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## Structure and Reactions of Illudin-S (Lampterol)

During our structural studies on lampterol, the antitumor factor isolated[1,2] from the Japanese mushroom, *Lampteromyces Japonicus* (KAWAM.) SING., planer structures (I) and (II) were proposed,[3] respectively, for illudin-S and -M isolated from *Clitocybe illudens.*[4] The same conclusion was reached by our independent investigations, and a subsequent direct comparison[5] showed lampterol and illudin-S to be identical. The structure has received full support from an X-ray analysis[6] on the *p*-iodobenzoate of its acyloin rearrangement product, isoilludin-S, and in conjunction with optical data the relative and absolute configurations have been clarified.[7]

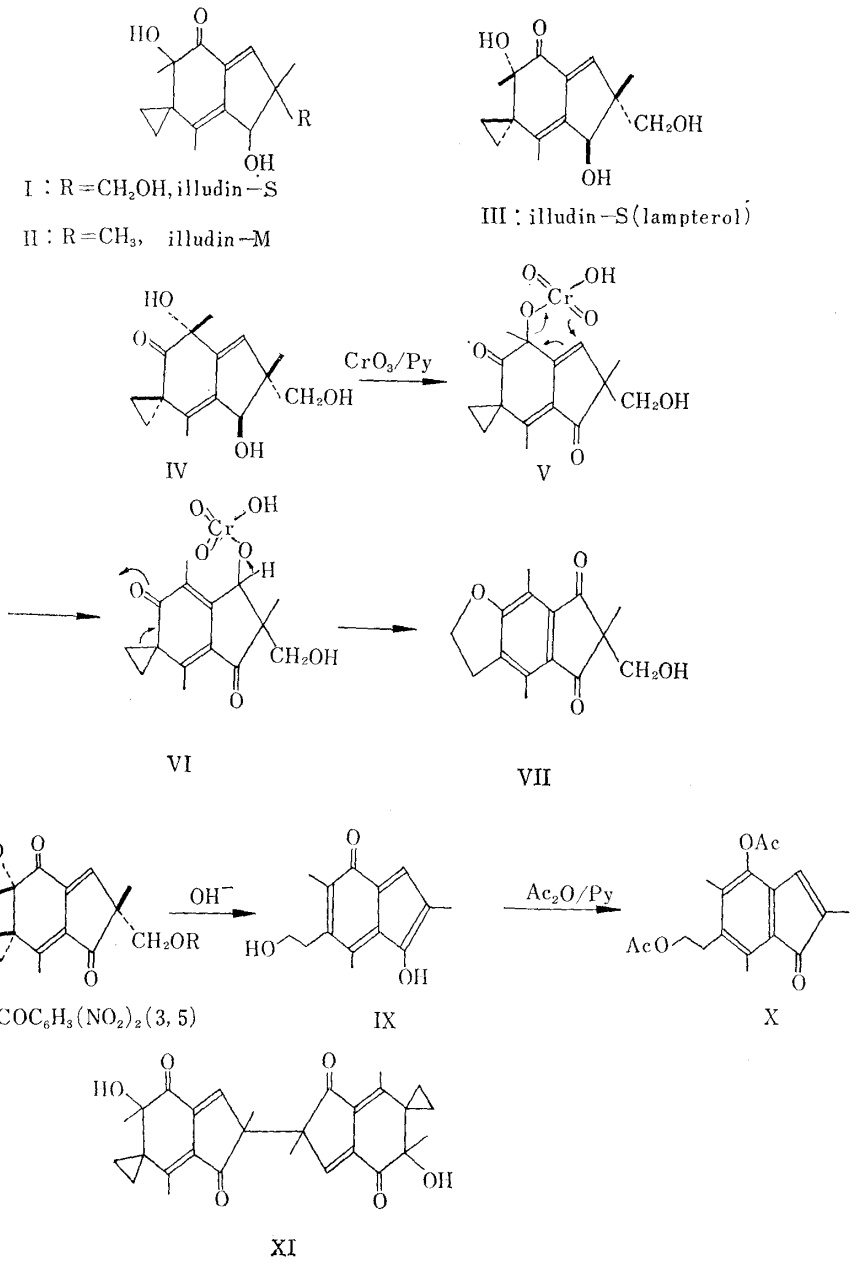
The nature of all twenty protons of illudin-S (III), m.p. 124~126°, $C_{15}H_{20}O_4$ ($M^+$ peak at 264), UV $\lambda_{max}^{MeOH}$ mμ (log ε) : 235 (4.10), 320 (3.54); IR $\nu^{CHCl_3}$ $cm^{-1}$ : 3629, 3605 (free OH), 3500 (bonded OH of α-ketol), 1698 and 1606 (*cisoid* α,β-unsaturated ketone), and 1651 (C=C); $[\phi]_{589}$ −459°, $[\phi]_{375}$ −4,435° (25°, MeOH, c=0.0069),*1 were easily disclosed by comparing its 100 Mc. nuclear magnetic resonance spectrum*2 with that of the diacetate. Oxidation of illudin-S with aqueous potassium permanganate afforded 1,1-cyclopropanedicarboxylic acid, which together with the high field nuclear magetic resonance peaks established the spirocyclopropane moiety.

When the chloroform solution of illudin-S is passed through a column of alumina it is isomerized to isoilludin-S (IV), m.p. 179~180°, UV $\lambda_{max}^{EtOH}$ mμ(log ε) : 252 (4.31); IR $\nu^{KBr}$ $cm^{-1}$: 3400 (br), 1697, 1645 (strong *cisoid* $\nu_{C=C}$ band significantly absent); $[\phi]_{589}$ + 499°, $[\phi]_{312}$ +21,380°, $[\phi]_{280}$ −22,440°, $[\phi]_{269}$ 0.00° (25°, MeOH, c=0.0013). This isomer, in contrast to illudin-S, forms a triacetate, m.p. 112~113°, upon conventional treatment with acetic anhydride pyridine. The nuclear magnetic resonance spectra of illudin-S and its isomer (or their acetates) were quite similar excepting that in the case of the isomer the cyclopropyl protons were shifted lower by ca. 0.7 p.p.m. whereas the olefinic proton singlet was shifted higher by 0.5 p.p.m.

Oxidation of isoilludin-S with chromic acid/pyridine at 50° afforded the dihydro-5*H*-indano[5,6-*b*]furan-5,7(6*H*)-dione (VII), m.p. 198~199°, $C_{15}H_{16}O_4$, UV $\lambda_{max}^{EtOH}$ mμ (log ε) :

*1 ORD curve measured with Japan Spectroscopic Company ORD/UV-5 spectropolarimeter.
*2 NMR spectra measured with Varian A-60 and HR-100 models, $CDCl_3$ solvent, TMS internal reference, chemical shifts in p.p.m. coupling constants in c.p.s.

1) K. Nakanishi, M. Tada, Y. Yamada, M. Ohashi, N. Komatsu, H. Terakawa : Nature, **197**, 292 (1963); K. Nakanishi, M. Ohashi, N. Suzuki, M. Tada, Y. Yamada, S. Inagaki : Yakugaku Zasshi, **83**, 377 (1963).
2) H. Shirahama, Y. Fukuoka, T. Matsumoto : Bull. Chem. Soc. Japan, **35**, 1047 (1962); Nippon Kagaku Zasshi, **83**, 1289 (1962).
3) T.C. McMorris, M. Anchel : J. Am. Chem. Soc., **85**, 831 (1963).
4) M. Anchel, A. Hervey, W.J. Robbins; Proc. Natl. Acad. Sci. U.S., **36**, 300 (1950); **38**, 927 (1952).
5) Private communication from Professor T. Matsumoto, Hakkaido University.
6) Private communication from Professor Y. Saito, University of Tokyo. To be published.
7) K. Nakanishi, M. Tada, Y. Yamada : This Bulletin, **12**, 856 (1964).




256 (4.14), 296 (3.44), 330 (3.14); IR $\nu^{KBr}$ $cm^{-1}$ : 3525, 1731, 1687. The NMR peaks (see Fig. 1) at 2.55 and 2.64 p.p.m. for aryl methyls are unusually low and can only be accounted for by placement of *peri*-carbonyl groups. The 2.64 p.p.m. methyl and 3.28 p.p.m. methylene signals are somewhat broad, and spin-decoupling experiments showed that they are weakly coupled to each other. The chemical shifts and coupling constants for the two methylene groups are very typical for a dihydrobenzofuran moiety.[8] When the sample was shaken in deuterium oxide, the doublet at 3.90 p.p.m. (J=5.5) was reduced to a singlet while the 1.92 p.p.m. triplet (J=5.5) disappeared.

These nuclear magnetic resonance data and the similarity of the infrared*3 and ultraviolet[9] spectra with model indane-1,3-diones permitted one to assign the unequivocal structure (Ⅶ) to this oxidation product, and this in fact had given the first clue

*3 For example, indane-1,3-dione has bands at 1743 and 1708 $cm^{-1}$ (KBr).

8) "High Resolution NMR Spectra Catalog," No. 300, Varian Associates, Palo Alto (1960).
9) M. Carmark, M. B. Moore, M. E. Bolis : J. Am. Chem. Soc., 72, 844 (1950).

regarding the arrangement of the carbon skeleton. The formation of this dihydrobenzofuran derivative can be rationalized by an allylic rearrangement of the chromate group and a net isomerism of the cyclopropane system (Structures (Ⅳ) to (Ⅶ)).

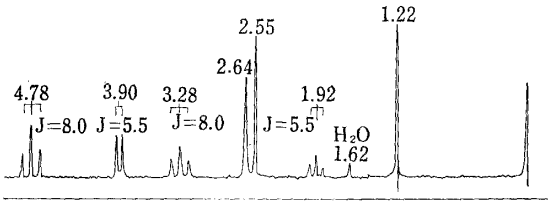



Fig. 1. NMR Spectrum of Dihydro-5*H*-indano-[5,6-*b*]furan-5,7(6*H*)-dione (Ⅶ) ($CDCl_3$ 100 Mc.)

Oxidation of illudin-S mono-3,5-dinitrobenzoate (Ⅲ, *prim*-OH esterified), m.p. 177~178°, with chromic acid/pyridine yielded the diketone (Ⅷ), m.p. 175~176°, UV $\lambda_{max}^{EtOH}$ mμ (log ε) : 294(4.09); IR $\nu^{KBr}$ $cm^{-1}$ : 3460, 1743, 1726, 1709, 1623, 1606 (all strong). On treatment with alkali, the double *s-cis*-α,β-unsaturated ketone (Ⅷ) was converted into a red pigment (Ⅸ), $C_{14}H_{16}O_3$ ($M^+$ peak at 232), m.p. 207~209°, UV $\lambda_{max}^{EtOH}$ mμ (log ε) : 249 (4.30), 374 (3.43), 440 (3.20); IR $\nu^{KBr}$ $cm^{-1}$ : 3360, 1681, which by usual acetylation afforded a yellow diacetate (Ⅹ), m.p. 147~148°; UV $\lambda_{max}^{EtOH}$ mμ (log ε) : 248 (4.57), 344 (3.36), 400 (2.08); IR $\nu^{KBr}$ $cm^{-1}$ : 1759, 1730, 1703; $\delta^{CDCl_3}$ 1.83 (doublet, J=2.0, olefinic methyl), 2.06 and 2.38 (acetate methyls), 2.13 and 2.52 (aromatic methyls), 2.96 and 4.10 (set of two triplets, J=7.5, $-CH_2-CH_2-$), 6.93 (quartet, J=2.0, olefin H). These spectroscopic data, especially the unusually low chemical shift of one of the aryl methyls (2.52 p.p.m.) and the high infrared frequency of the carbonyl group[10] (1703 $cm^{-1}$) are in full agreement with structure (Ⅹ), but the free compound is better represented by the tautomeric form (Ⅸ) in view of its ultraviolet spectrum.

Oxidation of illudin-S (Ⅲ) itself with chromic acid/pyridine afforded a syrup, which upon base treatment was also converted to the red pigment (Ⅸ). Besides this, there was obtained as a by-product the dimer (Ⅺ), the structure of which was deduced from spectroscopic data : the ultraviolet with $\lambda_{max}^{EtOH}$ mμ (log ε) : 302 (4.42) was very similar to the curve obtained by subtracting the absorption of ethyl 3,5-dinitrobenzoate from the diketonic ester (Ⅷ); the infrared spectrum with strong bands at 1705 (broad), 1610 and 1596 $cm^{-1}$ showed the presence of two *cisoid* α,β-unsaturated ketones; in the nuclear magnetic resonance spectrum the olefin and methyl signals all appeared as twin peaks, and the two olefinic methyls resonated at the unusually low field of 2.02 and 2.07 p.p.m. The optical rotatory dispersion of the dimer exhibited a negative Cotton effect with a trough at 403 mμ; $[\phi]_{589}$ −758°, $[\phi]_{403}$ −2,710°, $[\phi]_{390}$ −2,100° (25°, dioxane, c=0.042).

Formation of this dimer presumably proceeds *via* a radical intermediate. The isomerization of illudin-S to isoilludin-S is apparently an acyloin rearrangement which can be affected by passage through alumina, by sublimation, or by heating in a sealed capillary at 140°.

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10) E. D. Berhmann : "Progress in Organic Chemistry," edited by J. W. Cook, Vol. 3, p. 117, Butterworths Scientific Publisher, London (1953).