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SYNTHESIS OF (±)-LOLIOLIDE ((±)-DIGIPROLACTONE)*

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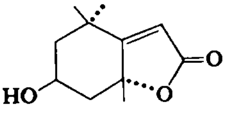
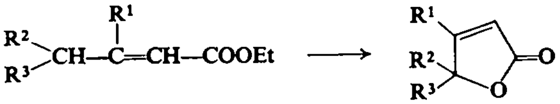
Abstract—(±)-Loliolide ((±)-digiprolactone) (I) has been synthesized from isophorone (IV) by two routes. The first utilized the oxidative lactonization of the mono-unsaturated acetoxy-ester XIb with selenium dioxide as a key step, while the second involved the cyclization of the doubly unsaturated keto-ester XVa to XVI with conc. sulphuric acid. The synthetic racemic compound proved to be identical with a sample prepared from natural optically active loliolide.

LOLIOLIDE, isolated from *Lolium perenne*, [1,2] has been shown to possess structure I.[1] This compound proved to be identical with a substance obtained from *Fumaria officinalis*[3] and from *Digitalis lanata*,[4] as well as with digiprolactone, from *Digitalis purpurea* (which independently was found to possess structure I).[5-8]


I

We have been interested in the selenium dioxide oxidation of αβ-unsaturated esters (II) to butenolides (III).[9-11] This type of reaction appeared to be applicable to the synthesis of loliolide. In the present paper, we describe the realization of this objective, as well as an alternative synthesis of loliolide.


II III

The starting material was isophorone (IV), which was isomerized to the βγ-unsaturated ketone V, as described previously.[12] Oxidation of V with peracetic acid and

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* Dedicated to Sir Robert Robinson on the occasion of his 80th birthday.

[1] R. Hodges and A. L. Porte, *Tetrahedron* **20**, 1463 (1964).

[2] See also E. P. White, *N.Z. J. Agric. Res.* **1**, 859 (1958).

[3] R. H. F. Manske, *Canad. J. Res.* **B16**, 438 (1938).

[4] R. Tschesche and G. Buschauer, unpublished; G. Buschauer, Dissertation, Hamburg, 1957; cf. first footnote in Ref. 2.

[5] D. Satoh, H. Ishii, Y. Oyama, T. Wada and T. Okumura, *Chem. Pharm. Bull. Japan* **4**, 284 (1956).

[6] T. Wada and D. Satoh, *Chem. Pharm. Bull. Japan* **12**, 752 (1964).

[7] T. Wada, *Chem. Pharm. Bull. Japan* **12**, 1117 (1964).

[8] T. Wada, *Chem. Pharm. Bull. Japan* **13**, 43 (1965).

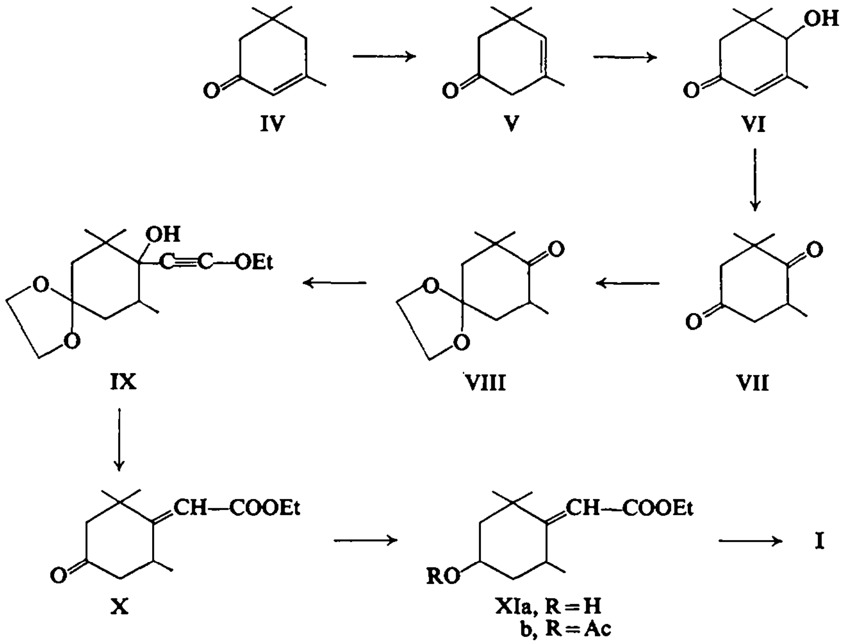
[9] N. Danieli, Y. Mazur and F. Sondheimer, *Tetrahedron Letters* 310 (1961).

[10] N. Danieli, Y. Mazur and F. Sondheimer, *J. Amer. Chem. Soc.* **84**, 875 (1962).

[11] N. Danieli and F. Sondheimer, unpublished experiments

[12] M. S. Kharasch and P. O. Tawney, *J. Amer. Chem. Soc.* **63**, 2308 (1941).

subsequent treatment with sodium hydroxide has been shown to lead to the hydroxyketone VI.[13] In our hands, this reaction was found to proceed in improved yield when *m*-chloroperbenzoic acid was used. Rearrangement of VI with *p*-toluenesulphonic acid in benzene led to the saturated diketone VII,[13] which was treated with ethylene glycol and *p*-toluenesulphonic acid. The resulting monoketal VIII[13] was found to be contaminated with the corresponding diketal, but no separation was carried out.



Reaction of the crude monoketal VIII with lithium ethoxyacetylide yielded the ethoxyacetylenic carbinol IX. Treatment with dilute sulphuric acid resulted in rearrangement of the side-chain,[14] as well as in removal of the protecting group, and led to the $\alpha\beta$-unsaturated ester X. The latter was obtained apparently as a mixture of double bond isomers, from which one pure crystalline isomer could be separated. The crystalline substance was reduced with sodium borohydride, and the resulting alcohol XIa (which appeared to consist of only one isomer) was acetylated to give XIb. The last-mentioned substance was then oxidized with selenium dioxide in boiling acetic acid, and the acetate grouping was removed by treatment with sodium bicarbonate. This procedure led to (±)-loliolide (I; m.p. 140–141°), although the yield in the selenium dioxide step was poor.

The synthetic (±)-loliolide proved to possess IR, NMR and mass spectra identical to those of the natural optically active compound. As further confirmation of structure, (±)-loliolide was prepared from the natural material.

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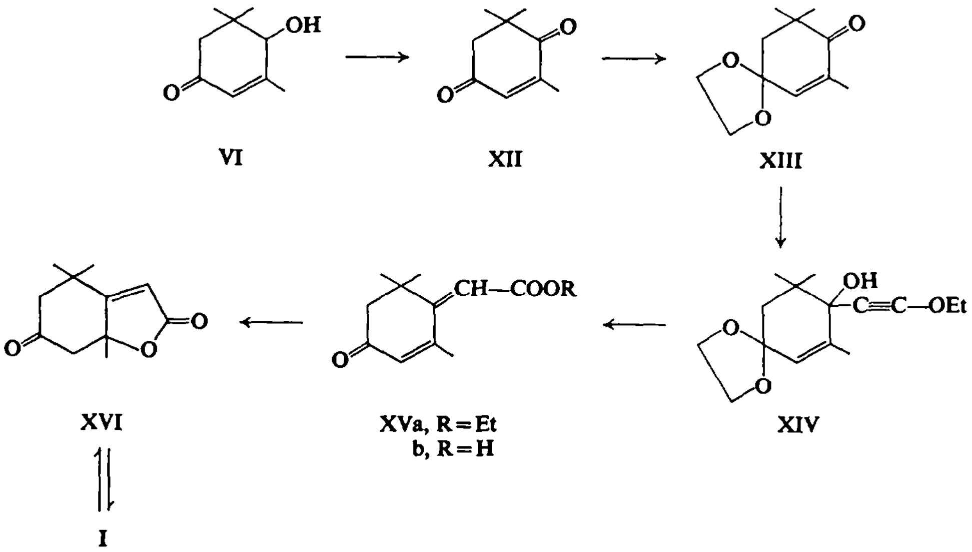
[13] O. Isler, H. Lindlar, M. Montavon, R. Rüegg, G. Saucy and P. Zeller, *Helv. Chim. Acta* **39**, 2041 (1956).

[14] See J. F. Arens, *Advances in Organic Chemistry, Methods and Results* (Edited by R. A. Raphael, E. C. Taylor and H. Wynberg) Vol. II; pp. 159 160. Interscience, New York (1960) and Refs. cited there.

Oxidation of natural loliolide with chromium trioxide has been shown previously to give rise to the optically active ketone XVI,[1,6,8] which could be reconverted to loliolide by sodium borohydride reduction.[8] Further, it has been reported that the optically active ketone XVI is racemized on treatment with sodium hydroxide and subsequent acidification.[1] We have obtained the (±)-ketone XVI by this method, and reduced it with sodium borohydride. The resulting (±)-loliolide showed a m.p. (140–141°) identical to that of the synthetic material, and there was no depression on admixture.

The fact that the optically active ketone XVI is racemized with base (presumably via the salt of the *"cis"*-isomer of the dienone-acid XVb)[1] suggested an alternative synthesis of (±)-loliolide. The hydroxy-ketone VI was oxidized with chromium trioxide (Jones' reagent)[15] to the unsaturated diketone XII; these conditions resulted in a considerably higher yield than had been obtained with chromium trioxide in acetic acid.[13] Treatment of XII with ethylene glycol and *p*-toluenesulphonic acid then yielded the monoketal XIII.[16]



As in the saturated series, the monoketal XIII was allowed to react with lithium ethoxyacetylide, and the product XIV was treated with dilute sulphuric acid in acetone. The resulting dienone-ester (XVa; UV maximum at 274 mμ) consisted of a non-crystalline mixture of double bond isomers, which were not separated.

The ester XVa could be cyclized to the butenolide XVI under various conditions. The most favoured involved treatment with conc. sulphuric acid, to give a mixture showing UV maxima at 215 mμ (due to XVI) and 274 mμ (presumably due to the *"trans"*-isomer of XVa, see below) of about equal intensities. Reduction of this mixture with sodium borohydride then yielded (±)-loliolide (m.p. 140–141°), identified with that obtained previously. This is the preferred synthetic route to this substance.

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[15] *Inter al.*, K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.* 39 (1946); R. G. Curtis, I. M. Heilbron, E. R. H. Jones and G. F. Woods, *ibid.* 457 (1953).

[16] See F. Hoffmann-La Roche, *Brit. Patent* 791,953 (March 19, 1958); *Chem. Abstr.* 53, 1190 (1959).

Saponification experiments carried out with the ester XVa indicated that it was a mixture of double bond isomers, and also provided a route to (±)-loliolide. Treatment with aqueous sodium carbonate at room temp apparently hydrolysed the "*cis*"-isomer (the "*cis*"-isomer is considered to be the one with the ester grouping nearer to the ring double bond), but not all of the "*trans*"-isomer. This follows from the fact that extraction of the basic solution with ether gave recovered ester XVa (UV maximum at 274 mμ), which must be the "*trans*"-isomer since treatment with conc. sulphuric acid as described above led to *no* appearance of the 215 mμ UV band of XVI. The basic solution must have contained the "*cis*"-isomer of the acid XVb, since acidification and ether extraction gave material with a UV maximum at 215 mμ (due to XVI) as well as at 274 mμ. Reduction of this material with sodium borohydride then again yielded (±)-loliolide (m.p. 139–140°), identified with the sample obtained from the natural product.

EXPERIMENTAL

M.ps (Kofler hot-stage) and b.ps are uncorrected. IR spectra: unless otherwise stated on a Perkin-Elmer Infracord recording spectrophotometer. UV spectra: 95% EtOH on a Cary model 14 recording spectrophotometer. NMR spectra: CCl_4 on a Perkin-Elmer model R-10 60Mc instrument, TMS as internal standard. Mass spectra: on an AEI MS9 spectrometer. TLC on microscope slides impregnated with Kieselgel G; the eluents were pet. ether–AcOEt mixtures, and the plates were developed with I vapours.

Hydroxy-ketone VI

Solid *m*-chloroperbenzoic acid. (15·5 g, 85% pure; 0·076 mole) was added during 10 min to a stirred solution of V (10·0 g; 0·072 mole)[12] in chf (200 ml) with external cooling, the temp being allowed to reach ca. 50°. A clear soln resulted, but *m*-chlorobenzoic acid then slowly precipitated. The mixture was allowed to stand for 1 hr without cooling, filtered, and the filtrate was evaporated under reduced press. Pet. ether was added to the residue, another crop of crystals was removed by filtration, and the filtrate was evaporated. VPC of the liquid product (6 ft Apiezon grease column, 150°) showed that it consisted of a ca. 1:1 mixture of VI (ret. time, 6·5 min) and the unrearranged 3,4-oxido-3,5,5-trimethyl-1-cyclohexanone (ret. time, 1·8 min), together with small amounts of isophorone (ret. time, 2·2 min) and *m*-chlorobenzoic acid.

The product was dissolved in ether (30 ml), H_2O (30 ml) was added, and the pH was adjusted to 11–12 by addition of NaOH aq. The mixture was stirred for 3 hr at room temp, and the ether layer was then washed with water. Drying and evaporation yielded VI (9·71 g; 87%; reported yield, 57%[13]) as an almost colourless oil, contaminated with only a trace of isophorone (VPC), which was used in the following steps. A distilled sample showed b.p. 98–103°/0·5 mm; IR bands at 3420 cm^{-1} (hydroxyl) and 1665 ($\alpha\beta$-unsatd ketone); NMR peaks at τ4·24 (1H, broad), 5·52 (1H, v broad), 6·05 (1H, broad), 7·67 (2H, AB quartet, $\delta_{AB} \simeq 10$ c/s, $J_{AB} = 15$ c/s), 7·95 (3H, singlet), 8·94 (3H, singlet) and 9·01 (3H, singlet).

Diketone VII

A soln of crude VI (4·70 g) in benzene (50 ml) containing *p*-toluenesulphonic acid (0·3 g) was boiled for 16 hr. Direct crystallization of the product from pet. ether gave VII (3·68 g; 78%), m.p. 64–67°; reported: m.p. 65–67°.[13]

Ketal VIII

The diketone VII (3·53 g) was converted to VIII, as described.[13] Distillation gave 4·15 g (91%), b.p. 77–80°/0·4 mm, n_D^{22} 1·469; IR bands at 1715 cm^{-1} (satd ketone) and 1100 (ketal). This material, which was used in the next step, was contaminated with ca. 20–25% of the corresponding diketal (NMR analysis, and isolation after reaction with lithium ethoxyacetylide, see below). Redistillation effected little further purification.

Ethoxyacetylenic carbinol IX

A soln of ethoxyacetylene (3·5 g; 50 mmoles; Pfister Chemical Works Inc., Ridgefield, N.J.; freshly distilled before use) in benzene (70 ml) was added dropwise to an ether soln of MeLi (70 ml, 0·65 N; 45·5 mmoles; prepared from Li and MeI) during 10 min, with stirring under N. The mixture was cooled in ice, and a soln of VIII (2·0 g; 10 mmoles) in benzene (20 ml) was added dropwise with continued cooling. The mixture was stirred at room temp for 4 hr, and was then poured into ice-water. The organic layer was separated, and the basic aqueous soln was extracted well with ether. The combined organic extracts were washed with water, dried, and evaporated. The resulting crude oily IX (2·57 g; 95%) showed IR bands at 3420 cm^{-1} (hydroxyl), 2260 (acetylene) and 1095 (ketal). This material (which showed two spots on TLC) was used in the next step.

In one experiment, the crude IX was chromatographed on neutral Al_2O_3. This resulted in the separation of the diketal of VII, which was eluted (with benzene) before IX. The diketal was an oil; IR band at 1100 cm^{-1} (ketal), no carbonyl bands; NMR peaks at τ 6·02 (4H, singlet), 6·19 (4H, multiplet) 8·3–8·8 (5H, complex multiplet), 8·90 (3H, singlet), 9·22 (3H, singlet) and 9·22 (3H, doublet, J = 6 c/s).

Unsaturated ester X

A soln of crude IX (2·57 g) in acetone (20 ml) containing 2 N H_2SO_4 (2 ml) was allowed to stand for 16 hr at room temp under N. Dilution with water, removal of the acetone under reduced press, and ether extraction, gave an oil, which was chromatographed on a column of silica gel (30 × 2 cm). Elution with benzene–ether (9:1 to 4:1) yielded X (1·08 g; 48% based on VIII) as a mixture of double bond isomers. It was a colourless oil, IR bands (CCl_4) at 1,705 cm^{-1} (ketone and unsatd ester) and 1625 (double bond); UV max at 223 mμ; NMR peaks at τ 4·15 (1H, singlet), 5·88 (2H, quartet, J = 7 c/s). 7·4–7·7 (5H, multiplet), and 8·58–8·80 (12H, multiplet).

Slow evapn of an ether soln of a middle chromatography fraction produced crystals. Seeding and crystallization from pet. ether then yielded one pure isomer of X (0·51 g; 23% based on VIII), m.p. 55·5–56·5°; IR and NMR spectra very similar to those of the mixture. (Found: C, 69·79; H, 8·72. $C_{13}H_{20}O_3$ requires: C, 69·61; H, 8·98%). The remaining material (0·57 g), which could not be induced to crystallize, is presumably a mixture of isomers.

Hydroxy-ester XIa *and acetoxy-ester* XIb

A soln containing crystalline X (0·5 g) and $NaBH_4$ (0·5 g) in MeOH (45 ml) and H_2O (5 ml) was allowed to stand at room temp for 1 hr. Dilute HCl aq was then added, the solvent was removed under reduced press, and the product was extracted with ether. The resulting oily XIa (0·45 g) appeared to be homogeneous by TLC; IR bands at 3400 cm^{-1} (hydroxyl), 1705 (unsatd ester) and 1625 (double bond); NMR spectrum similar to that of X, except for the additional presence of a broad peak at τ 6·65 (1H).

Acetylation was carried out with Ac_2O and pyridine for 16 hr at room temp. Isolation with ether yielded the oily acetate XIb (0·48 g; 80% based on X); homogeneous by TLC; IR bands at 1735 and 1240 cm^{-1} (acetate), 1705 (unsatd ester) and 1625 (double bond).

(±)-*Loliolide* (I) *from* XIb

A soln containing XIb (0·42 g; 1·57 mmole) and SeO_2 (0·15 g; 2·5 mmole; freshly sublimed) in glacial AcOH (30 ml) was boiled under reflux for 2 hr. The precipitated Se was removed by filtration, the solvent was removed under reduced press, and the residue was extracted with ether. The organic extract was washed with $NaHCO_3$ aq, dried, and evaporated.

The product (IR bands at 3400, 1705–1735 and 1630 cm^{-1}) was saponified by being allowed to stand in MeOH (30 ml) and 10% Na_2CO_3 aq (3 ml) for 16 hr at room temp. Water was added, and extraction was carried out with ether from the basic solution. Drying and evapn led to material, which showed four separate spots on TLC; the third in order of elution had a R_f value identical to that of natural loliolide. The material was then chromatographed on a column of silica gel (25 × 2 cm). The solid fractions eluted with benzene–ether (3:7) on crystallization from acetone–pet. ether yielded (±)-loliolide (7·5 mg; 2·5% based on XIb), m.p. 140–141°. (Found: C, 67·33; H, 8·03. $C_{11}H_{16}O_3$ requires: C, 67·31; H, 8·22%). The mass spectrum showed a mol ion at *m/e* 196. This spectrum and the IR spectrum (chf) were identical to those determined by us for natural loliolide, and the NMR spectrum was identical to the published one.[1]

(±)-Loliolide (I) *from natural loliolide*

Natural loliolide was oxidized to the optically active ketone XVI (m.p. 103–104°), and then racemized, as described previously.[1] The resulting crude racemic XVI was reduced directly with $NaBH_4$ in MeOH aq under the conditions described above. Isolation with ether, followed by direct crystallization from pet. ether–acetone, gave (±)-loliolide, m.p. 140–141°, undepressed on admixture with the synthetic compound.

Diketone XII

A standard 8 N soln of CrO_3 in H_2SO_4 aq (16 ml)[15] was added dropwise during 5 min to a stirred solution of VI (9·71 g; 0·063 mole) in acetone (100 ml; freshly distilled from $KMnO_4$) at room temp. Stirring was continued for a further 10 min, and MeOH was then added. The solvent was evaporated under reduced press, and the product was isolated with ether in the usual way. Distillation gave XII (8·19 g; 85%), b.p. 50–52°/0·2 mm; IR bands at 1665 cm^{-1} ($\alpha\beta$-unsatd ketone) and 1600 (double bond), no hydroxyl band; UV max at 240 mμ; NMR peaks at τ 3·51 (1H, multiplet), 7·37 (2H, singlet), 8·02 (3H, doublet, J = 2 c/s) and 8·78 (6H, singlet). The substance solidified at 0°, but remelted at room temp. The published method of oxidation[13] resulted in XII contaminated with much starting material.

Ketal XIII

The diketone XII (14·76 g; 0·097 mole) and *p*-toluenesulphonic acid (0·4 g) in benzene (100 ml) and ethylene glycol (9·0 g; 0·145 mole) was boiled for 12 hr, with removal of the resulting H_2O. The cooled soln was poured into $NaHCO_3$ aq, and the aqueous layer was washed with ether. The combined organic extracts were washed with H_2O, dried and evaporated. Two successive distillations gave XIII (13·50 g; 71%), b.p. 76–80°/0·5 mm, n_D^{20} 1·4910; IR bands at 1680 cm^{-1} ($\alpha\beta$-unsatd ketone) and 1100 (ketal); UV max at 226 mμ; NMR peaks at τ 3·80 (1H, multiplet), 6·07 (4H, singlet), 8·00 (2H, singlet), 8·24 (3H, doublet, J = 2 c/s) and 8·85 (6H, singlet).

Ethoxyacetylenic carbinol XIV

The ketal XIII (1·96 g; 0·01 mole) was allowed to react with lithium ethoxyacetylide, exactly as described above for the prep of IX. The resulting crude XIV (2·20 g; 83%) was obtained as an oil, homogeneous on TLC, which showed IR bands at 3450 cm^{-1} (hydroxyl), 2260 (acetylene), 1670 (double bond) and 1095 (ketal).

Dienone ester XVa

A soln of crude XIV (2·20 g) in acetone (20 ml) containing 2 N H_2SO_4 (2 ml) was allowed to stand for 16 hr at room temp under N. Dilution with H_2O and isolation with ether gave material, which was chromatographed on a column of silica gel (40 × 2 cm). Elution with benzene gave an oil (0·43 g), which was not investigated further. Elution with benzene–ether (19:1) yielded XVa (1·07 g) as an oil; IR bands at 1725 cm^{-1} (unsatd ester), 1675 (unsatd ketone), 1635 and 1595 (double bonds); UV max at 274 mμ; NMR peaks at τ 4·10 (2H, multiplet), 5·83 (2H, quartet, J = 7 c/s), 7·70 (2H, singlet), 7·90 (3H, doublet, J = 2 c/s), and 8·70–8·82 (9H, multiplet); mass spectrum, mol ion *m/e* 222. Further elution with benzene–ether (4:1) gave a mixture (0·56 g), which on rechromatography led to a further 0·23 g XVa (total yield, 1·30 g; 59% based on XIII). This material was a mixture of double bond isomers (see below), although it appeared to be homogeneous on TLC.

The rechromatography in addition to XVa gave a more polar substance as an oil, which is probably the hydroxy-ester derived by hydration of the acetylenic bond of XIV[17] (and removal of the ketal). It showed an IR band at 3400 cm^{-1} (hydroxyl), and could be dehydrated to XVa in low yield with thionyl chloride and pyridine.

(±)-Loliolide (I) *from* XVa

(a) *With sulphuric acid.* The ester XVa (0·44 g) was added slowly to conc. H_2SO_4 (5 ml), with stirring and ice-cooling. The brown soln was then allowed to warm to room temp, and to stand overnight. The solution was poured into ice-water, and the product was extracted with ether. Drying and evaporation yielded an oil (0·26 g) containing XVI, UV max at 215 and 274 mμ (approx. equal intensities), which showed four spots on TLC. Attempted chromatography on SiO_2 or Al_2O_3 resulted in extensive

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[17] See G. E. Arth, G. I. Poos, R. M. Lukes, F. M. Robinson, W. F. Johns, M. Feurer and L. H. Sarett, *J. Amer. Chem. Soc.* 76, 1715 (1954).

decomposition. A solution of this material and $NaBH_4$ (0·25 g) in MeOH (20 ml) and H_2O (2 ml) was allowed to stand at room temp for 1hr. Dil. HCl aq was added, the solvent was removed under reduced press, and the product was extracted with ether. The resulting oil (0·17 g), which showed three spots on TLC, was chromatographed on a column of silica gel (15 × 2 cm). The fractions eluted with benzene–ether (1:1 to 3:7) on crystallization from pet. ether–acetone gave (±)-loliolide (14 mg; 3·6% based on XVa), m.p. 140–141°. The IR and NMR spectra were identical to those of the sample obtained by the SeO_2 method, and there was no m.p. depression on admixture.

(b) *With sodium carbonate.* 10% Na_2CO_3 aq (2 ml) was added to XVa (200 mg) in MeOH (20 ml), and the soln was allowed to stand at room temp for 16 hr under N. Addition of water, and ether extraction, gave an oil (90 mg), which must be the "trans" isomer of XVa; IR, UV and NMR spectra essentially identical to those of starting material. Treatment of this product with conc. H_2SO_4 under the above described conditions did not result in the appearance of the UV band at 215 mμ due to XVI.

The aqueous soln from the Na_2CO_3 hydrolysis was acidified with HCl aq, and re-extracted with ether. Drying and evapn gave an oil (70 mg) containing XVI; UV max at 215 and 274 mμ (approx. equal intensities). $NaBH_4$ reduction, followed by chromatography and crystallization, as described above, then yielded (±)-loliolide (2·5 mg), m.p. 139–140°. There was no m.p. depression on admixture with the previously described compound, and the IR spectra were identical.

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