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# TERPENOIDS—XXXIX*

## THE SYNTHESIS OF TETRAHYDROSAUSSUREA LACTONE

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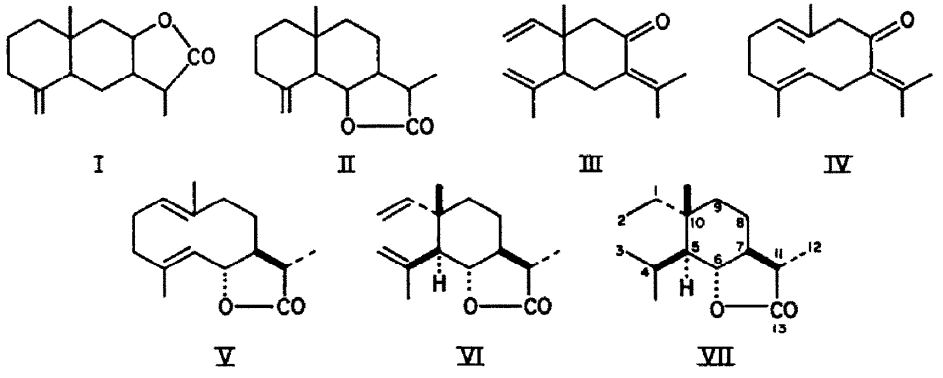
**Abstract**—An unambiguous total synthesis of tetrahydrosaussurea lactone using santonin as the starting material has been established. This synthesis confirms the structure and absolute configuration of tetrahydrosaussurea lactone as well as that of saussurea lactone, as previously established from this laboratory.[3]

SAUSSUREA lactone was isolated by Rao and Varma[1] from higher boiling fractions of vacuum distilled (180–200°/11 mm) costus root oil. Subsequently, Rao *et al.*[2] suggested tentative bicyclic structures (I or II) for this lactone on the basis of degradative studies. These structures were later disproved by Bhattacharyya *et al.*[3] who on the basis of spectral evidences and hydrogenation data showed that saussurea lactone contains two double bonds one of which is methylenic and the other of vinyl type (C=$CH_2$; —CH=$CH_2$). They also showed by analogy with the formation of pyrogermacrone (III) from germacrone (IV), that dihydrocostunolide (V) on pyrolysis (200–220°/50 mm) affords saussurea lactone. They further found that saussurea lactone on heating (at 180–190°) in the presence of *p*-nitro-benzoic acid underwent cyclization forming santenolide which on hydrogenation gave santanolide "c". Consequently, it was proved that the absolute configuration of saussurea lactone is represented by the structure VI and that of tetrahydrosaussurea lactone† by VII.



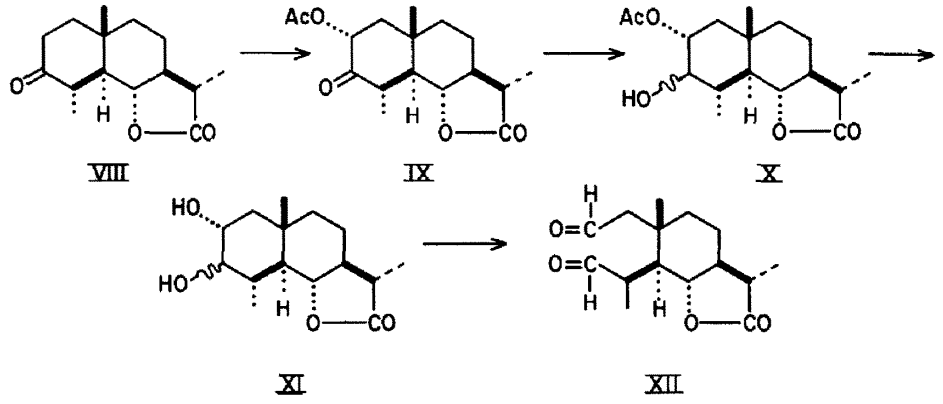

* Contribution No. 536 from the National Chemical Laboratory, Poona, India.

† In view of recent publication by J. D. M. Asher and G. A. Sim, *Proc. Chem. Soc.* 111 (1962); D. H. R. Barton, T. Miki, J. T. Pinhey and R. J. Well, *Ibid.* 112 and *J. Chem. Soc.* 3472 (1962), the methyl group at $C_{11}$ carbon atom in saussurea and tetrahydrosaussurea lactone and all the allied santonin derivatives mentioned in this paper is shown to be α-oriented and not β-oriented as was previously considered to be correct.

[1] P. S. Rao and B. S. Varma, *J. Sci. Ind. Res.* **10B**, 166 (1951).
[2] P. S. Rao, B. S. Varma, N. R. Ghosh and P. C. Dutta, *J. Sci. Ind. Res.* **17B**, 228 (1958).
[3] A. S. Rao, A. Paul, Sadgopal and S. C. Bhattacharyya, *Tetrahedron* **13**, 319 (1961).

In view of the unusual structural features of saussurea and tetrahydrosaussurea lactones, it was desirable to confirm their absolute configuration by unambiguous synthesis. This was considered important as we have found tetrahydrosaussurea lactone an excellent reference material for the elucidation of the stereochemistry of the sesquiterpenes of the elemane group.*

As starting material for the synthesis of tetrahydrosaussurea lactone, α-tetrahydrosantonin (VIII) of known absolute configuration was considered suitable. In the first approach, an attempt was made to obtain the dialdehydo-lactone (XII) which could then be converted to saussurea lactone (VI) or tetrahydrosaussurea lactone (VII) through known reactions.




Initially the *trans*-ketol-acetate (IX) was prepared from α-tetrahydrosantonin (VIII) following the procedure of Yamakawa.[4] This on hydrogenation was converted to hydroxy acetate (X) which presumably was a mixture of two epimers and consequently showed a wide melting point range (63–140°). But as the mixture of these two isomers was not expected to interfere with our objective the isomers were not separated. On saponification, this hydroxy acetate consumed two equivalents of alkali. Acidification of the saponified material afforded a gummy product which from its I.R. spectrum was considered to be lactone diol (XI) having bands at 3333 $cm^{-1}$ (hydroxyl group) and 1760 $cm^{-1}$ (γ-lactone). On treatment with sodium metaperiodate or periodic acid in dioxan solution instead of the expected dialdehyde (XII) only a polymeric product was obtained.

Subsequently, it was felt desirable to employ a new approach in which the bond between $C_2$ and $C_3$ carbon atoms had been already opened.

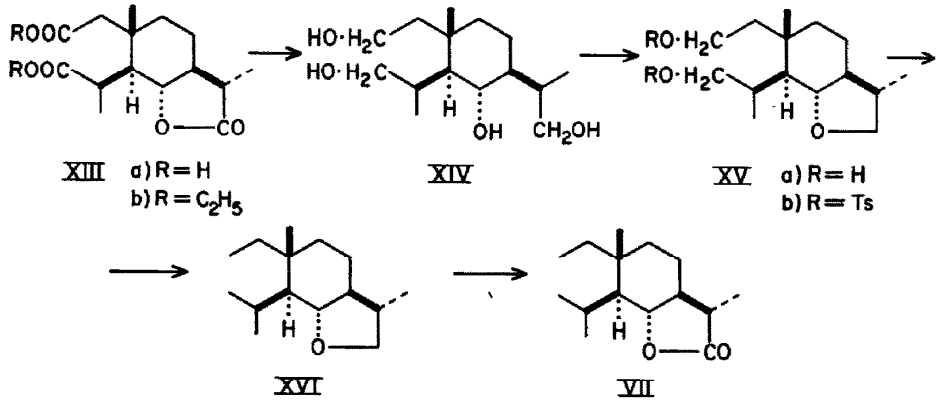
The crystalline dicarboxylic acid (XIIIa) prepared from α-tetrahydrosantonin (VIII) according to known procedure[4] was reduced with lithium aluminium hydride. The tetrol (XIV) thus obtained, because of its high polarity easily dehydrated to a diol-oxide considered to be (XVa) from its I.R. spectrum and elemental analysis.

It was felt that the diol-oxide (XVa) on tosylation (XVb) and subsequent reduction would afford the oxide (XVI) which on oxidation should form tetrahydrosaussurea lactone (VII).

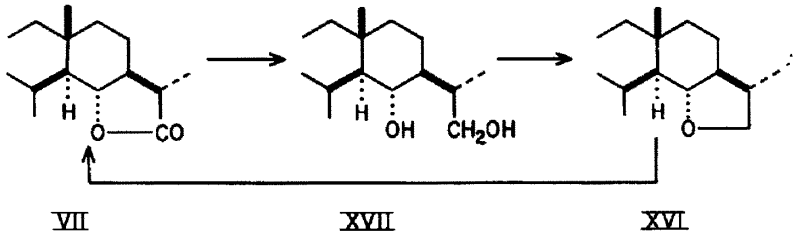
In anticipation, tetrahydrosaussurea lactone (VII) was reduced with lithium

* Unpublished data to be communicated.

[4] K. Yamakawa, *J. Org. Chem.* **24**, 897 (1959).




aluminium hydride to the crystalline diol (XVII), m.p. 91–93°, which on treatment with *p*-toluenesulphonic acid was converted to the oxide (XVI). This oxide has the



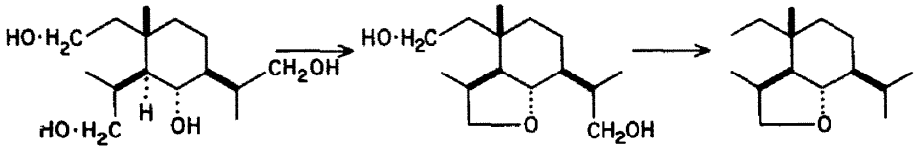

following properties; $[\alpha]_D$ −18·66°; $n_D^{28}$ 1·4755 and on chromic acid oxidation in acetic acid was reconverted to tetrahydrosaussurea lactone in high yield. The conversion of the oxide (XVI) to tetrahydrosaussurea lactone (VII) indicates that their stereo-orientation is of the same type. The molecular rotation differences between lactone (VII) and the diol (XVII), as well as between lactone (VII) and oxide (XVI) are in both the cases positive, indicating that the potential lactonic hydroxyl group is in α-orientation[5] and this is in agreement with the structure (VI) assigned to saussurea lactone.[3]

The oxide which was obtained from santonin, via dicarboxylic acid (XIIIa), tetrol (XIV) etc., however, even after purification by chromatography and redistillation over sodium did not show the same properties as the oxide (XVI) obtained from saussurea lactone. The oxide from santonin was a liquid, with correct elemental analysis and comparable boiling point to the oxide (XVI) obtained from saussurea lactone, but it showed much higher laevorotation, $[\alpha]_D$ −51·77°, a higher index of refraction, $n_D^{26}$ 1·4801 and its I.R. spectrum showed some distinct difference in the finger print region.

The failure of this approach could be explained in the following way. The tetrol (XIV) may also take up an orientation represented by the structure (XIV′) in which case one can expect in the subsequent stages formation of the diol (XVIII) and finally the oxide (XIX).

It is quite reasonable to assume that the oxide obtained from santonin was a

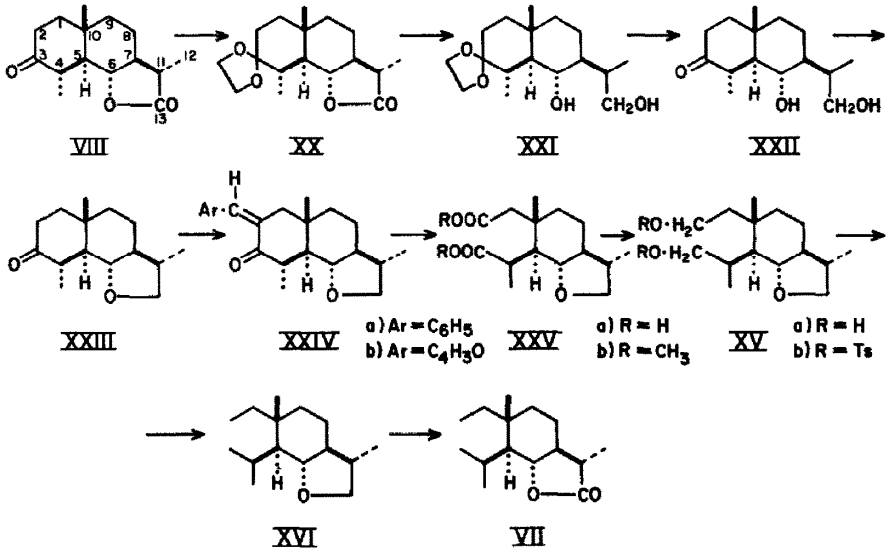
[5] V. Sykora and M. Romanuk, *Coll. Czech. Chem. Comm.* **22**, 1909 (1957).



XIV′ XVIII XIX

mixture of XVI and XIX. Because of their similar properties, it was not possible to separate these two oxides or the pure tetrahydrosaussurea lactone from the lactonic mixture formed by chromic acid oxidation of the mixture of these two oxides.

It was now clear that a successful unambiguous synthesis required first the formation of a suitable oxide ring between $C_6$ and $C_{13}$ to be followed by opening of the ring between $C_2$ and $C_3$ carbon atoms. Consequently, the following sequence of reactions resulted in the synthesis of tetrahydrosaussurea lactone (VII).



VIII XX XXI XXII

XXIII XXIV a) Ar = $C_6H_5$ b) Ar = $C_4H_3O$ XXV a) R = H b) R = $CH_3$ XV a) R = H b) R = Ts

XVI VII

The compounds XX to XXIII have been described in the literature[6] and the properties are in agreement with those obtained in the present investigation with the exception that the keto-oxide (XXIII) in our hands showed negative optical rotation. ($[\alpha]_D$ −10·76°) and not positive ($[\alpha]_D$ +11·8°) as previously reported.[6b]

To open the ring between $C_2$ and $C_3$ carbon atoms, the keto-oxide (XXIII) was subjected to Claisen-Schmidt's condensation as adopted by Johnson *et al.*[7–10] Preparation of benzylidene derivative followed by ozonization and subsequent oxidation with hydrogen peroxide in acetic acid, afforded an acidic product but it also showed

[6a] H. Matsumura, I. Iwai and E. Ohki, *J. Pharm. Soc, Japan* **75**, 687 (1955); [b] H. Ogura, *J. Org. Chem.* **25**, 679 (1960).

[7] W. S. Johnson, D. K. Banerjee, W. P. Schneider, C. D. Gutsche, W. E. Schelberg and L. J. Chinn, *J. Amer. Chem. Soc.* **74**, 2832 (1952).

[8] W. S. Johnson, E. R. Rogier, J. Ackerman, *J. Amer. Chem. Soc.* **78**, 6322 (1956).

[9] W. S. Johnson, B. Bannister, R. Pappo and J. E. Pike, *J. Amer. Chem. Soc.* **78**, 6354 (1956).

[10] W. S. Johnson, I. A. David, H. C. Dehm, R. J. Highet, E. W. Warnhoff, W. D. Wood and E. T. Jones, *J. Amer. Chem. Soc.* **80**, 661 (1958).

the presence of a small amount of lactone (a shoulder at 1780 $cm^{-1}$). To avoid undesirable lactone formation at this stage, the reaction with hydrogen peroxide was done in alkaline medium. The keto-oxide was converted to the furfurylidene derivative (XXIVb) following the procedure of Johnson,[9] and crystallized from methanol m.p. 114° with the expected U.V. absorption ($\lambda_{max}$ 323 m$\mu$, $\varepsilon = 25{,}860$).[10] On alkaline peroxide cleavage, the desired dicarboxylic acid (XXVa) was isolated as its dimethyl ester (XXVb). This was reduced with lithium aluminium hydride to the crystalline diol (XVa), m.p. 142–143°. Its I.R. spectra showed an intense peak for the hydroxyl group (3250 $cm^{-1}$) and the oxide ring (1035 $cm^{-1}$). On treatment with *p*-toluenesulphonylchloride in pyridine solution, it formed the ditosylate (XVb). Pure tosylate now obtained on reduction with lithium aluminium hydride afforded the desired oxide (XVI) completely identical in all respects including I.R. spectra with the oxide (XVI) obtained from saussurea lactone.

The properties of the two oxides are recorded below:

| | | |
|---|---|---|
| Oxide (XVI) obtained from saussurea lactone | $n_D^{28.5}$ 1·4755 | $[\alpha]_D$ −18·66° (*c*, 12·7; alcohol). |
| Oxide (XVI) obtained from santonin | $n_D^{28}$ 1·4757 | $[\alpha]_D$ −17·21° (*c*, 7·0; alcohol). |

The oxide (XVI) on oxidation with chromic acid gave tetrahydrosaussurea lactone (VII) as mentioned earlier.

As total synthesis of santonin has been achieved by earlier workers[11,12] results reported now amount to a total synthesis of tetrahydrosaussurea lactone. It has confirmed the absolute configuration of tetrahydrosaussurea lactone and consequently that of saussurea lactone itself, as previously established by Bhattacharyya *et al.*[3]

## EXPERIMENTAL

Melting and boiling points are uncorrected, U.V. spectra were determined in ethanol solution on Beckman DK-2 recording spectrophotometer. I.R. spectra were determined with Perkin–Elmer infracord spectrophotometer model 137-B and model 221. The sign (s) or (w) in I.R. data means strong and weak peak. Petroleum ether refers to the fraction, b.p. 60–80°. Microanalyses were carried out by Mr. Pansare and colleagues and I.R. and U.V. measurements by Mr. Gopinath and Miss Prabhu.

### α-*Tetrahydrosantonin* (VIII)

α-Tetrahydrosantonin was prepared from santonin (25 g) (May & Baker) by hydrogenation in acetone (250 ml) solution containing palladium charcoal (1 g, 7%) as described.[13] Hydrogenation was followed by isomerization of β-tetrahydrosantonin to α-tetrahydrosantonin with hydrochloric acid (50 ml, 15%); yield 62% (15·75 g), m.p. 152–54°; $[\alpha]_D$ +22·6° (*c*, 7·0; alcohol); lit.[13] records: m.p. 153°; $[\alpha]_D$ +23·4°.

### Trans-*Ketol-acetate* (IX)

α-Tetrahydrosantonin (2·02 g) and freshly prepared lead tetracetate (4·0 g) were dissolved in glacial acetic acid (400 ml) and the mixture refluxed on a heating mantle for 6 hr. The residue after removal of acetic acid, was extracted with chloroform, washed with saturated aqueous sodium

[11] Y. Abe, T. Harukawa, H. Ishikawa, T. Miki, M. Sumi and T. Toga, *Proc. Japan Acad.* **28**, 425 (1952); **29**, 113 (1953); **30**, 116 (1954); **30**, 119 (1954); *J. Amer. Chem. Soc.* **75**, 2567 (1953).
[12] M. Matsui, K. Toki, S. Kitamura, Y. Suzuki, M. Hamuro, *Bull. Chem. Soc., Japan* **27**, 7 (1954).
[13] M. Yanagita and A. Tahara, *J. Org. Chem.* **20**, 959 (1955).

bicarbonate followed by water, and dried ($Na_2SO_4$). The product (2·3 g, 92·4%) melted over a range 180–200°, but after recrystallization from ethanol afforded crystals, m.p. 198–202° identical with that described.[4] I.R. spectrum (in Nujol): Bands at 1761 $cm^{-1}$ ($\gamma$-lactone); 1736 $cm^{-1}$ (acetyl group), 1715 $cm^{-1}$ (cyclohexanone ring); other bands at 1449, 1370, 1235 (s), 1202, 1136, 1096, 1016 (s), 984 (s), 936 (w), 902 (w), 852 (w), 725 $cm^{-1}$.

*Hydroxy-acetate* (X)

The ketol-acetate (IX; 1·0 g) in glacial acetic acid (50 ml) was hydrogenated in the presence of Adams catalyst (70 mg). Hydrogen corresponding to one double bond (85 ml, 26°, 715 mm) was absorbed during 1 hr with no further absorption. The catalyst was filtered off, and acetic acid neutralized with dil potassium hydroxide solution at low temperature (+5°). After working up in the usual way, the residual white amorphous product (0·71 g; 70·8%) could not be crystallized. After sublimation amorphous material was obtained melting over a wide range 63–140° (Found: C, 66·27; H, 8·54. $C_{17}H_{26}O_5$ requires: C, 65·78; H, 8·44%). I.R. spectrum (in Nujol): Bands at 3472 $cm^{-1}$ (hydroxyl group); 1761 $cm^{-1}$ ($\gamma$-lactone); 1718 $cm^{-1}$ (acetyl group); other bands at 1238, 1139, 1019, 980, 933, 855, 726 $cm^{-1}$.

*Lactone-diol* (XI)

Hydroxy-acetate (X; 0·62 g) was dissolved in 0·5N alcoholic potassium hydroxide (20 ml) and refluxed for 3 hr. The saponification value 154·3 obtained after titration with 0·5N hydrochloric acid correspond to a molecular weight of 308·6 (expected 310·36). After removal of alcohol the residual solution was mildly acidified with a saturated aqueous solution of potassium dihydrogen phosphate (20 ml), extracted with chloroform and worked up in the usual way; the yield was 0·4 g I.R. spectrum: Bands at 3333 $cm^{-1}$ (hydroxyl group); 1760 $cm^{-1}$ ($\gamma$-lactone); other bands at 1453, 1370, 1144 (s), 1073, 1050, 1017 (s), 985, 926, 885 (w), 855 (w), 763 (w), 726 $cm^{-1}$.

*The attempted oxidation of lactone-diol* (XI) *to dialdehyde-lactone* (XII)

(a) Lactone-diol (XI; 0·4 g) was dissolved in dioxan (10 ml) and a saturated solution of sodium metaperiodate (15 ml) was added. The mixture was stirred overnight in a nitrogen atmosphere after which it was extracted with chloroform. The chloroform solution after working up, left 0·25 g which failed to give any semicarbazone and subsequently resinified.

(b) Lactone-diol (XI) was dissolved by stirring in dioxan (25 ml) in a nitrogen atmosphere. A solution of periodic acid dihydrate (750 mg) in distilled water (15 ml) was added and the stirring under nitrogen atmosphere at room temp continued overnight. The solvent was removed at room temp *in vacuo* and the residue diluted with water and extracted with ether. The ethereal extract after washing with sodium carbonate solution and water was dried, the ether removed and the residue in a few ml ethanol treated with semicarbazide solution, but no semicarbazone could be obtained.

*Lactone-diacid* (XIIIa)

A conical flask (1 l.) containing ammonium vanadate (0·4 g) and fuming nitric acid (100 ml, $d$ 1·52) was fitted with a magnetic stirrer and α-Tetrahydrosantonin (9·4 g) added. A vigorous exothermic reaction ensued with evolution of a brown-red gas. When the reaction subsided, the product was decanted into another flask and three other batches were similarly oxidized. The combined reaction products were diluted with water (380 ml) and then concentrated under reduced pressure. The residual red viscous oil in ethyl acetate was extracted with aqueous sodium carbonate solution. Acidification of this solution deposited crystalline diacid (XIIIa) which after crystallization from water afforded 14·6 g (32·6%), m.p. 193–194°, $[\alpha]_D$ −88·61° ($c$, 2·11; alcohol) (Found: C, 60·63; H, 7·35. $C_{15}H_{22}O_6$ requires: C, 60·39; H, 7·43%). I.R. spectrum (in Nujol): Bands at 2941, 2660 and 1709 $cm^{-1}$ (carboxyl group); 1779 $cm^{-1}$ ($\gamma$-lactone); other bands at 1626, 1457, 1408 (w), 1391 (w), 1370, 1295 (s), 1269, 1242 (w), 1220, 1205, 1190, 1161, 1124, 1103 (w), 1081 (w), 1057, 1042, 1020, 1002, 985 (w), 950, 920, 888, 847, 806 (w), 749 (w), 724 $cm^{-1}$. lit.[4] records: m.p. 193–195°; $[\alpha]_D^{26}$ −15·0° (EtOH, $c$, 1·27).

*Lactone-diethylester* (XIIIb)

Lactone-diacid (XIIIa; 12·9 g) was azeotropically esterified with ethanol in the usual way, yielding 14·9 g of the lactone-diethylester (XIIIb) which was distilled in a diffusion pump (210°/2 × $10^{-2}$ mm) (Found: C, 64·0; H, 8·6; $C_{19}H_{30}O_6$ requires: C, 64·38; H, 8·53%).

*Tetrol* (XIV)

Lactone-diethylester (14·2 g) was reduced with lithium aluminium hydride (15·5 g) in dry ether solution (600 ml). After refluxing for 6 hr excess lithium aluminium hydride was destroyed with alcohol (30 ml, 90%), water (50 ml) and sulphuric acid (600 ml, 10%). The aqueous layer which contained the desired tetrol was separated, and the ether-layer was washed 3 times with water (3 × 50 ml). The combined aqueous solution was neutralized with 50% aqueous potassium hydroxide (pH 6·5–7). The precipitate formed was filtered off and the filtrate concentrated under reduced pressure. The oily residue formed was mechanically separated and combined with the extracts obtained subsequently after continuous extraction of the aqueous portion with chloroform. The crude tetrol (10·8 g), a viscous oil, could not be crystallized and was used as such for further reaction. I.R. spectrum: Bands at 3240, 1026 $cm^{-1}$ (hydroxyl group); absence of any peak in region between 1600–2000 $cm^{-1}$; other bands at 2860, 1447, 1378, 1291 (w), 1254, 1119 (s), 1080, 973, 887 (w), 869 (s) $cm^{-1}$.

*Diol-oxide*

The crude tetrol (XIV; 6 g) was dehydrated with *p*-toluenesulphonic acid (1·3 g) in dry dioxan (120 ml). After refluxing for 45 min, dioxan was removed *in vacuo* and water (100 ml) added. The mixture was extracted with ether and the aqueous portion subjected to continuous extraction with chloroform for 24 hr. After working up in the usual way, the ether and chloroform solutions yielded the crude diol-oxide (4·3 g) which was combined with the product from another batch similarly obtained and distilled under high vacuum, b.p. 200° (bath)/8·5 × $10^{-4}$ mm, yielding 5·3 g of light greenish viscous oil (Found: C, 69·6; H, 11·3. $C_{15}H_{28}O_3$ (XVa or XVIII) requires: C, 70·2; H, 11·0%). I.R. spectrum: Bands at 3472, 1040 $cm^{-1}$ (hydroxyl group) other bands at 1462, 1391, 961 $cm^{-1}$.

*Ditosyl-oxide*

The above diol-oxide (5·2 g) was dissolved in freshly distilled anhydrous pyridine (100 ml) and *p*-toluenesulphonylchloride (14·4 g) was added. After warming (at 60°, for 10 min) the mixture was kept in a desiccator at room temp for 3 days. Water (150 ml) was added, and the solution extracted with ether. The ether solution was washed with 10% solution of hydrochloric acid, water, aqueous sodium carbonate and finally with water. After drying and evaporation of ether the crude ditosyl oxide (6·0 g) was chromatographed an alumina III. The tosyl derivative (5·5 g) was obtained in the petroleum ether–benzene (1:1) extract. I.R. spectrum: Bands at 2990 (s), 1595, 1449, 1387, 1355 (s), 1302 (w), 1289 (w), 1188 (s), 1174 (s), 1098, 1044, 1019, 960 (s), 816 (s), 794, 775, 742 (w), 708 (w), 682 (s) $cm^{-1}$.

*Reduction of ditosyl oxide with lithium aluminium hydride*

The ditosyl oxide (5·1 g) described above dissolved in dry ether (180 ml) was slowly added under stirring to lithium aluminium hydride (10 g) in dry ether. After 8 hr stirring and refluxing with the help of an I.R. lamp excess of lithium aluminium hydride was decomposed in the cold with ethanol (60 ml, 96%) and aqueous hydrochloric acid (400 ml, 15%). The ether portion after usual treatment afforded 3·1 g of a crude oxide. On chromatography on alumina III (150 g), the pet ether–benzene (1:1) eluate gave 2·6 g of a mobile colourless oil which was distilled twice over sodium b.p. 165° (bath)/12 mm, $n_D^{26}$ 1·4801, $[\alpha]_D$ −51·77° (*c*, 6·5; alcohol).

The product was fractionated by using a small column and divided into 3 fractions.

*Fraction* I. (0·8 g), b.p. 128–135°/7 mm; $n_D^{26}$ 1·4788; $d_4^{30}$ 0·9234; $[\alpha]_D$ −48·39° (*c*, 16·5; alcohol) (Found: C, 80·74; H, 12·52. $C_{15}H_{28}O$ requires: C, 80·29; H, 12·58%). I.R. spectrum: Bands at 2990, 1451 (s), 1370 (s), 1325 (w), 1236 (w), 1202 (w), 1174, 1125, 1098 (s), 1055, 1033 (s), 1019 (s), 983, 952, 909, 861 (w), 779 (w) $cm^{-1}$.

*Fraction* II. (0·85 g), b.p. 135–140°/7 mm; $n_D^{26}$ 1·4795; $[\alpha]_D$ −53·23° (*c*, 11·2 alcohol) (Found:

C, 80·35; H, 12·71. $C_{15}H_{28}O$ requires: C, 80·29; H, 12·58%). I.R. spectrum is superimposable with the spectrum of Fraction I.

*Fraction* III. (0·15 g) b.p. over 140°/7 mm, $n_D^{26}$ 1·4821.

*Chromic acid oxidation of Fraction* I

Fraction I (0·32 g) was dissolved in acetic acid (8 ml) and to this solution chromic acid (0·38 g) dissolved in acetic acid (0·38 g) was added. After shaking for 15 min on a water bath (70–80°) methanol (4 ml) was added followed by water (80 ml) and the mixture extracted with ether. After working up in the usual way, the residue was saponified by refluxing with alcoholic potassium hydroxide (10 ml, 10%) for 2 hr. Alcohol was removed and water (20 ml) was added. After washing with ether to remove neutral material, if any, the aqueous portion was acidified and extracted with ether. The ether solution was worked up to afford a mixture of lactone and unreacted hydroxy-acid according to I.R. spectrum. The product was chromatographed on alumina III and eluted with pet ether to furnish 80 mg of a white amorphous substance, the I.R. spectrum of which showed the presence of lactone group, but it could not be identified as tetrahydrosaussurea lactone. I.R. spectrum (in Nujol): Bands at 2940, 1770, 1453, 1379, 1290 (w), 1263 (w), 1215 (s), 1160, 1075 (w), 1036 (s), 1005 (s), 980 (s), 913, 831 (w), 815 (w), 781 (w), 730, 690 $cm^{-1}$.

*Tetrahydrosaussurea-6,13-diol* (XVII)

Tetrahydrosaussurea lactone (VII; 10·1 g) dissolved in dry ether (150 ml) was added carefully under stirring to a mixture of lithium aluminium hydride (5·9 g) and anhydrous ether (150 ml). The reaction product was stirred and refluxed for 3 hr and then decomposed in the usual way under cooling with ethanol (35 ml, 96%) and hydrochloric acid (170 ml, 15%).

The ethereal layer was washed with 2% potassium hydroxide solution and water and ether removed. The residue was refluxed with alcoholic potash solution (100 ml, 10%) to remove any unreacted lactone. Alcohol was removed and the product was extracted with ether; after working up it furnished a viscous diol (XVII) 10·25 g (quantitative) which soon crystallized. After a few recrystallizations from pet ether–benzene mixture (1:1) and sublimation it was obtained as shining crystals, m.p. 91–93°, $[\alpha]_D$ −6·3° (*c*, 8·5; alcohol) (Found: C, 74·7; H, 12·6. $C_{15}H_{30}O_2$ requires: C, 74·32; H, 12·48%). I.R. spectrum (in Nujol): Bands at 3425, 1022 $cm^{-1}$ (hydroxyl group); other bands at 2941, 1460, 1400 (w), 1379, 1335, 1299 (w), 1238 (w), 1176 (w), 1139 (w), 1127 (w), 1100 (w) 1087, 1042, 1022 (s), 1005, 980, 970, 930 (w), 917 (w), 871 (w), 869, 833 (w), 826 (w), 803 (w), 781 (w), 719 $cm^{-1}$.

*Tetrahydrosaussurea-6,13-oxide* (XVI)

The diol (XVII; 10 g) was dissolved in dry benzene (180 ml) containing *p*-toluenesulphonic acid (1·2 g) and refluxed for 1 hr. The solvent was removed, the residue treated with water (100 ml) and extracted with ether. The ether solution afforded 9·4 g of crude oxide which on standing for 2 days gave 1·3 g of the unreacted diol in crystalline form which was separated by filtration. The liquid portion was chromatographed on alumina III. The oxide (7·5 g, 93% on the basis of used diol), eluted with pet ether, on distillation twice over sodium, b.p. 160–165° (bath)/12 mm, was obtained as a mobile liquid $n_D^{28\cdot5}$ 1·4755; $d_4^{30}$ 0·9212; $[\alpha]_D$ −18·66° (*c*, 12·7; alcohol) (Found: C, 80·3; H, 12·6. $C_{15}H_{28}O$ requires: C, 80·29; H, 12·58%). I.R. spectrum: Bands at 1032 $cm^{-1}$ (oxide); other bands at 2930, 1451, 1370, 1340 (w), 1316 (w), 1274 (w), 1195, 1178, 1136, 1101, 1032 (s), 1001 (s), 983 (s), 960, 924 (w), 914 (w), 866 (w), 834 (w), 819, 779 (w) $cm^{-1}$.

*Chromic acid oxidation of tetrahydrosaussurea-6,13-oxide to tetrahydrosaussurea lactone* (VII)

Tetrahydrosaussurea-6,13-oxide (XVI; 0·75 g) in glacial acetic acid (17 ml) was oxidized with chromic oxide (0·7 g) dissolved in water (2 ml) and acetic acid (15 ml). The mixture was heated on a water bath (70–80°) for 15 min and after cooling methyl alcohol (5 ml) was added. After addition of water (100 ml) the mixture containing suspended white crystals was extracted with ether and the ether solution washed with aqueous sodium carbonate and water and finally the ether was removed. The residue was saponified with alcoholic potassium hydroxide (15 ml, 10%), the alcohol removed and the residue diluted with water (25 ml). The aqueous solution was washed with ether and later acidified to congo-red. The white crystals after purification afforded 0·55 g (69%) which after recrystallization

from alcohol had m.p. 123–124° not depressed with an authentic sample of tetrahydrosaussurea lactone; $[\alpha]_D$+ 41·2° (*c*, 3·2; alcohol); I.R. spectra superimposable with that of tetrahydrosaussurea lactone.

*α-Tetrahydrosantonin-3-ketal* (XX)

A mixture of α-tetrahydrosantonin (20·2 g) freshly distilled ethylene glycol (160 ml) and dry toluene (600 ml) was refluxed under stirring during 1 hr and a small amount of separated water was tapped out using a continuous water removal head. *p*-Toluenesulphonic acid (0·5 g) was added and stirring with reflux continued for 6 hr and separated water removed. Subsequently the reaction mixture was washed with sodium bicarbonate solution and the toluene layer separated and worked up. An oily material which soon crystallized, after two recrystallization from alcohol furnished pure ethylene-ketal derivative (XX; 18·2 g, 77%), m.p. 170–71°; $[\alpha]_D$ +23·5° (*c*, 10·7; chloroform) (Found: C, 69·3; H, 9·2. $C_{17}H_{26}O_4$ requires: C, 69·36; H, 8·9%). I.R. spectrum (in Nujol): Bands at 1776 $cm^{-1}$ (γ-lactone); 1098 $cm^{-1}$ (ethylene ketal);[14] other bands at 2985, 1453, 1404 (w), 1377, 1346, 1330, 1314, 1281 (w), 1267, 1250, 1235, 1211, 1193, 1182, 1155 (s), 1139, 1140, 1132, 1116, 1062 (s), 1028, 1010, 980, 961, 946, 917 (s), 897, 867 (w), 857, 772 (w), 749 (w), 718 $cm^{-1}$. Lit.[6] records: (a) m.p. 167–168·5°; $[\alpha]_D^8$ +23·4°; (b) m.p. 168°; $[\alpha]_D^{14}$ +26·1° (*c*, 5·4; chloroform).

*α-Tetrahydro-santan-6,13-diol-3-ketal* (XXI)

The ketal (XX; 18 g) in ether–benzene mixture (6:1; 500 ml) was reduced with lithium aluminium hydride (8·5 g) in ether benzene mixture (6:1; 210 ml) under stirring. After refluxing for 4 hr excess of lithium aluminium hydride was decomposed with alcohol (30 ml, 96%) followed by water (150 ml); no mineral acid was employed. The clear ether layer was separated and worked up. Removal of ether afforded the ketal-diol (15·7 g) (86%) as white crystals and was recrystallized from alcohol, m.p. 149–151°; $[\alpha]_D$ −8·3° (*c*, 7·2; chloroform) lit.[6] records: (a) m.p. 149–51°; $[\alpha]_D^8$ −14·0° (b) m.p. 149–51°; $[\alpha]_D^8$ −14·0°.

3-*Keto-α-santan-6,13-diol* (XXII)

The ketal-diol (XXI) was deketalized by refluxing in acetone solution with sulphuric acid. The product was actually a mixture of keto-diol (XXII) and the keto-oxide (XXIII). The latter was formed by simultaneous dehydration of the keto-diol (XXII) in presence of acid. A typical experiment is described below:

Ketal-diol (XXI; 15 g) was dissolved in acetone (300 ml) containing dil sulphuric acid (25 ml, 15%) and the mixture refluxed for 1 hr. The mixture was neutralized with aqueous sodium carbonate solution and acetone was subsequently removed. The residual floating oil was taken up in ether and worked up in the usual way. It afforded 9·4 g of viscous oil which after treatment with small amount of ether and cooling deposited certain quantity of keto-diol in the form of crystals. After recrystallization from ether–acetone mixture, 2·3 g of pure keto-diol (XXII) was obtained. A further quantity (0·9 g) of crystalline keto-diol was obtained by continuous extraction of the aqueous bicarbonate portion with chloroform. The combined mother liquor (9·6 g) after removal of crystalline keto-diol (XXII) was used for direct preparation of keto-oxide (XXIII) described subsequently. Keto-diol (XXII; 3·2 g) showed the following properties, m.p. 116–118°; $[\alpha]_D$ +26·0° (*c*, 2·6; chloroform) (Found: C, 70·94; H, 10·18. $C_{15}H_{26}O_3$ requires: C, 70·83; H, 10·30%). I.R. spectrum (in Nujol): Bands at 3350 $cm^{-1}$ (hydroxyl group); 1709 $cm^{-1}$ (keto group); other bands at 3000, 1460, 1379, 1351, 1328, 1299, 1266, 1233, 1220, 1176, 1149, 1126 (s), 1062 (s), 1044 (s), 1031 (s), 1002, 982 (w), 960, 943, 928, 909, 877 (w), 847, 772, 725 $cm^{-1}$. Lit.[6] (a) m.p. 117–118°; (b) m.p. 119–120°; m.p. 117–118°.

3-*Keto-α-santan-6,13-oxide* (XXIII)

This could be obtained from the crystalline keto-diol (XXII) or from the residual mother liquor.

(a) *Keto-oxide* (XXIII) *from keto-diol.* Dehydration of keto-diol (XXII; 0·5 g) was accomplished following the procedure described in the literature,[6b] in toluene solution (10 ml) with hydrochloric acid (4 ml, 20%) and refluxing in an oil bath for 16 hr. It afforded 0·46 g (quantitative) of mobile oil which soon crystallized. Recrystallization from pet ether afforded pure crystals of keto-oxide (XXIII), m.p. 84–86°; $[\alpha]_D$ −7·5° (*c*, 5·0; chloroform).

[14] S. Bernstein, R. Lenhard and J. Williams, *J. Org. Chem.*, **18**, 1172 (1953).

(b) *Keto-oxide* (XXIII) *from the deketalization mother liquor.* After separation of keto-diol (XXII) the residual mother liquor (9·6 g) was directly processed in toluene solution (200 ml) containing hydrochloric acid (80 ml, 20%) as described above under (a). The crude crystals of keto-oxide (7·9 g) were dissolved in pet ether, treated with active carbon and then passed through a column of alumina III (20 g). After elution with pet ether and recrystallization from the same solvent, 7·3 g of keto-oxide (XXIII) was obtained, m.p. 85–86°; $[\alpha]_D$ −10·76° (*c*, 12·2; chloroform). (Found: C, 76·3; H, 10·1. $C_{15}H_{24}O_2$ requires: C, 76·22; H, 10·24%). I.R. spectrum (in Nujol): Bands at 2985, 1712, (cyclohexanone ring); 1460, 1420 (w), 1374, 1337, 1314, 1285, 1279, 1252, 1232, 1212, 1189, 1163, 1149, 1134, 1121, 1074, 1056, 1030, 1000, 968, 950, 926, 901, 885, 841, 780, 709 $cm^{-1}$.

*Benzylidene-keto-oxide* (XXIVa)

To a boiling solution of the keto-oxide (XXIII) (2·0 g) in methanol (100 ml), freshly distilled benzaldehyde (1·2 g) was added followed by aqueous solution of sodium hydroxide (10 ml, 33%) and the mixture left under nitrogen atmosphere at 44° for 3 days. After removal of a portion of alcohol (about 50 ml) at room temp, water (100 ml) was added and the viscous oily material which separated was extracted with ether. The ether solution was worked up in the usual way to provide the benzylidene derivative which was chromatographed on alumina I (60 g). In the first 4 fractions (I—Pet ether–benzene 1:1, 0·72 g; II—Pet ether–benzene 1:2, 0·61 g; III—benzene, 0·58 g; IV—benzene–ethyl acetate 5:1, 0·9 g) the presence of benzylidene derivative was established from the U.V. spectra ($\lambda_{max}$ 290 m$\mu$)[10,15] and $\varepsilon$ values between 14,200 and 17,500. The third fraction (Found: C, 81·7; H, 9·1. $C_{22}H_{28}O$ requires: C, 81·44; H, 8·7%), showed the following spectral characteristics. I.R. spectrum: Bands at 2950, 1689 (keto-group); 1597, 1572, 1493, 1449 (s), 1379, 1307 (w), 1285 (w), 1235 (s), 1193 (s), 1175, 1155, 1140, 1122, 1067, 1036 (s), 1019 (s), 1000 (s), 972 (s), 958 (s), 926, 898 (w), 858 (w), 838 (w), 759 (s), 712, 694 (s) $cm^{-1}$.

*Furfurylidene-keto-oxide*(XXIVb)

Keto-oxide (XXIII; 4·66 g) was dissolved in ice-cooled methanol (150 ml). To this, a solution of sodium hydroxide (23 ml, 33%) was added, followed by freshly distilled furfural (10 ml). The mixture was kept overnight under a slow current of nitrogen at room temp. Methanol was removed *in vacuo* at 40–50° and the residue diluted with water (100 ml). The oily product which separated after working up was dissolved in pet ether and passed through alumina III (50 g), furnishing 6·07 g (98%) of furfurylidene derivative ($\lambda_{max}$ 323 m$\mu$, $\varepsilon$ = 23,050) which on addition of small amount of methanol and leaving at room temp furfurylidene derivative crystallized out. After recrystallization from methanol, it showed m.p. 114°, $[\alpha]_D$ −2·98° (*c*, 5·7; alcohol) (Found: C, 76·8; H, 7·9. $C_{20}H_{26}O_3$ requires: C, 76·4; H, 8·3%). U.V. spectrum: $\lambda_{max}$ 323 m$\mu$, $\varepsilon$ = 25860. I.R. spectrum (in Nujol): Bands at 3125 (w), 2941, 1669, 1597, 1538, 1453, 1374, 1348 (w), 1314, 1279 (w), 1245 (s), 1203 (s), 1176 (w), 1153, 1142, 1122, 1070, 1031 (s), 1015, 1001, 970, 952, 926, 881, 855, (w) 836 (w), 823 (w), 778 (s), 684 $cm^{-1}$.

*Dimethylester-oxide* (XXVb)

Furfurylidene derivative (XXIVb; 1·47 g) dissolved in methanol (30 ml) was added to a solution of sodium methoxide (sodium 6·5 g, dry methanol 170 ml). To this solution hydrogen peroxide (50 ml, 30%) was added and the mixture stirred in a "Waring blendor" (7,000–10,000 r.p.m.) for 6 hr. Subsequently, the solvent and residual hydrogen peroxide were removed under reduced pressure in nitrogen atmosphere. The residue was dissolved in water and extracted with ether. The alkaline aqueous extract was acidified with dil sulphuric acid and the liberated organic acid was extracted with ether. The ether extract was washed with aqueous solution of ferrous sulphate, water and dried over sodium sulphate. Removal of ether furnished 1·17 g of crude oily acid. From 3 such experiments, the combined acidic product (3·3 g) was esterified with diazomethane and the crude diester oxide (XXVb) was dissolved in pet ether–benzene (1:1) passed through a column of alumina III (40 g) and eluted with the same solvent mixture. The residue was distilled b.p. 165° (bath)/0·3 mm to furnish the diester oxide (XXVb), 2·0 g (46%) (Found: C, 65·36; H, 9·03. $C_{17}H_{28}O_5$ requires: C, 65·67;

[15] A. L. Wilds, L. W. Beck, W. J. Colse, C. Djerassi, J. A. Johnson, T. L. Johnson, C. H. Chunk, *J. Amer. Chem. Soc.* **69**, 1985 (1947).

H, 9·04%). I.R. spectrum: Bands at 1748 $cm^{-1}$ (ester); 1037 $cm^{-1}$ (oxide); other bands at 3012, 1462, 1441, 1387, 1357, 1208 (s), 1170 (s), 1134, 1114, 1053, 1005 (w), 966, 926 (w), 893 (w), 847, 772 (w), 725 (w) $cm^{-1}$.

*Diol-oxide* (XVa)

A solution of the diester-oxide (XXVb; 1 g) in dry ether (30 ml) was reduced in the usual way with lithium aluminium hydride (2·0 g) in anhydrous ether (70 ml). After refluxing for 5 hr the reaction product was decomposed in cold with ethanol (20 ml, 96%) and hydrochloric acid (80 ml), 15%). The ether extract was worked up in the usual way and after removal of ether left a viscous oily residue of the diol, which on mixing with a little ether crystallized. After recrystallization from benzene, 0·31 g of the pure diol oxide (XVa) was obtained, m.p. 142–43°; $[\alpha]_D$ −23·4° (*c*, 7·0; alcohol); (Found: C, 70·52; H, 11·18. $C_{15}H_{28}O_3$ requires: C, 70·27; H, 11·01%). I.R. spectrum (in Nujol): Bands at 3226 $cm^{-1}$ (hydroxyl group); 1035 $cm^{-1}$ (oxide); other bands at 2924, 1700 (w), 1493 (w), 1458, 1374, 1342 (w), 1299, 1217 (w), 1199 (w), 1176, 1148, 1130, 1099, 1085, 1064, 1010 (s), 998 (s), 980, 955 (s), 938, 909, 865 (w), 833, 781, 735 $cm^{-1}$.

*Ditosyl-oxide* (XVb)

Diol-oxide (XVa; 0·45 g) was treated in dry pyridine (20 ml) with *p*-toluenesulphonylchloride (2 g). Subsequently the mixture was heated for 5 min at 50° and then kept at room temp in a desiccator for 4 days. The reddish-brown solution was diluted with water (50 ml) and extracted with ether. After working up the ether solution, 0·54 g of crude tosylate was obtained which was dissolved in pet ether–benzene (1:1) and passed through a column of alumina III (15 g) and eluted with the same solvent mixture. After removing the solvent the oily tosylate (XVb; 0·49 g; 46%) was obtained. I.R. spectrum: Bands at 3003, 1608, 1495, 1464, 1368 (s), 1309 (w), 1294 (w), 1253 (w), 1212, 1192 (s), 1176 (s), 1122 (w), 1100, 1036, 1000, 961, 840 (s), 817 (s), 795, 775, 732, 708, 680 (s) $cm^{-1}$.

*Tetrahydrosaussurea*-6,13-*oxide* (XVI)

The tosylate (XVb; 0·45 g) dissolved in dry ether (50 ml) was reduced by stirring with lithium aluminium hydride (1·5 g) in dry ether (100 ml). The mixture was refluxed for 5 hr after which the reaction product was worked up in usual way to furnish the oxide (XVI) as a mobile oil. It was filtered through alumina III (10 g) and eluted with pet ether. Removal of solvent afforded 0·15 g of the oxide which was distilled, b.p. 170° (bath)/14 mm, twice over sodium to give the pure oxide 85 mg (47·5%) as a colourless mobile oil, $n_D^{28}$ 1·4757; $[\alpha]_D$ −17·21° (*c*, 7·0; alcohol) (Found: C, 80·13; H,12.46· $C_{15}H_{28}O$ requires: C, 80·29; H, 12·58%). I.R. spectrum and all the properties were identical with those of the oxide (XVI) obtained from tetrahydrosaussurea lactone.

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