogeno-ketones in this study (Table 1 and below) show the shift to lower wavelength of about 20 $cm.^{-1}$ * that would be expected on the same dipole-interaction grounds that account [11] for the shift in saturated α-halogeno-ketones. For instance, the α-isochlorohydrin (1679 $cm.^{-1}$) absorbs only 4 $cm.^{-1}$ above dihydrosantonin B (1675 $cm.^{-1}$), while the chlorohydrin (equatorial chlorine; 1688 $cm.^{-1}$) absorbs 13 $cm.^{-1}$ higher. Thus the chlorohydrin has an equatorial α-chloro-atom and the α-isochlorohydrin

* The average for the dihydrosantonins is 1671 ± 4 $cm.^{-1}$; that for three α-chloro-compounds is 1691 ± 3 $cm.^{-1}$ (the chlorohydrin and dichloride of santonin and 2α-chlorodihydrosantonin A).

[9] Wedekind and Tettweiler, *Ber.*, 1931, **64**, 387, 1796.

[10] Shriner, Fuson, and Curtin, "The Systematic Identification of Organic Compounds," Wiley, New York, 4th edn., 1956.

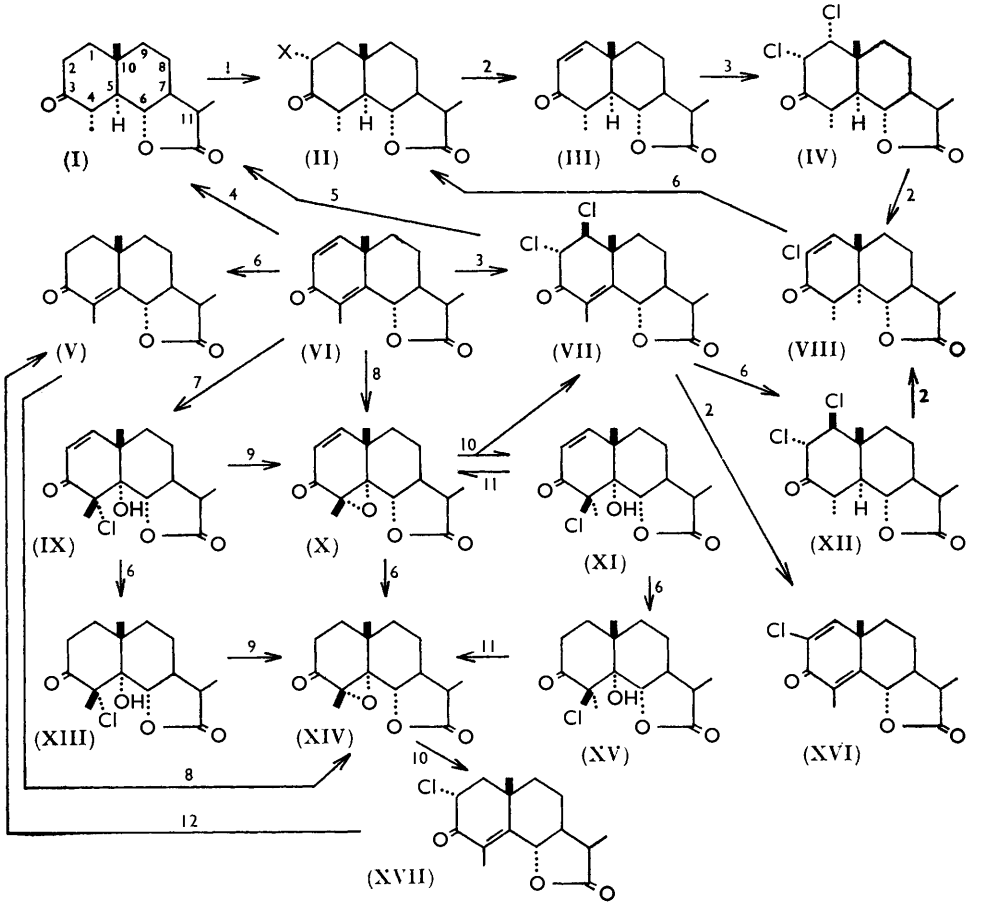
[11] Bellamy, "The Infrared Spectra of Complex Molecules," Wiley, New York, 2nd edn., 1958, especially pp. 139, 400 *et seq.*

[12] Bird, Cookson, and Dandegaonker, *J.*, 1956, 3675.

[13] For several cases see Kirk, Patel, and Petrow, *J.*, 1956, 1184; 1958, 1334. The *R*-bands in our compounds were of little use generally as the spectra were in ethanol, the compounds not being soluble enough in the more useful hexane.[12]

an axial one. In the latter case the ready interconversion of the α-epoxide and α-isochlorohydrin dictate a *trans*-diaxial orientation of the substituents,[14] which is consonant with the spectral assignments.

Only two configurations are then possible for each of the chlorohydrins, one with a *cis*-decalin skeleton (5β-OH) and one with a *trans*-decalin (5α-OH), and optical rotatory



For names see Table 1. Also: IV, 1α,2α-dichloro-α-tetrahydrosantonin; VIII, 2-chlorodihydrosantonin B; X = halogen.

Reagents: 1, Halogen. 2, NR_3. 3, Cl_2. 4, $2H_2$. 5, $3H_2$. 6, H_2. 7, Cl_2–H_2O. 8, BzO_2H. 9, OH^-. 10, HCl. 11, Pyridine. 12, Zn.

dispersion measurements[3] distinguish between them. The dihydro-α-isochlorohydrin, with the axial α-chloro-atom, shows a strongly negative Cotton effect (trough: $[\alpha]_{330}$ = 1200°) consistent only with the *trans*-decalin skeleton, 4β-chloro-5α-hydroxy, as shown (XV). With the equatorial α-chloro-atom of dihydrosantonin chlorohydrin, the positive Cotton effect curve (peak: $[\alpha]_{320}$ +700°) is very similar to that of the *trans*-decalin octant-rule model, γ-tetrahydrosantonin (peak: $[\alpha]_{330}$ +500°), not to the *cis*-decalin, β-tetrahydrosantonin (trough: $[\alpha]_{310}$ −280°). The chlorohydrin is thus assigned the 4α-chloro-5α-hydroxy-configuration as shown (XIII) and is a *cis*-chlorohydrin, which is theoretically unexpected and discussed more fully below. The α-epoxide must have the α-orientation of the epoxy-group (X), so that the traditional designation of " α " is correct as a configurational label as well. The optical rotatory dispersion curve of the dihydro-α-epoxide

[14] Eliel in Newman, " Steric Effects in Organic Chemistry," Wiley, New York, 1956, pp. 61 *et seq.*; Barton and Cookson, *Quart. Rev.*, 1956, **10**, 44.

shows a strongly negative Cotton effect, which is consistent only with the boat form of ring A in the dihydro-α-epoxide (XVIIIa), the octant-rule projections [3] showing that as the dihydro-α-epoxide passes through a conformational transition from chair to boat in ring A, the octant-rule prediction passes from a positive to a negative Cotton effect. On semiquantitative conformational grounds also, the epoxy-grouping is apparently more stable with the boat form of ring A, in harmony with this observation. For the chlorohydrins, passage from chair to boat form does not alter the octant-rule prediction, so that their assignments are not subject to this uncertainty.

If the chlorohydrins and epoxide are formed by reaction of the 4,5-double bond, it is clear that santonin dichloride is formed by reaction at the 1,2-double bond. The ultraviolet spectrum (251 mμ) shows the tetrasubstituted 4,5-olefin, while the nuclear magnetic resonance spectrum shows no olefinic hydrogen (3—4 τ) and does show the olefin-attached methyl group at 7·95 τ; also the vicinal pair of hydrogen atoms attached to carbon bearing chlorine shows as a pair of mutually split doublets at 5·40 and 5·87 τ, not seen in any of the derivatives considered above. The ready conversion of santonin into 2-chlorosantonin (XVI) by mild bases requires hydrogen and chlorine to be placed respectively α and β to the ketone; appropriately, 2-chlorosantonin shows only a single, unsplit olefinic-hydrogen resonance, at 3·56 τ. Finally, the infrared spectrum (1694 cm.$^{-1}$) indicates that the α-chloro-atom of santonin dichloride is equatorial, as indeed its formation from the epoxide with hydrochloric acid also requires, these being equilibrating conditions.

We have prepared a dihydrosantonin dichloride (m. p. 229—230°) [different from that (m. p. 145°) reported [9] to be formed by hydrogenation of santonin dichloride *] by chlorination of dihydrosantonin B in chloroform. Our product shows an equatorial chlorine atom α to the ketone group (1727 cm.$^{-1}$) and is formulated as a *cis*-dichloride (IV) on the basis of *trans*-diaxial chlorination followed by epimerization of the α-chlorine to an equatorial orientation.† The two dihydrosantonin dichlorides apparently yield the same 2-chlorodihydrosantonin B on dehydrochlorination (m. p., our product, 150°; reported,[9] 160°), $\lambda_{max.}$ 246 mμ (log ε 4·0). Since both the dihydro-dichlorides possess equatorial (α) 2-chlorine they can differ only at position 1, and since our new isomeric compound, by normal *trans*-diaxial addition of chlorine to a rigid *trans*-decalin (dihydrosantonin B), must have the 1α-axial chlorine atom, santonin dichloride (XXIIa) must have 1β-equatorial chlorine. Further support is provided by the nuclear resonance splitting constant (J_{AB} = 11·0 c.p.s.) of the hydrogen on carbon atoms bearing chlorine in santonin dichloride, which is constant only with the 180° dihedral angle between them proposed here, and not with the 60° dihedral characteristic of any other configuration.[8,15]

The physical data are thus all consistent with the formulations made here but they render at least unusual, and perhaps suspect, the chemical interrelations previously reported; so we re-examined these. Santonin dichloride is reported to be the major product, and the α-isochlorohydrin the minor product, on treatment of the α-epoxide with hydrogen chloride, and the same conversion is reported in the dihydro-series.[9] We have confirmed the former observation, but not the latter. Dihydrosantonin α-epoxide, when dissolved in cold hydrochloric acid, affords in fact a high yield of a new compound, 2α-chlorodihydrosantonin A. Its structure (XVII) was proved by analysis, its ultraviolet spectrum (248 mμ) indicating a 4,5-double bond, and its infrared spectrum (1690 cm.$^{-1}$) showing equatorial chlorine α to the ketone group, and was confirmed by formation of dihydrosantonin A on reduction by zinc, and finally by the absence of an olefinic hydrogen peak in the nuclear magnetic resonance spectrum, but the presence of one due to the methyl

* In our hands, this yielded only tetrahydrosantonin and starting material.

† This very ready epimerization, presumably involving enolization, is common in the santonin series and noteworthy in the neutral hydrogenation of santonin to α-tetrahydrosantonin, which requires epimerization of the 4-methyl group after *cis*-addition of hydrogen.

[15] Conroy, " Advances in Organic Chemistry, Methods and Results," Interscience Publ., Inc., New York, 1960, Vol. II, pp. 310—311.

group attached to an olefin (7·90 τ). This compound melts (m. p. 170°) at about the same temperature as that reported (175°) for dihydrosantonin α-isochlorohydrin. The latter is, however, prepared easily by hydrogenation of the α-isochlorohydrin and is readily convertible into the dihydro-α-epoxide simply by boiling water.

The second reported product from the dihydro-epoxide cleavage was said to be dihydrosantonin dichloride, identical with the hydrogenation product of santonin dichloride. We failed to duplicate this hydrogenation (cf. footnote *, p. 1682) but the reported melting point (145°) is virtually the same as that of the dihydroepoxide and suggests merely isolation of some starting material from the hydrogen chloride reaction, a result we also observed.

These revisions make the entire chemistry self-consistent.

Several theoretical aspects of the above reactions merit further attention. Some conformational peculiarities will be considered first. The *trans*-decalin α- and γ-forms of tetrahydrosantonin are conformationally rigid, but, unlike simple *cis*-decalins, so are the *cis*-decalin β- and δ-forms since inversion to the alternative *cis*-decalin form would force the *trans*-linked lactone into a *trans*-diaxial fusion, which is not allowable. This inversion would, however, become possible in basic media, wherein the lactone is opened to give a salt of a santoninic acid. Boat forms of the A-ring must also be considered owing to the multiplicity of groups in these complex derivatives. For 4,5-unsaturated derivatives interconversion between a *quasi- cis-* (cf. XXVII), and a *quasi-trans*-decalin (cf. XXII) is easy; the latter has generally been assumed [12,13] to be the more stable and both models and crude calculations of conformational stability [16] seem to bear this out; ‡ but the difference is slight and a single axial substituent at position 1 or 2 in the *quasi-trans*-decalin may well suffice to invert the molecule to the *quasi-cis*-conformation in order to afford that substituent an equatorial orientation.

Attack of santonin by peracids should theoretically occur at the more highly substituted double bond,[17] as the present revised formulation requires. Consideration of steric hindrances makes choice between attack above or below the molecular plane less clear and several investigators have reported small yields of a second epoxide from the reaction; [4] on the present basis, this is probably the β-epoxide (XIXa) (we have not succeeded in isolating it) while the major epoxide product (XVIIIa) arises by attack of the reagent from below the molecular plane of santonin.

One of the most curious features of this new formulation is the conversion of the 4,5-epoxide (X) into the 1,2-dichloride (VII) by hydrogen chloride. This ditertiary epoxide is apparently sufficiently hindered to render normal opening to the α-isochlorohydrin (XI) relatively difficult. However, 1,4-addition of hydrogen chloride to the unsaturated ketone can occur and models of the boat ring in (XVIIIa) suggest that addition from above at position 1 is reasonable. Such an addition would produce an allylic tertiary epoxide (XXa) subject (when protonated) to S_N2' displacement from below at position 2 by chloride ion, to yield compound (XXIa); and this enol is converted into santonin dichloride (VII; XXIIa) on elimination of water. Santonin α-isochlorohydrin (XV), the minor product of attack by hydrogen chloride, is produced by normal *trans*-diaxial opening of the epoxide; it is not an intermediate in the reaction producing santonin dichloride, as is shown by complete recovery of the α-isochlorohydrin after subjection to these reaction conditions.

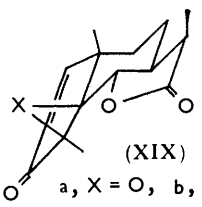
The attack of hydrogen chloride on the dihydro-α-epoxide is similar. While the oxide is relatively stable to normal cleavage, enolization (see footnote †, p. 1682) provides for the same series of steps leading to 2α-chlorodihydrosantonin A (XXIIb). When the reaction was allowed to proceed for only five minutes there was isolated in very small

‡ A consideration of the optical rotatory dispersions of several relevant unsaturated ketones [3] in terms of their octant-rule projections also indicates a preferred *quasi-trans*-decalin geometry.

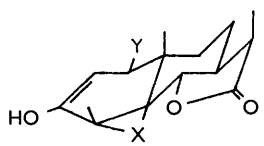
[16] Hendrickson, *J. Amer. Chem. Soc.*, 1961, **83**.
[17] Swern, *Org. Reactions*, 1953, **7**, 378.

amount a crystalline mixture the infrared spectrum of which showed a saturated α-chloroketone (1720 cm.$^{-1}$), an unsaturated ketone (1675, 1615 cm.$^{-1}$), and a large hydroxyl band

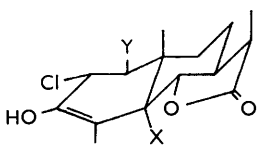
(XVIII) a, X = O; b, X = Cl$^+$



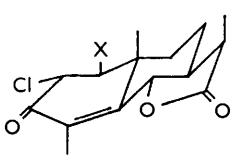
(XIX) a, X = O, b, X = Cl$^+$



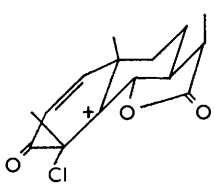
(XX) a, X = O, Y = Cl
b, X = Cl$^+$, Y = Cl



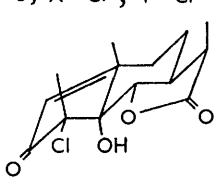
(XXI) a, X = OH, Y = Cl
b, X = Y = Cl
c, X = OH, Y = H



(XXII) a, X = Cl
b, X = H



(XXIII)

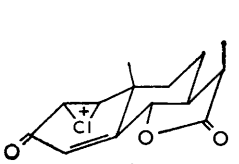


(XXIV)

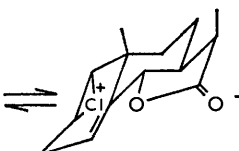
(3470 cm.$^{-1}$). This mixture, melting at 185°, probably contains some dihydro-α-isochlorohydrin as well as the hydroxy-ketone intermediate corresponding to the keto-form of (XXIc) and the normal product (XXIIb). The mother-liquors contained unchanged epoxide, which was recovered.

In the chlorination of santonin, the initial chloronium ion formed at the more reactive double bond must have structure (XVIIIb or XIXb), which will open by preference **at** position 5 rather than afford a 4-carbonium ion. The resulting ion (XXIII) is similar to santonin in geometry, so that attack by water at position 5 from below is not unreasonable, and it yields the chlorohydrin (XXIV). The non-epimerizable 4α-chlorine of this product (XXIV) thus attests to the attack of chlorine on santonin from below (cf. XVIIIb), as is the case with attack by per-acid.

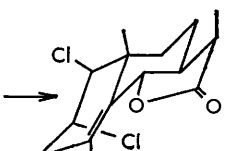
In the case of santonin dichloride, however, chlorination (in chloroform) appears to have attacked the less reactive, though less hindered, 1,2-double bond. Since the decalin forms of dihydrosantonin A are readily interconverted, the two possible chloronium ions (α and β) can each tautomerize between *quasi-cis-* and *quasi-trans*-decalin forms; one of these, in each case, will be the more readily opened by chloride ion, since it will involve breaking of the bond which is both equatorial and β to the ketone, to give the *trans*-diaxial product. For example, if attack by chlorine is from below (as in water), the chloronium ion will undergo the conformational interconversion (XXV) ⇌ (XXVI), in which the former is probably the more stable although the latter should react more rapidly with chloride (for the reasons above), to give *trans*-diaxial normal product (XXVII) which is then conformationally inverted to the more stable santonin dichloride (XXIIa). Attack



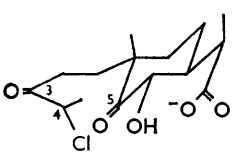
(XXV)



(XXVI)



(XXVII)



(XXVIII)

by chlorine from above would give the 1α,2β-isomer. It was considered, however, that this attack should occur first at the more reactive bond, in chloroform as in water, only to be followed by secondary rearrangement to the 1,2-positions. Such a scheme would follow the path outlined above for epoxide cleavage [cf. XVIIIb ⟶ XXb ⟶ XXI ⟶

santonin dichloride (XXIIa)]. In this case, production of the ion (XXb) requires the intermediacy of hydrogen chloride, so that we next carried out the chlorination in chloroform in the presence of pyridine to suppress catalysis by acid. The yield was lowered from quantitative to 80%, but the only other material isolated was unchanged santonin; so we concluded that chlorination proceeds directly on the 1,2-double bond in chloroform despite the preference for 4,5-attack in other cases discussed.* It should be noted that in the hydrogenation the first mol. is also added to the 1,2-bond.[2] In summary, in all of the cases studied (hydrogenation, chlorination, and epoxidation) attack of the reagent occurs from below, owing to the steric hindrance by the angular methyl groups, which moreover in the steroid system leads to the same result.

Since the chlorohydrin has a *cis*-orientation, normal epoxide formation in alkali is not possible. However, the presence in the chlorohydrin of a β-hydroxy-ketone system greatly facilitates opening of the A-ring by a retroaldol reaction, which produces compound (XXVIII). Rotation around the 3,4-bond is now free and reclosure can occur by attack on the enol at position 4 from either above or below the 5-ketone group, to produce four possible chlorohydrins, which may all, therefore, be considered to be in equilibrium. The *trans*-chlorohydrin pair would, however, close to epoxides in the alkali, rapidly and irreversibly; we conclude that reclosing acid (XXVIII) by attack from above the 5-ketone group (to form the more stable *trans*-decalin) is substantially faster since in practice only one epoxide results.

This mechanistic course involves the known α-isochlorohydrin as an intermediate; the rapid conversion of this into the epoxide in base has been demonstrated, and the dihydro-α-isochlorohydrin obtained by hydrogenation in fact reverts in boiling water.[9] The mechanism does not implicate that 1,2-double bond since the dihydro-chlorohydrin yields the dihydro-epoxide also.†

It might be argued that a different chlorohydrin is the first product of reaction in water and that in a secondary reaction a retroaldol equilibrium provides the chlorohydrin obtained. This, however, requires that the chlorohydrin produced be thermodynamically the most stable of the four which can arise by reclosure of acid (XXVIII) and it can be shown that it is not. Both the chlorohydrin obtained and its unknown 4-epimer exhibit 1,3-diaxial crowding with the angular methyl group, but in the epimer this occurs with the less bulky chlorine, and the epimer is further preferred by removal of the unfavourable dipole interaction [13,18] of the carbonyl and the equatorial chlorine which destabilizes the chlorohydrin. Hence the observed chlorohydrin is not the most stable one possible and so it may be reasoned that this secondary retroaldol reaction does not occur during addition in water.

Another area of past confusion involves the reactions of santonin with ozone and permanganate. Ozonolysis of the α-epoxide (or directly of santonin) was said to yield a C_{15}-acid, m. p. 208°, characterized as an α-dicarbonyl compound by its derivative with *o*-phenylenediamine and formulated as (XXIX) [19] ‡ since the dihydro-derivative was said to be identical with the product of ozonolysis of the dihydro-α-epoxide. Thus the double bond was presumed to be left intact while ozone attacked the epoxide group. Inasmuch as this seemed unprecedented we repeated the experiment; we prepared the same acid,

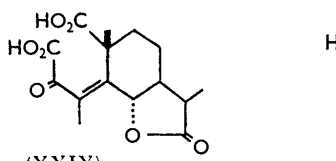
* Presumably some 4,5-dichloride should have appeared on suppression of this acid catalysis. Since it did not, we can only rationalize primary 4,5-addition by affirming the efficacy of pyridine hydrochloride catalysis (in 1,4-addition to XXIIb), or postulating 1,4-addition of another XY species. Both these possibilities seem remote.

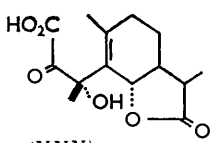
† A Favorski reaction might also be considered to account for epoxide formation, the 4-chloro-atom being displaced by the 2-enolate and the intermediate cyclopropanone then attacked by the 5α-hydroxy-group.

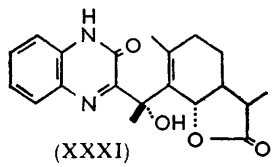
‡ The phenylenediamine derivative was characterized only by a nitrogen analysis. The formula (XXIX) was based on the incorrect epoxide structure in which the epoxy-group is attached at positions 1 and 2.

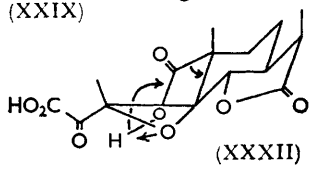
[18] Corey, *J. Amer. Chem. Soc.*, 1953, **75**, 2301.
[19] Wedekind, *Ber.*, 1915, **48**, 891; 1931, **64**, 1796.

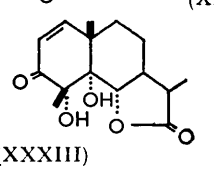
m. p. 209—210°, but find it has the empirical formula $C_{14}H_{18}O_6$.* We have reformulated the acid as (XXX) on the following grounds. The infrared spectrum shows the hydroxyl (3580 cm.$^{-1}$) and two carbonyl peaks (lactone at 1785, keto-acid at 1720 cm.$^{-1}$) with no evidence of a conjugated double bond, nor does the latter appear in the ultraviolet spectrum, which shows only end-absorption down to 215 mμ. The nuclear magnetic resonance spectrum lacks the characteristic pair of olefinic doublets shown by the other 1,2-olefins in the santonin series but shows the methyl group attached to an (unconjugated) double bond at 8·34 τ. Analysis of the *o*-phenylenediamine derivative is in accord with formula


(XXIX)


(XXX)


(XXXI)


(XXXII)


(XXXIII)

(XXXI) as are the infrared bands at 3620 (OH), 3370 (NH), 1785 (lactone), 1665 (lactam), and 1600 (imine). The derivative is insoluble in aqueous sodium hydrogen carbonate, as required, whereas the derivative from acid (XXIX) should be soluble. Wedekind [19] formulated the acid (XXIX) as a diacid lactone although his tritation values fit a monoacid lactone better.†

These experiments confirm structure (XXX) for the product of ozonolysis of the epoxide, showing clearly that it is the double bond of the epoxide which is attacked, as might be expected, and that the correlation through the dihydro-compounds must be in error (no analyses were reported for the dihydro-acid ‡). The reaction may be presumed to provide the normal diacid (XXXII) as the first product which is readily decarboxylated, with epoxide opening, as shown, to yield the product (XXX).

Mild permanganate oxidation of santonin was reported [20] to afford dihydroxysantonin, formulated originally as a $\Delta^{1,2}$-derivative. However, it was reported to be stable to Tollens's reagent but to give a positive iodoform test, both of which results are more compatible with formulation as the $\Delta^{4,5}$-derivative, the iodoform arising by oxidation of the Me·CH(OH)· grouping afforded by a retroaldol reaction under basic conditions. This dihydroxysantonin is converted into the acid (XXX) on further oxidation with permanganate, so it may be formulated with some assurance as (XXIII), the stereochemistry being based on *cis*-hydroxylation of the acid (XXX). This formulation is consistent with that of the other derivatives in showing attack of the reagent at the underside of the more reactive double bond of santonin.

Now that the interrelations of the oxidation products have been clarified, the way is open for study of the rearrangement of the decalin to the perhydroazulene skeleton.

* Wedekind obtained lower carbon values, fitting $C_{15}H_{18-20}O_7$, after recrystallization from ethyl acetate; we also obtained low carbon values from this solvent but several consistent analyses for $C_{14}H_{18}O_6$ after sublimation of the acid, which sublimes very cleanly *in vacuo*.

† Calculated as $C_{15}H_{20}O_7$, the acid neutralized 1·11 and 1·07 millimoles of cold hydroxide and 2·63 millimoles of hot sodium hydroxide; calculated as $C_{14}H_{18}O_6$, the acid neutralized 1·00 and 0·96 millimole of cold and 2·37 millimoles of hot hydroxide (data from ref. 21).

‡ See footnote † preceding.

[20] Angeli and Marino, *Memoire r. Accad. Lincei*, 1908, **6**, 13; *Chem. Abst.*, 1908, **2**, 1953.

[21] Wedekind and Koch, *Ber.*, 1905, **38**, 429.

Experimental

The following compounds were prepared as described in the literature except as noted (yields in parentheses):

Santonin chlorohydrin (reaction for 66 hr.; 59%), m. p. 235—238° (lit.,[9] 235—237°). It was recovered unchanged after being heated at 100° for 45 min. in pyridine.

Santonin α-epoxide (perbenzoic acid;[9] 68%), m. p. 214° (lit.,[9] 214°). The same product was obtained in slightly lower yield by use of peracetic acid. Attempts to isolate the reported β-epoxide [9] were unsuccessful. The α-epoxide was also obtained as reported [9] from the two chlorohydrins.

Santonin dichloride (reaction in $CHCl_3$; 90%), m. p. 175°; recrystallized from benzene–light petroleum (b. p. 36°), it had m. p. 183—185° (decomp.) (lit.,[21] 173°). When 1·1 equiv. of pyridine was added the yield was 80%, and 19% of santonin was recovered. The dichloride was also obtained from the α-epoxide with hydrochloric acid.[9]

Santonin α-isochlorohydrin (27%), m. p. 210° (decomp.) [lit.,[9] 210° (decomp.)]. It was recovered unchanged (93%) when it (10·5 mg.) was left in hydrochloric acid (concentrated, 5 ml.; plus water, 15 ml.) at 0° overnight.

Dihydrosantonin chlorohydrin (hydrogenation in ethanol over palladised strontium carbonate;[22] 88%), m. p. 216° (lit.,[9] 214°).

Dihydrosantonin α-epoxide (hydrogenation in ethyl acetate over palladised charcoal; 87%), m. p. 142° (lit.,[9] 142—143°). There was no indication of another isomer (cf. ref. 9). It was also prepared (93%) from dihydrosantonin chlorohydrin and potassium hydroxide in methanol.[9]

2-Chlorosantonin (from santonin dichloride;[9] 97%), m. p. 223° (no decomp.) [lit.,[9] 224° (decomp.)].

2α-Bromo-α-tetrahydrosantonin (from γ-tetrahydrosantonin;[23] 79%), m. p. 148° (lit.,[23] 147°).

2α-Chloro-α-tetrahydrosantonin (from α-tetrahydrosantonin;[9] 30—35%), m. p. 215° (lit.,[9] 215°).

Attempted Oxidation of Santonin Chlorohydrin with Chromium Trioxide.—The chlorohydrin only was recovered after oxidation as follows: (*a*) 0·596 g. with chromic oxide (0·60 g.) in pyridine at 15° for 24 hr.; (*b*) 200 mg. with chromic oxide (360 mg.) in acetic acid (20 ml.) containing water (2 ml.) and concentrated sulphuric acid (4 drops) at 50° for 30 min. and at room temperature for 42 hr.; (*c*) 200 mg. with a chromic oxide reagent (0·183 ml.) (made from 26·7 g. of oxide in 23 ml. of concentrated sulphuric acid, diluted to 100 ml. with water) at room temperature for 10 min.

Dihydrosantonin α-Epoxide.—Dihydrosantonin A (100 mg.) in chloroform (10 ml.) was refluxed with 0·44N-perbenzoic acid (3 ml.) for 12 hr. Further perbenzoic acid solution (3 ml.) was then added and the solution refluxed again for 12 hr. After cooling, benzoic acid was removed by aqueous sodium hydrogen carbonate, and the solution was dried (Na_2SO_4) and evaporated, yielding a semi-solid residue (70·9 mg.). The infrared spectrum identified this residue as a mixture of an epoxide and a hydroxy-benzoate. The residue was treated with potassium hydroxide (0·2 g.) in methanol (15 ml.) overnight at room temperature, chloroform (25 ml.) was added, and the base extracted in 10% hydrochloric acid. The chloroform solution was dried (Na_2SO_4) and evaporated, giving a solid residue (54 mg.), which after several recrystallizations from aqueous ethanol afforded dihydrosantonin epoxide (6 mg.), m. p. 142° (no depression on mixture with the authentic dihydro-epoxide), with an infrared spectrum (KBr) identical with that of dihydrosantonin epoxide.

2α-Chlorodihydrosantonin A.—Dihydrosantonin epoxide (300 mg.) was dissolved in concentrated hydrochloric acid (40 ml.) and poured into water (150 ml.). Crystals appeared after a few minutes and the suspension was left at room temperature overnight. After filtration, drying, and recrystallization from benzene–light petroleum (b. p. 36°), 2α-chlorodihydrosantonin (245 mg., 76%), m. p. 168—170°, was obtained (Found: C, 63·8; H, 6·6; Cl, 12·5. Calc. for $C_{15}H_{19}ClO_3$: C, 63·7; H, 6·8; Cl, 12·5%). In an attempt to isolate dihydrosantonin isochlorohydrin as described by Wedekind and Tettweiler [9] the aqueous filtrate was exhaustively extracted with ether but only small amounts of 2α-chlorodihydrosantonin A were found.

Brief Treatment of Dihydrosantonin Epoxide with Hydrochloric Acid.—Dihydrosantonin

[22] Woodward, Sondheimer, Taub, Heusler, and McLamore, *J. Amer. Chem. Soc.*, 1952, **74**, 4223, footnote 72.

[23] Yanagita and Tahara, *J. Org. Chem.*, 1955, **20**, 959.

epoxide (100 mg.) was dissolved in concentrated hydrochloric acid (20 ml.) at room temperature and as soon as dissolution was complete (~5 min.) the whole was poured into water (80 ml.) and extracted with dichloromethane (3 × 20 ml.). Evaporation of the extracts yielded a semisolid residue (103·2 mg.) which after several recrystallizations from chloroform–light petroleum (b. p. 65°)–light petroleum (b. p. 36°) yielded several mg. of crystals, m. p. 185°. The infrared spectrum (1775, 1720, 1675, 1615 $cm.^{-1}$) indicated a mixture. The mother-liquor yielded impure dihydrosantonin epoxide, m. p. 100—120°, with the correct infrared spectrum.

Dihydrosantonin B.—2α-Bromo-α-tetrahydrosantonin (2·67 g.) in γ-collidine (25 ml.) was refluxed for 36 hr. under nitrogen. After cooling, the solution was diluted with ether (50 ml.), and the resulting precipitate of collidine hydrobromide was filtered off (1·61 g., 98·3%). The ether was extracted with 10% hydrochloric acid (4 × 25 ml.), dried (Na_2SO_4), and evaporated. The residue (1·65 g.) did not crystallize from a variety of solvents and was sublimed at 160°/0·017 mm., giving crystals (0·91 g.) that, recrystallized from benzene–light petroleum (b. p. 65°), afforded dihydrosantonin B (0·90 g., 45%), m. p. 138—140° (Found: C, 72·65; H, 8·3. Calc. for $C_{15}H_{20}O_3$: C, 72·55; H, 8·1%).

Dihydrosantonin A.—(*a*) Santonin was hydrogenated in benzene over Raney nickel (British Drug Houses, Ltd.; wax pellets) as described by Banerji, Barton, and Cookson,[2] but with only 30—40% yields. Chromatography on alumina (activity III) gave dihydrosantonin A, m. p. 102° (lit.,[2] 102°), by elution with 20% of light petroleum (b. p. 65°) in ether. Other data agreed with those in the above reference.

(*b*) 2α-Chlorodihydrosantonin A (100 mg.) in ethanol (15 ml.) and water (1·5 ml.) was refluxed with zinc dust (100 mg.) for 30 hr. After removal of the zinc, chloroform (25 ml.) was added and the mixture was extracted once with water and with saturated aqueous sodium hydrogen carbonate (2 × 15 ml.). The chloroform solution was dried (Na_2SO_4) and evaporated, giving a residue (81 mg.), m. p. 94—96°. Recrystallization failed and the compound was sublimed at 137°/0·023 mm., to give dihydrosantonin A, m. p. and mixed m. p. 102°, with the correct spectra.

1α,2α-Dichloro-α-tetrahydrosantonin.—Dihydrosantonin B (100 mg.) was dissolved in dichloromethane (10 ml.) and chlorine was bubbled in at 0°. The solvent was removed and the residue was recrystallized from chloroform–light petroleum (b. p. 36°), giving 1α,2α-dichloro-α-tetrahydrosantonin (106 mg., 84%), m. p. 229—230° (no decomp.) (Found: C, 56·2; H, 6·4. Calc. for $C_{15}H_{20}Cl_2O_3$: C, 56·4; H, 6·3%).

2-Chlorodihydrosantonin B.—1α,2α-Dichloro-α-tetrahydrosantonin (104·7 mg.) in chloroform (10 ml.) and pyridine (1 ml.) were refluxed for 30 min. After removal of the pyridine in 10% hydrochloric acid and evaporation, the residue recrystallized from chloroform–light petroleum (b. p. 36°), to give 2-chlorodihydrosantonin B (36·2 mg., 40%), m. p. 150° (Found: C, 63·5; H, 6·95; Cl, 12·8. Calc. for $C_{15}H_{19}ClO_3$: C, 63·7; H, 6·8; Cl, 12·5%).

α- and γ-Tetrahydrosantonin.—Santonin (8·00 g.) in ethyl acetate (240 ml.) was hydrogenated over 2% palladised strontium carbonate at room temperature and pressure. After 21 min. uptake stopped at 2 mol. (1615 ml.), and the catalyst and solvent were removed. Recrystallization from aqueous acetone and thrice from aqueous ethanol gave γ-tetrahydrosantonin (3·52 g., 43%), m. p. 146° (lit.,[2] 146—147°). No attempt was made to isolate other products.

γ-Tetrahydrosantonin (1·00 g.) in ethanol (50 ml.) and 70% perchloric acid (2 drops) was refluxed for 12 hr. After 2 recrystallizations from aqueous ethanol α-tetrahydrosantonin (0·85 g.), m. p. 157° (lit.,[2] 154—155°), was obtained.

Dihydrosantonin α-Isochlorohydrin.—Santonin α-isochlorohydrin (300 mg.) in dry ether was hydrogenated over palladised charcoal, and the catalyst and solvent were removed. Recrystallization from ether–light petroleum (b. p. 36°) gave dihydrosantonin α-isochlorohydrin (82·5%), m. p. 185—186° (lit.,[9] 175°), that gave a positive chlorine test and a negative test with periodate. Treatment of it with boiling water gave a quantitative yield of the dihydro-α-epoxide.

Optical Rotatory Dispersion Measurements.—Dihydrosantonin epoxide. In methanol (0·004M), 28°; $[\alpha]_{589}$ −125·0°, $[\alpha]_{400}$ −67·3°, $[\alpha]_{390}$ −134·6°, $[\alpha]_{380}$ −211·5°, $[\alpha]_{370}$, −298·1°, $[\alpha]_{360}$ −413·5°, $[\alpha]_{350}$ −673·1°, $[\alpha]_{340}$ −1278·9°, $[\alpha]_{330}$ −1586·5°, $[\alpha]_{320}$ −1298·1°, $[\alpha]_{310}$ −211·5°, $[\alpha]_{300}$ +1269·2°, $[\alpha]_{290}$ +2355·8°.

Dihydrosantonin chlorohydrin. In methanol (0·0036M), 28°; $[\alpha]_{589}$ +233·7°, $[\alpha]_{400}$ +458°, $[\alpha]_{390}$ +373·8°, $[\alpha]_{380}$ +299·1°, $[\alpha]_{370}$ +401·9°, $[\alpha]_{360}$ +439·3°, $[\alpha]_{350}$ +486·0°, $[\alpha]_{340}$ +486·0°, $[\alpha]_{330}$ +607·5°, $[\alpha]_{320}$ +700·9°, $[\alpha]_{310}$ +532·7°, $[\alpha]_{300}$ +177·6°, $[\alpha]_{290}$ −102·8°.

Dihydrosantonin α-isochlorohydrin. In methanol (0·004M), 28°; $[\alpha]_{700}$ +154·9°, $[\alpha]_{600}$ −45·8°, $[\alpha]_{589}$ −7·5°, $[\alpha]_{536}$ −10·0°, $[\alpha]_{500}$ −73·3°, $[\alpha]_{450}$ +19·2°, $[\alpha]_{400}$ −206·6°, $[\alpha]_{390}$ −75·0°, $[\alpha]_{380}$ −416·5°, $[\alpha]_{370}$ −533·9°, $[\alpha]_{360}$ −520·6°, $[\alpha]_{350}$ −603·9°, $[\alpha]_{340}$ −1042·1°, $[\alpha]_{330}$ −1161·2°, $[\alpha]_{320}$ −459·0°.

Ozonolysis of Santonin Epoxide.—Santonin epoxide (500 mg.) in chloroform (25 ml.) was ozonized for 2 hr. (1·1 mequiv. of O_3/min.) in an ice–salt bath. The mixture was poured into boiling water (300 ml.) and refluxed for 1 hr. after the chloroform had evaporated. Cooling and filtration gave starting material (52 mg.). Extraction of the aqueous solution with chloroform gave a compound (271 mg.), m. p. 207—208° [from ethyl acetate–light petroleum (b. p. 36°)]. Sublimation at 195—200°/0·027 mm. gave the same compound, m. p. 210° (lit.,[9] 207—208°), $\nu_{max.}$ 1775, 1740, 1610 (small), 3580 (broad), having log ε 1·61 at 215 mμ (no maximum) and τ 8·9 (normal *C*-Me), 8·34 (Me attached to C=C) (Found: C, 59·4; 59·8, 59·6; H, 6·6, 6·5, 6·4. Calc. for $C_{14}H_{18}O_6$: C, 59·6; H, 6·4%). This compound gave negative tests with sodium hypoiodite, bismuth oxide, bromine, and ferric chloride, and positive tests with Tollens's reagent, and periodic acid. It dissolved in aqueous sodium hydrogen carbonate.

The hydroxy-keto-acid (50 mg.) was refluxed overnight in ethanol (4 ml.) with *o*-phenylenediamine (25 mg.). Dilution with water and three crystallizations of the precipitate from aqueous ethanol, followed by two from benzene–light petroleum (b. p. 36°) gave the *quinoxalone* (XXXI) (18 mg.), m. p. 283—284°, $\nu_{max.}$ 3620, 3370, 1785, 1665, and 1600 cm.$^{-1}$ (Found: C, 67·7; H, 6·2. Calc. for $C_{20}H_{22}N_2O_4$: C, 67·8; H, 6·3; N, 7·9%). Wedekind and Tettweiler report [9] only N, 7·67%); this fits $C_{20}H_{22}N_2O_4$ better than their formula $C_{21}H_{22}N_2O_5$ (N, 7·33%).

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