889. *Photochemical Transformations. Part IX.* The Stereochemistry of Lumisantonin.*[1]

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The stereochemistry of lumisantonin has been evaluated at every centre of asymmetry. The cyclopropane ring is fused *cis* to its attached five- and six-membered rings. The photochemical rearrangement of santonin that affords lumisantonin is stereospecific, involving an inversion of configuration at the angular methyl group. Its course is comparable with that of two other examples of bond-crossing photochemical rearrangements.

Irradiation of santonin (I) in neutral solution affords [2,3,4] the isomeric lumisantonin with the constitution [3,4] depicted in (II). The purpose of the present communication is to show that formula (II) also represents the correct stereochemistry of lumisantonin.

The centres of asymmetry at position 6, 7, and 11 are not altered in the photoisomerisation. First, these centres do not have bonds attached which would permit the absorption of ultraviolet light of the type needed for the reaction. Secondly, all four possible santonins epimeric at $C_{(6)}$ and $C_{(11)}$ have been irradiated and shown to furnish four different transformation products,[5] a fact best explained if $C_{(6)}$, $C_{(7)}$, and $C_{(11)}$ are not altered in any way on irradiation.

That the relation between the 3,4- and 1,5-bonds in (II) is *cis* has already been proved.[4] Thus the dicarboxylic acid obtained by opening ring A of (II) gives spontaneously the anhydride (IV). This would not, of course, be possible if the two carboxyl groups of the acid were attached in the *trans*-manner to the cyclopropane ring.

The configuration of the methyl group attached to $C_{(10)}$ in (II) was determined as follows. Dihydrolumisantoninic acid [2] (III) was oxidised with chromic acid to the diketo-acid (VI). This showed an interesting ultraviolet absorption spectrum * with $\lambda_{max.}$ 220 mμ (ε 5900). By analogy with the ready reduction of the system $-CO-\overset{|}{C}=\overset{|}{C}-CO-$ to

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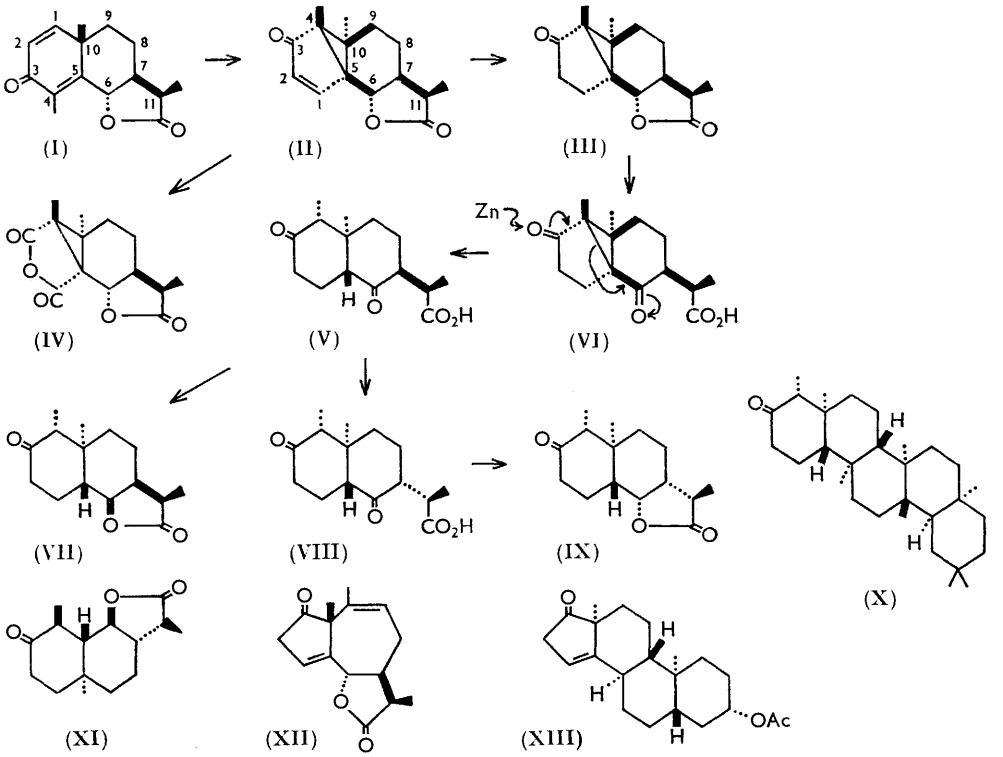
* Recently Kosower [6] suggested that the absorption spectrum recorded by us [4] for dihydrolumisantonin [$\lambda_{max.}$ 214 mμ (ε 4600)] was probably in error. We supplied Dr. Kosower with a specimen of dihydrolumisantonin for which he found (in EtOH) $\lambda_{max.}$ 211 mμ (ε 4000) using the Cary model 14 spectrometer. Having regard to differences in instrumentation these results are identical. In a letter dated June 5th, 1959, Dr. Kosower kindly records the opinion that " substitution on the cyclopropane (of a cyclopropyl ketone) has a marked effect on the maximum." We thank Dr. Kosower for his collaboration in settling this point.

[1] For a preliminary communication see Barton and Gilham, *Proc. Chem. Soc.*, 1959, 391.
[2] Cocker, Crowley, Edward, McMurry, and Stuart, *J.*, 1957, 3416.
[3] Arigoni, Bosshard, Bruderer, Büchi, Jeger, and Krebaum, *Helv. Chim. Acta*, 1957, **40**, 1732.
[4] Barton, de Mayo, and Shafiq, *Proc. Chem. Soc.*, 1957, 205; *J.*, 1958, 140.
[5] Barton, *Proc. Chem. Soc.*, 1958, 61; *Helv. Chim. Acta*, 1959, **42**, 2604.
[6] Kosower, *J. Amer. Chem. Soc.*, 1958, **80**, 3261.

-CO-CH-CH-CO- by dissolving metals we predicted that there would exist a cyclopropylogous reaction of the type

which could be applied to the diketo-acid (VI) (see arrows). In the event, reduction of the acid (VI) with a zinc–copper couple in acetic acid proceeded smoothly at steam-bath temperature to furnish the diketo-acid (V). The infrared spectrum of this acid indicated the presence of two cyclohexanone carbonyl groups. Reduction with borohydride gave a dihydroxy-acid which lactonised spontaneously. Oxidation with chromic acid then afforded the keto-lactone (VII). The stereochemistry of the ring junction in this keto-lactone was established by comparing its rotatory dispersion curve,[7] which showed a single Cotton effect with a trough [8] at 310 mμ ([*M*] −2400°), with that [9] of friedelin [10] (X) to which it is analogous. The dispersion curve also corresponded, but with inversion of sign,



to the mirror-image type chromophore [9] of α-tetrahydrosantonin (XI). The configuration of the keto-lactone (VII) at position 4 is regarded as equatorial (α) because this lactone was stable to digestion with alkali. If we assume that reduction of the diketo-acid (V) with borohydride and subsequent manipulations have not inverted the configuration at

[7] Djerassi, " Optical Rotatory Dispersion," McGraw-Hill Book Co. Inc., New York, 1960.
[8] Djerassi and Klyne, *Proc. Chem. Soc.*, 1957, 55.
[9] Djerassi, Riniker, and Riniker, *J. Amer. Chem. Soc.*, 1956, **79**, 6362.
[10] Brownlie, Spring, Stevenson, and Strachan, *J.*, 1956, 2419; Corey and Ursprung, *J. Amer. Chem. Soc.*, 1956, **78**, 5041.

position 4, then this compound must also be formulated as already indicated in (V) with a 4α-methyl group.

Treatment of the diketo-acid (V) with N-sodium hydroxide on the steam-bath gave a non-crystalline isomer (VIII). Reduction with borohydride gave a dihydroxy-acid which spontaneously lactonised. Without isolation this was oxidised with chromic acid to a new keto-lactone (IX). This showed a rotatory dispersion curve which had a single Cotton effect with a trough at 310 mμ ([*M*] −3800°) very similar to that recorded above for the isomer (VII). These results are most simply interpreted in the following way. Since the diketo-acid has already the more stable *trans*-decalin ring fusion and, almost certainly, an equatorial 4-methyl group, the only configuration that can be inverted by the mild treatment with alkali must be that at position 7. This, in fact, is the expected behaviour based on a stereochemistry for lumisantonin shown in (II). Thus the hydroxyl group and propionic side chain of (III) must, because of the ring fusion, both be axial. This is also in agreement with the fact that lumisantoninic acid and its dihydro-derivative do not lactonise except under forcing conditions.

The configurations at position 6 in the two keto-lactones (VII) and (IX) are regarded as β and α respectively, because of the changes in rotation [11] that they show on opening of the lactone ring in alkali (see p. 4599). The lactone rings in both these compounds are formed spontaneously from the parent hydroxy-acids. Since the propionic acid side chain of (VII) is β (axial) (see above) spontaneous lactonisation is, in any case, only possible if the configuration is β at position 6 (*cis*-lactone formation).

The configuration at position 4 in lumisantonin was determined in the following way. In our earlier work [4] we showed that lumisantonin, on treatment with hydrogen bromide under carefully defined conditions, gave the doubly unsaturated keto-lactone (XII). In this compound the configuration of lumisantonin at position 4 is preserved. The rotatory disperion curve of the compound (XII) showed a single Cotton effect with a trough near 330 mμ ([*M*] −5700°) of enantiomeric type to that of a comparable model steroid (XIII).[12] The latter had a single Cotton effect with a peak near 330 mμ ([*M*] +4800°). The configuration at position 4 in lumisantonin must therefore be opposite to that at position 13 in (XIII), as already written into formula (II).

The stereochemistry of lumisantonin at every centre of asymmetry is thus defined. The fusion of the five- and six-membered rings to the cyclopropane ring is *cis* in both cases. This is not unexpected since no case of *trans*-fusion, which would be very strained, is, as yet, known for either a cyclopropane or a 1,2-epoxide. The irradiation process which converts santonin into lumisantonin is stereospecific and the crossing of bonds leads to an inversion of configuration of the angular 10-methyl group.

This is the same result as has already been demonstrated [13] in the formation of photodehydro-ergosterol and -lumisterol. Such stereospecificity may be characteristic of bond-crossing photochemical rearrangements.

Experimental

M. p.s were taken on the Kofler block. Unless specified to the contrary, $[\alpha]_D$ refer to $CHCl_3$, ultraviolet absorption spectra to EtOH, and infrared absorption spectra to $CHCl_3$ solutions. Light petroleum refers to the fraction of b. p. 60—80°. The rotatory dispersion curves were determined for MeOH solutions.

Chromic Acid Oxidation of Dihydrolumisantoninic Acid.—Dihydrolumisantoninic acid [2] (615 mg.) in " AnalaR " acetic acid (5 ml.) was treated overnight with chromium trioxide (166 mg.). The mixture was poured into water and extracted with chloroform. Removal of the solvent

[11] Klyne, *Chem. and Ind.*, 1954, 1198; see also Novotny, Herout, and Šorm, *Coll. Czech. Chem. Comm.*, 1960, **25**, 1500.

[12] St. Andre, MacPhillamy, Nelson, Shabica, and Scholz, *J. Amer. Chem. Soc.*, 1952, **74**, 5506; Sondheimer and Burstein, *Proc. Chem. Soc.*, 1959, 228.

[13] Barton and Kende, *J.*, 1958, 688; Barton, Bernasconi, and Klein, *J.*, 1960, 511.

gave the *diketo-acid* (VI). Recrystallised from benzene this (440 mg.) had m. p. 190—192°, $[\alpha]_D$ −91° (*c* 3·90), $\lambda_{max.}$ 220 (ε 5900) and 292 mμ (ε 190), $\nu_{max.}$ 1680 and 1710 cm.$^{-1}$ (in Nujol) (Found: C, 68·5; H, 7·5. $C_{15}H_{20}O_4$ requires C, 68·15; H, 7·65%).

Reduction of the Diketo-Acid (VI).—The diketo-acid (VI) (820 mg.) in acetic acid (20 ml.) was heated on the steam-bath with stirring with zinc–copper couple (10 g.; moistened with ethanol) for 6 hr. (disappearance of band at 220 mμ). The couple was prepared by shaking zinc dust (100 g.) with 1% aqueous copper sulphate (200 ml.), followed by washing with water and then ethanol. Crystallisation of the product from light petroleum furnished the *diketo-acid* (V) (413 mg.), m. p. 110—113°, $[\alpha]_D$ +5° (*c* 2·50), $\nu_{max.}$ 1710 cm.$^{-1}$ (Found: C, 67·9; H, 8·45. $C_{15}H_{22}O_4$ requires C, 67·65; H, 8·35%).

Formation of the Keto-lactone (VII).—The diketo-acid (V) (80 mg.) in water (2 ml.) containing potassium borohydride (200 mg.) was left overnight at room temperature. Acidification with 2N-hydrochloric acid and extraction into chloroform gave a product (68 mg.), $\nu_{max.}$ 1770 and 3550 cm.$^{-1}$, which was dissolved in " AnalaR " acetic acid (2 ml.) and treated overnight at room temperature with chromium trioxide (25 mg.). Dilution with water, extraction into chloroform, and crystallisation from light petroleum afforded the *keto-lactone* (VII) (45 mg.), m. p. 130°, $[\alpha]_D$ −53° (*c* 1·9), $\nu_{max.}$ 1710 and 1770 cm.$^{-1}$ (Found: C, 71·9; H, 8·95. $C_{15}H_{22}O_3$ requires C, 71·95; H, 8·85%).

In 1 : 1 water–dioxan this keto-lactone had $[M]_D$ −140° (*c* 1·1) and in the same solvent mixture made N with sodium hydroxide it showed $[M]_D$ +26° (*c* 1·3).

The keto-lactone (VII) (36 mg.) in aqueous N-sodium hydroxide (4 ml.) was heated under nitrogen on a steam-bath for 1 hr. Acidification with hydrochloric acid, extraction into chloroform, and crystallisation from light petroleum gave back unchanged keto-lactone (27 mg.), identified by m. p. and mixed m. p.

Formation of the Keto-Lactone (IX).—The diketo-acid (V) (65 mg.) in aqueous N-sodium hydroxide (4 ml.) was heated under nitrogen on a steam-bath for 1 hr. Acidification as above and extraction into chloroform gave a product (60 mg.) which did not crystallise. It was treated overnight with potassium borohydride (150 mg.) in water (2 ml.). Acidification and extraction as above gave material (50 mg.) which was taken up in " AnalaR " acetic acid (2 ml.) and oxidised overnight with chromium trioxide (20 mg.). Dilution with water and extraction into chloroform gave the *keto-lactone* (IX) which was chromatographed over silica gel in benzene. Recrystallised from light petroleum this lactone (15 mg.) had m. p. 166°, $[\alpha]_D$ +5° (*c* 2·0), $\nu_{max.}$ 1710 and 1770 cm.$^{-1}$ (Found: C, 72·05; H, 9·05. $C_{15}H_{22}O_3$ requires C, 71·95; H, 8·85%).

In 1 : 1 water–dioxan it showed $[M]_D$ +34° (*c* 1·8) and in the same solvent mixture adjusted to N with sodium hydroxide $[M]_D$ −130° (*c* 2·1). Acidification of the latter solution gave back unchanged keto-lactone (IX) (m. p. and mixed m. p.).

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