Tetrahedron, 1965, Vol. 21, pp. 1247 to 1261. Pergamon Press Ltd. Printed in Northern Ireland

STEREOSPECIFIC SYNTHESES OF IRIDOMYRMECIN AND RELATED IRIDOLACTONES

J. WOLINSKY, T. GIBSON,[1] D. CHAN and H. WOLF
Department of Chemistry, Purdue University, Lafayette, Indiana

(*Received* 18 *December* 1964)

Abstract—Stereospecific syntheses of 6 (I, II, XVI, XXV, XXVI and XXXII) out of 8 of the possible iridolactones are described. The lactone IV, produced by lactonization of *trans*-pulegenic acid (III), was converted by LAH reduction and acetylation to 3-(α-hydroxyisopropyl)-2-acetoxymethyl-1-methylcyclopentane (*cis-trans*-V). Dehydration of V with refluxing acetic anhydride gave 2-acetoxymethyl-3-isopropenyl-1-methylcyclopentane (*cis-trans*-VII). Hydroboration of VII followed by oxidation and hydrolysis gave (−)-iridomyrmecin (I) which was epimerized with sodium methoxide to (+)-isoiridomyrmecin (II). The *cis-cis*-iridolactones XXV and XXVI were produced in similar fashion from the *cis-cis*-lactone XVII. Treatment of the lactones IV and XVII with hydrogen chloride in methanol gave methyl *trans-trans* and *trans-cis*-chloropulegenates X and XXVII, respectively. These esters were then transformed into iridolactones XVI and XXXII.

The biosynthesis of iridomyrmecin is discussed.

THE ant lactones, iridomyrmecin (I) and isoiridomyrmecin (II),[2] isolated from *Iridomyrmex humilis* Mayr.[3] and *Iridomyrmex nitidus* Mayr.,[4] respectively, have attracted considerable attention because of their use, by the ant, as agents of defence against preying insects and as possible means of communication.[5] These lactones are also found in the plant kingdom; they are minor components of matatabilactone,[6,7] a cat-attracting oil isolated from *Actinidia polygama*. In addition to these intriguing properties, Pavan has claimed that iridomyrmecin is a potent insecticide[8] and exhibits antibiotic action.[9] Syntheses have been reported for the racemic and optically active modifications of I and II.[10,11] Several of these approaches afford lactones of the proper stereo-chemistry more on the basis of chance than on design. Furthermore, these synthetic methods do not lend themselves for the selective construction of isomeric iridolactones. It was our intention to devise highly stereoselective routes to these lactones with the view in mind of examining certain aspects of the stereochemistry of the cyclopentane ring and of studying the effect of molecular geometry on the biological activity of the iridolactones.

[1] National Institutes of Health Predoctoral Fellow, 1961–1963.

[2] The name iridolactone, originally suggested by G. W. K. Cavill, *Chem. & Ind.* 465 (1959), will be used to designate stereoisomers of I and II.

[3] M. Pavan, *Ricerca Sci.* **19**, 1011 (1949); R. Fusco, R. Trave and A. Vercellone, *Chim. Ind., Milan* **37**, 251, 958 (1955).

[4] G. W. K. Cavill, D. L. Ford and H. D. Locksley, *Austr. J. Chem.* **9**, 288 (1956).

[5] L. M. Roth and T. Eisner, *Ann. Rev. Entomol.* **7**, 107 (1962).

[6] T. Sakan, A. Fujino, F. Murai, A. Suzui and Y. Batsugan, *Bull. Chem. Soc. Japan* **32**, 1154 (1959); T. Sakan, A. Fujino and F. Murai, *Nippon Kagaku Zasshi* **81**, 1320 (1960).

[7] Metatabilactone is largely comprised of two isomeric dihydronepetalactones. Details of the determination of the constitution of matatabilactone will be given in a forthcoming publication.

[8] M. Pavan, *Ricerca Sci.* **20**, 1853 (1950).

[9] M. Pavan, *Z. Hyg. Infection-krankh.* **134**, 136 (1952).

[10] F. J. Clark, G. I. Fray, R. H. Jaeger and R. Robinson, *Tetrahedron* **6**, 217 (1959).

[11] F. Korte, J. Falbe and A. Zschocke, *Tetrahedron* **6**, 201 (1959); F. Korte, K. H. Buche and A. Zschocke, *Chem. Ber.* **94**, 1952 (1961).

trans-Pulegenic acid (III),[12–15] obtained stereoselectively or stereospecifically by the action of sodium methoxide or sodium ethoxide on pulegone dibromide, provided a convenient starting material for this work. By proper manipulation of the sequence of events *trans*-pulegenic acid has been converted in a stereorational fashion into 6 of the 8 possible iridolactones.

(−)-*Iridomyrmecin* (I) *and its conversion to* (+)-*isoiridomyrmecin* (II)

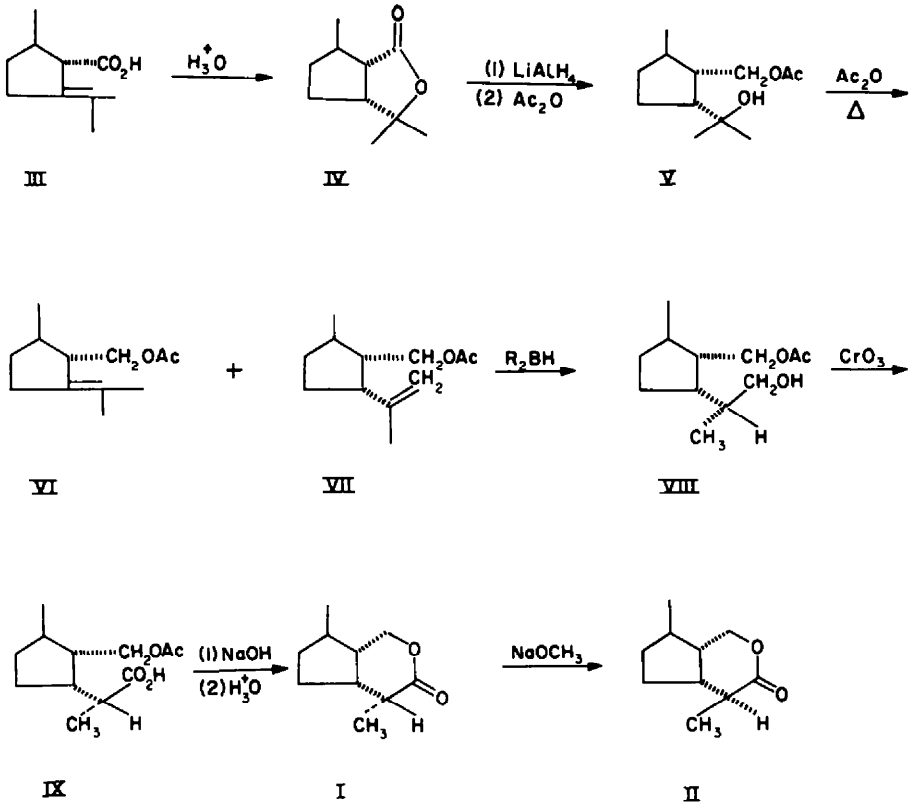
trans-Pulegenic acid (III) was smoothly transformed into *cis-trans*-pulegenolide (IV) by heating with dilute hydrochloric acid. The lactonization establishes the stereochemistry desired for the elaboration of iridomyrmecin and from this point reactions were chosen which would not alter the arrangement of the three asymmetric centres on the cyclopentane ring.

LAH reduction of IV afforded a syrupy glycol which was converted with acetic anhydride and a trace of pyridine to the crystalline mono-acetate (V). Dehydration of V can lead to two products; either 2-acetoxymethyl-3-isopropylidene-1-methylcyclopentane (VI) or the desired 2-acetoxymethyl-3-isopropenyl-1-methylcyclopentane (VII). Common dehydrating agents produced the undesired isomer VI in greater proportion. Using phosphorus oxychloride in pyridine or *p*-toluenesulphonyl chloride in 2,6-lutidine the ratio of VI to VII was 5:1. The situation was not markedly improved employing phosphorus oxychloride in 2,6-lutidine although the isomer ratio was lowered to 1·7:1. It was accidentally discovered that dehydration of the tertiary alcohol took place during the acetylation of the glycol when the excess acetic anhydride was distilled at atmospheric pressure. On further investigation it was determined that acetic anhydride at its b.p. converted the glycol, in high yield, to a mixture of the two unsaturated acetates containing as much as 78% of the desired isomer VII.

Selective conversion of VII to VIII was accomplished by hydroboration[15] with bis-3-methyl-2-butylborane. The unreacted isomer VI was readily separated from VIII by distillation.

Oxidation of the hydroxyl group in VIII was accomplished by the Jones procedure.[16] The removal of the protecting acetate group from the intermediate IX was effected by heating with aqueous alkali. Neutralization of the alkaline solution gave crude (−)-iridomyrmecin (I), which after two recrystallizations showed m.p. 60·5–61°, $(\alpha)_D$ −199° and proved to be identical with natural (+)-irodomyrmecin in every respect but the sign of optical rotation. The mother liquor from recrystallization of iridomyrmecin was analysed by vpc and showed the presence of 10–15% of another isomer, presumedly isoiridomyrmecin (II).[17]

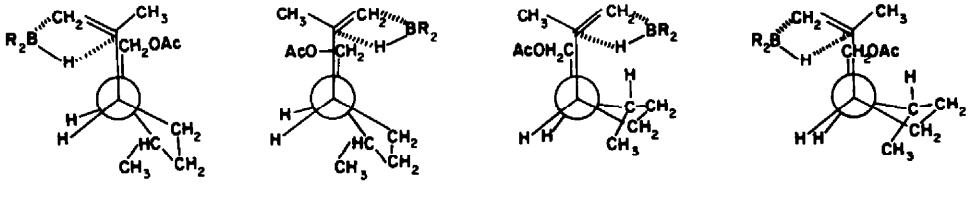
[12] J. Wolinsky, H. Wolf and T. Gibson, *J. Org. Chem.* **28**, 274 (1963).
[13] H. Rupe and K. Schafer, *Helv. Chim. Acta* **11**, 463 (1928).
[14] S. A. Achmad and G. W. K. Cavill, *Austr. J. Chem.* **16**, 858 (1963).
[14a] J. Wolinsky and D. Chan, *J. Org. Chem.* **30**, 41 (1965).
[15] H. C. Brown and G. Zweifel, *J. Amer. Chem. Soc.* **83**, 1241 (1961).
[16] Bowers, Halsall, E. R. H. Jones and A. J. Lemin, *J. Chem. Soc.* 2548 (1953).
[17] The almost exclusive formation of iridomyrmecin demonstrates that the hydroboration of the unsaturated acetate VII has proceeded with high stereoselectivity. This can be attributed to the formation of the non-crowded transition state A, rather than transition states B-D where appreciable non-bonded interactions arise (see opposite page).



When (—)-iridomyrmecin was subjected to the action of sodium methoxide in methanol a mixture rich in isoiridomyrmecin (II) resulted. A pure sample of (+)-isoiridomyrmecin (II) was isolated by recrystallization and sublimation and exhibited m.p. 56–57°, $[\alpha]_D$ +59° and proved to be identical, except for the sign of optical rotation, with an authentic sample of (—)-isoiridomyrmecin.[18]

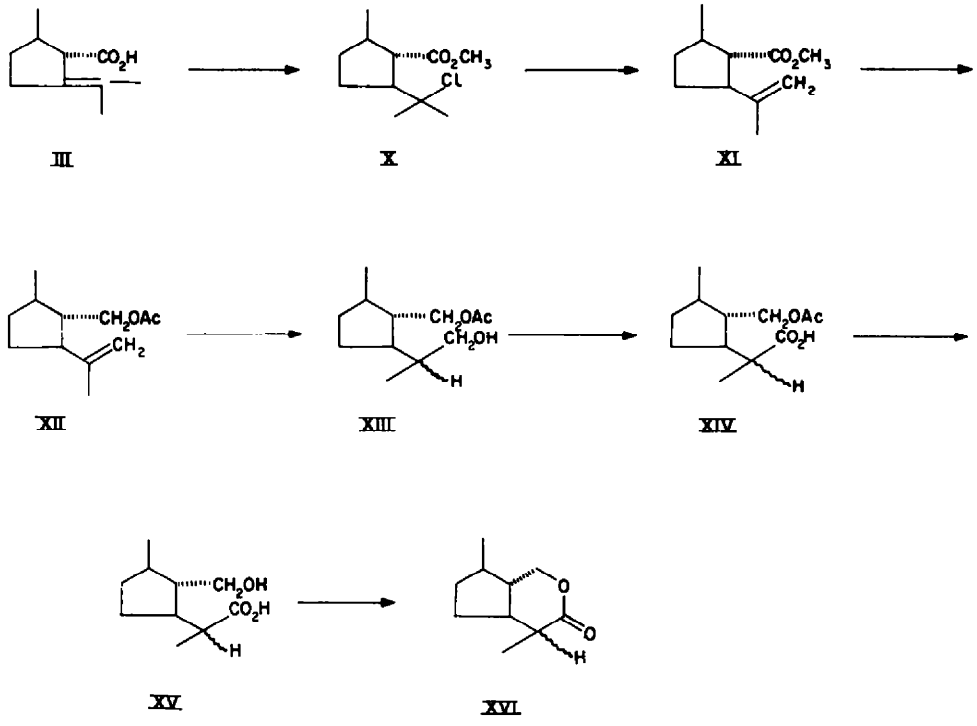
trans-trans-*Iridolactone* (XVI)

It was originally considered that the action of hydrogen chloride in methanol on IV would result in a kinetically controlled ring opening to afford a methyl chloro ester of *cis-trans*-configuration which might be used as an intermediate for the production of iridomyrmecin. This possibility was eliminated when it was discovered



[18] The authors wish to express their appreciation to Professor G. W. K. Cavill for kindly supplying the sample of (—)-isoiridomyrmecin.

that brief treatment of *trans*-pulegenic acid (III) or IV with hydrogen chloride in methanol gave methyl *trans*-pulegenate exclusively. Prolonged treatment finally gave a methyl chloro ester (X) which must have arisen from the thermodynamically controlled addition of hydrogen chloride to the isopropylidene double bond of methyl pulegenate. The methyl chloro ester can therefore be formulated as the thermodynamically more stable *trans-trans*-isomer (X). That this is the case was ultimately shown by the transformations described below which led to *trans-trans*-iridolactone (XVI).

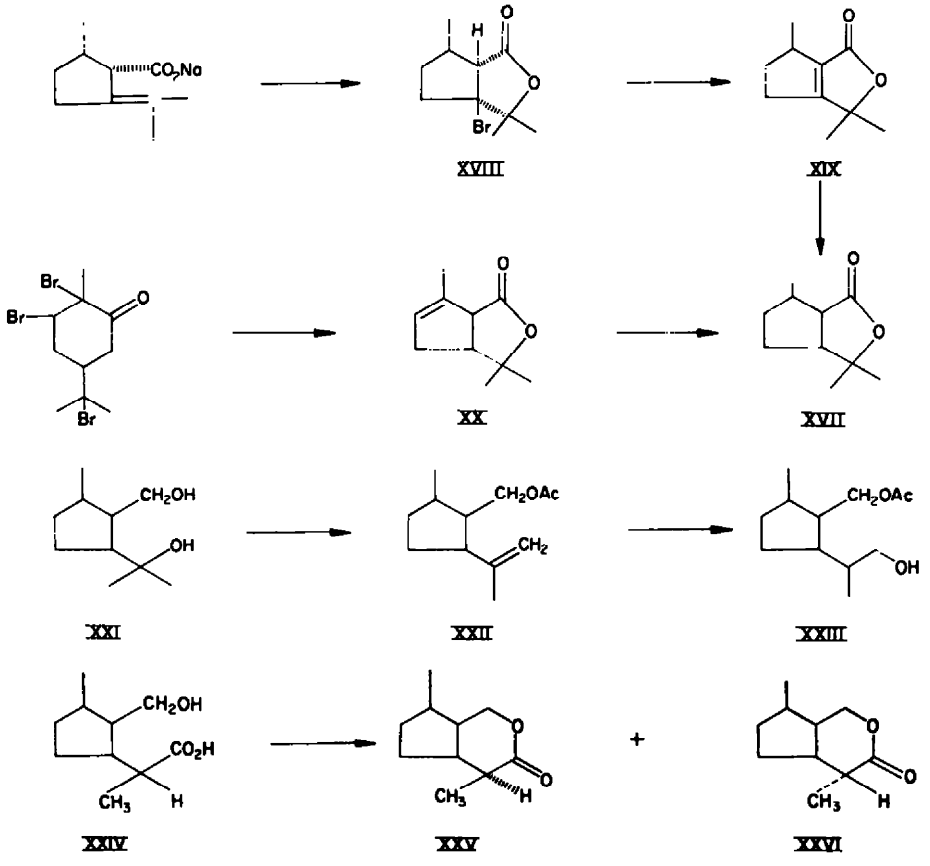


Dehydrochlorination of X with 2,6-lutidine led to a mixture of unsaturated esters in which methyl *trans-trans*-5-isopropenyl-2-methyl-1-cyclopentanecarboxylate (XI) predominated over methyl *trans*-pulegenate by a ratio of about 4:1. LAH reduction of the ester mixture, followed by acetylation, gave a mixture of the unsaturated acetate (XII) and 2-acetoxymethyl-3-isopropylidene-1-methylcyclopentane. The action of bis-3-methyl-2-butylborane[15] on this mixture of acetates led to the exclusive conversion of XII into XIII. Oxidation of XIII gave XIV which was converted with alkali to XV, which proved, contrary to the experience with the corresponding hydroxy acid derived from iridomyrmecin, extremely difficult to lactonize. Even after 6 sublimations at temperatures from 100–180° and pressures from 1·0–300 mm the resulting XVI was contaminated by appreciable amounts of XV. Heating XV with acetic anhydride produced *trans-trans*-iridolactone (XVI) contaminated by what appeared to be the acetate derivative of the mixed anhydride of XV. A pure sample of XVI was finally isolated by vpc. The lactone appeared to be unstable when exposed to moisture, reverting to the original XV. An attempt to crystallize the lactone from petroleum ether gave an oil whose IR spectrum was identical with that of XV.

cis-cis-*Iridolactones* (XXV *and* XXVI)

The synthesis of *cis-cis*-iridolactone according to the method of attack followed for the preparation of iridomyrmecin required a convenient preparation of XVII. Favorskii rearrangement of pulegone dibromide with aqueous alkali[12,14a] affords a mixture of almost equal parts of *cis*-and *trans*-pulegenic acid. Unfortunately, the *cis*-acid or the *cis-cis*-lactone (XVII) derived from it, could not be readily separated from the *trans*-acid or the corresponding *cis-trans*-lactone (IV). For this reason stereospecific routes originating from *trans*-pulegenic acid and (+)-carvone, respectively, were developed for the preparation of XVII.

The addition of bromine to sodium *trans*-pulegenate gave XVIII, which was cleanly dehydrobrominated to the conjugated lactone (XIX)[12] using potassium



[13] The bromolactone (XVIII) was not affected appreciably by heating with triethylamine in benzene. Dehydrobromination was brought about by prolonged heating with triethylamine in xylene. The difficulty encountered in dehydrobrominating XVIII with triethylamine is to be contrasted with the ease, 1 hr. heating in benzene, with which the bromolactone derived from *cis*-pulegenic acid is converted to unsaturated lactone XIX.[12] The formation of the conjugate lactone XIX from both isomeric bromolactones and the rapid elimination of HBr from the bromo lactone derived from *cis*-pulegenic acid is in best accord with the involvement of a *cis* E-2 elimination. For other *cis*-eliminations see: C. H. DePuy, R. D. Thurn and G. E. Morris, *J. Amer. Chem. Soc.* **84**, 1314 (1962).

t-butoxide.[19] Catalytic hydrogenation proceeded selectively to give the desired XVII contaminated with 10–20% of the isomer IV. Pure XVII was readily isolated from this mixture by recrystallization.

An alternate and overall more satisfactory method of preparing XVII involved the stereospecific addition of hydrogen to carvenolide (XX), produced by the action of ammonia on carvone tribromide.[12,20]

With pure XVII in hand, its conversion into *cis-cis*-iridolactone was patterned after the approach used for the preparation of (−)-iridomyrmecin. LAH reduction of XVII afforded the crystalline XXI, which was simultaneously acetylated and dehydrated by heating with acetic anhydride to afford an unsaturated acetate mixture comprised of 51% of *cis*-2-acetoxymethyl-3-isopropylidene-1-methylcyclopentane and 49% of the desired *cis-cis*-2-acetoxymethyl-3-isopropenyl-1-methylcyclopentane (XXII).

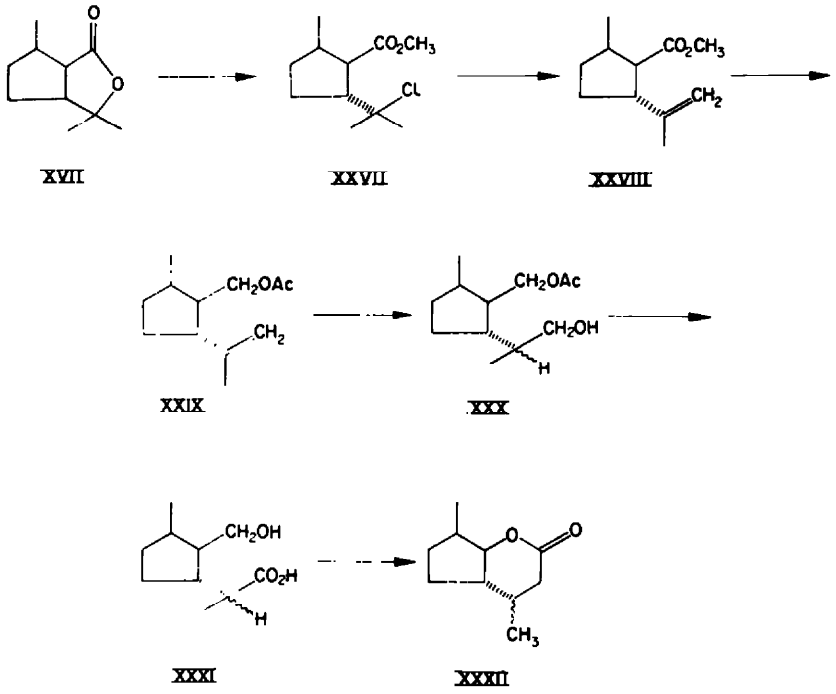
Hydroboration[15] of the unsaturated acetate mixture gave XXIII which was indicated by gas chromatographic analysis to be a mixture of stereoisomers, presumedly epimeric at the side chain CH_3—CH—CH_2OH group. Oxidation of XXIII and hydrolysis with dilute alkali gave, on rapid acidification, an insoluble hydroxy acid (XXIV) and a soluble mixture of lactones. Gas chromatographic separation of the lactone mixture gave two solids, *cis-cis*-iridolactone (XXV), m.p. 31–32°, $[\alpha]_D$ +172° and *cis-cis*-iridolactone (XXVI), m.p. 64–65°, $[\alpha]_D$ −53°. Sublimation of XXIV gave only the *cis-cis*-iridolactone (XXV), m.p. 31–32°. The stereochemical assignments to the *cis-cis*-iridolactones (XXV and XXVI) rest on a comparison of their optical rotations with those of natural (+)-iridomomyrmecin, $[\alpha]_D$ +210° and (−)-isoiridomyrmecin, $(\alpha)_D$ −59°. These assignments are valid providing the assumption is made that a change in configuration of the methyl group at C-1 does not drastically alter the conformation of the entire molecule.

trans-cis-*Iridolactone* (XXXII)

The synthesis of XXXII was patterned after the procedure employed for *trans-trans*-iridolactone (XVI). Prolonged treatment of XVII with hydrogen chloride in methanol gave the methyl *trans-cis* chloro ester (XXVII). Dehydrochlorination of XXVII with 2,6-lutidine led to a mixture of methyl *trans-cis*-5-isopropenyl-2-methyl-1-cyclopentane carboxylate (XXVIII) and methyl *cis*-pulegenate in a ratio of ca. 3:1. LAH reduction and acetylation gave the corresponding mixture of *trans-cis* unsaturated acetate (XXIX) and *cis*-2-acetoxymethyl-3-isopropylidene-1-methylcyclopentane.

Hydroboration of the unsaturated acetate mixture with bis-3-methyl-2-butylborane gave XXX which was converted by oxidation and hydrolysis to XXXI. A satisfactory method for the lactonization of this hydroxy acid was not found. Sublimation at temperatures from 150–200° gave small amounts of *trans-cis*-iridolactones, largely unchanged acid and some polymeric material. Treatment with acetic anhydride at 100° gave a lactone mixture contaminated with acetyl containing by-products. Samples of two isomeric *trans-cis*-iridolactones were isolated by gas chromatography. However, lactonization of XXXI after it had been kept at room temperature for several months gave only one of the two isomeric lactones (XXXII). Owing to the difficulty experienced in the lactonization of XXXI, the *trans-cis*-iridolactones have not been characterized completely.

[20] O. Wallach, *Liebig's Ann.* **414**, 233 (1918).



Spectral and stereochemical considerations

The IR spectra of the isomeric iridolactones are quite distinct, and, coupled with their different retention times on a Carbowax 20M column, provide a ready means for their identification.

We find, on the other hand, that the IR spectra of the various intermediates leading to the iridolactones do not always permit the differentiation of one stereoisomer from another. This is particularly true for the isomeric 2-acetoxymethyl-3-isopropenyl-1-methylcyclopentanes (VII, XII, XXII and XXIX). Close examination of the NMR spectra of these acetates provides certain generalizations which not only readily distinguish one isomer from another but suggest a simple tool to apply in connection with problems of stereochemistry which may arise with compounds derived from other iridoid terpenes[21] and alkaloids.[22]

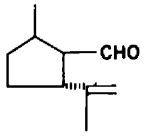
TABLE 1. NUCLEAR MAGNETIC RESONANCE SPECTRA OF ISOMERIC 2-ACETOXYMETHYL-3-ISOPROPENYL-1-METHYLCYCLOPENTANES

Isomer	—C=CH_2	—CH_2OAc	CH_3CO	CH_3C=C	CH_3—CH—
cis-trans-VII	4·78, 4·68	3·86, 3·77, 3·64	1·94	1·78	1·09, 1·00
cis-cis-XXII	4·80, 4·68	3·88, 3·78	1·94	1·79	1·10, 0·99
trans-cis-XXIX	4·68	3·97, 3·87	1·93	1·68	0·96, 0·84
trans-trans-XII	4·68	4·07, 3·98, 3·89	1·94	1·69	1·08, 1·00

[21] G. W. K. Cavill, *Rev. Pure Appl. Chem.* **10**, 169 (1960); G. W. K. Cavill and H. Hinterberger, *J. Austr. Chem.* **14**, 143 (1961).

[22] E. J. Eisenbraun, A. Bright and H. H. Appel, *Chem. & Ind.* 1242 (1962); L. Kawasaki, *Nippon Kagaku Zasshi* **81**, 154 (1960); G. Jones, H. M. Fales and W. C. Wildman, *Tetrahedron Letters* 397 (1963).

Examination of Table 1 indicates that the relationship between the isopropenyl group at C-3 and the acetoxymethyl group at C-2 can be decided by the appearance of a singlet for the olefinic protons when the substituents are *trans* and a doublet when they are *cis*.[23] This can be attributed to hindered rotation in the *cis*-isomers which places the two olefinic hydrogens in different environments. A further check on this assignment is provided by the signal of the methyl of the isopropenyl group which is found at 1·78 when the substituents are *cis* and at 1·69 when they are *trans*. The stereochemical relationship between the methyl group at C-1 and the acetoxymethyl group at C-2 can be decided on the basis of the smaller spin coupling constant of the CH_3—CH— group when the substituents are *trans* (J 4·8–5·4 c/s) than when they are *cis* (J 6·0–6·6 c/s).[24] In addition, the —CH_2OAc protons appear as triplets when the groups are *trans* and as a singlet accompanied by a close doublet when they are *cis*. These data have made possible the assignment of stereochemistry to aldehyde XXXIII[24a] obtained by photocyclization of citral.[25]



XXXIII

Biosynthesis of the iridolactones

Although experimental evidence is not available, several investigators[10,26] have discussed possible biogenetic routes to the ant lactones and related nepetalactones.[27,28] Citronellal has been considered as a possible precurser and according to Robinson[10] is converted to iridomyrmecin by an allylic oxidation, followed by an intramolecular Michael cyclization and intramolecular hydride transfer as indicated on the opposite page.

Cookson,[25] on the other hand, has obtained aldehyde XXXIII by irradiating citral. Enzymatic oxidation of XXXIII could give dolichodial (XXXIV)[2] which after reduction to iridodial (XXXV) and disproportionation would afford iridomyrmecin or isoiridomyrmecin.

Still another scheme visualizes (−)-limonene as a precursor. Oxidation of limonene to XXXVI, aldol cyclization to the unsaturated aldehyde XXXVII and enzymatic reduction would afford XXXIII. Aldehyde XXXIII might then proceed to the iridolactones in the manner described above. The plausibility of this scheme

[23] For additional data on the NMR signals of isopropenyl protons see Kondo, Kondo, Takemoto and Ikenove, *Bull. Chem. Soc. Japan* **35**, 1899 (1962).

[24] This difference in spin coupling constant does not appear to be generally applicable; thus *cis*- and *trans*-2-acetoxymethyl-3-isopropylidene-1-methylcyclopentane both show a spin coupling constant of 6·1 c/s.

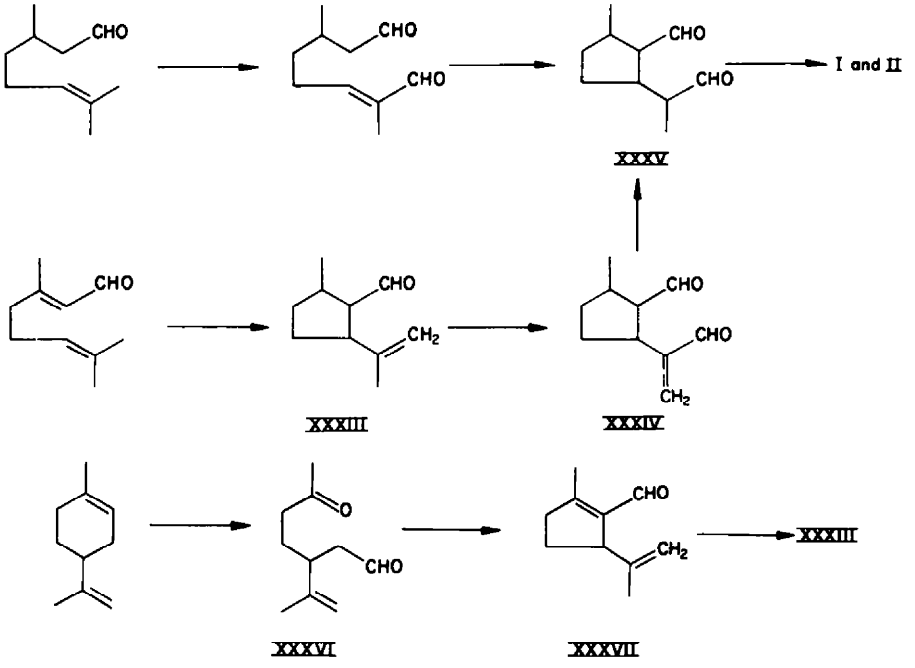
[24a] R. C. Cookson, Private communication.

[25] R. C. Cookson, J. Hudec, S. A. Knight and B. Whitear, *Tetrahedron Letters* 79(1962); *Tetrahedron* **19**, 1995 (1963).

[26] R. Thomas, *Tetrahedron Letters* 544 (1961); E. Wenkert, *J. Amer. Chem. Soc.* **84**, 99 (1962).

[27] J. Meinwald, *J. Amer. Chem. Soc.* **76**, 4571 (1954).

[28] R. B. Bates, E. J. Eisenbaum and S. M. McElvain, *J. Amer. Chem. Soc.* **80**, 3420 (1958).



is suggested by the preparation of XXXVII from the keto-aldehyde XXXVI.[30] The chemical reduction of XXXVII has now been examined under a variety of conditions and it has been found that 1,2-reduction of the aldehyde group predominates using sodium in ethanol, whereas, sodium or potassium in liquid ammonia reduces both the aldehyde group and the conjugated double bond to give a mixture of the 4 isomeric 2-hydroxymethyl-2-isopropenyl-1-methylcyclopentanes. Lithium in liquid ammonia produces a mixture in which the isomeric aldehydes XXXIII predominate.[31]

TABLE 2. REDUCTION OF 5-ISOPROPENYL-2-METHYL-1-CYCLOPENTENE-1-CARBOXALDEHYDE (XXXVII) TO 2-HYDROXYMETHYL-3-ISOPROPENYL-1-METHYLCYCLOPENTANES[a]

Reducing agent	*trans-cis*[b] XXIX *and* *cis-trans*[b] VII	*trans-trans* XII	*cis-cis* XXII
Na, EtOH	trace[c]	33%	20·5%
Na, liq. NH_3, EtOH	62%	32%	6%
K, liq. NH_3, EtOH	66·5%	30·5%	3%
Li, liq. NH_3, EtOH	58·2%	38%	4%

[a] The crude product was treated with aluminum hydride and acetylated.

[b] *trans-cis* XXIX and *cis-trans* VII were not separated cleanly by v.p.c. and the percentage of the mixture of the two is given. In each instance there was approximately equal amounts of the two isomers present.

[c] The major product, 46·5% was 2-hydroxymethyl-3-isopropenyl-1-methyl-1-cyclopentene.

[30] J. Wolinsky, M. Slabaugh and T. Gibson, *J. Org. Chem.* **29**, 3740 (1964).

[31] For a study of the effect of solvents and metals on the course of the reduction of a conjugated system see G. E. Arth, G. I. Poos, R. M. Lukes, F. M. Robinson, W. F. Johns, M. Feurer and L. H. Sarett, *J. Amer. Chem. Soc.* **76**, 1715 (1954).

In order to better determine the exact steric course of these reductions the crude products were treated with an excess of LAH and the resulting alcohols were acetylated and analyzed by vpc to give the data presented in Table 2.

The conversion of XXXVI into XXXIII demonstrates that limonene may serve as biosynthetic intermediate for iridoid compounds. We plan to test these ideas by *in vivo* experiments involving the incorporation of tagged intermediates into iridomyrmecin and related compounds.

EXPERIMENTAL

All b.ps and m.ps are uncorrected. IR spectra were determined with a Perkin Elmer Infracord spectrometer and optical rotations were measured with a Zeiss polarimeter. Vpc separations and analyses were conducted with a Carbowax 20 M column. NMR spectra were measured at 60 mc by Mr. W. E. Baitinger with the Varian Associates V-4300-B and A-60 spectrometers. Chemical shifts are given with reference to tetramethylsilane as an internal standard. Microanalyses were performed by Dr. C. S. Yeh and associates.

Synthesis of (−)-*Iridomyrmecin* (I)

3-(α-*Hydroxyisopropyl*)-2-*acetoxymethyl*-1-*methylcyclopentane*, (cis-trans-V)

A solution of 5·15 g (0·031 mole) of IV in anhydrous ether was added dropwise to an excess of LAH in ether. The resulting slurry was stirred for 30 min and the complex was decomposed with water. The inorganic salts were removed by filtration and after drying ($MgSO_4$), the ether was removed to give a viscous oil which could not be induced to crystallize. The oil was dissolved in acetic anhydride, three drops of pyridine were added, and the solution was allowed to stand at room temp overnight. Excess acetic anhydride was removed by vacuum distillation leaving an oil which slowly crystallized. Recrystallization from pet. ether gave 5·09 g (78%) of a white solid, m.p. 59–61°. Sublimation *in vacuo* gave a sample of V which showed $[\alpha]_D^{25°}$ +46°, (*c*, 4·53, CCl_4), IR bands at 2·75, 2·83, 5·79 and 8·1 μ, and NMR signals at 0·92, 1·03 (CH_3—CH—), 1·18, 1·28 ($(CH_3)_2C$—O), 1·97 (CH_3—CO—), and a multiplet centered at 4·08 ppm (—CH_2—O—). (Found: C, 67·60; H, 10·21. Calc. for $C_{12}H_{22}O_3$: C, 67·25; H, 10·35%.)

2-*Acetoxymethyl*-3-*isopropenyl*-1-*methylcyclopentane*, (cis-trans VII)

A. *Phosphorus oxychloride dehydration.* To a stirred solution of 1.35 g of V in 30 ml of dry pyridine at 0° was added dropwise 5·0 ml $POCl_3$. After standing at room temp overnight, the solution was poured into ice water and extracted with ether. The ether solution was washed with dil. HCl, dried and distilled to yield 1·13 g (92%) of a yellow oil. Vpc analysis of this oil indicated the presence of VII and *trans*-2-acetoxymethyl-3-isopropylidene-1-methylcyclopentane in a ratio of 17:83. Samples of these acetates were collected by vpc and identified by their IR spectra.

B. *Phosphorus oxychloride-2,6-lutidine dehydration.* A mixture of 1·0 g of V and 5 ml $POCl_3$ in 2,6-lutidine was heated at 50° for 1 hr. On working up a quantitative yield of unsaturated acetates was obtained. Gas chromatographic analysis indicated the presence of 32% of VII and 68% of *trans*-2-acetoxy-methyl-3-isopropylidene-1-methylcyclopentane.

C. *Acetic anhydride dehydration.* A solution of 37·4 g (0·217 mole) of the crude *cis-trans*-glycol, obtained as described above, in 150 ml acetic anhydride containing 1·0 ml pyridine was kept overnight and then the acetic anhydride was removed *in vacuo*. Fresh acetic anhydride was added and the resulting solution was heated at reflux for 5 hrs, after which most of the acetic anhydride was distilled. Distillation of the residue gave 33·9 g (81%) of a colourless liquid, b.p. 92–94° (5 mm), n_D^{25} 1·4589. Vpc analysis indicated the presence of 78% of VII and 22% of the isopropylidene isomer.

A pure sample of VII, isolated by vpc, showed n_D^{25} 1·4559, $[\alpha]_D^{25}$ +88° (*c*, 1·59 EtOH), IR bands at 5·77, 6·10 and 11·25 μ and NMR signals at 1·00, 1·06 (CH_3—CH—), 1·75 (CH_3C=C), 1·93 (CH_3—CO—), a triplet at 3·75 (—CH_2—O) and 4·68, 4·78 (C=CH_2) ppm. (Found: C, 73·58; H, 10·17. Calc. for $C_{12}H_{20}O_2$: C, 73·43; H, 10·27%.)

Hydroboration of VII; cis-trans-*hydroxyacetate* VIII

To a solution of 7·50 g (0·107 mole) of 2-methyl-2-butene in anhydrous tetrahydrofuran at 0° was added 30·0 ml of a 0·83 M solution of diborane in tetrahydrofuran.[15] After stirring for 3 hr at 0°,

15·6 g (0·079 mole) of a mixture of unsaturated acetates containing 64% of VII was added. The solution was cooled to 0° and there was added simultaneously, with vigorous stirring over a 90 min period, 16·5 ml of 30% H_2O_2 and 16·5 ml 3·0 N NaOH. After stirring an additional hr, the mixture was neutralized with acetic acid and the solvent removed (red. press.) The resulting mixture was extracted with methylene chloride. Distillation gave 9·2 g of a mixture of starting acetates, enriched in *trans* 2-acetoxymethyl-3-isopropylidene-1-methylcyclopentane, b.p. 80–84° (3 mm) and 7·02 g of VIII, b.p. 137–142° (3 mm). Vpc appeared to indicate the presence of single product. An evaporatively distilled sample of VIII showed n_D^{25} 1·4670, $[\alpha]_D^{25}$ +37° (*c*, 5·68, EtOH), IR bands at 2·73, 2·85, 5·78 and 8·13 μ and NMR signals at 0·98, 1·05 ($2CH_3$—CH—), 1·99 (CH_3—C=O), 2·86 (—OH), and a complex multiplet between 3·3 and 4·3 ppm (—CH_2—O—). (Found: C, 67·72; H, 10·48. Calc. for $C_{12}H_{22}O_2$: C, 67·25; H, 10·35%.)

cis-trans-*Acetoxy acid* (IX)

A solution of 5·30 g VIII in 300 ml purified acetone was titrated with 8 N CrO_3 in H_2SO_4–water. Only 67% of the theoretically calculated amount of oxidant was consumed. After removal of the insoluble salts and distillation of acetone, ether was added and the resulting solution was extracted with Na_2CO_3aq. The alkaline solution was acidified and extracted with methylene chloride. The methylene chloride solution was dried and the solvent removed to leave 3·04 g (54%) oil which after evaporative distillation showed n_D^{27} 1·4633, $[\alpha]_D^{25}$ 0°, IR bands at 5·75 and 5·87 μ and NMR signals at 0·96, 1·07 (CH_3—CH—), 1·21, 1·31 (CH_3—CH—CO_2), 1·98 (CH_3—C=O), a quartet at 3·92 (CH_2—O) and 11·30 ppm (—CO_2H). (Found: C, 63·32; H, 8·80. Calc. for $C_{12}H_{20}O_4$: C, 63·13; H, 8·83%.)

(−)-*Iridomyrmecin* (I)

A solution of 2·5 g IX in dil NaOHaq was heated for 2 hr. After cooling, the solution was acidified and extracted with methylene chloride to yield 2·25 g yellow oil. Recrystallization from pet. ether gave 0·94 g white crystals, m.p. 58–61°. Vpc of the mothor liquor indicated it was comprised of iridomyrmecin contaminated with 10–15% of an unidentified substance. Another recrystallization of the solid, followed by vacuum sublimation gave a sample of (—)-iridomyrmecin, m.p. 60·5–61°, $[\alpha]_D$ −199° (*c*, 3·77, EtOH). Reported for (+)-iridomyrmecin, m.p. 60–61°, $[\alpha]_D$ +210°. The IR spectrum of the synthetic lactone, in $CHCl_3$ solution, was essentially identical with that reported for the natural lactone.[10] The NMR spectrum of the lactone exhibited signals at 1·01, 1·11 ($2CH_3$—CH—), 1·81, 2·55 and 4·12 ppm. (Found: C, 71·42; H, 9·81. Calc. for $C_{10}H_{16}O_2$: C, 71·39; H, 9·59%).

(+)-*Isoiridomyrmecin* (II)

A solution of 338 mg of (−)-iridomyrmecin in 15 ml MeOH containing NaOMe was refluxed for 48 hr. The MeOH was removed and the residue acidified with dil. HCl. Extraction with ether gave an oil which was recrystallized from pet. ether to give, after 2 recrystallizations, 70 mg white needles, m.p. 56–57°, $[\alpha]_D$ +59° (*c*, 1·935, CCl_4). Reported for (−)-isoiridomyrmecin, m.p. 56–57°, $[\alpha]_D$ −59°.[22] The IR spectrum of (+)-isoiridomyrmecin was identical with that of an authentic sample of (−)-isoiridomyrmecin.[23]

trans-trans-*Iridolactone* (XVI)

trans-*Methyl pulegenate*. A solution of 20 g IV in MeOH was saturated with dry HCl and kept for 6 hr. The solvent was removed and distillation afforded 20 g of a colourless liquid, b.p. 93° (4 mm) which was identified as methyl pulegenate[12] by IR and Vpc comparison. A similar result was noted when *trans*-pulegenic acid was kept for 6–10 hr in MeOH saturated with HCl.

A pure sample of methyl pulegenate, obtained by diazomethane esterification of *trans*-pulegenic acid, showed n_D^{25} 1·4636, 5·80 μ and NMR signals at 0·96, 1·05 (CH_3—CH—), 1·56, 1·66 ($(CH_3)_2C$=C) 2·82–3·0 (CO—CH—C=C) and 3·61 (—OCH_3) ppm. (Found: C, 72·05; H, 9·98. Calc. for $C_{11}H_{18}O_2$: C, 72·49; H, 9·96%.)

trans-trans-*Methyl chloropulegenate* (X)

A solution of 33 g *trans-pulegenic* acid in MeOH was saturated with dry HCl gas and kept at room temp for 72 hr. The mixture was poured into ice and water and extracted with ether. The

[22] G. W. K. Cavill and H. D. Locksley, *Austr. J. Chem.* **10**, 752 (1957).

[23] The authors wish to express their appreciation to Professor G. W. K. Cavill for supplying the sample of (—)-isoiridomyrmecin.

ether solution was dried, the ether removed and distillation gave 30·5 g colourless liquid, b.p. 84–89° (2 mm) 72–74° (0·85 mm), n_D^{25} 1·4604. The IR spectrum of the chloro ester was similar to that of methyl pulegenate, but exhibited several new peaks in the region 10·0 to 11·5 μ. The NMR spectrum, 1·0, 1·1 (CH_3—CH—), 1·43, 1·53 ((CH_3)$_2$C—Cl) and 3·67 ppm (—OCH_3), indicated the absence of methyl pulegenate. Vpc of the chloro ester at 190° led to dehydrochlorination and the formation of approximately equal amounts of methyl pulegenate and XI. A sample of the chloro ester after standing 2 weeks did not give a test with $AgNO_3$aq.

Prolonged treatment of IV with HCl and MeOH gave the same chloro ester described above.

Methyl 5-isopropenyl-2-methyl-1-cyclopentanecarboxylate (trans-trans XI)

trans-trans Methyl chloropulegenate, 30·5 g, was heated at reflux in a N_2 atm. for 12 hr with 48 ml 2,6-lutidine. The mixture was added to ether and water, the layers were separated and the ether solution was washed with dil HCl, 5% $NaHCO_3$aq and water. After drying, the ether solution was distilled to give 21 g colourless liquid, b.p. 72–83° (2 mm). Vpc of this liquid indicated the presence of ca. 68% XI and 32% *trans*-methyl pulegenate. A pure sample of XI, isolated by vpc, showed n_D^{25} 1·4575, IR bands at 5·77, 6·10 and 11·25 μ, and NMR signals at 0·97, 1·07 (CH_3—CH—), 1·68 (CH_3—C=C), 3·60 (—OCH_3) and 4·69 ppm (C=CH_2). (Found: C, 72·43; H, 10·10. Calc. for $C_{11}H_{18}O_2$: C, 72·49; H, 9·96%.)

2-*Acetoxymethyl-3-isopropenyl-1-methylcyclopentane* (trans-trans-XII)

To a stirred slurry of 1·5 g LAH in 100 ml dry ether was slowly added an ether solution of 10·7 g of the mixture of methyl pulegenate and XI. After stirring for 1 hr the complex was decomposed with dil H_2SO_4. The mixture was filtered and the ether solution dried. The ether was removed and the residue was dissolved in 60 ml acetic anhydride and 0·5 ml pyridine. After 40 hr, the solution was distilled to give 10 g colourless liquid, b.p. 63–65° (1 mm). A pure sample of XII, isolated by vpc, showed n_D^{24} 1·4612, λ_{max} 5·74, 6·07 and 11·30 μ and NMR signals at 1·0, 1·08 (CH_3—CH—), 1·69 (CH_3—C=C), 1·94 (CH_3—CO_2—), 3·89, 3·98, 4·07 (—CH_2—O) and 4·68 ppm (C=CH_2). (Found: C, 73·75; H, 10·53. Calc. for $C_{12}H_{20}O_2$: C, 73·43; H, 10·27%.)

Hydroboration of XII, *hydroxy acid* XV

A solution of 12·62 ml 2-methyl-2-butene in dry tetrahydrofuran was added to 60 ml 0·89 M solution of diborane in tetrahydrofuran[15] at 0°. After 6 hr a tetrahydrofuran solution of 8·31 g of the mixture of unsaturated acetates containing XII was added and the solution was stirred at room temp for 7 hr. To this solution was added 11 ml 30% H_2O_2 and 11 ml 3 N NaOH. The tetrahydrofuran was distilled *in vacuo* and the residue extracted with ether. The ether solution was dried and the ether removed to leave a viscous oil which showed hydroxyl and acetate peaks in the IR and which was not purified further.

To a solution of the oil obtained above in pure acetone at 0° was added a solution of CrO_3 in H_2SO_4–water until an orange colour persisted. Isopropyl alcohol was added to destroy the excess oxidant and the green inorganic salts were removed by filtration and washed thoroughly with methylene chloride. The solvents were removed and the residue was warmed with NaOHaq. The alkaline solution was acidified and extracted with ether. The ether solution was dried and the ether removed to leave 3·4 g viscous oil which displayed broad absorption between 2·80 and 3·30 + 5·80 μ. A sample purified by evaporative distillation was analyzed. (Found: C, 64·50; H, 9·47; Calc. for $C_{10}H_{18}O_3$: C, 64·49; H, 9·74%.)

trans-trans-*Iridolactone* (XVI)

Sublimation of XV at 150° and 1 mm gave a mixture of acid and lactone. Lactonization was never complete by this procedure even after 5 successive sublimations at 200° and 100 mm. Treatment of XV with acetic anhydride and a trace of pyridine gave what appeared to be an acetate–anhydride derivative on the basis of peaks at 5·50, 5·60, 5·74 and 5·84 μ.

The lactone was best prepared by heating a small sample of XV with acetic anhydride at 100° for 20 hr. The acetic anhydride was removed and the residue evaporatively distilled. (Found: C, 70·37; H, 9·75. Calc. for $C_{10}H_{16}O_2$: C, 71·39; H, 9·59%.)

cis-cis-*Iridolactones* (XXV *and* XXVI)

Bromolactone XVIII

The addition of Br_2 to *trans*-pulegenic acid in CCl_4 at 0° gave XVIII as described earlier.[13] However, when the reaction was repeated on a larger scale a 1:1 mixture of IV and XVIII was produced. The lactone IV presumedly arose via lactonization promoted by HBr.

The bromolactone XVIII, free of IV, was obtained by the following procedure. *trans*-Pulegenic acid, 26·5 g, was dissolved in NaOHaq at 0° and a slight excess of Br_2 was added with stirring. The heavy oil which immediately separated was taken up in methylene chloride. The organic layer was dried and the solvent removed to give 38·1 g light brown oil whose IR spectrum was identical with that of pure XVIII.[13] This oil was not purified further but was used directly in the next step.

Pulegenolide XIX. Dehydrohalogenation of the bromolactone with excess triethylamine in refluxing benzene gave only 12% of the amine hydrobromide in 20 hr. Complete dehydrobromination with triethylamine could be effected by refluxing in xylene for 96 hr.

Pulegenolide was best prepared in the following manner. The bromolactone XVIII, from 26·5 g pulegenic acid, was added dropwise at room temp to a stirred solution of 7·5 g K in dry *t*-butyl alcohol. A precipitate formed immediately and after 1 hr the mixture was poured into ice water, neutralized with dil HCl and extracted with methylene chloride. The extract was dried, decolorized with charcoal, and the solvent removed. Distillation afforded an oil, b.p. 92–95° (2 mm) which was crystallized from pet. ether to give 15·6 g (60%) XIX, m.p. 40–41°.

cis-cis-*Puleganolide* (XVII)

Pulegenolide XIX; 15·3 g, was hydrogenated in ethyl acetate containing 1 ml acetic acid using PtO_2. The catalyst and solvents were removed to give 15·3 g oil which was shown to be comprised of 81% *cis-cis* XVII and 19% *cis-trans*-IV by vpc. Crystallization from pet. ether gave 8·37 g pure *cis-cis*-XVII, m.p. 47–48°.

Hydrogenation of 5·40 g carvenolide[13] (XX) using the same conditions described above afforded 5·14 g (94%) pure XVII, m.p. 49–50°.

3-(α-*Hydroxyisopropyl*)-2-*hydroxymethyl*-1-*methylcyclopentane* (cis-cis-XXI)

To an ether solution containing 8·30 g (0·05 mole) XVII was added 2·0 g (0·053 mole) LAH in ether. After stirring for 30 min, the complex was destroyed with water, the salts removed by filtration and the ether solution dried. The ether was removed leaving an oil which crystallized on standing. Vacuum sublimation afforded a sample which exhibited m.p. 41–44°, $[\alpha]_D$ +3·4 (*c*, 2·91, CCl_4), 3·1 μ and NMR signals at 0·91, 1·00 (CH_3CH—), 1·17, 1·34 ($(CH_3)_2CO$—), 1·79, 1·85, a doublet at 3·52 (—CH_2OH) and 5·3 ppm. (2 —OH). (Found: C, 70·20; H, 11·78. Calc. for $C_{10}H_{20}O_2$ C, 69·72; H, 11·70%.)

cis-cis-3-(α-*Hydroxyisopropyl*)-2-*acetoxymethyl*-1-*methylcyclopentane*

The XXI obtained above was dissolved in acetic anhydride containing a few drops pyridine and the solution was kept at room temp for 24 hr. Distillation gave 9·72 g (92%) hydroxyacetate, b.p. 100–102° (0·4 mm). A sample collected by vpc showed n_D^{22} 1·4642 and NMR signals at 0·95, 1·06 (CH_3CH) 1·14, 1·31 ($(CH_3)_2C$—O), 1·85, 1·97 (CH_3—CO), 2·20 (—OH) and an octet centered at 4·22 ppm. (—CH_2OAc). (Found: C, 67·83; H, 10·30. Calc. for $C_{12}H_{22}O_3$: C, 67·25; H, 10·35%.)

2-*Acetoxymethyl*-3-*isopropenyl*-1-*methylcyclopentane* (cis-cis XXII)

A solution of 9·5 g *cis-cis*-hydroxy acetate in 20 ml acetic anhydride was heated at 144° for 9 hr. Part of the excess anhydride was removed by distillation at atm. press. The residue was distilled (red. press.) to give 7·42 g (85%) of a colourless, oil, b.p. 88–90° (3·5 mm). Vpc indicated the oil was a mixture comprised of 49% of the desired XXII and 51% of *cis*-2-acetoxymethyl-3-isopropylidene-1-methylcyclopentane. A pure sample of XXII, isolated by vpc, exhibited n_D^{25} 1·4600, IR bands at 5·78, 6·12, 8·15 and 11·27 μ and NMR signals at 0·98, 1·10 (CH_3—CH), 1·81 (CH_3—C=C), 1·93 (CH_3—CO—), a doublet at 3·79 (—CH_2—O), and 4·68, 4·78 (C=CH_2). (Found: C, 73·75; H, 10·45. Calc. for $C_{12}H_{20}O_2$: C, 73·43; H, 10·27%.)

cis-cis-3-(β-*Hydroxyisopropyl*)-2-*acetoxymethyl*-1-*methylcyclopentane* (XXIII)

To a solution of 7·8 g (0·111 mole) 2-methyl-2-butene in pure tetrahydrofuran was added 0·70 g (0·025 mole) diborane in tetrahydrofuran. The solution was kept at 0° for 2 hr and then 7·0 g (0·0357

mole) of the mixture of unsaturated acetates containing XXII was added. The reaction was allowed to warm to room temp and was left for 24 hr. The solution was cooled and 16·0 ml 30% H_2O_2 and 16 ml 3 N NaOH were added simultaneously. After 1 hr most of the tetrahydrofuran was removed, water was added and the mixture was extracted with ether. The ether was removed and distillation afforded 3·0 g colourless oil, b.p. 117–119° (0·25 mm). Vpc on a silicone rubber column indicated the oil was a mixture of two closely related isomers. A vpc sample of this poorly resolved mixture showed n_D^{27} 1·4682, λ_{max} 2·92, 5·80 and 8·1 μ and NMR signals at 0·98, 1·07 (CH_3—CH), 1·98 (CH_3—CO), 2·17 (—OH), a multiplet centered at 3·4 (—CH_2OH) and a doublet centered at 4·0 ppm. (—CH_2OAc). (Found: C, 68·27; H, 10·51. Calc. for $C_{12}H_{22}O_3$: C, 67·25; H, 10·35%.)

cis-cis-*Iridolactone* (XXV *and* XXVI)

To an acetone solution of 3·8 g of the hydroxyacetates (XII) was added 7·1 ml 8 N CrO_3 in H_2SO_4–water. After 3 hr the excess oxidant was destroyed with isopropyl alcohol. The mixture was filtered and the acetone removed. The residue was taken up in ether, washed with water and dried. The ether was removed and the IR spectrum of the residue indicated the presence of an alcohol so that the oxidation was repeated and again worked up as just described. The residue obtained after removal of ether was heated for 2 hr with 2·0 g NaOH in 50 ml water. After cooling the solution was extracted with ether and acidified with dil. HCl. A white solid, m.p. 116–119°, immediately precipitated. The IR spectrum of this solid (nujol mull) showed it be a hydroxy acid. Extraction of the aqueous filtrate gave 1·27 g oil which was shown by vpc to be a 1:1 mixture of two lactones. Vacuum sublimation of the hydroxy acid at 60°, followed by recrystallization from pet. ether gave a single lactone, m.p. 30·5–32°, which was identical to one of the lactones in the 1:1 mixture. The second lactone was isolated from the lactone mixture and showed m.p. 64–65°. The amount of the 30–32° isomer in the total mixture was estimated to be 70%, while the 64–65° isomer amounted to 30%.

A pure sample of XXV m.p. 31–32°, showed $[\alpha]_D$ +172° (*c*, 2·40, CCl_4), λ_{max} 5·74 μ and NMR signals at 1·01, 1·05, 1·12, 1·16 (2 CH_3—CH—), 1·50 and 4·25 (—CH_2—O) ppm. (Found: C, 71·70; H, 9·73. Calc. for $C_{10}H_{16}O_3$: C, 71·39; H, 9·59%.)

A sample of XXVI, m.p. 64–65°, exhibited $[\alpha]_D^{25}$ −53·2° (*c*, 3·58, CCl_4), λ_{max} 5·74 μ, and NMR signals at 0·91, 1·02, 1·07, 1·17 (2 CH_3—CH—) 1·65, 2·10, a doublet at 3·94 and a singlet at 4·09 (—CH_2—O) ppm. (Found: C, 71·94; H, 9·61. Calc. for $C_{10}H_{16}O_3$: C, 71·39; H, 9·59%.)

trans-cis-*Iridolactone* (XXXII)

Methyl-5-isopropenyl-2-methylcyclopentane-1-carboxylate (trans-cis XXVIII)

A solution of 14·9 g (0·0887 mole) XVII in 600 ml MeOH saturated with dry HCl was kept at room temp for 6 days. The solution was poured into ice-water and extracted with ether. The IR spectrum of the crude organic residue indicated the presence of unreacted lactone, consequently, the above treatment with MeOH saturated with HCl was repeated. After the usual work up the residue did not exhibit a significant lactone peak and was used without purification in the next step.

A solution of the crude chloro ester and 40 ml 2,6-lutidine was heated at reflux for 18 hr, cooled, dissolved in ether and extracted with 5% HCl. The ether solution was dried and distilled to give 15·8 g (98%) colourless oil, b.p. 85–105° (7·8 mm). Vpc analysis indicated that the XXVIII was contaminated with 27% methyl *cis*-pulegenate. A pure sample of XXVIII showed n_D^{25} 1·4575, IR bands at 5·80, 6·12 and 11·26 μ and NMR signals at 0·83, 0·95 (CH_3—CH—), 1·68 (CH_3—C=C), 3·60 (—OCH_3) and 4·68 ppm (C=CH_2). (Found: C, 72·14; H, 10·64. Calc. for $C_{11}H_{18}O_2$: C, 72·49; H, 9·96%.)

2-*Acetoxymethyl*-3-*isopropenyl*-1-*methylcyclopentane* (trans-cis-XXIX). To an ether solution of 10·31 g of the esters obtained above was added 1·5 g LAH in ether. After 2 hr the complex was decomposed with water, the mixture filtered and the ether solution was dried. The ether was removed and the residue dissolved in 25 ml acetic anhydride containing 3 drops pyridine. The solution was kept 20 hr and then distilled to give 10·08 g (91%) oil, b.p. 68–86° (0·23 mm). A pure sample of XXIX showed n_D^{25} 1·4600, IR bands at 5·77 and 6·10 μ and NMR signals at 0·86, 0·96, 1·70 1·95, 3·90 (doublet), 4·0 (singlet) and 4·70 ppm. (Found: C, 73·71; H, 10·57. Calc. for $C_{13}H_{20}O_3$: C, 73·43; H, 10·27%.)

trans-cis-*Hydroxy acid* XXXI.

To a solution of 16 g (0·23 mole) 2-methyl-2-butene in dry tetrahydrofuran at 0° was added 67 ml 0·88 M diborane in tetrahydrofuran. After stirring for 2 hr, 10 g XXIX mixture was added. The

solution was allowed to warm to room temp and stand for 24 hr. The solution was cooled in an ice bath and 35 ml 30% H_2O_2 and 35 ml 3 N NaOH were added simultaneously. The usual work-up afforded, after distillation, 4·78 g XXX b.p. 131–132° (0·5 mm). The residue from distillation, 2·0 g, showed the same IR spectrum as the distilled hydroxyacetate.

A solution of 6·75 g XXX in purified acetone was oxidized according to the Jones procedure.[16] The crude acetoxy-acid, so obtained, was warmed with dil. NaOHaq. Acidification and extraction with ether gave a light tan oil, 4.90 g. Evaporative distillation afforded a colourless oil, λ_{max} 2·9–3·8 and 5·88 μ. (Found: C, 65·02; H, 9·73. Calc. for $C_{10}H_{16}O_3$: C, 64·49; H, 9·74%).

trans-cis-*Iridolactones* XXXII

A small amount of hydroxy-acid was heated at 160° and atm. press. in a sublimation flask. The IR spectrum of the sublimate indicated it was composed of the unaltered hydroxy acid.

A sample of the hydroxy acid was heated at 100° in acetic anhydride for 15 hr. The acetic anhydride was removed *in vacuo* and the residue evaporatively distilled. The resulting oil was further purified by vpc to give a small sample of XXXII, λ_{max} 5·82 μ, NMR signals at 0·88, 0·98, 1·09, 1·21, 3·55, and 4·0 ppm. Elementary analysis gave a low value for carbon, indicating the possibility that hydrolysis due to moisture had occurred.

Chemical reduction of 2-methyl-5-isopropenyl-1-cyclopentene-1-carboxaldehyde (XXXVII)

A. *Sodium and ethanol.* To a solution of 1·50 g (0·01 mole) XXXVII in 150 ml absolute EtOH was added 4·6 g (0·20 g atom) Na in portions at a rate sufficient to keep the solution refluxing moderately. Most of the solvent was removed under red. press. and 100 ml water was added to the dark residue. The resulting solution was extracted thoroughly with ether to give 1·12 g oil which displayed IR absorption at 3·00, 6·10 and 11·25 μ.

The oil was dissolved in 5 ml acetic anhydride containing several drops pyridine. After standing overnight, distillation gave 0·5 g liquid, b.p. 68° (0·60 mm). The analysis of this material is given in Table 2.

B. *Sodium in Liquid ammonia.* To a magnetically stirred solution of 4·6 g (0·20 g atom) Na in ca. 100 ml liquid ammonia was added over a period of 1 hr, 1·50 g (0·01 mole) XXXVII in 25 ml ether containing 2·30 g (0·05 mole) absolute EtOH. After stirring for 5½ hr., NH_4Cl was added cautiously until the blue colour disappeared. The ammonia was allowed to evaporate and 150 ml water was added to the residue. The solution was extracted thoroughly with ether to afford 1·53 g oil which showed a strong —OH peak at 3·00 μ and a weak carbonyl peak at 5·84 μ.

The oil dissolved in 25 ml ether was added dropwise to a stirred mixture of 0·38 g (0·01 mole) LAH and 50 ml ether. The reaction mixture was worked up in the usual manner to give an oil which was acetylated with acetic anhydride and pyridine. Distillation gave 0·85 g of an acetate mixture, b.p. 68° (0·4 mm). The analysis of this material is given in Table 2.

C. *Lithium in liquid ammonia.* The aldehyde XXXVII (1·50 g, 0·01 mole) in 25 ml ether containing 2·30 g absolute EtOH was added over a period of 8 min to a magnetically stirred solution of 1·39 g (0·20 g atom) Li in ca. 100 ml liquid ammonia. After the work up described previously, the residual oil was distilled to give 0·5 g liquid b.p. 32–82° (0·35 mm) and 0·3 g, b.p. 104–142° (0·35 mm). The IR spectrum of the first fraction indicated it was predominantly XXXIII contaminated with a small amount of the isomeric 2-hydroxymethyl-3-isopropenyl-1-methylcyclopentanes. The IR spectrum of the higher boiling suggested it was the ammonia adduct of XXXIII.