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STRUCTURE OF LAMPTEROL (ILLUDIN S)[1]

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Abstract—The structure of lampterol, an antitumor substance isolated from *Lampteromyces japonicus* has been established in I.

IN PREVIOUS papers[2] isolation of an antitumor substance lampterol $C_{15}H_{20}O_4$; m.p. 127–129°, from *Lampteromyces japonicus* has been reported. During structural studies on lampterol, the structure I was proposed for illudin S isolated from *Clitocybe illudens*.[3] The identity of these two substances was confirmed by direct comparison of their NMR and IR spectra as well as mixed m.p. determination. This paper presents evidence which leads to the formula I for lampterol by independent investigations.

The UV and IR absorption maxima of lampterol (I) point to the presence of a cisoid α,β-unsaturated ketone group (ν_{max} 1692, 1602 cm^{-1}) in a cross conjugated dienone system[4] (λ_{max} 235, 325 mμ; log ε, 4·1, 3·5). The NMR spectrum characterizes whole hydrogen atoms of I as follows; six tertiary methyl protons (τ 8·81 s,[5] 8·63 s), three vinylic methyl protons (8·33 s), four cyclopropane protons (8·60 – 9·80 m), two hydroxyl protons (8·11 s), a hydroxyl proton (6·43 s), two methylene protons α to hydroxyl group (6·50 s), a proton α to hydroxyl group (5·29 s) and a vinylic proton (3·53 s). The diacetate of lampterol (II), $C_{19}H_{24}O_6$, m.p. 98–99°, exhibits an hydroxyl band in the IR spectrum at 3480 cm^{-1}. Therefore, out of four oxygen atoms in lampterol, two are present as acylable hydroxyl groups and one as a nonacylable hydroxyl group. The intensity of the near IR spectrum of II reveals that II has two methylene groups of a cyclopropane ring[6] (λ_{max} 1·63 mμ; ε, 0·76). The above results indicate the presence of the moieties in Fig. 1 in lampterol.

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[1] Reported at the IUPAC Symposium on the chemistry of Natural Products, Kyoto, Japan, April, 1964.

[2] H. Shirahama, Y. Fukuoka and T. Matsumoto, *Bull. Chem. Soc. Japan* **35**, 1047 (1962); *Nippon Kagaku Zasshi* **83**, 1289 (1962). See also K. Nakanishi, M. Tada, Y. Yamada, M. Ohashi, N. Komatsu and H. Terakawa, *Nature, Lond.* **197**, 292 (1963); K. Nakanishi, M. Ohashi, N. Suzuki, M. Tada, Y. Yamada and S. Inagaki, *J. Pharm. Soc. Japan* **83**, 377 (1963); M. Tada, Y. Yamada, N. S. Bhacca, K. Nakanishi and M. Ohashi, *Chem. Pharm. Bull.* **12**, 853, 856 (1964).

[3] T. C. McMorris and M. Anchel, *J. Amer. Chem. Soc.* **85**, 831 (1963). We express our sincere thanks to Dr. M. Anchel for generous gift of a sample of illudin S. Our thanks are also due to Professor K. Nakanishi, Tohoku University, for helpful discussion.

[4] L. F. Fieser, K. Nakanishi, W. Y. Huang, *J. Amer. Chem. Soc.* **75**, 4719 (1953).

[5] Multiplicities are indicated by the usual symbols s singlet, d doublet, q quartet, m multiplet, AB AB type quarted and b broad.

[6] P. G. Gassman, *C and E News* **49**, April 9 (1962).

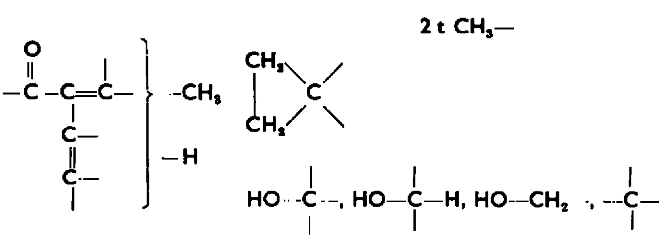


FIG. 1

Reduction of II with sodium borohydride gave a dihydro compound (VI), $C_{19}H_{26}O_6$, m.p. 80–82° (λ_{max} 257 mμ; log ε, 4·37), whose NMR spectrum showed a doublet (J = 2c/s) at τ 3·62 (a vinylic proton) coupled with a peak (τ 5·67; J = 2c/s) due to a proton α to the newly formed hydroxyl group. This indicates that I has a vinylic proton at the β position of the *cisoid* enone system. Chromatography of I on alumina resulted in isomerization to isolampterol (III), $C_{15}H_{20}O_4$, m.p. 179–180° (λ_{max} 252 mμ; log ε, 4·3). The UV absorption maximum is not ascribable to an α,β-unsaturated carbonyl group but to a conjugated diene system, since the solvent effect was not observed in the spectrum of its triacetate (IV), $C_{21}H_{26}O_7$, m.p. 110–111°. The diene is probably *transoid* since tetracyanoethylene did not add to IV. The IR strong band at 1600 cm^{-1} common to the *cisoid* α,β-enone system is no longer recognized in III and IV. The absorption band at 1690 cm^{-1} of isolampterol may be attributable to the six membered carbonyl group adjacent to a cyclopropane ring. The NMR spectrum of III exhibits peaks corresponding to those of I; four cyclopropane protons (τ 8·9–7·7 m), nine methyl protons (8·84 s, 8·49 s, 8·32 s), three hydroxyl protons (7·55 b), two protons α to an hydroxyl group (6·61 s), a proton α to an hydroxyl group (6·4 s) and a vinylic proton (4·3 s). The presence of a spiro cyclopropane ring in III is also confirmed by the NIR spectrum.

The evidence described above suggests that the isomerization of I to III is concerned with the carbonyl group. One possibility is the acyloin rearrangement. If I has a ketol system, the hydroxyl group of the ketol should be tertiary, since in the NMR spectrum of III, a proton α to the newly formed hydroxyl group shows only long range coupling with the vinylic proton. In this connection, it is interesting to note that the iso-compound does not reduce Fehling solution while I does. Now, if the primary alcohol group is placed at a δ position α,β-unsaturated ketone group, the reducing function of I in alkaline medium is smoothly explained by formation of formaldehyde (Fig. 2). The conversion from I to III is consequently explained as in Fig. 3. The shift of NMR peak due to the vinyl proton to higher field in III compared to I supports this explanation and the hypothesis is proved by the following reaction.

Hydrogenation of III over platinum oxide afforded a saturated alcohol, hexahydroisolampterol (V), $C_{15}H_{26}O_4$, m.p. 183–186°. Periodate oxidation of V yielded

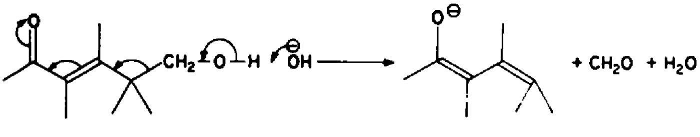


FIG. 2

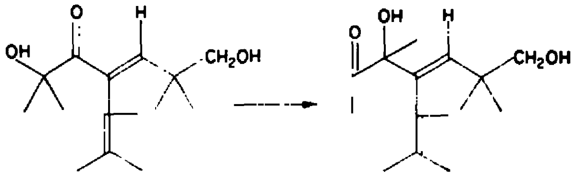


FIG. 3

a paste which reduced triphenyltetrazolium chloride and gave a positive iodoform test. These results suggest that the product is an aldehydic methyl ketone. Chromatography of the pasty substance yielded an α,β-unsaturated ketone (VII), $C_{15}H_{22}O_3$, m.p. 183–186°, whose UV absorption maximum (λ_{max} 253·5 mμ; log ε, 4·21) indicates that the conjugation extended to the cyclopropane ring. The ketol was obviously oxidized to produce an aldehydic methyl ketone which in turn converted to an α,β-enone by aldol condensation. The fact that NMR signals due to cyclopropyl protons of III appeared at an unusually low field, coupled with the position of UV absorption maximum of VII, shows the vicinal arrangement of a cyclopropane ring and a carbonyl group in III. The series of reactions are then expressed as shown in Fig. 4.

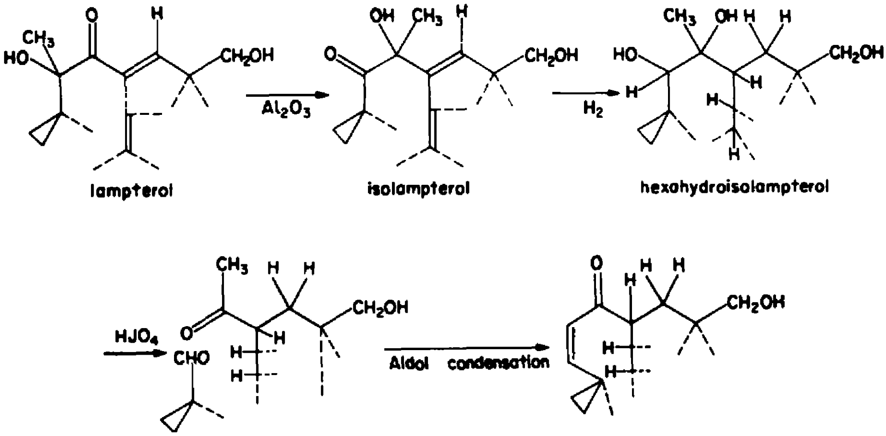
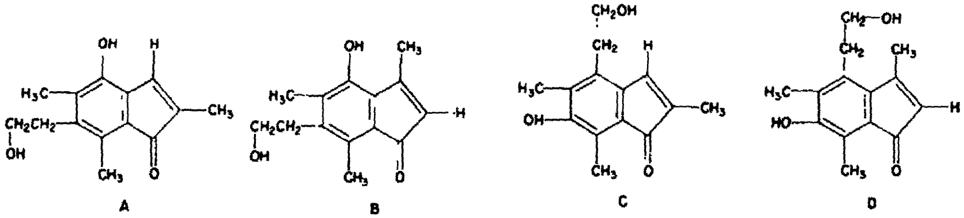


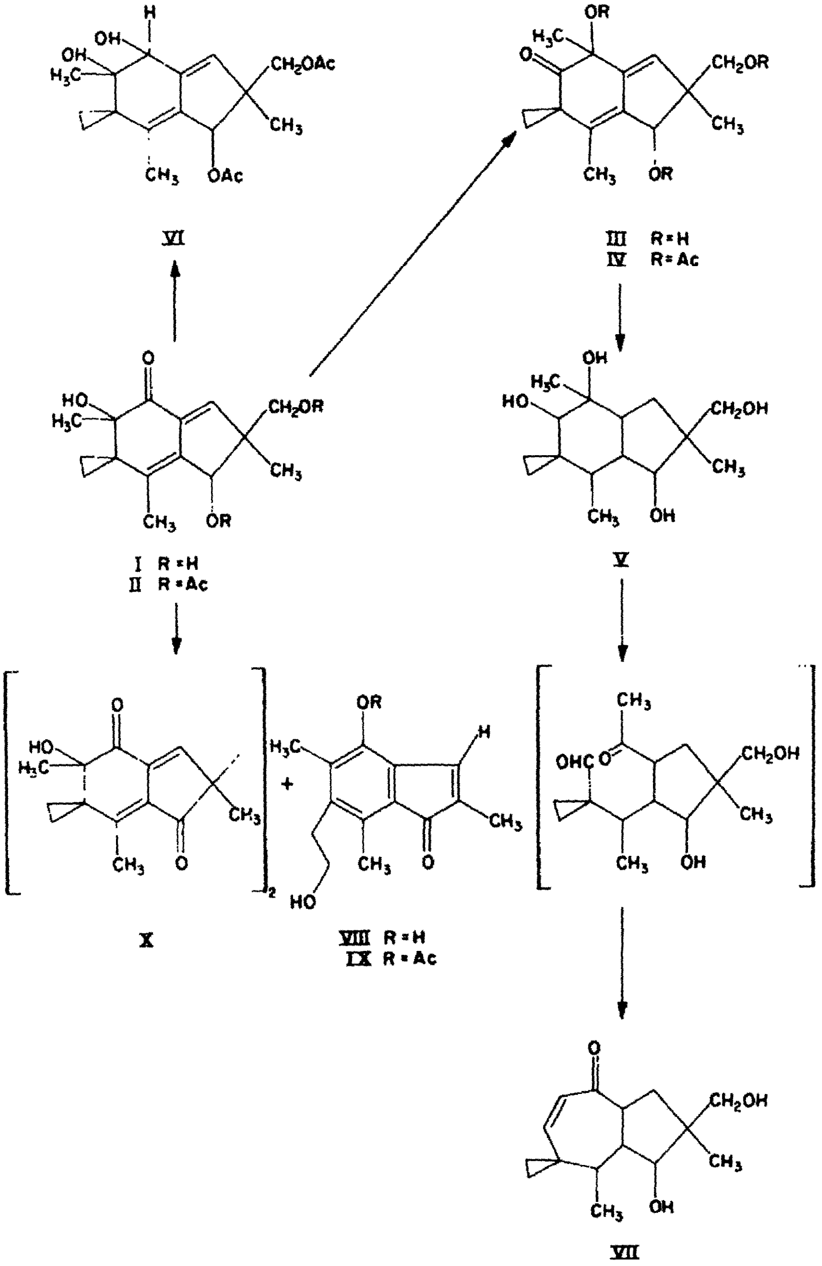
FIG. 4

Oxidation of I with pyridine–chromium trioxide afforded, besides a dimeric norketone (X), $C_{28}H_{30}O_3$, m.p. above 200°, a red crystalline phenol (VIII), $C_{14}H_{16}O_3$, m.p. 190–192°, whose monoacetate (IX), $C_{16}H_{18}O_4$, m.p. 143–144° showed NMR signals at τ 8·38 s (a hydroxyl group), 8·12 d (J = 2 c/s, a vinylic methyl group), 7·59 s (an acetate methyl proton), 7·82 s (an aromatic methyl group), 7·43 s (an aromatic methyl group located near the carbonyl group), 6·29–7·10 m (two methylene groups between aromatic and hydroxyl group) and 3·01 q (J = 2 c/s, a vinylic proton). The IR spectrum of VIII in carbon tetrachloride solution revealed the absence of an intramolecular hydrogen bond. The spectroscopic evidence suggests the following



A B C D

FIG. 5



VI

III R = H
IV R = Ac

I R = H
II R = Ac

V

X

VIII R = H
IX R = Ac

VII

FIG. 6

four possible structures for VIII (Fig. 5). In consideration of the partial formulae given to I, A is clearly the correct representation of VIII. The structure of lampterol (I) is therefore expressed by I.

The dimeric norketone obtained by oxidation of I is formulated as X on the basis of its spectroscopic data; λ_{max} 305 mμ (log ε, 4·11), ν_{max} 3460, 1706, 1615, 1600 cm^{-1}, NMR signals at τ 8·88, 8·80, 8·69, 8·65, 7·98, 7·93 each s (six methyl groups), 9·60–8·20 m (eight protons due to two cyclopropane ring), 6·41 s (two hydroxyl proton) and 3·95, 3·84 each s (two vinylic protons). The compounds produced by the series of reactions are depicted in Fig. 6.

EXPERIMENTAL[7]

Lampterol diacetate (II). A sample of lampterol was dissolved in a mixture of acetic anhydride and pyridine and the solution set aside for a day. Removal of the solvent gave a good yield of diacetate which was recrystallized from light petroleum (b.p. 45–80°), m.p. 98–99°, λ_{max}^{EtOH} 227, 317 mμ (log ε 4·1, 3·5), $\lambda_{max}^{isooctane}$ 222·5, 249 shoulder, 308 mμ (log ε 4·20, 4·04, 3·60), ν_{max}^{KBr} 3480, 1730, 1695, 1680, 1605, 1230, 1110, 1035 cm^{-1}, NMR spectrum: τ 9·79–8·61 m (4H), 8·91, 8·64, 8·49, 7·98, 7·91 each s (5 × 3H), 6·94 s (1H), 5·87 and 6·14 AB (2H), 4·25 s (1H), 3·62 s (1H), $\lambda_{max}^{CCl_4}$ 1·63 mμ (ε 0·76), m/e 43 (100), 173 (67), 213 (33), 215 (30) 233 (25), 331 (14), 348 (M$^+$) (22). (Found: C, 65·38; H, 7·09. $C_{19}H_{24}O_6$ requires: C, 65·50; H, 6·94%.)

Dihydrolampterol diacetate (VI). To a solution of lampterol diacetate (300 mg) in 5 ml MeOH was added a solution of $NaBH_4$ (500 mg) in 2 ml MeOH. After the solution was set aside, the solvent was removed and the residue extracted with ethyl acetate. Chromatography of the product on a column of silicic acid (5 g) using a mixture of dichlorethane and MeOH (5%) as a eluant afforded 120 mg of crude dihydro compound. The product was recrystallized from dichloroethane to yield pure VI as colourless needles, m.p. 80–82°, λ_{max}^{EtOH} 257 mμ (log ε 4·37), $\nu_{max}^{CHCl_3}$ 3430, 3085, 1720, 1647, 1623, 1112, 1040 cm^{-1}, NMR spectrum: τ 9·01, 8·88, 8·60 each s (3 × 3H), 9·60–8·50 m (4H), 7·90 b (2H), 7·85 s (6H), 6·43 s (2H), 5·67 d (J = 2 c/s 1H), 4·42 d (J = 2 c/s 1H), 4·24 s (1H). (Found: C, 64·84; H, 7·76. $C_{19}H_{26}O_6$ requires: C, 65·12; H, 7·48%.)

Isolampterol (III). Lampterol (2 g) was dissolved in ethyl acetate and poured on to a column packed with 100 g of alumina and then developed to be absorbed on alumina with the same solvent. After setting aside 3 days, the column was eluted with MeOH. Removal of the solvent left crystalline isolampterol, which was recrystallized from ethyl acetate to give pure compound in 80% yield, m.p. 179–180°, λ_{max}^{EtOH} 252 mμ (log ε 4·3), ν_{max}^{KBr} 3420, 1690, 1645, 1395, 1365, 1018 cm^{-1}, NMR spectrum: τ 8·84, 8·49, 8·32 each s (3 × 3H), 8·9–7·3 m (4H), 7·54 b (3H), 6·61 bs (2H), 5·40 s (1H), 4·30 s (1H). (Found: C, 67·84; H, 7·28. $C_{15}H_{20}O_4$ requires: C, 68·16; 7·63%.) Isolampterol did not reduce Fehling solution and triphenyltetrazolium chloride, consumed one mole of periodate and gave a negative iodoform test. Lampterol exhibits a positive iodoform test.

Isolampterol triacetate (IV). Treatment of a sample of isolampterol with acetic anhydride and pyridine for a day gave triacetyl lampterol in good yield. Light petroleum (b.p. 45–80°) was a suitable solvent for recrystallization: m.p. 110–111°, λ_{max}^{EtOH} 253 mμ (log ε 4·3), $\lambda_{max}^{isooctane}$ 250 mμ (log ε 4·18), ν_{max}^{KBr} 1730, 1700, 1240 cm^{-1} NMR spectrum: τ 8·93 s (3H), 8·44 s (6H), 7·94 s (6H), 7·86 s (3H), 5·83 and 6·14 AB (2H), 4·56 s (1H), 4·10 s (1H), $\lambda_{max}^{CCl_4}$ 1·635 mμ (ε 0·755), m/e 43 (100), 173 (8), 201 (24), 215 (24), 228 (34), 229 (25), 331 (4), 390 (M$^+$) (4). (Found: C, 64·68; H, 6·76. $C_{21}H_{26}O_7$ requires: C, 64·60; H, 6·71%.)

Hexahydroisolampterol (V). A solution of isolampterol in EtOH was hydrogenated in the presence of PtO_2. Consumption of 3·5 moles H_2 completed the absorption. The catalyst and the solvent were then removed to leave a crystalline mass of product in good yield, m.p. 170–180°. Recrystallization from ethyl acetate raised the m.p. to 183–186°, ν_{max}^{nujol} 3580, 3383, 1115, 1075, 922 cm^{-1}, NMR spectrum in deuterated pyridine: τ 8·51 d (J = 6 c/s 3H), 9·60–8·75 m (4H). (Found: C, 66·44; H, 9·60. $C_{15}H_{26}O_4$ requires: C, 66·63; H, 9·69%.) This compound did not reduce Fehling solution or triphenyltetrazolium chloride.

Oxidation of hexahydroisolampterol with sodium periodate. To a solution of V (550 mg) in 4 ml EtOH was added a solution of sodium periodate (485 mg) in 15 ml water. After standing overnight

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[7] M.ps are uncorrected. NMR spectra were run in $CDCl_3$ unless otherwise specified.

the reaction mixture was extracted with ethyl acetate. Evaporation of the solvent left a glass which gave a positive iodoform test and reduced triphenyltetrazolium chloride in alkaline medium. Chromatography of the product on silicic acid using a mixture of dichlorethane and MeOH (2%) as an eluant and subsequent recrystallization from EtOH gave 150 mg of crystalline α,β-unsaturated ketone, m.p. 183–186°, $\lambda_{\text{max}}^{\text{EtOH}}$ 253·5 (log ε 4·21), $\nu_{\text{max}}^{\text{nujol}}$ 3470, 3075, 1706, 1642, 1617, 1100, 1035 cm^{-1}, m/e 250 (M$^+$). (Found: C, 72·38; H, 8·66. $C_{15}H_{22}O_3$ requires: C, 71·97; H, 8·86%.) The crystalline ketone no longer reduced triphenyltetrazolium chloride and gave a negative iodoform test.

Oxidation of lampterol with chromium trioxide. To a solution of lampterol (500 mg) in 3 ml pyridine was added a mixture of 600 mg CrO_3 and 3 ml pyridine. After being set aside for 2 hr, the reaction mixture was diluted with a large quantity of ethyl acetate and the resultant precipitate collected. The pale yellow filtrate was extracted with 5% NaOH aq. The red alkaline extract was neutralized with dil HCl aq (colour was changed to yellow) and extracted with ethyl acetate. Evaporation of the solvent and recrystallization of the residue from EtOH–water yielded the phenolic indenone (VIII) as crystalline red needles, m.p. 190–192°, $\lambda_{\text{max}}^{\text{EtOH}}$ 247, 369, 440 mμ (log ε 4·26, 3·43, 3·24), $\nu_{\text{max}}^{\text{CHCl}_3}$ 3250, 1672, 1617, 1593, 1310, 1116, 1012, 886 cm^{-1}, $\nu_{\text{max}}^{\text{CCl}_4}$ (conc. 6·0 × 10^{-4} mol) 3618, 3603 cm^{-1}, NMR spectrum in pyridine: τ 8·23 d (J = 1·5 c/s 3H), 7·64 s (3H), 7·41 s (3H), 7·16–6·14 m (4H). (Found: C, 68·29; H, 6·07. $C_{14}H_{14}O_3$ requires: C, 68·28; H, 5·73%.)

A sample of 20 mg of the red substance, VIII, was dissolved in 1 ml of a mixture of pyridine and acetic anhydride (1/1). After being set aside overnight, the reaction mixture was diluted with water and extracted with ether. Thin layer chromatography of the product on silicic acid using a mixture of carbon tetrachloride and 5% MeOH afforded besides a small amount of a compound which appears to be diacetate ($\nu_{\text{max}}^{\text{CHCl}_3}$ 1765, 1740, 1708 cm^{-1}), 13 mg of monoacetate (IX). Recrystallization of the monoacetate from anhydrous methanol gave crystalline needles, m.p. 143–144°, $\lambda_{\text{max}}^{\text{EtOH}}$ 248·5, 340, 400 mμ (log ε 4·43, 3·18, 2·70), $\nu_{\text{max}}^{\text{CHCl}_3}$ 3480, 1768, 1707, 1610, 1190, 1100 cm^{-1}, NMR spectrum: τ 8·38 s (1H), 8·12 d (J = 2 c/s 3H), 7·59 s (3H), 7·82 s (3H), 7·43 s (3H), 7·10–6·29 m (4H), 3·01 q (J = 2 c/s 1H). (Found: C, 69·64; H, 6·49. $C_{16}H_{18}O_4$ requires: C, 70·05; H, 6·61%.)

In the working up of the oxidation products, extraction of the red phenol (VIII) with aqueous alkali left neutral products in organic solvent. The ethyl acetate solution was concentrated to afford a solid mass whose recrystallization from $CHCl_3$ yielded colourless crystalline dimer (X), m.p. above 200°, $\lambda_{\text{max}}^{\text{EtOH}}$ 305 mμ (log ε 4·11), $\nu_{\text{max}}^{\text{nujol}}$ 3460, 1706, 1615, 1600, 1107, 1050 cm^{-1}, NMR spectrum: τ 8·88, 8·80, 8·69, 8·65, 7·98, 7·93 each s (6 × 3H), 9·6–8·2 m (8H), 6·41 s (2H), 7·05 s (1H), 7·10 s (1H). (Found: C, 72·46; H, 6·60; $C_{28}H_{30}O_6$ requires: C, 72·71; H, 6·54%.)