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THE SYNTHESIS AND STEREOCHEMISTRY OF DESACETOXYMATRICARIN AND THE STEREOCHEMISTRY OF MATRICARIN[1]

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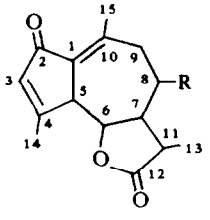
Abstract—Desacetoxymatricarin (IV), a sesquiterpene lactone found in the genus *Artemisia* and in the form of 8-hydroxy and acetoxy derivatives in the genus *Achillea*, has been synthesized from α-santonin by a sequence that allows assignment of the full stereochemistry. The stereochemistry of matricarin (V) has also been determined. The unusual stability to dehydration of some of the cyclopentyl-type alcohols, which were intermediates in the synthesis, is discussed.

RECENTLY, we isolated five sesquiterpene lactones from the wild flower *Achillea lanulosa* (Yarrow), and assigned structures Ia, IIa, IIIa, IIb, IIIb to these compounds.[2] Various interconversions showed that compounds Ia, IIa, and IIIa (the achillin series) had the same stereochemistry at carbons 5, 6, 7, and 11, and that compounds



Ia, b: R = H
IIa, b: R = OH
IIIa, b: R = O_2CCH_3

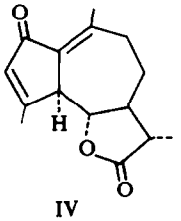
a = Achillin series
b = Matricarin series

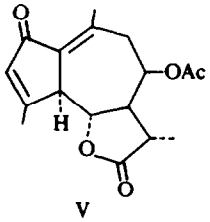
I–IIIb (the matricarin series) belonged to another series differing from the achillins only in the stereochemistry at those centers.[2] None of the members of the "a" series had been reported previously, and the name achillin was assigned to the parent compound, Ia. The "b" series was named from compound IIIb, matricarin, a compound which had been isolated from *Matricaria chamomilla*[3] and from *Artemisia tilesii*.[4] More recently, the isolation of desacetoxymatricarin (Ib)[2,*] itself has been reported from the plant species *Artemisia leukodes*,[5] *Artemisia austriaca*,[6] *Artemisia tridentata*,[7] and *Achillea santolina*;[8] also, a digitalis-like activity has been discovered for it.[9]

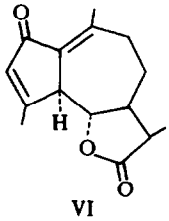
The structural work leading to formulas I–III did not define the stereochemistry at the four common asymmetric centers, however. We now report a synthesis of desacetoxymatricarin (Ib) that determines the stereochemistry as represented by formula IV.[1] We have also determined the configuration of the hydroxyl group at C-8 in desacetylmatricarin (IIb) by the method of Horeau,[10,11] and in combination with the earlier conversions of IIb into IIIb and into Ib,[2] can write expression V to illustrate the absolute configuration of matricarin. Since jacquenilin,[12] and arbiglovin

* Previously called leukodin[5,6] and santolin.[8]

(except at C-1 and C-10)[13] have been correlated with desacetoxymatricarin (IV), the stereochemistry of these compounds has been determined, as well, by the synthesis. Furthermore, in the paper that follows[14] we report a synthesis of achillin (Ia) that fixes the stereochemistry as represented in formula VI.


IV

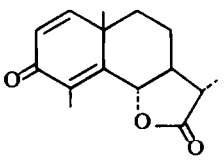

V


VI

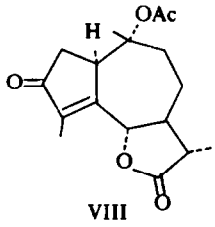
The relative stereochemistry of carbons 5, 6, and 7 of compounds I–III might appear, at first glance, to be determinable by NMR spectroscopy. However, as outlined briefly before[1], NMR spectroscopy alone is not a reliable tool for assigning stereochemistry to the lactone ring in molecules of this type, since models indicate that several of the possible isomers could account for the observed 10 Hz coupling of the C-6 proton with those at C-5 and C-7. The 7-membered ring distorts the 5-membered lactone ring sufficiently to allow a dihedral angle of near 0° for the C-6 and C-7 protons in an isomer with a *cis* fused lactone (J = 9 Hz in confertiflorin[15] and related compounds, which are known to have a *cis* lactone fusion[11]), and near 160–180° for all conformations for an isomer with a *trans* fused ring (compound IV and V have coupling constants of 9·5 and 10 Hz, respectively, for the C-6, 7 protons).[1,2,16] Thus the Karplus equation[17] predicts a large coupling for either isomer. Assignments of configuration based on the NMR spectra are unreliable even for simple systems as shown by the similarity in coupling constants for the *cis* and *trans* protons of model ketals and carbonates.[18]

Recently, Linde and Ragab have proposed that the C-11 Me group in desacetoxymatricarin (Ib = IV) is in the β configuration.[8] Our synthesis clearly shows, however, that the C-11 Me has the α configuration as illustrated in formula IV. Linde and Ragab assigned their configuration on the basis of an upfield shift of 0·35 ppm for the NMR signal of the C-11 Me group when the spectrum was run in benzene—relative to the position when the spectrum was run in deuteriochloroform. This assignment was based on the finding of Narayanan and Venkatasubramanian[19] that shifts of 0·46 ± 0·06 ppm were found for pseudo axial Me groups (β in their examples) and shifts of 0·23 ± 0·06 ppm for the pseudo equatorial d-Me groups in lactones fused to 6-membered rings (as in santonin). At about the same time, Bauer, *et al.*[16] reported that the corresponding solvent shift for the C-11 Me group in achillin was 0·37 ppm, and we have verified this value. Thus, the method of Narayanan and Venkatasubramanian[19] cannot be used in this case to determine stereochemistry. An examination of Dreiding models shows that the pseudo axial and pseudo equatorial designation vanishes when the lactone is fused to a 7-membered ring, since the Me group is about equally shielded in either epimer.

Since determination of the stereochemistry of I by degradative methods appeared to be a formidable problem, we turned to its synthesis to achieve this goal, especially since the absolute stereochemistry was known for the reasonable presursors α-santonin (VII)[20] and its photoproduct O-acetylisophotosantonic lactone (VIII).[20–22] Santonin (a eudesmanolide) and the matricarins (I–III; guianolides) are found in closely related plant species,[23] and in view of the common biogenetic origin of sesquiterpenes



VII



VIII

of the guianolide and eudesmanolide classes,[23] compounds of these classes might be expected to have a similar stereochemistry. In any case, six isomers of santonin[24] and several of the corresponding isomers of O-acetylisophotosantonic acid lactone[22,25] are known and each could be carried through the synthesis. Anticipating the final result, however, it turned out that α-santonin (VII) itself was transformed by the synthesis into desacetoxymatricarin (Ib = IV).

Synthesis of desacetoxymatricarin. The successful synthesis is outlined in Fig. 1. Photolysis of α-santonin in acetic acid gives O-acetylisophotosantonic lactone (VIII),[26] obtainable in 30% yield by direct crystallization. Catalytic hydrogenation (Pd/C) gives the dihydro product IX, which is readily epimerized at C-4 by acid, base, or alumina to give the isomer XII (an excess of catalyst in the hydrogenation leads in part to the hydrogenolysis product X). Compound XII has been prepared previously by acetylation of the corresponding hydroxy compound XI,[21,22] and its structure and stereochemistry have been determined with the aid of an x-ray analysis of the bromo derivative XIV;[20] the absolute stereochemistry (as shown in XIV) follows from the work of Barton.[25] Thus, compounds IX and XII would appear to be reasonable precursors for the synthesis of I. Such a synthesis would involve moving the ketone function to C-2 and introducing a double bond at C-3. A number of approaches were tried starting with compound XII, but these foundered on the difficulty in introducing a double bond into the 5-membered ring; as will be described later, the difficulty was traced to the configuration at C-4. The approach that proved successful was based on the introduction of the double bond before the functionality at C-2.

Reduction of the unisomerized ketone IX with sodium borohydride* or lithium tri-t-butoxyaluminum hydride gave a mixture of four alcohols, detectable by gas chromatography of the corresponding acetates, in the approximate ratio 1:2:4:5

* This step had been reported to give an amorphous mixture of alcohols.[44]

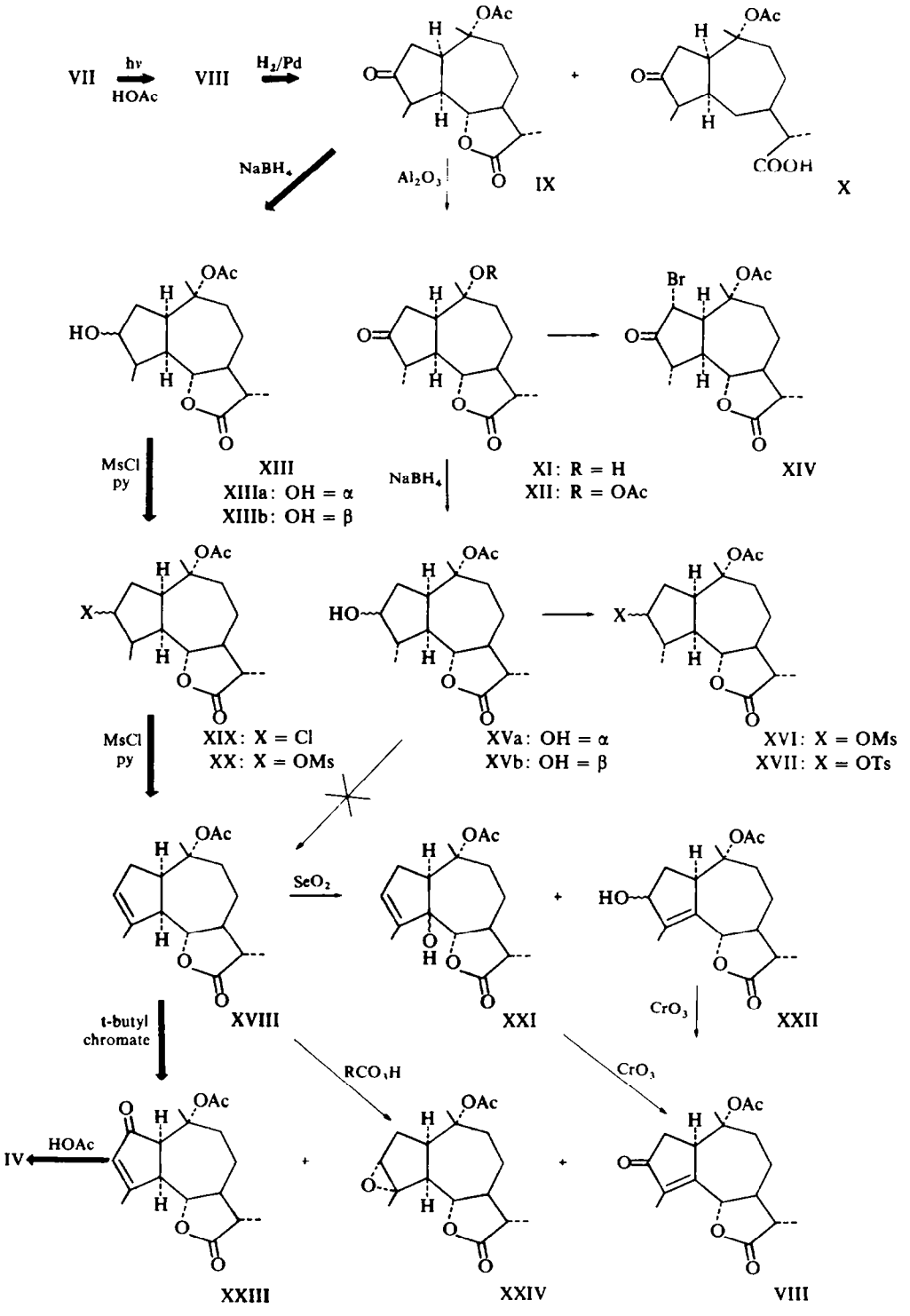


FIG. 1 Steps in the synthesis of desacetoxymatricarin (IV).

(for both reducing agents) in order of increasing retention time. In contrast, reduction of the epimerized ketone XII under the same conditions gave only two compounds in the ratio of ca. 1 : 4, corresponding to the two minor products in the above reduction. Thus the major products from IX are XIIIa and b. Conditions could not be found to prevent the partial isomerization of the C-4 Me in ketone IX from occurring during the reduction. The major isomer from the reduction of XII was obtained crystalline and it is represented as XVa on the basis of the following argument. The reduction of IX gives approximately equal amounts of XIIIa and b; the effect of epimerizing the C-4 Me to its α-position in XII can only have the effect of hindering approach to the bottom side of the molecule. Thus the principle isomer in the 1 : 4 mixture would be predicted to be that arising by β-attack of the hydrides to give XVa.

This conclusion was verified by determination of the absolute configuration of the alcohol function in XVa by the method of Horeau.[10,11] After esterification with excess racemic 2-phenylbutyric anhydride, the recovered α-phenylbutyric acid was found to be dextrorotatory (10% optical yield), which corresponds to the R configuration at C-3 as shown in XVa.

Treatment of the mixture of alcohols (XIII), obtained from ketone IX, with methanesulfonyl chloride in pyridine initially gave the corresponding mixture of mesylates; however, at least one isomer was unstable to the reaction conditions and it underwent elimination at 25° to give olefin XVIII. The reaction products, after 24 hr at room temperature, were olefin XVIII (45% yield), a mixture of two epimeric chlorides (presumably the 3-chloro analogs XIX) in 6% yield, and a mixture of mesylates (XX) in 32% yield. The latter mixture, from which one isomer was obtained crystalline (probably 3α Mes, 4β Me), was stable under the reaction conditions, and it gave only complex decomposition products on more drastic treatment. The position of the double bond in compound XVIII is assigned from the NMR spectrum, which shows a broadened singlet at 4·62 τ (1H) and a broadened singlet at 8·13 τ (3H), assigned to the vinyl proton at C-3 and the Me group attached to C-4 respectively.

In contrast, treatment of the alcohol mixture (XV) from ketone XII with methanesulfonyl chloride in pyridine gave less than 1% of olefin XVIII, 3% of chlorides, and 93% of stable mesylates (XVI). Furthermore, treatment of the major alcohol from the borohydride reduction (XVa) with toluenesulfonyl chloride and pyridine under conditions which have led to the dehydration of cyclopentanol,[27] in this case led to the corresponding tosylate (XVII) as the only recoverable product.

These results suggest that of the four epimeric alcohols XIIIa, XIIIb, XVa, and XVb, only isomer XIIIb, which can undergo ready *trans* elimination with the tertiary α C-4 proton, undergoes elimination under conditions mild enough for the remainder of the molecule to remain intact. The fact that XVa evidently doesn't eliminate under these conditions must reflect the greater steric hindrance to removal of the β-proton at C-4. This point is discussed in greater detail later in the paper.

To introduce oxygen at C-2, olefin XVIII was first treated with selenium dioxide in refluxing aqueous dioxane. Only two allylic alcohols, XXI and XXII, were formed, along with selenium-containing material; no detectable amount of the C-2 hydroxy compound was formed. The structures of XXI and XXII follow from their NMR spectra and their ready oxidation by the Jones reagent[28] to O-acetyl isophotosantonic lactone (VIII). Their formation is in accord with the most recently postulated mechanism for selenium dioxide oxidation,[29] which involves H_2SeO_3 attack on the

double bond in a Markownikov sense as the first step. Thus, one wouldn't expect other allylic oxidants such as $Pb(OAc)_4$ or $Hg(OAc)_2$[29] which react by this mechanism, to give the desired orientation either.

t-Butyl chromate,[30] on the other hand, appeared to be the reagent of choice, since the first step in its mechanism of action is postulated[29] to involve hydrogen or hydride ion abstraction from the allylic position. When the reaction of t-butyl chromate with compound XVIII was carried out in refluxing carbon tetrachloride containing acetic acid and acetic anhydride, compound IV was obtained which was identical in all respects with natural desacetoxymatricarin (Ib).[2]

The precursor β-acetoxy ketone XXIII was also formed, and this compound could be converted to desacetoxymatricarin by treatment with a mild base (such as sodium acetate). It was subsequently shown that the desacetoxymatricarin was not a primary product of the oxidation reaction, but rather was formed during the work-up procedure, which involved treatment with aqueous oxalic acid. When the oxidation was run with added sodium acetate, elimination of the acetoxyl function in XXIII was complete and desacetoxymatricarin was isolated in 15–20% yields.

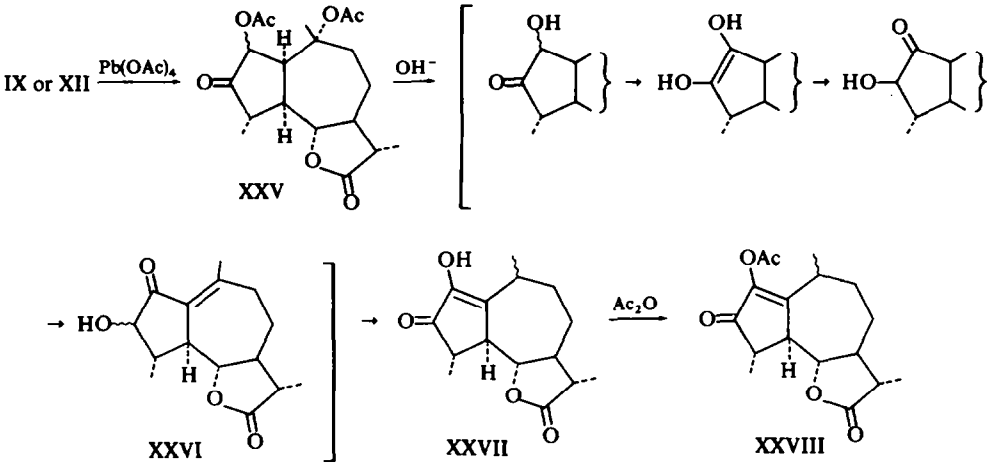
The reaction gave rise to two other products. One was O-acetylisophotosantonic lactone (VIII), which probably arose by oxidation at C-5 to give XXI, followed by allylic rearrangement and further oxidation. The other product was the epoxide XXIV (stereochemistry assigned on the basis of less steric hindrance to the α-side), which was independently synthesized by peracid oxidation of olefin XVIII. As far as we are aware, epoxide formation is without precedent for t-butyl chromate, although products arising by attack on the double bond followed by further oxidation, such as ketols[30,31] and cleavage products,[32] are known. The related reagent, chromic acid, has given rise to epoxides.[33]

Although the synthesis of desacetoxymatricarin is complete, the stereochemistry is defined as shown in formula IV only if no epimerization occurred during the synthesis. To show that this was the case, the steps in which epimerization might have occurred were carried out with deuterated reagents. Thus, treatment of olefin XVIII with the salt of pyridine and deuterium chloride in pyridine under the conditions of its formation gave no deuterium incorporation detectable by NMR spectroscopy. The more crucial step is the t-butyl chromate oxidation, which gives a molecule (IV) in which the C-5 proton is activated and epimerizable, in principle. However, carrying out the reaction with O-deuterioacetic acid as the only proton (deuteron) source, and work-up with deuterium oxide gave desacetoxymatricarin which had no deuterium in it. In particular, the NMR spectrum (100 MHz) showed the C-5 proton as a doublet, $J = 10$ Hz, and the C-6 proton as a triplet, $J = 10$, whereas the C-11 Me appeared as a normal doublet, $J = 7$; these facts preclude the possibility that deuterium had entered at either C-5 or C-11.

On treatment with strong base, the C-11 position of olefin XVIII could be epimerized and the new olefin, on oxidation with t-butyl chromate, converted into an isomer of desacetoxymatricarin; the new compound proved to be identical to achillin (VI = 1a)[1,2,16] (reported elsewhere).[14] Thus, these two compounds are shown to be C-11 epimers and they bear the same stereochemical relationship as α- and β-santonnin.[20,34]

Other approaches to desacetoxymatricarin (IV). The first attempt to synthesize IV involved the introduction of oxygen at C-2 before introduction of the double bond

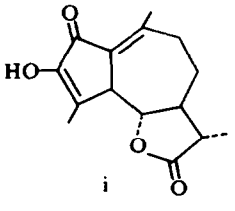
in the 5-membered ring. Treatment of either IX or XII with lead tetraacetate[35] in benzene gave approximately 30% yields of the 2-acetoxy derivative XXV (Eq. 1).*



EQ. 1

The NMR spectrum shows a new doublet (1H) at 4·66 τ (J = 9 Hz), and doublets (J = 6 Hz) at 8·73 and 8·77 τ assigned to the Me groups attached to carbons 4 and 11; the spectrum is consistent with structure XXV, although the structure with reversed ketonic and acetoxy functions at C-2 and C-3 is also possible. It was hoped that treatment of XXV with base would yield compound XXVI. The OH groups could presumably be replaced by halogen by the method of Landauer and Rydon,[36] and elimination of the hydrohalic acid would lead to IV. In fact, a further rearrangement by base occurred to give the keto-enol XXVII. This structure follows from the analysis, the positive reaction with ferric chloride, and the physical data. The IR spectrum showed a band at 2·87 μ (3490 cm^{-1}) in carbon tetrachloride and at 2·94 μ (3400 cm^{-1}) in a KBr matrix assignable to a highly associated OH group (House and Wasson[37] report the enol of 3-methyl-1,2-cyclopentane-dione absorbing at 3350 cm^{-1} in KBr). The UV absorption of XXVII is at 263 mμ (log ε 4·09) in ethanol, and at 304 mμ (log ε 3·95) in aqueous base (the values reported for 3-methyl-1,2-cyclopentanedione are 258 mμ (log ε 3·91) and 297 (log ε 3·79), respectively).[38] The pK_a of 8·8 is comparable with values of 9·14 reported for 1,2-cyclopentanedione and 9·60 for 3-methyl-1,2-cyclopentanedione.[39] The acetyl derivative XXVIII was readily prepared with acetic anhydride.

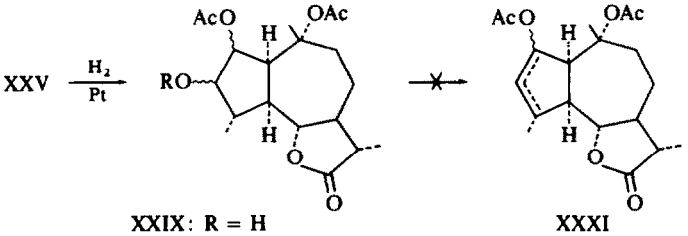
* Base treatment of the mother liquors has led to a compound assigned structure i. (Private communication from Drs. T. Sasaki and S. Eguchi, Nagoya University).



i

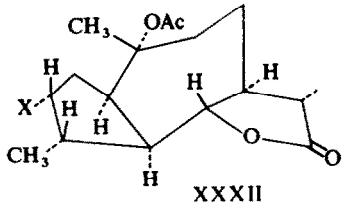
Saponification of XXV was carried out under milder conditions, but the spectra and TLC showed a large number of components.

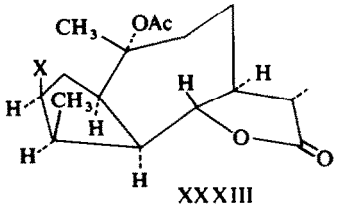
Attention was then shifted to the hydrogenation of compound XXV and the introduction of a double bond at this stage. The infrared spectrum of XXIX in a dilute solution in carbon tetrachloride at high resolution showed a band at 3622 cm^{-1}



EQ. 2

assigned to free OH, and a band at 3545 cm^{-1} assigned to a bonded form.* Treatment of XXIX with 4-nitrobenzenesulfonyl chloride in pyridine led only to the derivative XXX, and treatment of this compound with pyridine, triethylamine, or lutidine at higher temperatures in an attempt to introduce a double bond was unsuccessful. In view of the configuration at C-4, perhaps a solvolytic (S_N1) approach would have been more successful. Similarly, the application of the Chugaev reaction to XXIX was unsuccessful in that a complex product mixture and only small quantities of unsaturated materials were obtained. This resistance to dehydration is similar to that encountered with compound XVa (mentioned above). In view of the facile elimination from the mesylate of alcohol XIII, we are inclined to believe that α-derivatives at C-3 in either XVa or XXIX do not readily undergo *trans* elimination to the corresponding olefins because attack on the C-4 hydrogen is blocked. The *trans*-proton at C-4 in



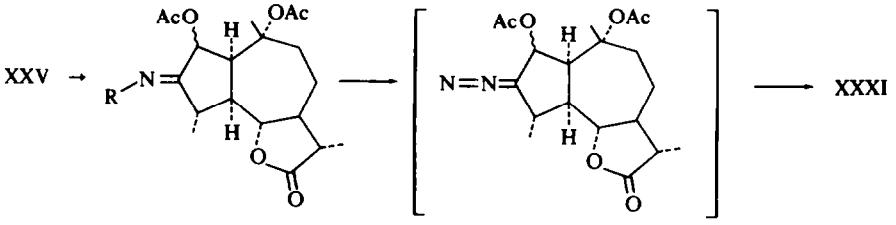


the diptych shaped molecule XXXII is well shielded by the 7-membered ring and the approach of an external base molecule is effectively blocked. A β-substituent at C-3, requiring a *cis* elimination, is similarly blocked. The derivatives containing a β-Me at C-4, on the other hand, are of a shape such that attack on the C-4 hydrogen occurs from the outside of the bent molecule (XXXIII); thus alcohol XIIIb readily led to olefin XVIII.

Attempts were also made to introduce a double bond through reactions in which

* We thank Dr. Lester P. Kuhn for measuring the IR absorption spectrum of compound XXVI at high dispersion.

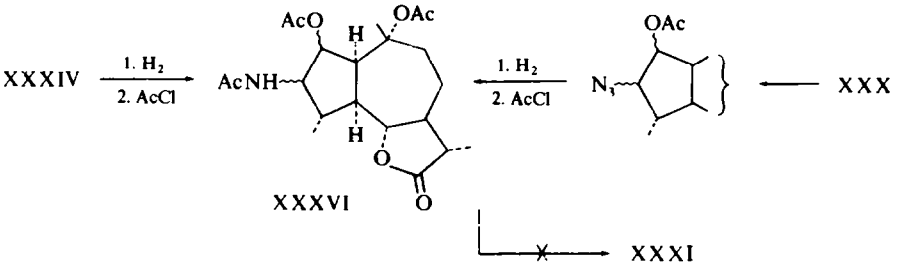
nitrogen was the leaving group. Olefins are known products of the thermal and photochemical decomposition of diazoalkanes. Compounds XXXIV and XXXV were readily prepared, but the yields, in preliminary work, of the diazo compound and the unsaturated product in the two reactions (Eq. 3) was quite small.



XXXIV: R = OH
XXXV: R = *p*-$CH_3C_6H_4SO_2NH$

EQ. 3

An alternative approach using an N-nitrosoamide as the olefin source[40a] was attempted (Eq. 4), but it was not possible to isolate the nitrosoamide, which, on the basis of model compounds, would be expected to decompose at a low temperature.[40b]



EQ. 4

EXPERIMENTAL

Determination of the alcohol configuration in desacetylmatricarin by the method of Horeau.[10] A soln of 0·0997 g of IIb, 0·1996 g racemic α-phenylbutyric anhydride, and 2 ml dry pyridine was allowed to stand at room temp overnight, then worked up exactly as described for similar compounds,[11] to give 0·1422 g (89%) of the α-phenylbutyric ester, pure by NMR and TLC, and 0·1330 g of α-phenylbutric acid. The recovered acid had $[\alpha]_D^{25}$ +5·0° (benzene), which corresponds to 5·0/50·5 = 10% optical yield, and which requires the R configuration for the alcohol.[10,11]

Photolysis of α-santonin (VII). A soln of 15·00 g (0·061 mole) α-santonin in 150 ml glacial AcOH was irradiated under N_2 for 22 hr with a 200 W Hanovia high press Hg lamp in a water-cooled quartz immersion well apparatus. Three runs were combined and the solvent was removed *in vacuo*. The remaining oil was dissolved in 75 ml MeOH and the soln was cooled to give 17 g slightly sticky, yellowish crystals. One crystallization from MeOH gave, in three combined crops, 16·20 g (0·0252 mole, 29%) of large needles, m.p. 180–181°, $[\alpha]_D^{24}$ +47·2° (*c*, 0·86 in Chf) (lit. 175–177°, $[\alpha]_D$ +58°, 0·53 in EtOH);[26a] 183°, $[\alpha]_D$ +59° (EtOH);[41] 176–177°, $[\alpha]_D$ +47° (*c*, 0·80 in Chf).[42]

This procedure is a simplified version of the one reported recently.[26]

A similar irradiation for 1·5 hr followed by chromatography on alumina yielded, in addition to VIII, lumisantonin (30%), m.p. 154–156° (lit.[43] 153–157°), UV in MeOH 237·5 mμ (log ε 3·61) (lit.[43] 237 (3·70)).

Catalytic reduction of O-acetylisophotosantonic lactone (VIII). A soln of 5·00 g of VIII in 250 ml EtOAc was hydrogenated over 0·50 g 10% Pd/C at ambient conditions. The H_2 uptake was 530 ml (1·3 equivs).

After 18 hr, the catalyst was removed by filtration, the solvent was evaporated *in vacuo* to 20 ml and the soln was cooled to give 2·96 g (59%) of glistening white crystals of IX, m.p. 168–171°, raised to 171–172·5° by one further crystallization; $[\alpha]_D^{24}$ −61·7°; NMR, 6·00 (broad t, J = 9 Hz, C-6 H), 6·6–7·8 (unresolved m), 7·90 (s, acetate), 8·47 (s, C-10 Me), 8·77 and 8·80 (d, J = 7, C-4 and 11 Me's). (Found: C, 66·08; H, 7·81. Calcd. for $C_{17}H_{24}O_5$: C, 66·21; H, 7·84%).

From the mother liquors was isolated 1·2 g of material, m.p. 130–145° (nor raised appreciably by further crystallization). Gas chromatography (SE-30 150 ft Golay Column at 225°) revealed that the latter material was a ca. 3:2 mixture of XII (ret time 8:0 min) (IX epimerizes on the column to give mainly XII, see below) and another similar compound (ret time 9·5 min), probably the C-5 epimer of IX. The glassy residue from the crystallization contains the two mentioned compounds in a ca. 1:1 ratio as well as at least five other compounds detectable by VPC.

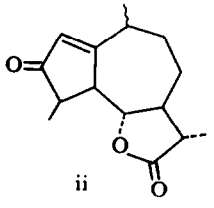
In a run in which five times as much catalyst was used, compound X was isolated (15% yield) by chromatography of the reaction mixture on neutral alumina (Act III), rechromatography of the slower running components on silica gel, and recrystallization from benzene–hexane mixtures; m.p. 156–157°; IR in KBr 3100 (very broad), 1745, 1730, and 1680 cm^{-1}; NMR 7·90 τ (s, acetate) 8·47 τ (s, C-15 Me), and 8·94 τ (unsymmetrical t, C-13 and 14 Me's).

Isomerization of C-4 *of dihydro*-O-*acetylisophotosantonic lactone* (IX). A soln of 300 mg of IX in 10 ml $CHCl_3$ was stirred for 2 hr with 2 g of activity I Alcoa alumina. The alumina was filtered off and washed well with acetone. The combined organic solvents were removed to give 299 mg of a white solid, which on crystallization from pet. ether–benzene, deposited 270 mg (90%) of XII, m.p. 164·5–1655°, $[\alpha]_D^{24}$ −26·6° (1% in Chf), (lit.[25] 165–167° and $[\alpha]_D$ −26°). Either IX or XII gave the same two peaks on VPC, ret time 8·00 and 9·30 min (Golay 150 ft SE-30 column at 225°) in a ratio of ca. 95:5, suggesting that equilibrium is reached between them on the column.

Alternatively, the isomerized ketone XII could be obtained directly from VIII in 70% yield by hydrogenation and then chromatography of the total product on alumina and elution with benzene, followed by crystallization as above.

The NMR spectrum (100 MHz showed the following peaks: 5·88 τ (t, J = 10 Hz, C-6 H), 6·71 (unsymmetrical q, J = 8, C-4 H probably), 7·62 (center of m, C-2 H ?), 7·98 (s, acetate), 8·56 (s, C-10 Me), 8·77 and 8·80 (d, J = 6·5 and 7, Me's at C-4 and 11).

Anhydrodihydroisophotosantonic acid lactone (ii) was prepared from XII by the method of Barton *et al.*[25] The physical properties of our sample agree with their reported ones with the exception of the m.p. which was observed to be 133–135° (lit. 151–155°):[25] UV in MeOH 227 mμ (log ε 4·21) (lit. 227 and 4·07):[25] IR in $CHCl_3$ 1770, 1700, and 1603 cm^{-1}): NMR 3·98 τ (unsymmetrical t, J = 1·5 Hz, C-2 H) and 6·12 τ (unsymmetrical t, J = 10·5, C-6 H). Since our m.p. decreased with fractional crystallization, we may have isolated a stereoisomer of ii (possibly at C-10 or C-11). (Found: C, 72·24; H, 7·92. Calcd. for $C_{15}H_{20}O_3$: C, 72·55; H, 8·12%).



ii

Sodium borohydride reduction of C-4-*epi-dihydro*-O-*acetylisophotosantonic lactone* (XII). To an ice-cold soln of 150 mg of XII in 10 ml MeOH was added 75 mg $NaBH_4$ with stirring. After 20 min, water was added, the MeOH was removed on an evaporator, and the residue was acidified with HCl and then extracted well with ether. The ether phase was washed with water, with NaCl aq, and then it was dried over $MgSO_4$. Removal of the ether and recrystallization from CCl_4 gave 129 mg (85%) of white microcrystals of XVa, m.p. 101–103°, raised to 108–109° by further crystallization; $[\alpha]_D^{24}$ −24°, (*c*, 0·85 in Chf); $\lambda_{max}^{CHCl_3}$ 3·15, 3·20, 5·63, 5·78 μ; NMR, 5·78 τ (C-6 H, t, J = 9 Hz), 6·36 (C-3 H, m), 8·01 (OAc), 8·53 (C-10 Me), 8·81 and 8·88 (C-4 and C-11 Me's, d, J = 6·5 Hz). (Found: C, 66·06; H, 8·32. Calcd for $C_{17}H_{26}O_5$: C, 65·78; H, 8·44%).

Acetylation (Ac_2O in pyridine) of the total product in another run gave a mixture of two acetates, in about a 4:1 ratio as judged by VPC (SE-30 Golay column at 215°); these alcohols were identical to the two minor isomers derived from IX (see below).

The toluenesulfonate (XVII) was prepared in unsuccessful attempts to dehydrate the alcohol. A mixture of the alcohol (22 mg, 0·070 mmole) and 4-toluenesulfonylchloride (19 mg, 0·01 mmole) was heated in 1 ml of pyridine at 100° for 1 hr. The product, which showed three spots on TLC, gave 5 mg crystals from a mixture of chloroform and hexane, m.p. 146–147°. (Found: C, 61·98; H, 7·17. Calcd for $C_{24}H_{32}O_7S$: C, 62·05; H, 6·94%).

This tosylate was stable for 10 hr in dry pyridine at 100°.

Determination of the alcohol configuration in C-4-*epi*-C-3-α-*tetrahydro*-O-*acetylisophotosantonic lactone* (XVa). The method of Horeau[10] was used, with the work-up procedures outlined for similar compounds.[11]

A soln of 0·1119 g of XVa and 0·1989 g of α-phenylbutyric anhydride in 2 ml of dry pyridine was allowed to stand overnight, then worked up as described.[11] There was recovered 0·1375 g (90%) of the α-phenylbutyric ester of XVa and 0·1236 g of α-phenylbutyric acid, $[\alpha]_D^{25}$ +7·8° (benzene), corresponding to an optical yield of 7·8/50·5 = 5·5%. This requires the C-3 OH to have the R absolute configuration.[10, 11]

Reduction of dihydro-O-*acetylisophotosantonic lactone* (IX). To a soln of 2·00 g (6·5 mmoles) of IX in 50 ml of dimethoxyethane (freshly distilled from NaH) was added 2·0 g lithium aluminum tri-t-butoxyhydride at 0° with stirring. After 2 hr, the cloudy soln was allowed to warm to room temp, water was added and most of the solvent was removed at reduced press. The residue was acidified with HCl, extracted well with ether, and the ether phase was separated and washed with water, then dried. Removal of the ether gave 2·02 g (100%) of a colorless, glassy material (XIII), showing one spot on TLC; $\lambda_{max}^{CHCl_3}$ 2·8 to 2·95, 5·65, 5·78 μ; NMR, 5·6–5·9 τ (m, C-3 and C-6 H), 8·02 (OAc), 8·52 (C-10 Me), 8·75, 8·85, 8·97 (broadened peaks, C-4 and C-11 Me). No crystals could be obtained from any solvent tried, and chromatography on silica gel or alumina effected little purification.

A portion of the mixture was acetylated (Ac_2O–pyridine) and the acetate mixture analyzed by VPC (SE-30 150 ft. Golay column at 215°); four acetates, in the approximate ratio 1:2:4:5, in order of increasing retention times, were detected. The first two corresponded to the two derived from the C-4 epimerized ketone XII (see above).

Reduction of IX with $NaBH_4$ in MeOH as reported[44] gave the same four compounds as outlined above in a slightly different ratio. The yield of XVIII in the following reactions was not as satisfactory, however, as when the reduction was carried out as described above.

Reaction of alcohol (XIII) *with methanesulfonyl chloride in pyridine. Formation of olefin* (XVIII). A soln of 2·02 g (6·50 mmoles) of XIII and 1·5 ml methanesulfonyl chloride in 20 ml pyridine was stirred for 24 hr at room temp. Most of the pyridine was removed *in vacuo*, the brown residue was dissolved in ether and the soln was washed with dilute HCl, with H_2O, then dried over $MgSO_4$. Evaporation of the solvent gave 2·3 g of a yellow oil, which still contained some of the methanesulfonyl chloride. An ether soln was taken to dryness with 4 g of silica gel and this was placed on a column of 50 g of silica gel; elution was then effected with pet. ether–ether, 9:1. Fractions were combined on the basis of TLC and NMR. The first 600 ml of solvent contained 35 mg of a non-polar material which was not characterized further. The next 900 ml contained 820 mg (2·80 mmoles, 43%) of XVIII, homogeneous by TLC. The material was rechromatographed whereupon a center fraction was obtained crystalline from MeOH at dry ice temps. Crystallization of the combined remaining material from MeOH-H_2O with seeding gave 520 mg of waxy white platelets in the first crop and 80 mg in the second, m.p. 66–67°; $[\alpha]_D^{24}$ +8° (*c*, 1·7 in Chf); $\lambda_{max}^{CCl_4}$ 5·60 and 5·75 μ (no absorption 5·9 to 6·2); NMR, 4·62 τ (broad s 7 Hz wide at half-height, C-3 H), 5·98 (C-6 H, t, J = 9·5 Hz), 8·04 (OAc), 8·13 (broad s, 5 Hz wide at half-height, C-4 Me), 8·57 (C-10 Me), 8·85 (C-11 Me, d, J = 6 Hz) (Found: C, 70·04; H, 8·17. Calcd for $C_{17}H_{24}O_4$: C, 69·84; H, 8·27%).

The material in the mother liquors showed no other olefinic signals by NMR and the spectrum was almost superimposable on that of the pure compound.

Further elution of the column with pet. ether–ether (4:1) gave 134 mg (0·41 mmole, 6%) of XIX as white crystals, which were recrystallized from ether, m.p. 162–163°; $[\alpha]_D^{24}$ −25° (*c*, 1·6 in Chf); $\lambda_{max}^{CCl_4}$ 5·60 and 5·75 μ; NMR 5·92 τ (C-6 H, broad), 8·03 (OAc), 8·52 and 8·56 (ratio 2:1), 8·77 (C-11 Me of one isomer and C-11 and C-4 Me of another, doublet, four protons total), 8·96 (C-4 Me of major isomer, d, two protons total). The NMR spectrum indicates that this material is a mixture of two isomers in the ratio of about 2:1. (Found: C, 62·38; H, 7·74; Cl, 10·61. Calcd for $C_{17}H_{25}ClO_5$: C, 62·09; H, 7·76; Cl, 10·79%).

Treatment of the mixed chlorides with a soln of t-BuOK in t-BuOH for 12 hr at 25° led to the destruction of the minor component (the NMR signal at 8·56 τ was lost). However, none of the olefin XVIII could be

detected by TLC and NMR analyses. The remaining chloride melted at 155–157° after recrystallization from ether.

Further elution of the column with pet. ether–ether (3:7) gave 820 mg (2·10 mmoles, 32%) of a mixture of XX. A central fraction crystallized when the solvent was allowed to evaporate slowly. The material was recrystallized with difficulty from ether, m.p. 134–135° (decomposes to purple melt); $[\alpha]_D^{24}$ −13° (*c*, 2·0 in Chf); $\lambda_{max}^{CCl_4}$ 5·60, 5·75, 8·50 and 8·55 μ; NMR, 5·13 τ (C-3 H, broad s, width at half height 9 Hz), 7·00 (CH_3SO_3), 8·04 (OAc), 8·51 (C-10 Me), 8·78 (C-11 Me, d, J = 6·5 Hz), 8·92 C-4 Me, d, J = 6·5 Hz). (Found: C, 56·48; H, 7·55; S, 8·36. Calcd for $C_{18}H_{28}SO_7$: C, 55·66; H, 7·27; S, 8·24%).

Treatment of the remaining crude mesylate from the mother liquor with methanesulfonyl chloride in pyridine for another 24 hr, then chromatography as before gave 175 mg further of XVIII, of which 83 mg crystallized. The total yield of XVIII was 995 mg (3·40 mmoles, 52%) of which 683 mg (2·34 mmoles, 36%) was obtained crystalline. In another run, with a reaction time of 48 hr, 43% of olefin was obtained (35% crystalline).

Preparation of the stable methanesulfonates (XVI). To a soln of 113 mg of the total reduction product of the C-4 epimerized ketone (XII → XV; containing two isomers, α and β) in 5 ml pyridine was added 0·2 ml methanesulfonyl chloride, and the mixture was stirred for 24 hr at 25°.

The pyridine was removed at aspirator pressures, ether was added, and the soln was washed well with dilute HCl, and then with water. Drying the soln and evaporation of the solvent gave a yellow oil, which was chromatographed on 10 g of silica gel. Elution with pet. ether–ether (9:1) gave ca. 1 mg (1%) of olefin XVIII. Elution with a 4:1 mixture gave 4 mg (3%) of a crystalline chloride (corresponding to XV), m.p. 160–162°. Finally, elution with pure ether, gave 131 mg (93%) of XVI, homogeneous by TLC, which could not be obtained crystalline; NMR 5·45 τ (C-3 H, q, J = 7 Hz), 5·85 (C-6 H, t, J = 9·5 Hz), 6·94 (OMs), 8·00 (OAc), 8·51 (C-10 Me), 8·81 and 8·82 (C-4 and C-11 Me, d, J = 7 Hz).

Selenium dioxide oxidation of olefin XVIII. A mixture of 225 mg (0·77 mmole) of XVIII in 20 ml H_2O + dioxan (1:9) and 85 mg (0·77 mmole) sublimed SeO_2 was refluxed 8 hr, then filtered to remove Se. The solvent was removed *in vacuo*, the residue was absorbed on 1 g silica gel and put dry onto a column of 10 g silica gel made up in pet. ether–ether (3:1). Elution with this solvent mixture gave, in fractions 8–20, 98 mg of a solid which showed a major and a minor spot by TLC. Rechromatography gave 62 mg (0·20 mmole, 26%) of a white solid which was crystallized from a ether–pet. ether mixture to give 39 mg of XXI, m.p. 147–149·5° raised by recrystallization to 151–151·5°; $[\lambda]_D^{24}$ −30° (*c*, 10 in Chf); λ_{max}^{Chf} 2·80, 5·62, 5·75 μ; NMR 4·47 τ (C-3 H, broad s, width at half height 7 Hz), 5·82 (C-6 H, sharp d, J = 9·5 Hz), 7·98 (OAc), 8·17 (C-4 Me, broad s), 8·49 (C-10 Me), 8·77 (C-11 Me, d, J = 6·5 Hz). (Found: C, 66·34; H, 8·01. Calcd for $C_{17}H_{24}O_4$: C, 66·21; H, 7·84%).

Further elution of the column with 50% ether in pet. ether gave 40 mg of fairly pure XXII in fractions 21–27, this material was rechromatographed to give 35 mg (0·14 mmole, 18%) of XXII, m.p. 150–151·5°; λ_{max}^{Chf} 2·66, 2·74, 5·62, 5·78 μ; NMR, 5·42 τ (C-6 H, t, J = 9·5 Hz), 6·3 (C-3 H, broad), 8·02 (OAc), 8·10 (C-3 broad s, width at half height 5 Hz), 8·80 (C-10 Me), 8·78 (C-11 Me, d, J = 6·5 Hz). (Found: C, 66·31; H, 7·89. Calcd. for $C_{17}H_{24}O_5$: C, 66·21 H 7·84%).

Further elution of the column with ether gave 47 mg of a brown Se-containing material which showed no OH absorption in the IR (spectra run in Chf) and from which no characterizable compounds could be isolated.

Brief treatment of either compound XXI or XXII with the Jones reagent[28] at 0° in acetone gave a smooth conversion to VIII, m.p. and mixture m.p. 180–181°.

Oxidation of olefin XVIII *with t-butyl chromate*

Synthesis of desacetoxymatricarin (IV). Olefin XVIII (500 mg, 1·71 mmoles) in 20 ml CCl_4 was refluxed for 8 hr under N_2 with 30 ml AcOH, 1·5 ml Ac_2O, and 12·0 ml of 1·0 N t-butyl chromate soln[30] (prepared by dissolving 1·36 g of CrO_3 in 4 ml of t-BuOH with cooling, diluting with 12 ml CCl_4, washing well with water, and drying over $MgSO_4$). The resulting mixture was cooled and then stirred 1 hr with 0·3 g oxalic acid in 20 ml water. The almost-colorless organic layer was separated, washed with water, dried, and the solvent was then removed. The resulting oil was chromatographed on 20 g silica gel (1·7 × 28 cm column). Elution with 10% ether in pet. ether gave 63 mg of recovered XVIII. Fractions (50 ml) eluted with 25% ether in pet. ether were combined (on the basis of their IR spectra in the CO region) as follows:

Fractions 2–6 (44 mg, 80% pure by NMR, 0·14 mmole, 8%), had $\lambda_{max}^{CHCl_3}$ 5·65 μ (lactone), 5·90 (conjugated ketone), 6·08 and 6·14 (double bonds) as well as 5·90 (acetate, weak). Three crystallizations from ether gave 15 mg of pure IV, m.p. 205–205·5° $[\alpha]_D^{24}$ +52·5° (1% in $CHCl_3$), no depression with an authentic

sample, m.p. 204–205°, prepared from matricarin.[2] (Lit: m.p. 196–198°, $[\alpha]_D$ +55·9°[2]; m.p. 202–203°, $[\alpha]_D$ +58°[5]); NMR (100 MHz) 3·87 τ (broad s, C-3 H), 6·46 (t, J = ca. 9–10, C-6 H), 6·65 (broad d, J = 10·5, C-5 H), 7·60 and 7·72 (broadened s, C-4 and 10 Me's), 8·75 (d, J = 6, C-11 Me). It was also identical by IR, TLC, NMR, and gas chromatography to an authentic sample. (Found: C, 73·26; H, 7·46. Calcd for $C_{15}H_{18}O_3$: C, 73·11; H, 7·36%).

This compound was not formed directly in the oxidation step, but arose in the hydrolysis step with oxalic acid, as was demonstrated by IR and TLC on the total product in another run (*vide infra*).

Fractions 7–9 contained 26 mg of crystals (0·084 mmole, 5%) which had $\lambda_{max}^{CHCl_3}$ 5·62 μ (lactone) and 5·78 (acetate). Two crystallizations from ether–pet. ether gave pure XXIV, m.p. 173–175°; $[\alpha]_D^{24}$ −25° (*c*, 1·1 in Chf); NMR, 5·97 τ (C-6 H, t, J = 9·5 Hz), 6·67 (C-3 H, broad s, width at half height 3 Hz) 7·98 (OAc), 8·41 (C-4 Me), 8·50 (C-10 Me), 8·79 (C-11 Me, doublet, J = 6 Hz). The compound was identical to a sample prepared by treatment of XVIII with 1 equiv *m*-chloroperbenzoic acid in $CHCl_3$ for 10 min at room temp. (Found: C, 66·02; H, 7·72. Calcd for $C_{17}H_{24}O_5$: C, 66·21; H, 7·84%).

Further elution with 35% ether gave, in fraction 10, 3 mg of a mixture which was not identified.

Fractions 11–16 (188 mg) had λ_{max}^{Chf} 5·62, (lactone), 5·78 (acetate), 5·90 (conjugated ketone), and 6·14 μ (double bond). Crystallization from pet. ether–ether gave, in the first crop, 60 mg of crude crystalline material, which was recrystallized to give 34 mg of VIII, m.p. 168–170° (0·11 mmole, 6·5%). The mother liquors (134 mg, 0·44 mmole, 25%) contained fairly pure XXIII, as determined by TLC and NMR. Two crystallizations from ether gave an analytical sample of XXIII, m.p. 146–148° $[\alpha]_D^{24}$ +45° (*c*, 1·0 in Chf); λ_{max}^{Chf} 5·62, 5·78, 5·90, 6·14 μ; NMR 5·95 τ (C-3 H, broad s, width at ½ height 5 Hz), 5·90 (C-6 H, t, J = 9 Hz), 7·72 (C-4 Me, broad s, width at ½ height, 5 Hz), 7·90 (OAc), 8·70 (C-10 Me, d, J = 6·5 Hz). Treatment of this compound with excess NaOAc in MeOH or HOAc at reflux gave IV in high yield.

In another run in which all conditions were identical to those described above, except that 0·5 g of NaOAc was added and the reaction time increased to 12 hr, no XVIII or XXIII was obtained, and the yield of desacetoxymatricarin after chromatography was 15%.

Control experiments with deuterated solvents

(A) *Olefin* XVIII. Olefin XVIII (50 mg) was dissolved in 15 ml pyridine (freshly distilled from CaH_2). To this soln was added 0·1 ml D_2O and 3 ml methanesulfonyl chloride, whereupon a ppt of pyridine · DCl formed. The mixture was stirred for 11 hr, then ether was added and the ppt removed by filtration. Evaporation of the ether and trituration of the residue with CCl_4 gave 45 mg of material which was essentially unchanged XVIII as judged by TLC, IR, and NMR. In particular, the triplet at 5·98 τ due to the C-6 proton was unchanged in intensity or multiplicity.

(B) *Desacetoxymatricarin* (IV). Olefin XVIII (150 mg) in 10 ml CCl_4 was refluxed for 6 hr with 3 ml Ac_2O to which had been added 0·1 ml D_2O, 0·1 g NaOAc and 3 ml 1·0 N t-butyl chromate soln in CCl_4 (which had been washed well with D_2O). The cooled mixture was diluted with $CHCl_3$ and filtered, then the organic soln was evaporated to dryness. The residue was triturated with CCl_4 and filtered. The CCl_4 soln contained 20 mg of oil which was ca. 25% IV (NMR analysis). The green solid which had been removed was stirred with D_2O and CCl_4 for 1 hr. The layers were separated, the CCl_4 phase was washed with D_2O and then dried. Removal of solvent gave 50 mg of an oil which deposited 15 mg of crystalline IV from CCl_4. Its NMR spectrum ($CDCl_3$) was identical to that of the natural compound. A 100 MHz spectrum resolved the C-5 proton signal into a doublet at 6·64 τ (J = 11 Hz) and the C-6 proton signal into a triplet at 6·40 τ (J = 9·5 Hz), thus precluding the possibility that deuterium had been incorporated into these centers.

O-*Acetyl*-2-*acetoxyisodihydroisophotosantonic lactone* (XXV). Compound XII, 308 mg, 1·0 mmole was dissolved in 60 ml benzene, which had been distilled from lead tetraacetate, and to this was added 665 mg (1·5 mmoles) lead tetraacetate, which had been freshly recrystallized from AcOH at 60°. The mixture was refluxed for 9 hr, or until tests with starch-iodide paper were negative. The reaction mixture was washed with water, dried with Na_2SO_4, and concentrated *in vacuo*. Chromatography of the residue (360 mg) on 9 g of neutral alumina (Alcoa, Activity II) gave 121 mg (0·33 mmole, 33%) of crude product, m.p. 161–164°. Two recrystallizations from benzene–hexane mixtures gave 81 mg (0·22 mmole, 22%) of pure XXV: m.p. 164–165°; $[\alpha]_D^{24}$ +26·0° (*c*, 1·00 in $CHCl_3$); IR in CCl_4, 5·60 μ (1785 cm^{-1}), 5·65 (1770), 5·72 (1748), 5·77 (1733); NMR, 4·66 τ (d, J = 9, C-2 hydrogen), 5·76 (t, J = 10, C-6 hydrogen), 6·54 (m, C-4 hydrogen), 7·84 and 7·95 (s, Me's of the acetate groups), 8·73 and 8·77 (d, J = 6, C-4 and C-11 Me groups). (Found: C, 62·40; H, 7·10. Calcd for $C_{19}H_{26}O_7$: C, 62·28; H, 7·15%).

The yields in this reaction were somewhat erratic, ranging from 20–40%. Either increasing or decreasing

the ratio of reagents decreased the yield somewhat. An investigation of the mother liquor has recently led to the isolation of a by-product, identified as i. (see footnote on p. 2104).

Treatment of O-*acetyl-2-acetoxyisodihydroisophotosantonic lactone* (XXV) *with base.* A suspension of compound XXV (230 mg, 0·63 mmole) in 10 ml of 0·72 N KOH was stirred under a N_2 atm for 3 hr; the resulting clear pale yellow soln was then allowed to stand at room temp for 16 hr. The soln was acidified with AcOH to a pH of 5·5. During the next 10 hr, a crystalline material (97 mg) separated, m.p. 153–171°. Concentration of the mother liquor yielded an additional 18 mg, both crops showing only a single spot on TLC (total yield 0·44 mmole, 70%). Extraction of the mother liquor with $CHCl_3$ yielded 25 mg of an oil that showed at least 3 spots on TLC. The crystalline fractions which gave a yellow-brown color with $FeCl_3$, were recrystallized from a water–MeOH mixture to give crystals of XXVII, m.p. 172–183° dec: IR in CCl_4 2·87 μ (3490 cm^{-1}), 5·58 (1792), 5·83 (1715), and 6·02 (1661); UV in 95% EtOH 263 mμ (log ε 4·09), and in 0·72 Naq KOH 304 mμ (log ε 3·95); NMR 3·17 τ (s, OH), 6·82 (m, C-4 hydrogen), 6·20 τ (t, J = 10, C-6 hydrogen). (Found: C, 68·18; H, 7·55. Calcd for $C_{15}H_{20}O_4$: C, 68·16; H, 7·63%).

When 73 mg of XXV in 20 ml MeOH was treated slowly with 32 ml 0·01 M Na_2CO_3 (the latter solution added slowly to maintain a pH of 7–8) during 3 hr, the recovered product, after acidification contained three components, but no starting material as shown by TLC.

Acetylation of ketal XXVII. Ac_2O (0·11 ml, 1·0 mmole) was added to a soln of the ketal (215 mg, 0·82 mmole) in 1 ml pyridine and the mixture was stirred at 24° for 12 hr. Water was added to precipitate the crude acetate (196 mg), which was recrystallized from a hexane–CH_2Cl_2 mixture to give 165 mg (0·54 mmole, 66%) of XVIII in the form of fine needles, m.p. 150–151°: IR in CCl_4 1780, 1730, and 1645 cm^{-1}; UV in MeOH 236 mμ (log ε 4·12); NMR 6·12 τ (unsym. t, J = 9·5, C-6 hydrogen), 6·94 τ (prob. C-4 hydrogen), and 7·72 τ (s, acetate methyl). (Found: C, 66·39; H, 7·06. Calcd for $C_{17}H_{22}O_5$: C, 66·65; H, 7·24%).

Attempts to prepare the oxime of the acetate in pyridine, led instead largely to the parent ketol (71% recovered).

Hydrogenation of O-*acetyl-2-acetoxyisodihydroisophotosantonic lactone* (XXV). The ketone XXV (1·22 g, 3·33 mmoles) was added to the prereduced catalyst (from 0·60 g PtO_2) in 300 ml MeOH, and the mixture was shaken with H_2. The uptake of H_2 was 83 ml in 22 hr (theory, 82 ml). The catalyst was removed by filtration through celite and the solvent was evaporated to dryness *in vacuo*. The residue was recrystallized from a benzene–hexane mixture to give 1·00 g (82%) of XXIX in the form of white needles, m.p. 179–181°. Recrystallization raised the m.p. to 181–182°; IR in CCl_4 3622, 3545, 1783, and 1742 cm^{-1}; NMR 4·98 τ (t, J = 6, C-2 hydrogen), 5·86 (t, J = 8·5, C-6 hydrogen), 6·46 (m, C-3 hydrogen), 6·74 (m, C-4 hydrogen, probably). (Found: C, 62·18; H, 7·54. Calcd for $C_{19}H_{28}O_7$: C, 61·94; H, 7·66%).

The 4-*nitrobenzenesulfonate ester* (XXX) of XXIX was prepared from 368 mg (1·0 mmole) of the alcohol and 243 mg (1·1 mmoles) 4-nitrobenzenesulfonyl chloride in 4 ml dry pyridine (24 hr at 25°). The mixture was poured into water and the ppt was chromatographed on silica gel. The ester was then recrystallized from a mixture of hexane and CH_2Cl_2 to give 360 mg (65%) of XXX as faintly yellow needles, m.p. 128–130° dec; IR in KBr 1764, 1733, 1605, 1534, 1374, and 840 cm^{-1}; NMR 1·72 τ (AB q, J = 9, aromatic hydrogen), 4·51 (4 peaks, C-3 hydrogen), 5·34 (q, J = 6 and 9·5. C-2 hydrogen), 5·91 (broad t, J = 9, C-6 hydrogen), 6·80 (broadened m, C-4 hydrogen?). (Found: C, 54·13; H, 5·69. Calcd for $C_{25}H_{31}NO_{11}S$: C, 54·24; H, 5·65%).

Attempts were made to eliminate 4-nitrobenzenesulfonic acid from XXX, using triethylamine, pyridine, and 2,6-lutidine at their b.ps. In general, starting material was recovered as well as what appeared to be an isomer of XXIX (possibly the C-3 epimer), m.p. 191–193°, NMR 4·99 τ (t, J = 5), 5·87 (t, J = 9), 6·53 (broad s), 6·82 (m), 7·90 and 8·07 (acetate Me's); and smaller amounts of many unidentified compounds. Similar results were obtained with XXX and neutral or basic alumina. Heating XXIX with 4-nitrobenzenesulfonyl chloride in pyridine also gave the isomer of XXIX mentioned above.

The oxime of O-*acetyl-2-acetoxyisophotosantonic lactone* (XXXIV). A mixture of 366 mg (1·00 mmole) of XXV and 105 mg (1·50 mmoles) hydroxylamine hydrochloride in 5 ml pyridine was stirred for 12 hr at 25°. Water and benzene were added and the benzene extract was dried and concentrated to 1 ml. The addition of hexane yielded a ppt, which after recrystallization from a benzene–hexane mixture gave 360 mg (94%) of XXXIV in the form of a fluffy solid, m.p. 110–115°, homogeneous by TLC; IR in CCl_4 3570 (sharp), 3300 (broad), 1783, 1751, 1745, and 1742 cm^{-1}; NMR 5·98 τ (t, J = 9·5, C-6 hydrogen), 6·70 τ (broad s, OH and C-4 hydrogen), 7·91 τ (two peaks, C-2 and C-10 acetates). (Found: C, 59·46; H, 7·23; N, 3·59. Calcd for $C_{19}H_{27}NO_7$: C, 59·83; H, 7·14; N, 3·67%).

Treatment of the oxime with hydroxylamine-O-sulfonic acid in aqueous pyridine at 25° did not lead to any appreciable amount of the unsaturated product. In a model study, camphor oxime was treated

with chloroamine in water at 25° for 1 hr; the IR spectrum of the product showed a weak band at 2260 cm^{-1}, a band at 1760 cm^{-1} (cyclopentanone), and olefinic bands at 1680 and 1640 cm^{-1}.

The tosylhydrazone of O-*acetyl-2-acetoxyisodihydroisophotosantonic lactone* (XXXV). A mixture of XXV (183 mg, 0·50 mmole) and *p*-toluenesulfonylhydrazide (93 mg, 0·50 mmole) in THF was refluxed for 20 hr under N_2. Evaporation to dryness and recrystallization from MeOH yield the tosylhydrazone as a white crystalline solid (21 mg, 0·039 mmole, 8%), m.p. 225–230° dec; IR in KPr 3220, 1780, 1720, 1725, 745, and 1600 cm^{-1}. (Found: C, 58·87; H, 6·30; N, 4·80. Calcd. for $C_{26}H_{34}N_2O_8S$: C, 58·42; H, 6·41; N, 5·24%).

Chromatography of the mother liquor on silica gel yielded another 2% of the tosylhydrazone and 30–50% of XXV. The yield was 10% for the reaction in EtOH (1 hr reflux), 18% in MeOH (20 hr reflux), and 0% in AcOH (6 hr at 25°).

The Li salt of the hydrazone was prepared in THF with BuLi. Evaporation of the solvent led to a yellow solid, which showed a weak band in the IR at 2060 cm^{-1}. The solid was heated to 120–140° in a sublimer at 10^{-3} Torr for 3 hr. The sublimate was complex and it showed no pronounced olefinic bands in the IR.

The acetamidoguaianolide XXXVI.

(A) *Preparation from the oxime* XXXIV. The oxime (649 mg) prepared from 615 mg (1·68 mmoles) of XXV was hydrogenated at 25° in MeOH (40 ml) in the presence of 1 atm H_2 and 900 mg 5% Rh on Al (PtO_2, Pt–C, and Ru–C catalysts were ineffective in this hydrogenation). After 30 hr, the uptake of H_2 had stopped, and TLC showed the absence of oxime. The catalyst was removed by filtration and the solvent removed to give 609 mg of a white fluffy solid. The IR spectrum showed a weak amide band at ca. 5·9 μ indicating that some acyl migration had occurred. The product was dissolved in 5 ml pyridine, and 0·20 ml (2·8 mmoles) acetyl chloride was added with stirring. After several hr, water and $CHCl_3$ were added and the $CHCl_3$ extract dried. Removal of the solvent gave 569 mg of a white solid, which was chromatographed on silica gel. The first fraction (125 mg) showed an IR band at 1130 cm^{-1}, and it might well contain an oxazoline. The third fraction (241 mg) appeared to contain an amino alcohol. The second fraction (283 mg) was recrystallized from a mixture of hexane and CH_2Cl_2 to give 145 mg (21% from XXV) of XXXVI, m.p. 90–94°; IR 3435, 1770, 1750, 1675, and 1515 cm^{-1}. (Found: C, 61·85; H, 7·84; N, 3·39. Calcd. for $C_{21}H_{31}NO_7$: C, 61·60; H, 7·63; N, 3·42%).

(B) *From the azide.* A mixture of XXX (554 mg, 1·00 mmole) and dry sodium azide (650 mg, 10·0 mmoles) in 10 ml of N-methylpyrrolidone (distilled from BaO) was stirred at 70° for 5 hr under an atm of N_2. The mixture was poured into water, and the product extracted into ether. Evaporation of the solvent yielded 258 mg of a yellow, sticky solid. A second extraction with CH_2Cl_2 yielded a further 146 mg of product. Chromatography on silica gel with $CHCl_3$ and $CHCl_3$ containing 3% MeOH yielded in successive fractions: 5 mg of yellow needles (m.p. 143–144°, no lactone or acetate bands in the IR), 107 mg of the crude azide, and 210 mg of a yellow, sticky solid (IR bands in the OH, lactone, and acetate regions of the spectrum, plus a band at 1670 cm^{-1}).

The azide (107 mg) was recrystallized from a mixture of benzene and hexane to yield 73 mg (19%) of yellow needles m.p. 115–116° dec; IR 2110, 1774, and 1740 cm^{-1}. (Found: C, 56·96; H, 6·83; N, 9·92. Calcd. for $C_{19}H_{27}N_3O_6$: C, 58·00; H, 6·92; N, 10·68%).

Hydrogenation of the azide in EtOH containing a trace of HCl in the presence of an equal weight of 10% Pd/C was complete in 5 hr at 27°. The product was acetylated with Ac_2O in pyridine to give the same amide obtained from the oxime, but in a less pure state.

Nitrosation of the amide was attempted with dinitrogen tetroxide in CH_2Cl_2 at 0°.[45] It was not possible to isolate a product showing an appreciable N-nitroso band at 6·6 μ, and the presence of a weak band at 6·06 μ indicated that some elimination had occurred during the synthesis. (Found: C, 63·15; H, 6·94. Calcd. for $C_{19}H_{24}O_7$: C, 62·63; H, 6·64%).

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