Tetrahedron Letters No. 8, pp. 331-337, 1962. Pergamon Press Ltd. Printed in Great Britain.

THE STRUCTURE OF PHOTOSANTONINIC ACID

I. Satoda and E. Yoshii

Research Laboratory, Nippon Shinyaku Co., Ltd.

Minami-ku, Kyoto, Japan

(Received 13 March 1962)

PHOTOSANTONINIC acid has been known as one of the phototransformation products of santonin.[1] Several years ago, Cocker *et al.*[2] and Arigoni *et al.*[3] observed the formation of this compound by the action of alcoholic potassium hydroxide on lumisantonin and reported some of its properties, but the structure remains unelucidated. In this communication, we wish to propose the structure (I, R=H) for photosantoninic acid based on the following evidence.

Empirical formula of photosantoninic acid has been reported to be $C_{30}H_{42}O_9$,[1,2,3] but analytical data of its derivatives disclosed that it is correctly represented by the Formula $C_{30}H_{40}O_8$. It takes up one molecule of water of crystallization which is difficult to remove without being converted into pyrophotosantoninic acid.[3] It was titrated as a dibasic acid (pk' 5.2 and 7.2 in 50% EtOH) and gave with CH_2N_2 a dimethylester (I, R=Me), m.p. 199°, $C_{32}H_{44}O_8$, which had one hydroxyl group (I.R.[4] band at 3497 cm^{-1} and modified Zerewitinoff method[5]).

---

[1] J. Simonsen and D.H.R. Barton, *The Terpenes* Vol. III, p. 292. Cambridge University Press (1952).

[2] W. Cocker, K. Crowley, J.T. Edward, T.B.H. McMurry and E.R. Stuart, J. Chem. Soc. 3416 (1957).

[3] D. Arigoni, H. Bosshard, H. Bruderer, G. Büchi, O Jeger and L.J. Krebaum, *Helv. Chim. Acta* **40**, 1732 (1957).

[4] Infra-red spectra were determined in $CHCl_3$ unless stated otherwise.

[5] T. Higuchi, *Organic Analysis* Vol. II. Interscience, New York (1954).

Pyrophotosantoninic acid (II, R=H, R'=R"=0), m.p. 284°, $C_{30}H_{38}O_7$, obtained by pyrolysis at 200° or more conveniently by refluxing the acetic acid solution of I(R=H), had the following infra-red bands: in $CHCl_3$ 1776(sh), 1745(sh), 1709 cm^{-1} (intensification of the band 1776 cm^{-1} to the normal and disappearance of the band 1745 cm^{-1} were observed by the addition of Et_3N); in Nujol 1767(γ-lactone), 1709(C=0), 1689 cm^{-1}(COOH), It was titrated as a monobasic acid (pk' 6.35 in 50% EtOH) and gave with CH_2N_2 a monomethylester (II, R=Me, R'=R"=0), m.p. 269°, $C_{31}H_{40}O_7$, which was also obtained by treatment of I(R=Me), with NaH[6] or $Al(i\text{-}PrO)_3$[7] in dry benzene. Infra-red spectrum of II(R=Me, R'=R"=0) showed no absorption band of hydroxyl and had the following bands: 1779(γ-lactone), 1718(COOMe), 1709 cm^{-1}(C=0). Pyrophotosantoninic acid is, therefore, not a dilactone as previously assigned from I.R. in $CHCl_3$[3] but a γ-lactonic acid.

Methyl pyrophotosantoninate (II, R=Me, R'=R"=0) was stable to O_3, perbenzoic acid, and OsO_4, and gave no color with tetranitromethane, suggesting the absence of a double bond. The ultra-violet absorption maxima of I(R=H) at 216 mμ(ε 9120) and 290 mμ(ε 110)[8] is, therefore, indicative of a ketone conjugated with a cyclopropane system.[9] Reduction of II(R=Me, R'=R"=0) with $NaBH_4$ in dioxane or by catalytic hydrogenation over Adams catalyst afforded a ketoalcohol (II, R=Me, $R'{=}{<}^{H}_{OH}$, R"=0), m.p. 247°, $C_{31}H_{42}O_7$, I.R.(Nujol): 3546(OH), 1770(γ-lactone), 1706 cm^{-1}(COOMe and cyclopropylketone[10]), U.V.: 211, 294 mμ(ε 4800, 65). This was oxidized with active MnO_2 in $CHCl_3$ or CrO_3 in C_5H_5N to give the starting ketone

---

[6] C. Djerassi, D. Marshall and T. Nakano, J. Amer. Chem. Soc. 80, 4853 (1958).

[7] R.B. Woodward, F.E. Bader, H. Bickel, A.J. Frey and R.W. Kiersted, Tetrahedron 2, 1 (1958).

[8] Ultra-violet spectra were measured in EtOH.

[9] Refs. 2 and 3, and literature cited therein.

[10] I.R. of disodium salt of the corresponding dicarboxylic acid, in C=0 stretching region, showed only one band of cyclopropylketone at 1715 cm^{-1} in Nujol.

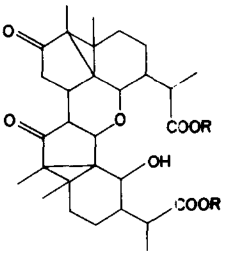
II(R=Me, R'=R"=O). Successful oxidation of cyclopropylcarbinols with MnO_2 is not unexpected, since applying this reagent Ohloff et al.[11] had converted carol-5 into carone, and we have found that dihydrolumisantoninol is readily oxidizable to dihydrolumisantonin. Further reduction of the remaining carbonyl group in II(R=Me, $R'=<^{H}_{OH}$, R"=O) was realized using $LiBH_4$ in tetrahydrofurane to give a diol (II, R=Me, $R'=R''=<^{H}_{OH}$), m.p. 235°, $C_{31}H_{44}O_7$, I.R.: 3460(OH), 1776(γ-lactone), 1724 cm^{-1}(COOMe). It showed no ketonic absorption in the ultra-violet region (ε 470 at 210 mμ) and gave with Ac_2O-C_5H_5N a diacetate (II, R=Me, $R'=R''=<^{H}_{OAc}$), m.p. 240°, $C_{35}H_{48}O_9$, I.R.: 1776(γ-lactone), 1724 cm^{-1}(AcO and COOMe), free from the absorption band of hydroxyl. The MnO_2 oxidation of the diol (II, R=Me, $R'=R''=\,^{H}_{OH}$) afforded a ketoalcohol (II, R=Me, R'=O, $R''=<^{H}_{OH}$), m.p. 236°, $C_{31}H_{42}O_7$, I.R.: 1776 (γ-lactone), 1721(COOMe), 1709 cm^{-1}(cyclopropylketone), U.V.: 220, 284 mμ (ε 4800, 60), along with the diketone II(R=Me, R'=R"=O). From the infrared and the ultra-violet spectra of these two isomeric monoketones: II(R=Me, $R'=<^{H}_{OH}$, R"=O) and II(R=Me, R'=O, $R''=<^{H}_{OH}$), coupled with their behaviour to MnO_2, it was concluded that photosantoninic acid has two five-membered ring ketones both of which are conjugated with cyclopropane systems.[9,12]

Dimethyl photosantoninate (I, R=Me) was recovered unchanged on an attempted acetylation with Ac_2O-C_5H_5N, whereas upon oxidation with CrO_3 in C_5H_5N it gave a triketone (III), m.p. 220°, U.V. 217, 295 mμ(ε 9340, 170). Therefore, the hydroxyl group in photosantoninic acid, which is at a γ-position relative to COOH, should be the secondary one, though it resisted to ordinary acetylation procedure. Reduction of I(R=H) with $NaBH_4$ in H_2O containing two equimolecular amounts of NaOH gave a tetrahydro-

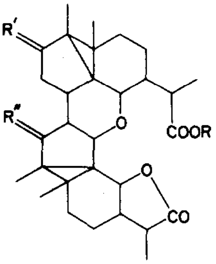
---

[11] G. Ohloff, E. Farnow, W. Philipp and G. Schade, Liebigs Ann. 625, 206 (1959).

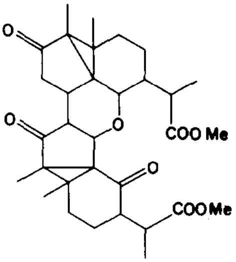
[12] Cyclohexanones conjugated with cyclopropane have the I.R. band of C=O at lower frequency than 1700 cm^{-1}. For example: G. Büchi, M. Schach, V. Wittenau and D.M. White, J. Amer. Chem. Soc. 81, 1968 (1959).



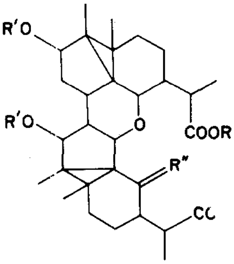
I



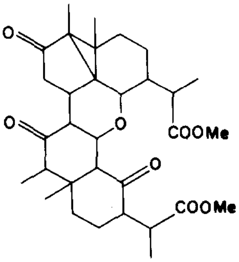
II



III



IV



V

derivative (IV, R=R'=H, $R''=<^{H}_{OH}$), m.p. 221°(d.). This was esterified with CH_2N_2 to give a dimethylester (IV, R=Me, R'=H, $R''=<^{H}_{OH}$), m.p. 230°, which had three hydroxyl groups[5] and two of them could be acetylated with $Ac_2O-C_5H_5N$ giving a diacetate (IV, R=Me, R'=Ac, $R''=<^{H}_{OH}$), m.p. 205°. This diacetate was oxidized with CrO_3 in C_5H_5N to a ketone (IV, R=Me, R'=Ac, R"=O), m.p. 223°, which exhibited a characteristic ultra-violet absorption of a ketone conjugated with a cyclopropane system at 210 mμ(ε 1800) and 284 mμ(ε 40). Consequently, the triketone (III) should have a system $-CO-\overset{C}{C}-C-CO-$, and, in accord with this, the cyclopropane ring in this moiety was cleaved hydrogenolytically by Zn-Cu couple[13] in acetic acid to afford a dihydro-derivative (V), m.p. 201°, $C_{32}H_{44}O_8$, U.V.: 212, 290 mμ(ε 6700, 130). These results indicated clearly that the hydroxyl group in photosantoninic acid is located at the position adjacent to a cyclopropane ring.

[13a] D.H.R. Barton and P.T. Gilham, Proc. Chem. Soc. 391 (1959); [b] G.L. Buchanan and J.K. Sutherland, J. Chem. Soc. 2620 (1956).

The foregoing findings establish the functions of seven oxygens out of eight in I(R=H), and the remaining unreactive one is assigned to be an ether. The NMR spectra[14] of I(R=H) and II(R=Me, R'=R"=O) showed, in ether proton region, the following peaks: I(R=H) 117(broad, unresolved), 146 (doublet, J=6.6), and 161 c.p.s.(doublet, J=8.7 c.p.s.); II(R=Me, R'=R"=O) 121(doublet, J=5.3), ca. 144(doublet, J=ca.6, overlapped with 142 c.p.s. peak of COOMe), and 162 c.p.s.(doublet, J=10.6 c.p.s.). These suggest the presence of the groupings $-CH-\overset{\overset{C}{|}}{C}H-O-\overset{\overset{C}{|}}{C}H-CH-$ and $-C-\overset{\overset{C}{|}}{C}H-OH$ in photosantoninic acid. In addition, I(R=H) contains six C-Me groups as determined by quantitative infra-red measurements.

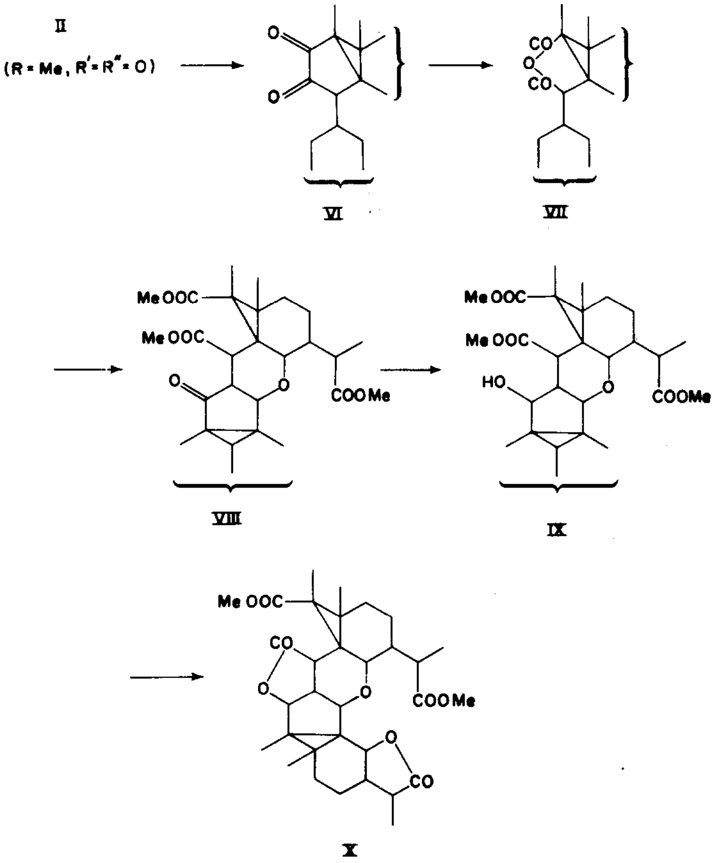
Selenium dioxide oxidation of II(R=Me, R'=R"=O) afforded a yellow α-diketone (VI), m.p. 250°(d.), $C_{31}H_{38}O_8$, I.R.: 1783(γ-lactone and CO-CO), 1764(CO-CO[15]), 1727 cm^{-1}(COOMe and cyclopentanone conjugated with cyclopropane), U.V.: 210, 280, 460 mμ(ε 6000, 2140, 40), which is enolizable, U.V.: in 0.1 n-KOH 370 mμ(ε 3300). This was further oxidized with H_2O_2 in acetic acid to an anhydride (VII), m.p. 230°, $C_{31}H_{38}O_9$, IR(Nujol): 1799 (anhydride), 1783(γ-lactone), 1742(anhydride), 1721 cm^{-1}(COOMe and cyclopentanone conjugated with cyclopropane). These anhydride bands in I.R. are the characteristics of a glutaric anhydride.[16] VII was treated with CH_2N_2 in the presence of methanol to give a trimethylester (VIII), m.p. 272°, I.R.: 1773(γ-lactone), 1733(sh, COOMe), 1718 cm^{-1}(COOMe and cyclopentanone conjugated with cyclopropane), U.V.: 211, 292 mμ(ε 5500, 70). Reduction of the ketone group in VIII was carried out with $LiBH_4$ in tetrahydrofurane to give an alcohol (IX), m.p. 205°, I.R.: 3510(OH), 1776(γ-lactone),

---

[14] NMR spectra were measured by Varian Associates instrument (40 Mc) using $CHCl_3$ as solvent and internal reference.

[15] K. Alder, H.K. Schafer, H. Krieger and R. Reubke, Liebigs Ann. 593, 23 (1955).

[16] H.E. Erdtman and T. Norin, Chem. & Ind. 622 (1960).

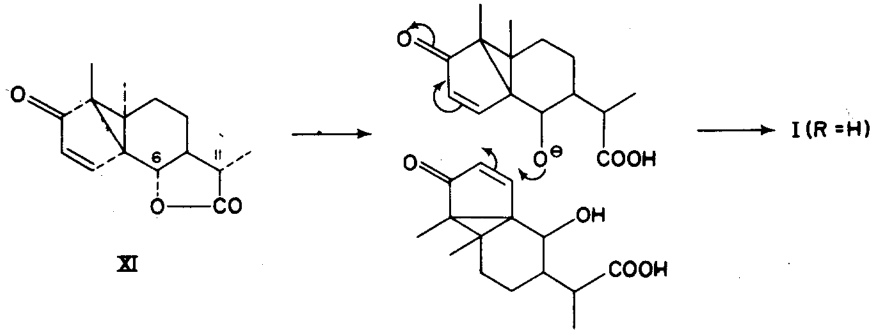


1727 cm^{-1}(COOMe). This alcohol lost an element of methanol when treated with NaH[6] in dry benzene, giving the compound $C_{32}H_{42}O_9$(X), m.p. 211°, I.R.: 1776(γ-lactone), 1736 cm^{-1}(COOMe). Integrated intensity measurement of the band 1776 cm^{-1} of X proved the presence of two γ-lactone groups.[17] suggesting 1,5-relation of two original ketones in photosantoninic acid.

All these results are in good agreement with the structure I(R=H) for photosantoninic acid which probably arises from lumisantonin (XI) by a base-catalysed process as shown on following page.

---

[17] II(R=Me, R'=R"=O) 6.78; VIII 6.86; and X 13.34 units. After the method of D.A. Ramsay, J. Amer. Chem. Soc. 74, 72 (1952).



In this mechanism, the ring system is such that C_6-O bond should require α-orientation (equatorial) as is the case of lumisantonin.[13a] In accord with this assumption, lumi-6-epi-santonin: m.p. 141°, α_D= -191°,[18] and lumi-6-epi-β-santonin: m.p. 160°, α_D= -180°, both of which have a C_6-βOH group respectively, were recovered unchanged on an attempted dimerzation with alcoholic potassium hydroxide, while lumi-β-santonin: m.p. 121°,[2] α_D= -102°, possessing an αOH at C_6 was converted by the same reagent into a dimer, which was named as metaphotosantoninic acid, m.p. 233°(d.), α_D= -38°, $C_{30}H_{40}O_8$, I.R.(Nujol): 3559(OH), 1712(cyclopentanone conjugated with cyclopropane), 1700 cm^{-1}(COOH), U.V.: 216, 289 mμ(ε 9020, 105).

Acknowledgements - The authors are indebted to Prof. K. Nakanishi, Tokyo Kyoiku University, for discussion on the infra-red spectra, and to Dr. Y. Sasaki, Osaka University, for NMR measurements. The authors appreciation is due to Prof. S. Uyeo, Kyoto University, for his valuable advise in preparing this manuscript.

---

[18] Rotations refer to $CHCl_3$ solution.