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THE STRUCTURE OF ILLUDOL*

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Abstract-Detailed evidence is given for the structure and partial stereochemistry of illudol, a sesquiterpenoid trio1 obtained from the Basidiomycete ***Clitocybe illudens.***

THE SESQUITERPENOID illudol (I) is produced by the Basidiomycete ***Clitocybe illudens*** along with several closely related compounds.[1] Detailed evidence for its structure is presented here,' and its relation to other sesquiterpenoids is discussed.

Illudol, m.p. 130–132°, $[\alpha]_D$ −116°, analysed for $C_{15}H_{24}O_3$. The mass spectrum did not show the molecular ion peak (mol. wt. 252) but gave peaks at m/e 234 (M-18) and 216 (M-36). The NMR spectrum in deuteriochloroform gave signals for three tertiary methyl groups (singlets at δ 0·97, 1·00, 1·08) and four protons a to oxygen: a two proton singlet at δ 4·22, a triplet at 3·95 (J = 7 Hz) for one proton and a very broad peak, partly hidden under the singlet and triplet, for the remaining proton. When the spectrum was taken in pyridine-d, the low field signals were spread out more and were thus easier to identify.

Treatment of illudol with acetic anhydride and pyridine gave a product whose NMR spectrum showed the presence of three acetate groups and the expected downfield shift of four protons a to the acetate groups.

There were no signals for vinyl protons in the NMR spectrum of illudol. The compound, however, showed a u.v. maximum at 207 nm (ε 9400) indicating the presence of a tetrasubstituted double bond. It followed from the molecular formula that illudol was tricyclic. The nature of the ring system was revealed by reaction with palladium-charcoal at 280". A mixture of hydrocarbons was obtained, the major component of which gave an NMR spectrum indicative of an indane. It was identified as 2,2,4,5,6-pentamethyl indane by comparison with the authentic compound which had been synthesized by de Mayo and co-workers.[3]

Catalytic hydrogenation of illudol with palladium-charcoal gave a mixture from which three crystalline compounds were isolated by chromatography. The major product was the diol (II) $C_{15}H_{26}O_2$, m.p. 95-96". Its NMR spectrum integral showed the presence of four methyl groups (signals at δ O-91, 1·01 and 1·05), indicating that hydrogenolysis of the primary hydroxyl group had taken place giving a new methyl group. In agreement there

* Part VII of the series "Metabolites of ***Clitocybe illudens";*** for Part VI, see PRATAP SINGH, M. S. R. NAIR, T. C. MCMORRIS and MARJORIE ANCHEL, ***Phytochem.*** (in press).

[1] M. ANCHEL, A. HERVEY and W. J. ROBBINS, ***Proc. Natl. Acad. Sci. U.S. 36,*** 300 (1950).
[2] T. C. MCMORRIS, M. S. R. NAIR and MARJORIE ANCHEL, ***J. Am. Chem. Soc.*** 89, 4562 ***(1967).***
[3] J. J. DUGAN, P. DE MAYO, M. NISBET, J. R. ROBINSON and M. ANCHEL, ***J. Am. Chem. Soc. 88,*** 2838 (1966).

were now only two protons *a* to oxygen : at $\delta 3{\cdot}4$ (broad singlet) and $4{\cdot}5$ (triplet, $J = 7$ **Hz).** When a few drops of trichloroacetyl isocyanate were added to the solution of (II) the dicarbamate derivative formed rapidly, and the signals for the two protons shifted downfield to $\delta 4{\cdot}9$ and $5{\cdot}3$.[4]

The second product of hydrogenation of (I) was the keto-alcohol (III) m.p. 110–112°, formed in low yield. The NMR spectrum showed that hydrogenolysis of the primary hydroxyl had occurred, but the most interesting feature of (III) was the carbonyl group, which gave a peak at 1709 cm^{-1} in the i.r. It evidently resulted from migration of the double bond in the allylic alcohol system during hydrogenation. The third product of hydrogenation was the alcohol (IV) and this confirmed the presence of two allylic hydroxyl groups in (I).

Oxidation of the diol (II) with Jones reagent[5] gave a diketone (V) whose i.r. spectrum, ν_{max} 1782, 1715 cm^{-1}, revealed the presence of a cyclobutanone and cyclohexanone. Similarly, oxidation of (III) afforded the diketone (V) while oxidation of (IV) gave a cyclobutanone. The mass spectra of (II) and (III) showed intense peaks at *m/e* 194 (M-44, 84 % of base peak) and *m/e* 192 (M-44, base peak), respectively, which are readily explained as resulting from cleavage of the cyclobutanol ring with loss of CH_2CHOH.[6]

The third ring of illudol was therefore four membered. It was cleaved in the reaction with palladium-charcoal and the product (2,2,4,5,6-pentamethyl indane) possessed two more methyl groups than illudol. One of these must have resulted from opening of the cyclobutane ring so that one methyl carbon in the indane was formerly a cyclobutane carbon. Bearing in mind the presence of primary and secondary allylic hydroxyl groups and of a tetrasubstituted double bond, only one structure (I) could be written which accommodated satisfactorily all the evidence. The hydroxyl group in the cyclobutane ring was probably not allylic since there was no indication of its hydrogenolysis when illudol was subjected to catalytic hydrogenation. Also, the signal of the proton a to the hydroxyl in (II) and (IV) appeared as a clear triplet ($\delta 4{\cdot}5$ J = 7 Hz) indicating it to be strongly coupled to two protons. The components of the triplet were not as sharp as the corresponding ones in the spectrum of illudol and suggested weak coupling to a third proton.

The location of the cyclobutanol hydroxyl was confirmed in the following way. Baeyer-Villiger oxidation of the diketone (V) with excess of 40% peracetic acid afforded a high yield of a crystalline keto-lactone (VI), $C_{15}H_{22}O_3$ (M^+ 250) m.p. 136–137°, ν_{max} 1770, 1712 cm-'. The NMR spectrum gave a singlet at $\delta 1{\cdot}50$ for the methyl *a* to the new oxygen function and there was no low field signal for a proton *a* to oxygen. Hence, the structure (VI) could be assigned unambiguously. The peracetic acid attacked only the cyclobutanone, giving the normal product with insertion of the oxygen atom between the carbonyl and the more highly substituted adjacent carbon atom.

When the keto-lactone (VI) was stirred at room temp. with dilute sodium hydroxide solution it gradually dissolved. Acidification gave a product which consisted of the starting compound ($\sim$ 10%) and an isomeric ketolactone ($\sim 90\%$), m.p. 138-139". The latter could have resulted from epimerization at either of the centers adjacent to the carbonyl group. A decision between the two possibilities was made by treating (VI) with acetic anhydride-perchloric acid in carbon tetrachloride. A single enol acetate (VII)

[4] **1. R. TREHAN, C. MONDER and A. K. BOSE,** *Tetrahedron Letters 67 (1968).*
[5] **A. BOWERS, T. G. HALSALL, E. R. H. JONES and A. J. LEMIN,** *J. Chem. Soc. 2548 (1953).*
[6] **Cf. cyclobutanol: H. BUDZIKIEWICZ, C. DJERASSI and D. H. WILLIAMS,** *Interpretation of Mass Spectra of Organic Compounds,* p. *42,* **Holden-Day, San Francisco (1964).**

m.p. 138–140°, was formed as indicated by TLC. The NMR spectrum (pyridine-d,) which showed four methyl singlets, 0·98, 1·03, 1·35 and 2-13 (gem dimethyl, methyl a to oxygen, and acetate) is consistent with the structure (VII). Had enolixation occurred in the alternative way the secondary methyl of (VI) would have become a vinyl methyl resulting in a spectrum with five methyl singlets. Alkaline hydrolysis of (VII) gave mainly the same keto-lactone, m.p. 138-l 39°, as obtained above. [Hydrolysis of (VII) in aq. acetic acid-hydrochloric acid gave the two keto-lactones in roughly the same amounts (TLC).] Therefore, the keto-lactones (VI) and (VIII) are epimeric at the ring junction next to the carbonyl group.

Evidence to be discussed later allows assignment of the *cis* fused hydrindane structure to (I) and also the configuration of the allylic methyl. Hydrogenation of (I) is expected to yield a *cis* fused cyclobutane rather than the more highly strained *trans* isomer. Since the net result of hydrogenation can be either *cis* or *trans* addition of hydrogen atoms,' the configuration of the secondary methyl in (II), (III) and (IV) remains uncertain. The partial stereochemistry of the keto-lactones (VI) and (VIII) follows from that of (II) because the Baeyer-Villiger reaction proceeds with retention of configuration.[8] It is not clear from Dreiding models which of the isomers should be more stable, though as we have seen earlier (VI) is largely converted to (VIII) under alkaline conditions. The circular dichroism curves of (VI) and (VIII) have been determined and it is interesting to note that the curve of (VI) shows a large negative molar ellipticity $[\theta]_{291.5} = -16{,}300$ while that of (VIII) has $[\theta]_{292} = +7090$. Of a number of possible conformations of (VI) there are two, a chair form and a twist form,[9] which have both lactone and cyclopentane rings falling in negative octants. Therefore, either of these would account for the large negative ellipticity. The *trans* isomer (VIII) is more rigid and can adopt a twist conformation in which the cyclopentane ring is in a positive octant and the lactone ring partly in a positive and partly in a negative octant. The resultant Cotton effect should therefore be positive, in agreement with the experimental result.

The ORD curve of the ketol (III) was also determined. It gave a strong negative Cotton effect: $[\Phi]_{370}$ -1650, $[\Phi]_{310}$ -10,000, $[\Phi]_{293}$ 0, $[\Phi]_{270}$ + 9700, $[\Phi]_{230}$ + 3900. The model of (III) can have two chair conformations, one of which is predicted to give a negative Cotton effect and the other a positive Cotton effect. The former is therefore more likely to be correct.

The structure (I) found for illudol is particularly interesting because it has the carbon skeleton of the hypothetical precursor (X) of a group of fungal metabolites: illudin S (XI), illudin M (XII),[10–12] marasmic acid (XIII),[3] illudinine (XIV), illudalic acid (XV), illudoic acid (XVI),[13] dihydroilludin S (XVII, R = OH),[14] dihydro illudin M (XVII, R = H)

[7] H. 0. HOUSE, *Modern Synthetic Reactions,* p. 19, Benjamin, New York (1965).
[8] H. 0. HOUSE, *Modern Synthetic Reactions,* p. 125, Benjamin, New York, (1965).
[9] C. DJERASSI and W. KLYNE, *Proc. Natl. Acad. Sci. U.S. 48, 1093 (1962).*
[10] T. C. MCMORRIS and M. ANCHEL, *J. Am. Chem. Soc. 87,* 1594 (1965).
[11] The stereochemistry indicated in (XI) was proposed originally by T. MATSUMOTO, Y. FUKUOKA, A. ICHIHARA, *Y.* MORI, H. SHIRAHAMA, *Y.* TAKAHASHI and M. WATANABE, *Bull. Chem. Soc. Japan* 37, 1716 (1964). The opposite absolute stereochemistry was assigned by Nakanishi and co-workers, but this has been revised to (XI). See N. HARADA and K. NAKANISHI, *Chem. Commun. 310,* (1970).
[12] *dl*-Illudin M has been synthesized: T. MATSUMOTO, H. SHIRAHAMA, A. ICHIHARA, H. SHIN, S. KAGAWA, F. SAKAN, *S.* MATSUMOTO and S. NISHIDA, *J. Am. Chem. Soc.* 90, 3280 (1968). See also T. MATSUMOTO, H. SHIRAHAMA, A. ICHIHARA, H. SHIN, S. KAGAWA and F. SAKAN, *Tetrahedron Letters* 1171 (1970).
[13] M. S. R. NAIR, H. TAKESHITA, T. C. MCMORRIS and M. ANCHEL, *J. Org. Chem. 34,240* (1969).
[14] A. ICHIHARA, H. SHIRAHAMA and T. MATSUMOTO, *Tetrahedron Letters 3965* (1969).

fomannosin (XVIII),' [5] and hirsutic acid C **(XIX).**[16] Recently, a second sesquiterpenoid possessing the skeleton (X), coriolin (XX), has been described."

Biosynthetic experiments with marasmic acid[3] and with illudin *S* and *M*[18] support the genesis of these compounds from mevalonic acid. The humulene type cation (IX) and cyclobutyl cation (X) may possibly be intermediates in the biosynthesis and at any rate provide a useful rationalization for the formation of these metabolites. (I) and (XX) are derived directly from (X) while cleavage of the six-membered ring of(X) leads to (XVIII). Compounds (XI-XVII) result from opening of the cyclobutane ring and more profound skeletal rearrangement gives hirsutic acid C **(XIX).**[16,19]

Sim has proposed that if a humulene type precursor (e.g. IX) is actually involved in the biosynthesis and if its conformation is similar to that of humulene in the humulene–$AgNO_3$ complex,[20] illudol might be expected to have a ***cis*** fused hydrindane system. In addition, the allylic tertiary methyl would be *trans* to the adjacent hydrogen in the cyclopentane ring, in the same way as the methylene of the lactone ring in fomannosin is *trans* to the adjacent hydrogen in the cyclopentanone ring. Supporting evidence for a similar relation in marasmic acid has been obtained from a chloro derivative of that compound.[3] A recent X-ray analysis of the chloro derivative shows it to possess a ***cis*** hydrindane ring fusion.*' It is therefore probable that illudol has a ***cis*** fused hydrindane system.

EXPERIMENTAL*

The isolation of (I) was described in Ref. 1. A sample crystallized from EtOAc had m.p. 130-132"; $[\alpha]_D$ = -- 116" (C O-42, 95 % EtOH); λ_{max} 207 nm (ϵ 9400). ν_{max} (Nujol) 3413, 3356, 3279, 1382, 1367, 1110, 1066, 1012, 1002 cm-'. δ ($CDCl_3$) 0.97, 1·00, 1·08 (singlets, 3 x 3 H); 2.37, (singlet, 3H. This was produced by the three OH protons. It did not disappear on adding D_2O. However, the peak did not appear in the spectrum taken in pyridine-d_5); 3.95 (triplet, J = 7 Hz, 1 H. This overlapped a very broad peak due to another proton as indicated by the integral count); 4.22 (singlet, 2 H). (pyridine-d_5) 0·93, 1.05, 1.25 (singlets, 9 H), 4.21 (triplet, J = 7 Hz 1 H), 4·7 (singlet, 2 H); mass spectrum, ***m/e*** (intensity relative to base peak) 234 (7, M-18), 216 (100, M-2 x 18), 20i (40, M-36-15), 188 (50, M-36-30), 187 (55), 160 (97, M-18-30-44). (Found: C, 70.82; H, 9.53; 0, 19.45; M.W. (Rast) 243. $C_{15}H_{24}O_3$ requires: C, 71·39; H, 9.59; 0, 19.02; M.W. 252.34.)

Acetylation. A solution of illudol (200 mg) in pyridine (2 ml) and Ac_2O (2 ml) was allowed to stand overnight then concentrated ***in vacuo*** and the colourless gummy residue purified by chromatography on silica gel 40 g (0·05–0·2 mm) with EtOAc-light petroleum (b.p. 60–80° 1: 4. The pure acetate (single spot on TLC) was not obtained crystalline. ν_{max} ($CHCl_3$) 1742, 1730, 1376, 1242 cm-'. δ ($CDCl_3$) 0.93, 0·97, 1·03 (3 singlets, 9 H); 2·0, 2·03 (singlets, 9 H); 4·53 (singlet, 2 H); 4.62 (triplet J = 7 Hz, 1 H): 5·3 (very broad peak, 1 H).

Illudol was sensitive to both acid and base. It reacted with CrO_3 in HOAc and with activated MnO_2 in acetone, but the products were complex mixtures which were not investigated further.

Aromatization. Illudol (1 g) was mixed with Pd/C (5 %, 1 g) and heated in a sealed tube at 280" for 2 hr. The tube was cooled, opened and the contents extracted with light petroleum to give a brown oil which was

* M.ps were taken on a Kofler hot stage and are uncorrected. I.r. spectra were determined on a Perkin-Elmer Model 21 spectrometer; NMR spectra were recorded on a Varian A-60A spectrometer with TMS as internal standard, and u.v. spectra on a Perkin-Elmer Model 450 spectrophotometer. Elemental analyses were carried out by Dr. Franz Pascher, Bonn, W. Germany and the mass spectra measurements by Morgan-Schaffer Corp., Montreal, Canada.

[15] J. A. KEPLER, M. E. WALL, J. E. MASON, C. BASSET, A. T. MCPHAIL and G. A. SIM, *J. Am. Chem. Soc. 89, 1260* (1967).

[16] F. W. COMER, F. MCCAPRA, I. H. QURESHI, J. TROTTER and A. I. SCOTT, *Tetrahedron 23, 4761 (1967).*

[17] *S.* TAKAHASHI, H. IINUMA, T. TAKITA, K. MAEDA, and H. UMEZAWA, *Tetrahedron Letters 4663 (1969).* The same authors have recently reported the structures of two closely related compounds, Coriolin B and C. *Tetrahedron Letters 1637* (1970).

[18] M. ANCHEL, T. C. MCMORRIS and PRATAP SINGH, *Phytochem.* (in press).

[19] W. PARKER, J. S. ROBERTS and R. RAMAGE, *Quart. Rev. London 21, 331 (1967).*

[20] *G.* A. SIM, personal communication.

distilled at 100" (O-25 mm) to give a colourless oil. GLC on a P column (diethylene glycol succinate) at 190° and column pressure of 15 psi, gave one main component (85 %). It had λ_{max} 271 nm (ε 1100) 276 (ε 950) and 281 nm (ε 1100). δ (CCl_4) 1·12 (singlet, 6 H), 2·1 (singlet 6 II), 2·2 (singlet, 3 H), 2.61 (singlet, 4 H) 6·68 (singlet, 1 H). The data are the same as those reported for 2,2,4,5,6-pentamethylindane by de Mayo et *al.*[3] Comparison of the i.r. spectrum with that of authentic compound established the identity.

A minor component of the reaction had a lower retention time and showed λ_{max} 263, 267, 271 and 276 nm but was obtained in too small amount to be positively identified.

Hydrogenation. A solution of illudol (1·5 g) in EtOH (60 ml) was stirred with Pd/C (5 %, 1 g) in H_2 at room temp. and pressure. Absorption ceased after about 2 hr. The catalyst was filtered off and the solvent removed, leaving a colourless gum. It was chromatographed on silica gel (110 g) with benzene containing gradually increasing amounts of Et_2O. The mono-alchol (IV) was eluted first (50 mg, m.p. 68-95"). It was further purified by preparative TLC with benzene-ether (3:1) and recrystallized from light petroleum (b.p. 60–80°), m.p. 100-101"; ν_{max} 3280 cm^{-1}. (Found: C, 81.58; H, 11.05; 0, 7·67. $C_{15}H_{26}O$ requires: C, 81·02; H, 11.79; 0, 7·20 %.)

Further elution gave the ketol (III) (30 mg) which was recrystallized from light petroleum, m.p. 110-l 12° ν_{max} 3290, 1709 cm^{-1}. Mass spectrum: 236 (0.3, M^+), 218 (0.7, M-18), 203 (2, M-18-15), 192 (100, M-44). ($CDCl_3$) 0.83, 0·93, 1·13 (singlets, 12 H), 6·1 (triplet, J = 7 Hz, 1 H).

The diol (II) was eluted with benzene–Et_2O (1: 1). The compound (600 mg) was purified by recrystallization from light petroleum. It formed colourless rods, m.p. 95–96°, ν_{max} 3540, 1389, 1370, 1117, 1080, 1053 cm^{-1}. δ ($CDCl_3$) O-91, 1·01, 1·05 (singlets, 12 H), 3·4 (broad singlet, 1 H), 4·5 (triplet, J = 7 Hz, 1 H). Mass spectrum: 220 (2, M-18), 205 (2, M-18-15), 202 (4, M-2 x 18), 194 (84, M-44), 43 (100). (Found: C, 75.35; H, 11.13; 0, 13·85. $C_{15}H_{26}O_2$ requires: C, 75·60; H, 10·90; 0, 13·50 %.)

Oxidation of diol (ZZ). A solution of II (50 mg) in acetone (50 ml) was cooled to 10" and CrO_3–H_2SO_4 in H_2O (Jones reagent)' was added dropwise until the yellow colour persisted. A drop of MeOH was added to destroy excess reagent, the solution concentrated under reduced pressure, H_2O added, and the mixture extracted with EtOAc giving a homogeneous colourless oil (V) ν_{max} 1782, 1715 cm^{-1}.

The ketol (III) on treatment with Jones reagent gave a product ν_{max} 1782, 1715, cm^{-1}. Similarly, the monoalcohol (IV) gave a product with ν_{max} 1782 cm^{-1}.

Baeyer–Villiger oxidation of the diketone (V). A solution of V (560 mg) in HOAc (5 ml) containing hydrated NaOAc (187 mg) was treated with 40% peracetic acid (0·18) ml and set aside in the dark at room temp. for 5 days. It was diluted with H_2O and extracted with EtOAc. The extract was washed with $NaHCO_3$ and H_2O, dried (Na_2SO_4), and the solvent removed, giving a partly crystalline solid (500 mg) which was purified by chromatography on a silica gel column (50 g) with EtOAc-light petroleum (1: 1). Recrystallization from light petroleum gave (VI) as colourless needles m.p. 136-137". ν_{max} 1770, 1712 cm^{-1}. δ ($CDCl_3$) O-98 (doublet, low field portion hidden under singlet at 1.02, J = 6 Hz, 3 H), 1·02, 1.13 (singlets, 6H), 1.48 (singlet, 3H) δ (pyridine-d_5) 0·88 (singlet, 3H) 1·00 (doublet, J = 6 Hz, 3 H), 1.02, 1.43 (singlets, 6 H). Mass spectrum: m/e 250 (35, M^+), 235 (18), 152 (35), 43 (100). (Found: C, 71.89; H, 9.09; 0, 19·13. $C_{15}H_{22}O_3$ requires: C, 71.97; H, 8.86; 0, 19·17 %; mol. wt. 250·33.)

Zsomerizution of (VI). The keto-lactone (VI, 20 mg) was stirred with NaOH (10 %, 5 ml) until dissolved completely (2 hr). Acidification and extraction with EtOAc gave a product which on preparative TLC yielded (VI) (cu. 2 mg) but mainly a slightly faster moving compound (VIII) (*ca.* 18 mg) which crystallized from light petroleum as needles m.p. 138–139°. ν_{max} 1773, 1712 cm^{-1}. δ (pyridine-d_5) 0·93 (singlet, 3 H); 1·1 (singlet, 3 H), 1·07 (doublet, low field portion hidden under singlet at 1·1, (J = 6 Hz, 3 H) 1.28 (singlet, 3 H). The mass spectrum was virtually the same as that of (VI). (Found: C, 71.86; H, 8·89; 0, 19.14. $C_{15}H_{22}O_3$ requires: C, 71.97; H, 8.86; 0, 19·17.)

Formation of enol acetate. The keto-lactone VI (20 mg) in CCl_4 (5 ml) was stirred overnight with 5 ml of Ac_2O and 1 drop of $HClO_4$ (70%). H_2O (5 ml) was added to the mixture and the stirring continued for 1 hr more. Then the aqueous layer was separated and extracted with CCl_4. The combined CCl_4 layer was washed with $NaHCO_3$, H_2O, dried (Na_2SO_4) and the solvent removed leaving partly solid material. It was dissolved in EtOAc-light petroleum (1: 1) and filtered through a column of silica gel to give a colourless crystalline solid m.p. 138-140" which was homogeneous (TLC) ν_{max} $CHCl_3$ 1767 cm^{-1}. δ (Pyridine-d_5) 0.98, 1·03, 1·35 (singlets, 9 H) 2.13 (singlet, 3 H). Treatment of (VII) with NaOH as in the case of (VI), afforded mainly the keto lactone (VIII). When a solution of (VII, 20 mg) in HOAc (2.4 ml) H_2O (1·5 ml) and conc. HCl (O-35 ml) was kept overnight then diluted with H_2O, it gave a product which showed two spots of approximately equal intensity (TLC) corresponding to (VI) and (VIII), as well as one which suggested the presence of unreacted (VII).

p-Bromo-phenylhydrazones of (VI) and (VIII). A solution of the compound (VI, 20 mg) in EtOH (1 ml) was heated at 100° (15 mins) with a solution of p-bromophenylhydrazine HCl-ide (100 mg) and NaOAc (160 mg) in aq. EtOH (1: 1, 2 ml). H_2O was added to the mixture and the precipitated solid was filtered off, washed with H_2O and crystallized from aq. EtOH as plates, m.p. 222-223". ν_{max} 3333, 1754, 1600 cm^{-1}.

Similar treatment of (VIII) gave a crystalline derivative, m.p. 215–216°, ν_{max} 3333, 1754, 1600 cm^{-1}.

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