Tetrahedron Vol 23, pp 4635 to 4652 Pergamon Press Ltd 1967 Printed in Great Britain

STRUCTURE AND STEREOCHEMISTRY OF BOSCHNIAKINE, BOSCHNIALACTONE, AND BOSCHNIALINIC ACID, AN OXIDATION PRODUCT OF BOSCHNIALACTONE

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(*Received in Japan 9 January 1967; accepted for publication 1 February 1967*)

Abstract Boschniakine, $C_{10}H_{11}NO$, and boschnialactone, $C_9H_{14}O_2$, were isolated as the physiologically active principles of *Boschniakia rossica* Hult, and their absolute structures have been determined. Four optically active stereoisomers of boschnialinic acid (2-carboxy-3-methylcyclopentylacetic acid), one of which is an oxidation product of boschnialactone, have been synthesized and their stereochemistries established.

A NUMBER of cyclopentanoid monoterpenes isolated from *Actinidia polygama* Miq. (Dilleniaceae) during the past 10 years were found to have an interesting physiological action on Felidae and Chrysopidae.[1] A plant, *Boschniakia rossica* Hult. (Orobanchaceae), is also liked by Felidae animals and two active substances, boschniakine and boschnialactone, isolated are described in the present investigation. Oxidation of boschnialactone gave a 2-carboxy-3-methylcyclopentylacetic acid which was named boschnialinic acid. In this paper the isolation and the structural determination of both active components, and the syntheses and the stereochemistry of four stereoisomers of boschnialinic acid are reported.

Isolation and structural determination of boschniakine and boschnialactone[2]

The dried terrestrial portion of *Boschniakia rossica* Hult., collected during the flowering season on Mount Fuji, was extracted with methanol. Boschniakine was isolated as a basic substance from the water-soluble portion of this extract, and boschnialactone as a lactonic substance from the volatile neutral fraction. Both substances have a marked physiological action on the cat, similar to the constituents of *Actinidia polygama*.

Boschniakine occurs as a fragrant liquid, b.p. 80–90°/3 mm, $[\alpha]_D$ +21·02°, corresponding to the formula $C_{10}H_{11}NO$. It forms a picrate, m.p. 126·5–128° and a semicarbazone, m.p. 227–228° (dec). The base obtained by Huang-Minlon reduction and its picrate agree with actinidine (II), a component of *Actinidia polygama*, and its picrate[3] in IR spectra. Since the UV and IR absorption maxima (λ_{max} 239, 268 and 282 mμ; ν_{max} 3050, 2725, 1700 and 1580 cm^{-1}) suggest the presence of an aldehyde

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[1] T. Sakan, S. Isoe, S. Be Hyeon, R. Katsumura, T. Maeda, J. Wolinsky, D. Dickerson, M. Slabaugh and D. Nelson, *Tetrahedron Letters*, 4097 (1965) and Refs. contained therein.

[2] T. Sakan and F. Murai, *Abstracts for the 16th Annual Meeting of the Chemical Society of Japan*, p. 82 (1963).

[3] T. Sakan, A. Fujino and F. Murai, *Nippon Kagaku Zasshi*, **81**, 1320 (1960); A. Fujino, *Ibid.* 1327 (1960).

group conjugated with a pyridine ring, the structure I was given to boschniakine.

Boschniakinic acid, $C_{10}H_{11}NO_2$, m.p. 215–220° (dec), was obtained from the high-boiling fraction by the distillation of boschniakine. Its IR spectrum exhibits absorption bands at 2450, 1950, 1700, 1602 and 1575 cm^{-1}, which were not inconsistent with a pyridinecarboxylic acid structure.[4] This acid seemed to be an auto-oxidation product of I, and its structure III was confirmed by the oxidation of boschniakine with silver oxide.

Boschnialactone occurs as a colourless liquid, b.p. 105–112°/6 mm, $[\alpha]_D$ −18·2°, corresponding to the formula $C_9H_{14}O_2$. Its IR spectrum exhibits an absorption band for a carbonyl group at 1743 cm^{-1}. Oxidation with alkaline potassium permanganate afforded a saturated dicarboxylic acid, boschnialinic acid, $C_9H_{14}O_4$, m.p. 82–83°. The NMR spectrum of the lactone shows a signal centered at 8·95τ (doublet, $J = 7$, 3H) for secondary methyl hydrogens as well as signals at 7·60 τ (doublet, $J = 6$, 2H) and 5·88 τ (doublet, $J = 6$, 2H). Consideration of the biogenesis and the physiological activity of the compound, suggest formula IV for the lactone and, therefore, formula V for boschnialinic acid. The conclusive evidence for these structures is provided by the synthetic studies described below.

Syntheses of DL-*boschnialactone and related lactones*[5]

The syntheses were based on the reaction of ethyl 3-methyl-2-oxocyclopentylacetate (VI)[6, 7] with triphenylmethoxymethylenephosphorane in dimethylsulfoxide (DMSO)[8] to afford a methoxymethylene compound VII, which was usually contaminated with the starting material in approximately equal quantities. Compound VII is readily hydrolysed in water and underwent considerable hydrolysis and autooxidation during purification by column chromatography yielding a half ester VIIIa of a dicarboxylic acid.[9, 10] A pure sample of VII could be isolated by preparative VPC, but the yield was poor. Therefore, a mixture of VI and VII was used, *per se*, for the next step.

Hydrogenation of the methoxymethylene ester VII gave a dihydro compound IX as a mixture of two stereoisomers (1 : 1). Both analytical values and mass spectra of the mixture and a pure isomer agree with each other and are compatible with the structure IX.

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[4] S. Bratož, D. Hadži and N. Sheppard, *Spectrochim. Acta*, **8**, 249 (1956).

[5] T. Sakan, Y. Hayashi, Y. Honda and M. Nakajima, *Abstracts for the 18th Annual Meeting of the Chemical Society of Japan*, p. 217 (1965).

[6] A. E. Bradfield, E. M. Francis, A. R. Penfold and J. L. Simmonsen, *J. Chem. Soc.* 1619 (1936).

[7] The ketoester VI gave only one peak on VPC under a variety of conditions, but its NMR spectrum showed two pairs of doublet signals (intensity ratio = 1 : 2), centered at 8·93 τ ($J = 7$) and 8·90 τ ($J = 6$), corresponding to the secondary methyl hydrogen. Therefore, this substance was considered to be a mixture of stereoisomers relative to the substituents in 1- and 3-position.

[8] [a] E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.* **84**, 866 (1962); E. J. Corey, R. B. Mitra and H. Uda, *Ibid.* **86**, 485 (1964); R. Greenwald, M. Chaykovsky and E. J. Corey, *J. Org. Chem.* **28**, 1128 (1963); [b] E. J. Corey, M. Chaykovsky, *J. Am. Chem. Soc.* **87**, 1345 (1965).

[9] Treatment of VII with acid gave the aldehyde-ester XII, whose reduction with $NaBH_4$ followed by hydrolysis afforded a hydroxy acid XIII. As XIII underwent lactonization to a very limited extent under usual acidic conditions and formed XIV by distillation, compound XIV was assumed to be a *trans*-lactone

[10] Alkaline hydrolysis of the half-ester VIIIa gave a dicarboxylic acid VIIIb, m.p. 123–124°, which was the racemate of a stereoisomer of boschnialinic acid. Further details on this compound will be given later in connection with the stereochemistry of other isomers

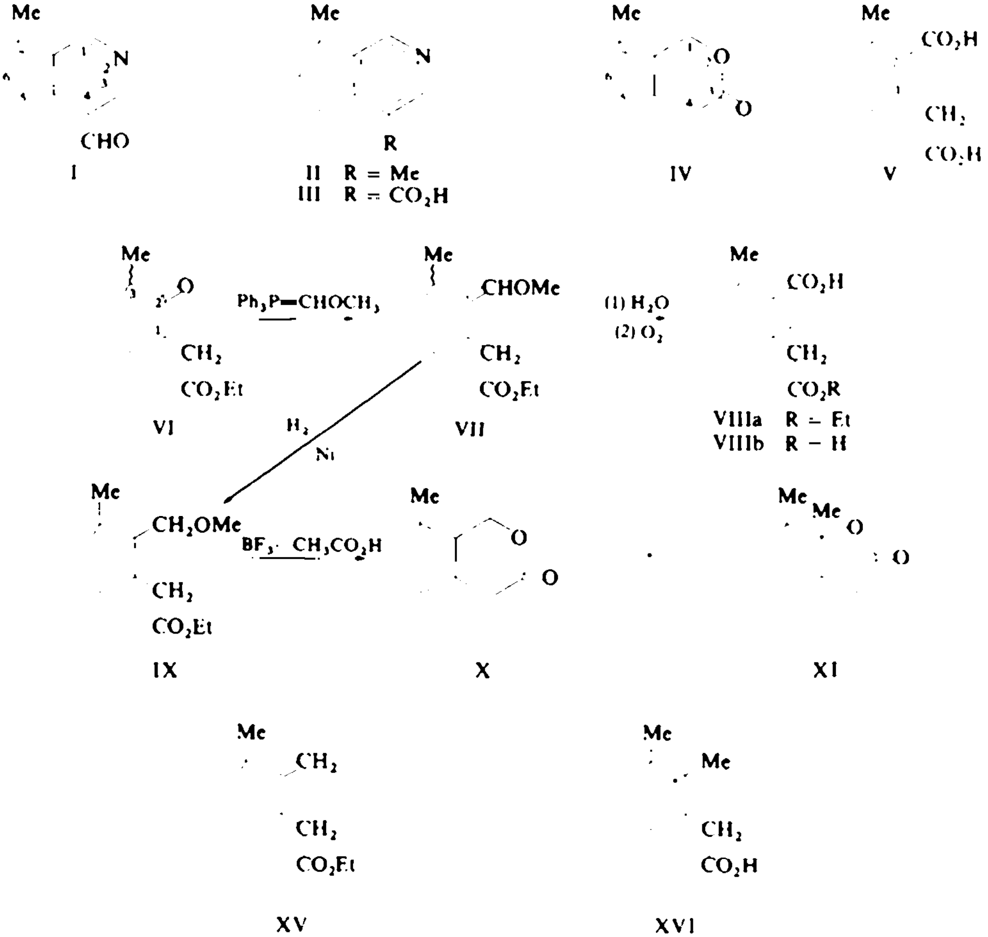
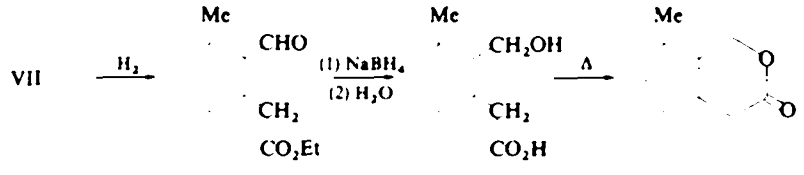


FIG. 1.

Compound IX was treated with a large excess of BF_3-acetic acid complex at the temperature of boiling dichloromethane. A liquid which gave 3 main peaks in VPC was obtained as the lactonic fraction of the reaction product. From this mixture, DL-boschnialactone (X) was isolated by silica gel chromatography. Compound X was a colourless fragrant liquid, and its IR and NMR spectra agree with those of the natural lactone. The mass spectrum of this lactone shows a molecular peak of *m/e* 154 and the mode of fragmentation is consistent with structure X. Since X is readily formed from the corresponding hydroxy acid by lactonization, the juncture of the lactone ring with the cyclopentane ring should be *cis*.[9] The relative configuration of a secondary methyl group attached to the cyclopentane ring and the absolute structure of the natural lactone will later be discussed on the basis of the oxidation product, boschnialinic acid.

Both the remaining lactones formed by the reaction of IX with BF_3 show a carbonyl absorption band at 1760 cm^{-1} and an NMR signal at 8·6 τ (singlet, 3H) besides that centered at 8·9 τ (doublet, $J = 5$, 3H) for a secondary methyl group. These facts suggest that they are stereoisomers of the 5-membered lactone represented by XI.

The lactones are probably formed via the carbonium ion XVI or its equivalent, since they are formed as a mixture of approximately the same composition from (a) reaction of the keto-ester VI with methylmagnesium iodide, (b) acid treatment of the exo-methylene ester XV[11] obtained from VI by the Wittig reaction, and (c) acid treatment of DL-boschnialactone.



XII XIII XIV

FIG. 2

In the conversion of IX into a mixture of the δ-lactone X and the γ-lactones XI, the ratio of XI to X formed increases by elevation of the reaction temperature and prolongation of the reaction time. Only the γ-lactones XI were formed by the use of 48% hydrobromic acid or concentrated sulfuric acid as the reagent.

Synthesis and absolute structure of boschniakine[12, 13]

Starting with 2-methoxycarbonyl-3-methylcyclopentanone (XIX),[14] derived from (+)-pulegone (XVII) via methyl pulegenate (XVIII),[15] the cyanopyridine derivative

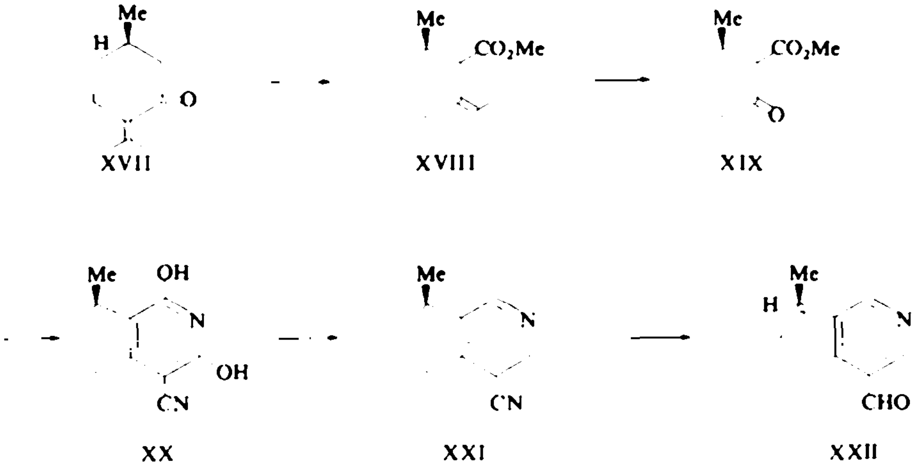


FIG. 3

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[11] K. Sisido, K. Utimoto and T. Isida, *J. Org. Chem.* **29**, 3361 (1964).

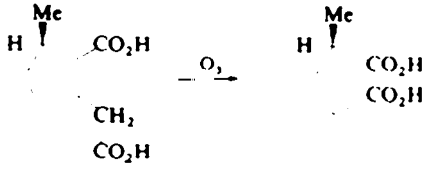
[12] T. Sakan, T. Shono and M. Kato, *Abstracts for the 17th Annual Meeting of the Chemical Society of Japan* p. 275 (1964).

[13] T. Sakan, Y. Hayashi, A. Otsubo and F. Murai, *Abstracts for the 19th Annual Meeting of the Chemical Society of Japan* Part IV; p. 15 (1966).

[14] T. Sakan, A. Fujino, F. Murai, Y. Butsugan and Y. Terashima, *Nippon Kagaku Zasshi* **81**, 1447 (1960).

[15] [a] H. Rupe and K. Schäfer, *Helv. Chim. Acta* **11**, 463 (1928); [b] J. Wolinsky and D. Chan, *J. Org. Chem.* **30**, 41 (1965); [c] S. A. Achmad and G. W. K. Cavill, *Austral J. Chem.* **16**, 858 (1963).

XXI was obtained via the dihydroxypyridine derivative XX.[16] The cyano derivative XXI was reduced with a large excess of stannous chloride and hydrogen chloride, and the resulting aldimine-stannic chloride complex was submitted to steam distillation, by which hydrolysis was effected together with isolation of the product to yield boschniakine (XXII), $[\alpha]_D$ +28·4°. The UV and IR spectra, and the specific rotation of this substance agree with those of the natural product. The asymmetric carbon atom in (+)-pulegone[17] was shown to have the R-configuration by the work of Freudenberg *et al.*[20] Therefore, the absolute structure of boschniakine was determined as XXII. Since all the bases having the iridoid skeleton reported previously[21] had the carbon atom in 7-position taking S-configuration, boschniakine is the first example of the base with a reverse configuration.



XXVIII

FIG. 4.

Syntheses of the stereoisomers of boschnialinic acid and stereochemistry of boschnialactone[13]

Four stereoisomers of boschnialinic acid (XXVI, XXVII, XXIX and XXX) were synthesized in the optically active forms and their stereochemistry established as follows:

Condensation of ethyl cyanoacetate with the β-ketoester XIX gave an unsaturated cyanodiester XXIV, whose structure was supported by analogy to similar reactions[16b, 22] and the NMR spectral evidence[23] of an unsaturated dicarboxylic acid

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[16] [a] T. Sakan, A. Fujino, A. Suzui and Y. Butsugan, *Nippon Kagaku Zasshi* **81**, 1445 (1960); [b] G. G. Ayerst and K. Schofield, *J. Chem. Soc.* 4097 (1958); M. Protiva, V. Mychajlyszyn and J. O. Jilek, *Chem. Listy* **49**, 1045 (1955); V. Prelog and O. Metzler, *Helv. Chim. Acta* **29**, 1170 (1946).

[17] Pulegone used here was of 89% purity with $[\alpha]_D^{18}$ +26·6° (reported,[18] $[\alpha]_D$ +21°). In order to confirm further the absolute configuration of the compounds used in a series of synthetic reactions, an intermediate XXVIII was submitted to ozonolysis and yielded (−)-2(R)-methylglutaric acid, m.p. 81–82°, $[\alpha]_D$ −21·1° (reported,[19] m.p. 82–83°, $[\alpha]_D$ −20·4°).

[18] A. Baeyer and F. Henrich, *Ber. Dtsch. Chem. Ges.* **28**, 653 (1895).

[19] V. H. T. James, *J. Chem. Soc.* 637 (1955).

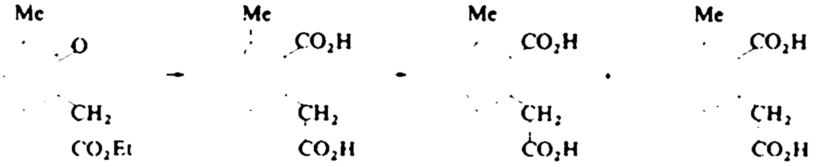
[20] K. Freudenberg and W. Hohmann, *Liebig's Ann.* **584**, 54 (1953).

[21] C. Djerassi, J. P. Kutney, M. Shamma, J. N. Shoolery and L. F. Johnson, *Chemi. & Ind.* 210 (1961); G. C. Casinovi, J. A. Garbarino and G. B. Marini-Bettolo, *Ibid.* 253 (1961); Y. Hammouda, M. Plat and J. LeMen, *Bull. Soc. Chim. Fr.* 2802 (1963); Y. Hammouda and J. Le Men, *Ibid.* 2901 (1963); G. Jones, H. M. Fales and W. C. Wildman, *Tetrahedron Letters* 397 (1963).

[22] [a] G. A. R. Kon and H. R. Nanji, *J. Chem. Soc.* 2426 (1932); A. C. Anderson, Jr., W. F. Harrison and R. G. Anderson, *J. Am. Chem. Soc.* **85**, 3448 (1963); [b] Kasturi and Srinivasan proposed a structure, having the exocyclic conjugated double bond, for an analogous compound to XXIV. The difference is probably due to the different reaction conditions of their preparations: T. R. Kastri and A. Srinivasan, *Tetrahedron* **22**, 2575 (1966).

[23] The acid XXVIII or its dimethyl ester exhibited two characteristic NMR signals at 8·88 τ (doublet, J = 7 c/s, 3H) for a secondary methyl group and around 6·3 τ (singlet, 2H) for the allylic side chain methylene group, and gave no olefinic proton signal.

XXVIII, a hydrolysis product of XXIV. Hydrogenation of XXIV over Pt catalyst in ethanol resulted in the formation of a saturated cyanodiester XXV with rapid absorption of hydrogen. Subsequent hydrolysis and decarboxylation gave two acids, XXVI m.p. 113°, $[\alpha]_D$ $-41{\cdot}1°$, and XXVII m.p. 85°, $[\alpha]_D$ $-33{\cdot}7°$. The acid, obtained from the natural boschnialactone, agreed with XXVII in mixed m.p. and the IR spectra of the acids and their esters. By heating under reflux with methanolic sodium methoxide,[24, 25] the dimethyl ester of XXVII was almost completely isomerized to the ester of an isomeric acid XXX, m.p. 110–111°, $[\alpha]_D$ $-65{\cdot}4°$ (an aforementioned DL-acid VIIIb was the racemate of XXX), and the dimethyl ester of XXVI was transformed into an equilibrium mixture of the esters of XXVI and a new acid XXIX, m.p. 103–105°, $[\alpha]_D$ $-25{\cdot}1°$ (the ratio of the ester of XXVI to XXIX was 40:60). The methyl ester of XXIX also gave the same mixture in approximately equal ratio by the same treatment. These facts suggest that the 1,2-relationship of XXVI and XXVII would be *cis*, and that of XXIX and XXX would be *trans*. This assignment was consistent with the results in the thermal equilibration of the acid anhydrides;[26] heating of the anhydride of XXIX at 180–200° followed by hydrolysis completely changed it to XXVI, while the anhydride of the other 1,2-*trans* acid (the racemate VIIIb was used in this case instead of XXX) gave an equilibrium mixture (*cis*:*trans* = 61:39) at 240–250°.



VI XXIII VIIIb

FIG. 5.

On the other hand, hydrogenation of the unsaturated acid XXVIII over Pt catalyst in acetic acid gave two isomeric 1,2-*trans* acids, (XXX and XXIX). It is noticeable that this hydrogenation did not proceed by the expected *cis* addition process, but the thermodynamically more stable 1,2-*trans* compounds were formed.[27]

The steric effect of the methyl group at 3-position on the composition of the foregoing equilibrium products was considered as follows. In the equilibration of two 1,2-*cis* dimethyl esters with basic catalyst, the 1,2-*cis*-2,3-*cis* compound (hereinafter the notations 1,2- and 2,3- will be omitted and only the notations *cis* and *trans* will be used) will be in equilibrium with the *trans-trans* compound formed by inversion at C-2, and the *cis-trans* compound will be in equilibrium with the *trans-cis* compound. Considering the non-bonding interaction among the substituents, the equilibrium of *cis-cis* ⇌ *trans-trans* compound will tend largely towards the latter, while in the equilibrium of *cis-trans* ⇌ *trans-cis* compound, ratio of two components

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[24] S. M. McElvain and E. J. Eisenbraun, *J. Am. Chem. Soc.* **77**, 1599 (1955).

[25] R. B. Bates, E. J. Eisenbraun and S. M. McElvain, *J. Am. Chem. Soc.* **80**, 3413 (1958).

[26] A. H. Cook and R. P. Linstead, *J. Chem. Soc.* 956 (1934).

[27] Hydrogenation of the double bond isomer XXIII, which was prepared as racemate from VI by the known method,[6] also gave two saturated 1,2-*trans* acids under the same condition.

should not be so large because there could not be much difference in the interaction between the ester group in 2-position and the substituent in 1- or 3-position. In the thermal equilibrium of the acid anhydrides the anhydride of the *trans-cis* acid would undergo inversion at the 2-position more easily than that of the *trans-trans* acid, and the ratio of formation of the 1,2-*cis* anhydride is likely to become larger.

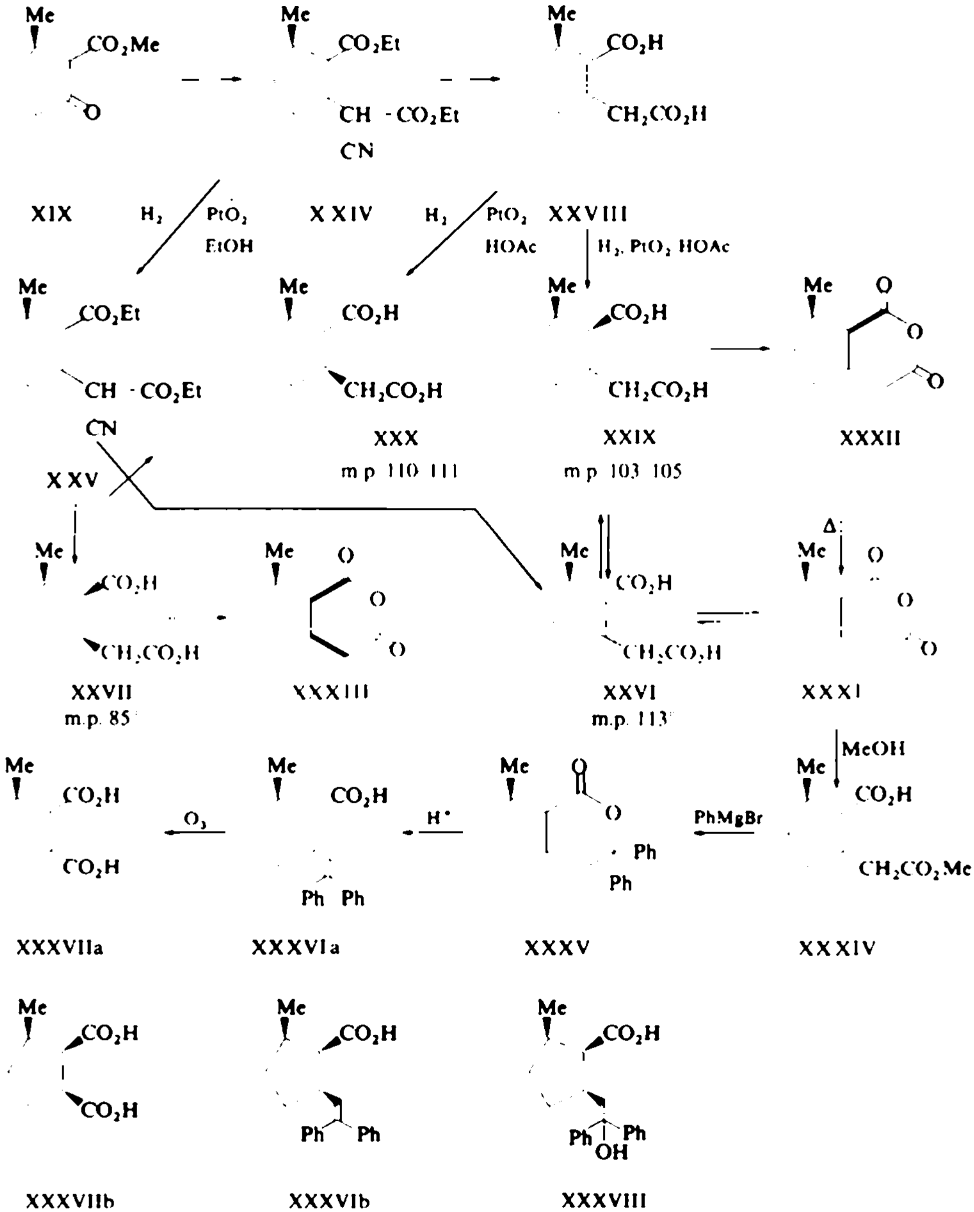

FIG. 6.

The behaviour of the esters and anhydrides summarized in Table 1 clearly indicate the effect of the C_3-methyl group and undoubtedly suggest that, of the 1,2-*cis* acids, the substance XXVII, m.p. 85° is the *cis-cis* acid and that XXVI, m.p. 113° is the *cis-trans* acid, and the 1,2-*trans* compounds, the substance XXX, m.p. 110–111° is the *trans-trans* and XXIX, m.p. 103–105° is the *trans-cis* acid.

TABLE 1. EQUILIBRATION BETWEEN THE ISOMERS OF BOSCHNIALINIC ANHYDRIDE AND DIMETHYL BOSCHNIALINATE

Starting material		Method	Composition of equilibrated mixture (%)			
Anhydride of	Dimethyl ester of		*cis-cis*	*trans-trans*	*cis-trans*	*trans-cis*
DL-*trans-trans* VIIIb		a	61	39		
3(R)-*trans-cis* XXIX		a			100	0
	3(R)-*cis-cis* XXVII	b	5	95		
	DL-*trans-trans* VIIIb	b	trace	ca. 100		
	3(R)-*cis-trans* XXVI	b			40	60
	3(R)-*trans-cis* XXIX	b			43	57

[a] Pyrolysis at 200–250°.

[b] Refluxing in MeOH with MeONa.

This conclusion was confirmed by transforming the two 1,2-*cis* isomers (XXVI and XXVII) to *cis-trans*- and *cis-cis*-nepetic acid, (XXXVIIa and XXXVIIb), the stereochemistry of which is known.[25] Methanolysis of the acid anhydrides (XXXI and XXXIII) gave half methyl esters of the dicarboxylic acid and subsequent reaction with phenylmagnesium bromide produced a lactone (XXXV) from XXXI and a comparatively stable, corresponding hydroxy acid (XXXVIII) from XXXIII.

Treatment of XXXV and XXXVIII respectively with 70% sulfuric acid yielded the unsaturated acids, XXXVIa and XXXVIb, the structures of which were based on the NMR spectra (around 3·8 τ, doublet, $J = 10$, 1H) and the UV spectra (253 mμ, log ε: 4·2) of 1,1-diphenylethylene type.[28] Ozonolysis of XXXVIa or XXXVIb afforded a dicarboxylic acid XXXVIIa, m.p. 132–133°, from XXXVIa, or XXXVIIb, m.p. 137–138°, from XXXVIb. The IR spectra of the dimethyl esters of these two acids agree well with those of the dimethyl esters of *cis-trans-* and *cis-cis-*nepetic acid, respectively, and reported by McElvain *et al.* Therefore, the structures of the two boschnialinic acids, XXVI and XXVII, are unambiguously established.

Since boschnialinic acid obtained from the natural lactone was found to be the 3(R)-*cis,cis*-acid, it is clear that the absolute structure of boschnialactone should be represented by the *cis,cis*-structure XXXIX with R-configuration at the 7-position. It is of interest that in the lactones with similar physiological activity obtained to date the carbon atom, to which the methyl group is attached in the cyclopentane ring, has the S-configuration.

Inoue and others[29] obtained a dicarboxylic acid, m.p. 104–106°, $[\alpha]_D$ +34·1°, from monotropein (XL) and gave the structure XLI to this acid. This substance was found to be the antipode of 3(R)-*cis-trans*-boschnialinic acid (XXVI) by direct comparison of the samples.

On the other hand, Djerassi *et al.*[30] obtained a dicarboxylic acid, m.p. 104·5–107·5°, $[\alpha]_D$ +20°, as a degradation product of genipin (XLII) and gave it the 3(R)-*cis-cis* structure (XXVII). Briggs *et al.*[31] reported that an acid of $C_9H_{14}O_4$, m.p. 107·5–108°, obtained from asperuloside (XLIII) agrees with the Djerassi's acid. Both these acids, however, apparently differ from 3(R)-*cis-cis*-boschnialinic acid. Through the courtesy of Professor L. H. Briggs, our synthetic 3(R)-*trans-trans*-boschnialinic acid was compared with the Briggs' acid and proved to be identical (mixed m.p., IR, and optical rotation[32] comparison). From this result, the degradation of asperuloside seems to proceed via an intermediate dialdehyde (XLIV) with a stable *trans-trans* configuration.

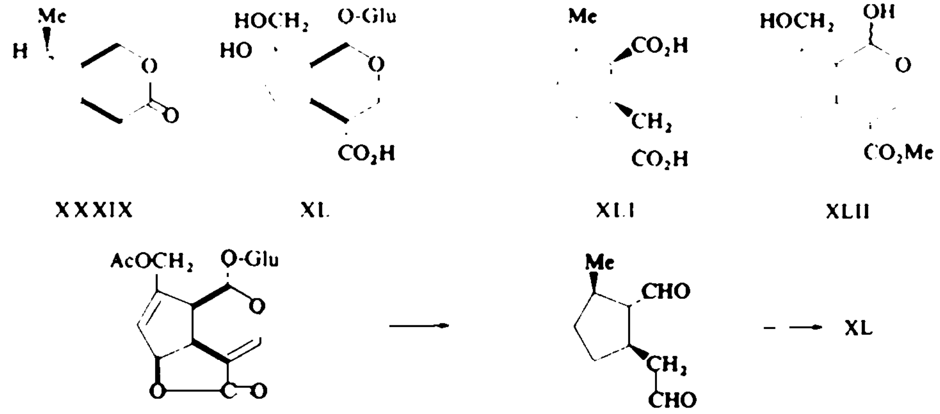

FIG. 7

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[28] D. Y. Curtin and Y. G. Hendrickson, *J. Org. Chem.* **21**, 1260 (1956).

[29] H. Inoue and T. Arai, *Chem. Pharm. Bull.* **12**, 968 (1964).

[30] C. Djerassi, T. Nakano, A. N. James, L. H. Zalkow, E. J. Eisenbraun and J. N. Shoolery, *J. Org. Chem.* **26**, 1192 (1961).

[31] L. H. Briggs, B. F. Cain, P. W. LeQuesne and J. N. Shoolery, *J. Chem. Soc.* 2595 (1965).

[32] Although Briggs *et al.* reported the optical rotation as $[\alpha]_D$ + 18° (MeOH), the present authors confirmed the value as $[\alpha]_D$ −46·5° (*c*: 1·32, $CHCl_3$).

The acid obtained by Djerassi *et al.* was not compared directly, but the IR spectrum of its dimethylester[33] was almost identical with that of the dimethyl ester of *cis-trans*-acid XXVI.

The stereochemistry of the isomers of DL- and 3(R)-boschnialinic acid, and their physical constants are summarized in Table 2.

TABLE 2. STEREOCHEMISTRY AND PHYSICAL CONSTANTS OF ISOMERIC DL- AND 3(R)-BOSCHNIALINIC ACIDS

Acid	Relative configuration C1:C2	Relative configuration C2:C3	M.p.	Specific rotation (in $CHCl_3$)
3(R)-*cis-cis* XXVII DL-*cis-cis*	*cis*	*cis*	85° 113–114°	−33·7°
3(R)-*trans-trans* XXX DL-*trans-trans* VIIIb	*trans*	*trans*	110–111° 123–124°	−65·4°
3(R)-*cis-trans* XXVII	*cis*	*trans*	113	−41·1°
3(R)-*trans-cis* XXIV DL-*trans-cis*	*trans*	*cis*	103–105° 108–111°	25·1

EXPERIMENTAL

All m.ps and b.ps were uncorrected. M.ps were taken on a hotstage in a Yanagimoto micro m.p. apparatus Model MPJ-2. IR spectra were taken on a spectrophotometer Model IR-S of Japan Spectroscopic Co., and UV spectra on a Hitachi recording spectrophotometer Model EPS-2. NMR spectra were determined at 60 mc/s with a NMR spectrometer Model JNM C-60 of Japan Electron Optics Laboratory Co. Chemical shifts were expressed in τ value and coupling constants were given in c/s. Mass spectra were obtained with a Hitachi mass spectrometer Model RMU-6. The spectral data are presented as ν_{max}^{state} in IR, $\lambda_{max}^{solvent}$ in UV., $\tau^{solvent}$ in NMR, and *m/e* in mass spectra. Optical rotations were measured with a Rex photoelectric polarimeter Model NEP-2. VPC analyses were carried out on either a Shimazu Model GC-1B or Yanagimoto Model GCG-220 apparatus using 4 mm × 2 m column packed with 20% SE-30 or Apiezon-L on chromosorb-P. The adsorbent used for column chromatography were Woelm neutral alumina or Mallinckrodt silicagel (100 mesh).

Separation of the volatile neutral and basic components of Boschniakia rossica *Hult.* The dried terrestrial portion of *Boschniakia rossica* Hult. (16 Kg) collected during the flowering season (July) from Mt. Fuji, was extracted 3 times with MeOH. Steam distillation of this extract followed by extraction of the distillate with ether gave 46 g of the volatile portion.

The ether soln of this material was washed with $NaHCO_3$ aq and cold 10% NaOH aq, dried, and evaporated to give 2·91 g of the neutral portion as a yellowish brown oil.

After washing with ether and then AcOEt, the residual aqueous portion from the above steam distillation was made alkaline with aqueous ammonia and extracted with $CHCl_3$. The $CHCl_3$ soln was shaken with 5% HCl aq. From the acid extract, the basic portion (3 g) was obtained as a dark oil.

Isolation of boschnialactone (IV). The above neutral portion was chromatographed on 60 g alumina (activity I). Elution with 300 ml ether and then with 400 ml AcOEt gave 1·300 g of the crude lactonic fraction, which was purified by alkaline hydrolysis and subsequent acidification. The resulting oil (400 mg) was rechromatographed on 8 g neutral alumina. Benzene and benzene–ether (4 : 1) eluted a yellow oil, which was distilled to give pure boschnialactone as a colorless liquid, b.p. 105–112°/6 mm, $[\alpha]_D^{21}$ −18·2° (c: 2·10,

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[33] A copy of the IR spectrum (in $CHCl_3$) of the dimethyl ester of Djerassi's acid was kindly sent here from Professor L. H. Briggs.

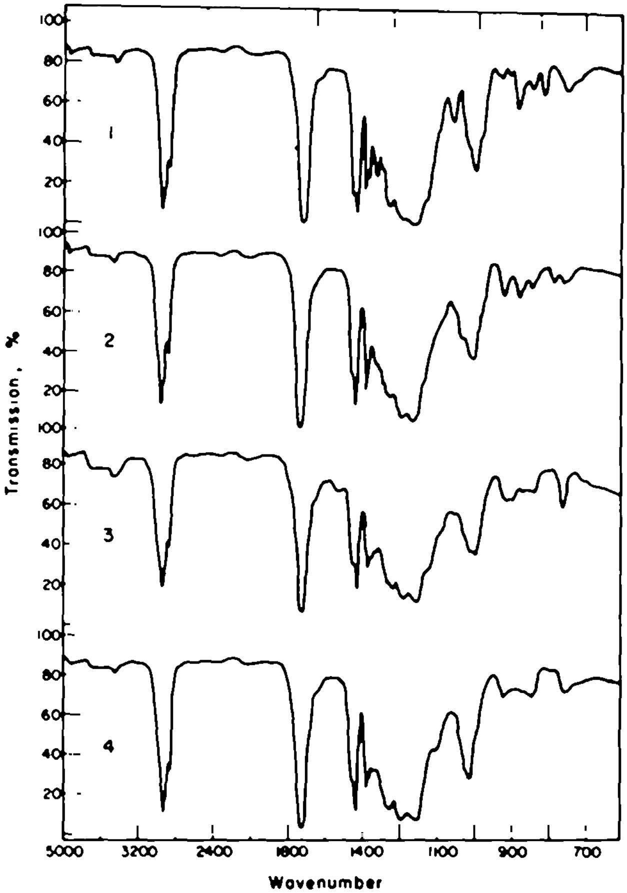

FIG. 8. IR spectra of isomeric dimethyl boschnialinates (liquid film). 1: *cis-cis* ester; 2: *cis-trans* ester; 3: *trans-cis* ester; 4: *trans-trans* ester.

$CHCl_3$), ν_{max}^{liquid} 1743, 1275, 1245, 1058, 1033, 835 cm^{-1}, τ^{CCl_4} 8·95 (doublet, J = 7, 3H), 7·60 (doublet, J = 6, 2H), 5·88 (doublet, J = 6, 2H). (Found: C, 70·11; H, 9·13. $C_9H_{14}O_2$ requires: C, 70·10; H, 9·15%.)

The lactone was also isolated by the preparative VPC. This substance crystallized on standing in a refrigerator and melted at room temp.

Isolation of boschniakine (I) *and boschniakinic acid* (III). The basic fraction, described above, was chromatographed on 3 g silicagel (activity I). Elution with $CHCl_3$ acetone (95:5) gave 1·01 g of a pale yellow oil, which was distilled to give 731 mg boschniakine as a fragrant colorless liquid, b.p. 80 90 3 mm; $[\alpha]_D^{20}$ +21·02° (c: 0·98, $CHCl_3$), n_D^{20} 1·5437, λ_{max}^{EtOH} 239, 268, 282 mμ (log ε: 3·75, 3·26, 3·19), ν_{max}^{liquid} 2725, 1700, 1577 cm^{-1}; Tollens' reaction— positive and semicarbazone, m.p. 277–278° dec; ν_{max}^{Nujol} 3410, 3210, 3145, 1690, 1605, 1575, 1455, 1150, 1120, 1100, 945, 930, 787 cm^{-1}. (Found: C, 60·79; H, 6·50; N, 25·66. $C_{11}H_{14}N_4O$ requires: C, 60·53; H, 6·47; N, 25·67%.)

An additional sublimable crystalline compound was obtained from the high-boiling fraction on distillation of boschniakine. Recrystallization from MeOH gave colourless crystals of III, m.p. 215 220° dec, ν_{max}^{Nujol} 2400, 1900, 1700, 1602, 1575 cm^{-1}. (Found: C, 67·78; H, 6·59; N, 7·93. $C_{10}H_{11}NO_2$ requires: C, 67·78; H, 6·26; N, 7·91%.)

Potassium permanganate oxidation of boschnialactone. Aqueous 3% $KMnO_4$ (20 ml) was added to a stirred soln of boschnialactone (300 mg) in 10 ml 5% KOH aq under ice cooling. After standing overnight at room temp, the reaction mixture was filtered, and the aqueous layer acidified with dil HCl. After extraction with ether, the ether soln was dried and evaporated to give a yellow viscous oil, which crystallized on standing. Recrystallization from pentane:ether (1:1) gave crystals of 3(R)-*cis-cis*-boschnialinic acid, m.p. 82–83°, $[\alpha]_D^{20}$ $-32.8°$ (c: 0·72, $CHCl_3$), ν_{max}^{Nujol} 1700, 1250, 1220, 898 cm^{-1}. Dimethyl ester: ν_{max}^{liquid} 1730, 1260, 1200, 1100 cm^{-1}.

Huang Minlon reduction of boschniakine. To a soln of 300 mg boschniakine in 1·0 ml diethylene glycol, 0·3 ml 90% hydrazine hydrate was added and the mixture heated at 110–120° for 10 min. After cooling, 0·3 g KOH was added and the mixture heated at 180–190° for 2 hr. The reaction mixture was then taken up in several portions of ether. The combined ether layer was washed with 30% $NaHSO_3$aq and extracted with 5% HCl. The acid extract was made alkaline with KOHaq and extracted thoroughly with ether. After drying and evaporation the ether soln gave 56 mg of a yellow oil, the IR spectrum of which was identical with that of natural actinidine[3]; picrate, m.p. 143–144°.

Oxidation of boschniakine with silver oxide. To a mixture of 200 mg boschniakine in 10 ml EtOH and 136 mg $AgNO_3$ in 1 ml water, 10 ml 0·5N NaOH, was added dropwise. The mixture was kept stirred at room temp for 3 hr. The black Ag suspension was filtered off and the filtrate was washed with ether, and brought to pH 6·2 with dil HCl, and extracted with $CHCl_3$. The $CHCl_3$ soln was dried and evaporated leaving a crystalline residue which from MeOH afforded an amino acid, m.p. 210–215° (dec), whose IR spectrum was identical with that of the boschniakinic acid described.

Syntheses of DL-*boschnialactone and related lactones*

Esters of 3-methyl-2-oxocyclopentylacetic acid. To a stirred suspension of the Na salt of ethyl 3-methyl-2-oxo-cyclopentanecarboxylate [prepared from 170 g (1 mole) of the ketoester, 23 g powdered Na and 500 ml anhyd benzene] 184 g (1·1 mole) ethyl bromoacetate was added dropwise. The mixture was stirred at room temp for 3 hr and then decomposed with cold dil HCl. The separated organic layer yielded 240 g which distilled at 4 mm to give 188 g (74%) of a colourless liquid, b.p. 134°/4 mm.

This product (50 g) was then heated under reflux with 200 ml 6N HCl and 100 ml AcOH for 5 hr. The oily acidic product, obtained by thorough extraction of the reaction mixture with ether and evaporation, was immediately esterified by refluxing with 200 ml MeOH and 5 drops of concd H_2SO_4 for 5 hr. Most of the MeOH was removed under reduced press and the residual oil taken up in benzene. The benzene soln was washed with $NaHCO_3$aq and water, dried and evaporated to give 30 g liquid, which distilled at 4 mm yielding 27·1 g (82%), b.p. 89–92°/4 mm and 2,4-dinitrophenylhydrazone, m.p. 135–136°. (Found: C, 51·56; H, 5·36; N, 15·93. Calc. for $C_{15}H_{18}N_4O_6$: C, 51·42; H, 5·18; N, 15·99%.)

Similarly, the ethyl ester was obtained using EtOH for the esterification.

Ethyl 2-methoxymethylene-3-methylcyclopentylacetate (VII). To a dimethyl sulfinyl carbanion soln [prepared from 0·02 mole sodium hydride (54·5% mineral oil dispersion 0·88 g) and 10 ml purified DMSO by the known method][8a] a soln of 6·85 g (0·02 mole) triphenylmethoxymethylphosphonium chloride in 20 ml DMSO was added dropwise at room temp. To the resulting dark red ylide soln, 3·68 g (0·02 mole) of VI was added at room temp. After stirring at 55–65° for 10 hr, the mixture was diluted with an equal volume of water, and extracted 5 times with hexane. The hexane soln was washed, dried and concentrated to yield a yellowish brown oil. Distillation at 3 mm gave 1·44 g of a colourless liquid, which was found by VPC to be a mixture of nearly equal amount of VI and VII. The methoxymethylene ester VII was isolated in a pure state by preparative VPC, 319 mg, ν_{max}^{liquid} 2860, 1740, 1690 cm^{-1}.

Methyl 2-methoxymethyl-3-methylcyclopentylacetate (IX). A soln of 11·25 g of the mixture of VI and VII, obtained by the above Wittig reaction, in 50 ml EtOH was hydrogenated under 15–20 atms at room temp with a teaspoonful Raney Ni (W-7) for 5 hr. After filtration of the catalyst and evaporation of the solvent, the residual oil (9·7 g) was hydrolysed by refluxing with 40 ml 10% NaOHaq and 20 ml EtOH for 4 hr. After removal of most of the EtOH by distillation, acidification with HCl and extraction with benzene, the benzene layer was worked up as usual. The neutral fraction, a colourless liquid (3·26 g), had the IR max at 1780 cm^{-1} and was identical with the lactone of 2-hydroxy-3-methylcyclopentylacetic acid prepared by direct hydrogenation and lactonization of VI. The crude acidic fraction (3·6 g) was treated with ethereal diazomethane and chromatographed on 72 g of alumina (activity II). Elution with benzene gave 2·270 g of a colourless liquid, which was subjected to repeated chromatography on 50 g silicagel. Elution with pet. ether:ether (5:1) gave 1·816 g of a liquid, which exhibited two close peaks on the VPC; ν_{max}^{liquid} 1735, 1200, 1155, 1110 cm^{-1}, τ^{CCl_4} 9·02 (doublet, $J = 6$, 3H), 6·75 (singlet, 3H), 6·72 (doublet, $J = 6$, 2H), 6·40 (singlet, 3H). (Found: C, 66·10, 66·00; H, 10·06, 10·11. $C_{11}H_{20}O_3$ requires: C, 65·97; H, 10·07%.)

Although a component of this mixture could be isolated in a pure state by careful chromatography on silicagel, the yield was very poor. Therefore, the mixture was used directly in the next step. The mass spectra of the mixture and a pure substance were almost identical. m/e 200 (molecular peak), 185, 168, 153, 108, 95, 81 (base peak), 67, 55, 45.

DL-*Boschnialactone* (X) *and the lactones* (XI) *of 2-hydroxy-2,3-dimethylcyclopentylacetic acids.* A mixture of 920 mg of IX (the mixture of two components), 13 ml of BF_3–AcOH complex, and 7 ml CH_2Cl_2 was heated under reflux for 6 hr. After cooling, the reaction mixture was decomposed with 30 ml ice-water and extracted with ether. The ether soln was washed with $NaHCO_3$aq (from this washing, 531 mg of the starting material was recovered after esterification), dried and evaporated to leave 618 mg of a brown oil, which was heated under reflux with 10 ml 1N NaOH for 15 min. The clear soln was washed with ether, acidified, heated at 100° for 5 min, and extracted with ether. After evaporation of ether, 233 mg of a yellow liquid (lactonic fraction) was chromatographed on 10 g silicagel with $CHCl_3$ containing 0·5% EtOH. The fraction was collected in 10 ml portions and the residual liquid from each fraction was analysed by VPC. The fractions 10 to 12 contained ca. 90% of DL-boschnialactone, IR and NMR spectra of which were identical with those of the natural lactone; m/e 154 (molecular peak), 95, 82, 81, 67 (base peak), 55, 41. The fractions 5 to 7 exhibited an IR max at 1760 cm^{-1} and were identical with the 5-membered lactones (XI) described below.

The hydrolysis of IX with 48% HBr or conc H_2SO_4 gave only the lactones (XI).

Ethyl 2-formyl-3-methylcyclopentylacetate (XII). A soln of 250 mg (1·18 mmole) of VII in 3 ml EtOH and 3 ml 2N HCl was heated at 60° for 1 hr under N_2, diluted with water, and extracted with pet ether (b.p. 40 60°). The pet ether soln was dried and evaporated to leave 183 mg (78%) of a liquid, ν_{max}^{liquid} 2740, 1730 cm^{-1}; and 2,4-dinitrophenylhydrazone, m.p. 119 121·5°. (Found: C, 54·04; H, 5·98; N, 14·90. $C_{17}H_{22}N_4O_6$ requires: C, 53·96; H, 5·86; N, 14·81%.)

The lactone (XIV) *of 1,2-trans-2-hydroxymethyl-3-methylcyclopentylacetic acid.* The aldehyde XII (150 mg, 0·76 mmole) in 20 ml MeOH was treated with $NaBH_4$ (90 mg, 2·38 mmoles) in 10 ml MeOH at 0°. After standing overnight, the reaction mixture was treated as usual to give 123 mg of a neutral oil, which was refluxed with 5% NaOHaq (10 ml) for 1 hr. The soln was acidified, heated for 1 hr, and extracted with ether to give 10 mg lactonic and 77 mg acidic fractions. The former was found to be a mixture of XI and XIV by the IR spectrum ($\nu_{C=O}$ 1780 1740, broad) and VPC. Distillation of the latter gave the lactone XIV, b.p. 125 145°/3 mm (bath temp), ν_{max}^{liquid} 1735, 1260, 1190, 1020, 800 cm^{-1}, m/e 154 (molecular peak), 95, 81 (base peak), 67. The mass spectrum of XIV was almost identical with that of the natural boschnialactone.

Ethyl 3-methyl-2-methylenecyclopentylacetate (XV). Compound XV was prepared from VI by the Wittig reaction in 1,2-dimethoxyethane as a solvent.[11] b.p. 65 75°/6 mm, ν_{max}^{liquid} 3060, 1730, 1660, 885 cm^{-1}.

Acid treatment of XV. A mixture of 30 mg of XV, 4 ml EtOH and 2 ml 2N HCl was heated under reflux for 2 hr and then concentrated under vacuum. A $CHCl_3$ soln of the residual oil was washed and evaporated to give a colourless liquid, which was a mixture of two components exhibiting two close peaks on VPC. (The same mixture was also formed from the reaction of VI with one equivalent of MeMgI.) The two components after separation by careful column chromatography (silicagel chloroform containing 0·5% EtOH) had the carbonyl absorption band at 1760 cm^{-1} and closely resembling finger print regions in IR spectra, one of them: ν_{max}^{liquid} 1760, 1240, 1150, 1105, 1027, 943 cm^{-1}, the other: ν_{max}^{liquid} 1760, 1240, 1160, 1110, 1045, 940 cm^{-1}. Their NMR spectra exhibited two kinds of methyl proton signal, τ^{CCl_4} 8·95 (doublet, $J = 5$, 3H), 8·60 (singlet, 3H). From these spectral data, both compounds were considered to be the stereoisomers of 5-membered lactone XI.

Partial isomerization of DL-*boschnialactone with acid.* A soln of 30 mg DL-boschnialactone in 2 ml EtOH and 1·5 ml 2N HCl was heated under reflux for 1 hr and then concentrated under vacuum. Chloroform extraction gave 8 mg of a colourless liquid, which was a mixture of X and XI by VPC.

Syntheses of boschniakine, DL-*boschniakine and other related pyridine derivatives*

DL-*4-Cyano-6,7-dihydro-1,3-dihydroxy-7-methyl-5(H)-2-pyrindine* (DL-XX). A mixture of 12·7 g (0·081 mole) of DL-XIX,[14] 40 ml 28% aqueous ammonia and 9·2 g (0·081 mole) ethyl cyanoacetate was stirred at room temp for 2 days to form a thick slurry. Cooling at 0° for 1 hr and filtration gave 9·0 g of a pale yellow powder, which was recrystallized from 6N HCl, 7·4 g (52%), m.p. 218 223°; λ_{max}^{EtOH} 261, 329 mμ (log ε: 4·03, 4·25); ν_{max}^{Nujol} 3220, 3000 2600, 2240, 1670, 1640, 1570, 1150, 860 cm^{-1}. (Found: C, 62·83, 62·94; H, 5·32, 4·97; N, 14·55. $C_{10}H_{10}N_2O_2$ requires: C, 63·15; H, 5·30; N, 14·73%.)

4-Cyano-6,7-dihydro-1,3-dihydroxy-7(R)-methyl-5(H)-2-pyrindine (XX) was prepared from XIX by the same method, m.p. 220 226°, $[\alpha]_D^{20}$ −86·6° (c: 1·0, $CHCl_3$).

DL-*4-Cyano-1,3-dichloro-6,7-dihydro-7-methyl-5(H)-2-pyrindine.* A mixture of 3·90 g (0·021 mole) of DL-XX and 20 ml (0·22 mole) $POCl_3$ was placed in a sealed tube and heated at 180° for 5 hr. After standing overnight at room temp, the reaction mixture was decomposed with ice and extracted with $CHCl_3$. The

$CHCl_3$ soln was washed with cold 5% NaOH aq and then with water, dried and evaporated to leave a brown liquid, which was distilled under vacuum, 3·41 g (80%); λ_{max}^{EtOH} 240, 283, 292 mμ (log ε: 4·05, 3·66, 3·67); ν_{max}^{liquid} 2240, 1565, 1362, 1210, 944, 765 cm^{-1}. (Found: C, 53·07, 53·15; H, 3·73, 3·80; N, 12·38, 12·15. $C_{10}H_8N_2Cl_2$ requires: C, 52·89; H, 3·55; N, 12·34%.)

4-Cyano-1,3-dichloro-6,7-dihydro-7(R)-methyl-5(H)-2-pyrindine was prepared from XX in 74% yield by the same method, $[\alpha]_D^{20}$ −53·8° (c: 1·8, $CHCl_3$).

DL-*4-Cyano-6,7-dihydro-7-methyl-5(H)-2-pyrindine* (DL-XXI). A soln of 5·263 g (0·023 mole) of DL-1,3-dichloro derivative in 120 ml MeOH was hydrogenated with 0·5 g $PdCl_2$ and 8·0 g AcOK at room temp for 4 hr under 50 atms H_2 press. After filtration of the catalyst and evaporation of the solvent, the residue was triturated with $NaHCO_3$ aq and extracted with ether. Evaporation of ether gave 2·95 g of a brown liquid, which was distilled twice, b.p. 100–110°/2 mm, 0·713 g (19·3%); λ_{max}^{EtOH} 272, 280 mμ (log ε: 3·29, 3·25). ν_{max}^{liquid} 2220, 1578, 1412, 903, 723 cm^{-1} (Found: C, 75·15, 74·99; H, 6·86, 6·83; N, 17·20, 16·70. $C_{10}H_{10}N_2$ requires: C, 75·92; H, 6·37; N, 17·71%.)

4-Cyano-6,7-dihydro-7(R)-methyl-5(H)-2-pyrindine (XXI) was obtained from the optically active 1,3-dichloro derivative by the same method.

DL-*Boschniakine*. A suspension of 1·5 g (7·9 mmole) anhyd $SnCl_2$ in 30 ml anhyd ether was saturated with dry HCl at 0° (1 hr) and then 144 mg (0·91 mmole) of DL-XXI was added to this mixture with vigorous stirring. The mixture was stirred while heated under reflux for 6 hr and HCl gas was passed continuously during this reaction period. The solvent was removed under vacuum and the residue steam distilled. The distillate was made alkaline with aqueous ammonia and extracted thoroughly with ether. Evaporation of ether and distillation of the residual oil gave a colourless liquid, whose IR and UV spectra were identical with those of the natural boschniakine.

7(R)-Boschniakine, $[\alpha]_D^{20}$ +28·4° (c: 0·7, $CHCl_3$), was obtained from XXI by the same method as DL-boschniakine and was identified with the natural boschniakine in all respects.

Syntheses of the stereoisomers of boschnialinic acid.

2-Methoxycarbonyl-3(R)-methylcyclopentanone (XIX). Methyl pulegenate (20 g) prepared from (+)-pulegone (89% purity, $[\alpha]_D^{18}$ +26·6°) according to Wolinsky's method,[15b] was saturated with O_3 at −20° in 70 ml CCl_4. After addition of an equal amount of water and warming at 60° for 10 min, the aqueous layer was separated and the organic layer extracted 3 times with cold 0·5N NaOH aq. The combined alkaline soln was acidified with dil H_2SO_4, saturated with salt, and extracted with ether. After washing with $NaHCO_3$ aq and drying, the ether soln was evaporated to give 8·4 g of a colourless liquid. Distillation under N_2 gave the product, 6·0 g (35%), b.p. 70–73°/3 mm; $[\alpha]_D^{20}$ −81·6° (neat), ν_{max}^{liquid} 1750, 1720 cm^{-1}; $FeCl_3$ reaction—deep violet.

Ethyl 2-ethoxycarbonyl-3(R)-methylcyclopent-1-enylcyanoacetate (XXIV). To a thick slurry of ethyl potassiocyanoacetate [prepared from 6·0 g (0·154 g atom) of K, 50 ml anhyd EtOH and 16·8 g (0·149 mole) ethyl cyanoacetate at 0°] 25 g (0·16 mole) of XIX was added dropwise with vigorous stirring at room temp. After standing overnight, the reddish brown soln was decomposed with dil HCl and extracted with ether. The ether soln was washed, dried and evaporated to give a dark red liquid, which was distilled under vacuum, b.p. 140–142°/3 mm, 15·3 g (36%); ν_{max}^{liquid} 2240, 1725, 1625, 1280, 1100, 1030, 860, 785 cm^{-1}.

Ethyl 2-ethoxycarbonyl-3(R)-methylcyclopentylcyanoacetate (XXV). A soln of 6·0 g of XXIV in 30 ml EtOH was hydrogenated at 20° under 1 atm with 200 mg of PtO_2 catalyst. After uptake of 730 ml of H_2 during 3·5 hr, absorption ceased (theoretical amount of H_2 — 540 ml) and the mixture was filtered and the filtrate evaporated. Distillation under vacuum gave 5·84 g (97%) of a colourless liquid, b.p. 122–123°/3 mm; ν_{max}^{liquid} 2260, 1735, 1250, 1200, 1175, 1030, 860 cm^{-1}.

3(R)-cis,trans-*boschnialinic acid* (XXVI) *and* 3(R)-cis,cis-*boschnialinic acid* (XXVII). A mixture of 11·2 g of XXV, 56 ml conc HCl and 28 ml water was refluxed for 4 hr to form a pale brown clear soln. After dilution with an equal volume of water, treatment with charcoal, and thorough extraction with ether, the combined ether soln was dried and evaporated to give 8·5 g of a yellow oil, which was developed on 100 g of silica gel with $CHCl_3$.

Elution with $CHCl_3$ containing 0·5% EtOH gave 2·005 g of colourless crystals, m.p. 100–106°, from which 1·100 g (14%) of XXVI was isolated by repeated recrystallization from pentane:ether (4:1), m.p. 113°, $[\alpha]_D^{22}$ −41·1° (c: 1·4, $CHCl_3$); ν_{max}^{Nujol} 1700, 1300, 1240, 1160, 945 cm^{-1}. (Found: C, 58·48, 58·30; H, 7·87, 7·79. $C_9H_{14}O_4$ requires: C, 58·05; H, 7·58%.) The dimethyl ester: ν_{max}^{liquid} 1735, 1200, 1170, 1015, 930, 890, 855, 800, 770 cm^{-1}.

A soln of 120 mg of XXVI in 2 ml Ac_2O was heated under reflux for 1 hr. The excess Ac_2O was removed under reduced press and the residual oil distilled at 130°/3 mm to give 3(R)-cis,trans-*boschnialinic anhydride* (XXXI) as a colourless liquid; 94 mg (87%), ν_{max}^{liquid} 1805, 1760, 1260, 1070, 1040, 970, 940, 860 cm^{-1}, τ^{CCl_4} 8·77 (doublet, $J = 6$, 3H).

From the fractions eluted with $CHCl_3$ containing 1% EtOH, 1·893 g crude crystals, m.p. 65–71° was obtained. Repeated recrystallization from pentane:ether (4:1) gave 0·684 g (8·8%) of XXVII, m.p. 85°, $[\alpha]_D^{22}$ −33·7° (*c*: 1·1, $CHCl_3$); ν_{max}^{Nujol} 1700, 1295, 1240, 1200, 1160, 1115, 1070, 1025, 995, 900, 730 cm^{-1}. (Found: C, 58·33, 57·91; H, 7·33, 7·43. $C_9H_{14}O_4$ requires: C, 58·05; H, 7·58%.) This acid was identical with the acid obtained from natural boschnialactone by the alkaline permanganate oxidation; the dimethyl ester: ν_{max}^{liquid} 1730, 1265, 1195, 1170, 1060, 1005, 890, 850, 820 cm^{-1}

3(R)-cis,cis-*Boschnialinic anhydride* (XXXIII) was prepared from 120 mg of XXVII and 2 ml Ac_2O as described above, 89 mg (82%), ν_{max}^{liquid} 1805, 1755, 1240, 1090, 1035, 975, 940, 890, 750 cm^{-1}, τ^{CCl_4} 8·91 (doublet, $J = 7$, 3H).

Base catalysed equilibration between isomeric dimethyl boschnialinates

(a) *Dimethyl* 3(R)-cis,trans- and 3(R)-trans, cis-*boschnialinate*. A mixture of dimethyl 3(R)-*cis,trans*-boschnialinate, prepared from 256 mg of the acid XXVI and ethereal diazomethane, and MeONa soln, prepared from 200 mg Na and 3 ml anhyd MeOH, was heated under reflux for 20 hr. After removal of MeOH under reduced press, the residue was taken up in ether and yielded 182 mg of a neutral oil, which was a mixture (60:40) of the dimethyl esters of *trans,cis*- and *cis,trans*-acid by VPC. Saponification of this product with 2N NaOH (100°, 3 hr) gave a mixture of dicarboxylic acids, from which 3(R)-trans,cis-*boschnialinic acid* (XXIX) was isolated by the fractional crystallization from pentane:ether (4:1), m.p. 99–101°, 54 mg (21%). An additional two recrystallizations gave a pure sample, m.p. 103–105°, $[\alpha]_D^{22}$ −25·1° (*c*: 1·2, $CHCl_3$); ν_{max}^{Nujol} 1700, 1320, 1240, 1180, 1110, 945, 750 cm^{-1}; the dimethyl ester: ν_{max}^{liquid} 1730, 1240, 1195, 1160, 1010, 970, 850, 770 cm^{-1}. The IR spectrum of the ester was identical with that of dimethyl DL-*trans,cis*-boschnialinate.

3(R)-trans,cis-*Boschnialinic anhydride* (XXXII) was prepared from 54 mg of the acid and 1·5 ml Ac_2O at room temp (5 hr) and distilled at 120°/0·1 mm, 45 mg (92·5%). This substance solidified on standing, m.p. 67–71°; ν_{max}^{Nujol} 1810, 1760, 1220, 1150, 1060, 1030, 985, 960 cm^{-1}, τ^{CCl_4} 8·94 (doublet, $J = 7$, 3H). The anhydride XXXII isomerized quantitatively to the *cis,trans*-anhydride XXXI by heating at 180–200° for 0·5 hr with Ac_2O (confirmed by the comparison of the IR and the NMR spectra). The acid, obtained by hydrolysis of the isomerized anhydride with water (100°, 15 min), had m.p. 110–111° and was not depressed by admixture with 3(R)-*cis,trans*-acid, m.p. 113°. VPC of the dimethyl ester of the acid showed no trace of the *trans,cis*-acid in this product.

The acidic product (78 mg) was also formed by the above equilibrium reaction. VPC of its methyl ester showed that this was a mixture (60:40) of the *trans,cis*- and *cis,trans*-acid. Recrystallization gave an additional portion (22 mg, 8·6%) of 3(R)-*trans,cis*-acid, m.p. 103–105°.

Dimethyl 3(R)-*trans,cis*-boschnialinate (from 20 mg of XXIX) was also submitted to the equilibration with MeONa in MeOH (60 mg of Na and 1 ml MeOH). The product was a mixture of the *trans,cis*- and the *cis,trans*-ester in ratio 57:43.

3(R)-*cis,trans*-boschnialinic acid remained unaffected on refluxing with 2N NaOH for 20 hr.

(b) *Dimethyl* 3(R)-cis,cis- *and* 3(R)-trans,trans-*boschnialinate*. Dimethyl 3(R)-*cis,cis*-boschnialinate, prepared from 109 mg of XXXVII, was refluxed for 14 hr with MeONa soln, prepared from 240 mg Na and 4 ml anhyd MeOH. Water (2 ml) was added and the mixture was heated under reflux for an additional 2·5 hr. The crude acidic product was a mixture of the *cis,cis*- and the *trans,trans*-acid in ratio 5:95 by VPC of its dimethyl ester. Recrystallization from pentane:ether (4:1) gave 79 mg (72·5%) of 3(R)-trans,trans-*boschnialinic acid* (XXX), m.p. 110–111°, $[\alpha]_D^{14}$ −65·4° (*c*: 2·3, $CHCl_3$); ν_{max}^{Nujol} 1700, 1245, 1160, 935, 710 cm^{-1}. (Found: C, 58·11, 58·02; H, 7·76, 7·91. $C_9H_{14}O_4$ requires: C, 58·05; H, 7·58%). The dimethyl ester: ν_{max}^{liquid} 1730, 1260, 1200, 1155, 1100, 1015, 925, 850, 760 cm^{-1}.

3(R)-*cis,cis*-Boschnialinic acid was unchanged by heating under reflux with 2N NaOH for 20 hr.

Hydrolysis of ethyl 2-ethoxycarbonyl-3(R)*-methylcyclopent-1-enylcyanoacetate* (XXIV). A mixture of 3·967 g of XXIV, 20 ml conc HCl, and 10 ml water was refluxed for 3 hr. After dilution with an equal volume of water, treatment with charcoal, and standing overnight, the crystalline ppt of XXVIII was collected by filtration, 767 mg (28%), m.p. 154–157° and after recrystallization from water, m.p. 157–158°; $[\alpha]_D^{20}$ +17·1° (*c*: 1·6, $CHCl_3$); ν_{max}^{Nujol} 1695, 1640, 1300, 950 cm^{-1}, $\tau^{DMSO\text{-}d_6}$ 8·88 (doublet, $J = 7$, 3H), 6·32 (singlet, 2H). (Found: C, 59·04, 59·00; H, 6·78, 6·82. Calc. for $C_9H_{12}O_4$: C, 58·69; H, 6·57%.) The dimethyl ester was prepared with ethereal diazomethane, ν_{max}^{liquid} 1735, 1710, 1645, 1260, 1200, 1130, 1045, 800 cm^{-1}, τ^{CCl_4} 8·88 (doublet, $J = 7$, 3H), 6·38 (singlet, 2H).

The aqueous filtrate was evaporated to dryness and the residue was triturated several times with ether. The ether soln was concentrated to give 1·155 g of a yellow oil, from which an additional crystal of XXVIII separated slowly. The ether insoluble solid was mixed with water and then filtered to give 729 mg of *6,7-dihydro-1,3-dihydroxy-7(R)-methyl-5(H)-2-pyrindine*. Recrystallization from EtOH gave a colourless needles, m.p. 159·5–160°, $[\alpha]_D^{18}$ −80·0° (*c*: 0·7, $CHCl_3$); ν_{max}^{Nujol} 3200–2400, 1660, 1610, 1565, 1340, 1255, 1130, 850 cm^{-1}. (Found: C, 65·37; H, 6·64; N, 8·34. $C_9H_{11}NO_2$ requires: C, 65·44; H, 6·71; N, 8·48%.)

Ozonolysis of XXVIII *to* 2(R)-*methylglutaric acid*. A soln of 800 mg of XXVIII in 15 ml glacial AcOH was ozonized at 20° for 2 hr. After addition of 10 ml water, the mixture was heated at 100° for 1 hr and evaporated to dryness. An acidic product (479 mg) obtained was chromatographed on 7 g silicagel with $CHCl_3$. Crude (−)-2(R)-methylglutaric acid, 145 mg (23%), m.p. 70–74°, was recrystallized from benzene: pentane to give 87 mg of the pure sample, m.p. 81–82°, $[\alpha]_D^{18}$ −21·2° (*c*: 2·8, H_2O). The IR spectrum of its dimethyl ester was identical with that of the authentic dimethyl DL-2-methylglutarate.

Hydrogenation of XXVIII. Unsaturated dicarboxylic acid XXVIII was hydrogenated under 1 atm at room temp with 100 mg Pt catalyst in AcOH. After 2 hr, the reaction mixture was worked up as usual. Two hydrogenation products, XXX, 61 mg, m.p. 107–108°, and XXIX, 28 mg, m.p. 97–98° could be isolated and identified with authentic specimens, respectively.

DL-trans,trans-*Boschnialinic acid* (VIIIb). The methoxymethylene ester VII was warmed with ethanolic HCl and then air was bubbled into the soln for 1 hr. The acidic product isolated as usual was further refluxed with 5% NaOHaq for 1 hr. The mixture was acidified and extracted with ether. The ether soln was evaporated to give an oil, which crystallized on standing, m.p. 119–123°. Recrystallization from pentane: ether, m.p. 123–124°, ν_{max}^{Nujol} 1700, 1300, 1230, 1160, 940 cm^{-1}. (Found: C, 58·05, 58·28; H, 7·77, 7·81. $C_9H_{14}O_4$ requires: C, 58·05; H, 7·58%.) The dimethyl ester: ν_{max}^{liquid} 1730, 1260, 1200, 1155, 1100, 1015 cm^{-1}; *m/e* 214 (molecular peak), 183, 182, 154, 141, 122, 95, 81 (base peak), 69, 59, 41.

A soln of 433 mg (2·33 mmole) of VIIIb in 3 ml Ac_2O was left standing overnight at room temp. The excess Ac_2O was removed under reduced press and the residue distilled to give 337 mg DL-*trans,trans*-boschnialinic anhydride, b.p. 120–130°/3 mm (bath temp), ν_{max}^{liquid} 1810, 1760 cm^{-1}; τ^{CCl_4} 8·76 (doublet, $J = 5$, 3H). The anhydride was hydrolysed with 5% NaOHaq at room temp for 5 hr or by refluxing with water for 2 hr to yield pure *trans,trans*-dicarboxylic acid, m.p. 123–124°.

The dimethyl ester of VIIIb remained unaffected on heating under reflux with excess methanolic MeONa for 2 hr.

DL-cis,cis-*Boschnialinic acid*

(a) *By oxidation of* DL-*boschnialactone* (X) *with alkaline potassium permanganate*. To a soln of 52 mg (0·34 mmole) DL-boschnialactone in 2·5 ml 3% KOHaq, 2·8 ml (0·91 mmole) 5% $KMnO_4$aq was added under ice cooling. After standing for 12 hr at 0–5°, the mixture was worked up as described in the oxidation of the natural lactone. The crude product (33 mg, 55%) recrystallized from pentane: ether (4:1), m.p. 107–109°; ν_{max}^{Nujol} 1700, 1350–1100 (9 small peaks), 930 cm^{-1}. The dimethyl ester: ν_{max}^{liquid} 1730, 1260, 1195, 1165, 1000 cm^{-1}, *m/e* 214 (molecular peak), 183, 182, 154, 141, 127, 95, 81 (base peak), 69, 59, 41. The IR spectrum and the VPC were identical with those of dimethyl 3(R)-*cis,cis*-boschnialinate obtained by oxidation of the natural lactone and the alternative synthesis described below.

(b) *By thermal isomerization of* DL-trans,trans-*boschnialinic anhydride*. The anhydride, prepared from 157 mg (0·84 mmole) DL-*trans,trans* VIIIb, was heated at 240–250° for 10 min. After distillation, the colourless distillate was hydrolysed with 2 ml water at 100°. On cooling, colourless crystals separated, 100 mg, m.p. 86–89°. This was a mixture of the *trans,trans*- and the *cis,cis*-acid in ratio 37:63 by VPC of its dimethyl ester. DL-*cis,cis*-boschnialinic acid (20 mg, 13%) was obtained by fractional crystallization from pentane: ether and was identified with the acid prepared by the method (a). (Found: C, 58·44, 58·24; H, 7·73, 7·78 $C_9H_{14}O_4$ requires: C, 58·05; H, 7·58%.) Evaporation of the mother liquor after hydrolysis of the isomerized anhydride gave additional crystals (19 mg), which were a mixture of the *trans,trans*- and *cis,cis*-acid in the ratio 10:9. Therefore, the total equilibration ratio of both acids in this reaction was 39:61.

DL-2-*Carboxy-3-methylcyclopent-2-en-1-ylacetic acid* (XXIII). Compound XXIII was prepared from VI by the method of Bradfield *et al.*[6], m.p. 192–193°, ν_{max}^{Nujol} 1700, 1680, 1660, 1630, 1300, 1270, 1220, 930 cm^{-1}, $\tau^{pyridine}$ 7·78 (doublet, $J = 1$, 3H), 6·2 (multiplet, 1H). (Found: C, 58·91, 58·53; H, 6·80, 6·71. Calc. for $C_9H_{12}O_4$: C, 58·69; H, 6·57%.)

Hydrogenation of XXIII. A soln of 680 mg (3·70 mmole) of XXIII in 12 ml glacial AcOH was hydrogenated with 100 mg PtO_2 at room temp under 1 atm. Approximately the theoretical amount of H_2 was absorbed over 2·5 hr. Filtration and evaporation gave a colourless viscous liquid. On standing, crystals separated, m.p. 90–100°. Fractional crystallization from benzene : hexane gave two pure substances, m.p. 120–122° (59 mg) and m.p. 108–111° (128 mg). The former was identified with DL-*trans,trans*-boschnialinic acid and the latter, ν_{max}^{Nujol} 1700, 1300, 1245, 1205, 1180, 1030 cm^{-1}, was found to be DL-*trans,cis*-acid by the comparison of the IR and the mass spectrum of its dimethyl ester (ν_{max}^{liquid} 1730, 1260, 1200, 1160, 1015, 925, 850, 760 cm^{-1}, *m/e* 214, 183, 182, 154, 141, 127, 95, 81, 69, 59, 41) with those of dimethyl 3(R)-*trans,cis*-boschnialinate.

Conversion of the boschnialinic acids into the nepetic acids

The lactone (XXXV) *of* 1,2-cis-1,5-trans-2-(*2′-hydroxy-2′,2′-diphenylethyl*)-5(R) *methylcyclopentanecarboxylic acid*. The anhydride XXXI (450 mg; 2·68 mmoles) was dissolved in 3 ml anhydrous MeOH and heated under reflux for 4 hr. Evaporation of the solvent gave the half methyl ester XXXIV of 3(R)-*cis,trans*-boschnialinic acid as a pale yellow liquid. ν_{max}^{liquid} 1725, 1700 cm^{-1}.

To a vigorously stirred soln of Grignard reagent, prepared from 250 mg (10·4 mg atom) Mg, 2·3 g (14·7 mmole) bromobenzene, and 10 ml anhyd ether, an anhyd benzene (4 ml) soln of the half ester was added while heating under reflux. The mixture was heated under reflux for another 7 hr, and decomposed with dil HCl under cooling. The ether layer was separated and the aqueous layer extracted 3 times with ether. The ether soln was washed with $NaHCO_3$aq, dried, and evaporated to give 1·7 g of an oil. Unchanged bromobenzene was removed under vacuum at 100°. The viscous residue was refluxed with 10 ml 2N NaOH for 2 hr. The mixture was washed with ether, acidified with HCl, and extracted with ether. Evaporation of ether afforded 559 mg of a yellow residue, which solidified on standing. Recrystallization from benzene : pentane gave 356 mg (43·4 %) of a colourless prism, m.p. 135°; $[\alpha]_D^{15}$ −106·4° (c: 1·0, C_6H_6); ν_{max}^{Nujol} 1725, 1595, 1490, 1240, 1200, 1065, 1050, 1000, 755, 715 cm^{-1}, τ^{CCl_4} 8·85 (doublet, $J = 6$, 3H). (Found: C, 82·18, 82·19; H, 7·42, 7·25. $C_{21}H_{22}O_2$ requires: C, 82·32; H, 7·24 %.)

1,2-cis-1,5-trans-2(*2′,2′-Diphenylethenyl*) 5(R)-*methylcyclopentanecarboxylic acid* (XXXVIa). A mixture of 380 mg (1·24 mmole) of the lactone XXXV and 17 ml of 70 % (v/v) H_2SO_4 was kept at 60° for 10 min with occasional shaking. The insoluble material was well crushed during this period. After standing at room temp for 12 hr, the yellowish brown suspension was diluted with ice-water and extracted with ether. The ether soln was washed twice with water, dried, and evaporated to give a solid in quantitative yield, m.p. 129°, which was recrystallized from pentane : ether, m.p. 137–138°; $[\alpha]_D^{17}$ −16·8° (c: 0·8, $CHCl_3$), λ_{max}^{EtOH} 253 mμ (log ε: 4·18); ν_{max}^{Nujol} 3300–3000, 1715, 1670, 1595, 1500, 1215, 1160, 885, 770, 705 cm^{-1}; τ^{CCl_4} 8·98 (doublet, $J = 6$, 3H), 3·89 (doublet, $J = 10$, 1H). (Found: C, 82·43, 82·23; H, 7·55, 7·51. $C_{21}H_{22}O_2$ requires: C, 82·32; H, 7·24 %.)

cis,trans-*Nepetic acid* (XXXVIIa). A soln of the methyl ester (267 mg, 0·833 mmole), prepared from XXXVIa and diazomethane, in CCl_4 (14 ml) was saturated with O_3 at −20° (2 hr). After standing overnight at 0°, the reaction mixture was added to a soln of 19 ml 5 % NaOHaq and 8 ml 30 % H_2O_2, and then stirred at room temp for 20 hr. The organic solvent was evaporated under reduced press and the aqueous layer was washed with ether, acidified, and extracted with ether. The ether soln was dried and evaporated to leave 100 mg of an oil. This material was heated with 3 ml 6N HCl at 100° for 2·5 hr. Treatment with charcoal and evaporation gave 50 mg of a liquid, which was chromatographed on 350 mg silicagel with $CHCl_3$. Colourless crystals (10 mg) were obtained, m.p. 123–126°, $[\alpha]_D^{16}$ −57·8° (c: 0·7, $CHCl_3$). Recrystallization from pentane : ether (4 : 1) gave pure 3(R)-*cis,trans*-XXXVIIa, m.p. 132–133°. The IR spectrum of its dimethyl ester was identical with that of dimethyl *cis*-nepetate reported by McElvain *et al.*[25]

1,2-cis-1,5-cis-2(*2′,2′-diphenylethenyl*) 5(R)-*methylcyclopentanecarboxylic acid* XXXVIb. A soln of the half methyl ester, ν_{max}^{liquid} 1725, 1700 cm^{-1}, of 3(R)-*cis,cis*-boschnialinic acid, prepared from 496 mg (2·95 mmole) anhydride XXXIII and 5 ml anhyd MeOH, in 3 ml anhyd benzene was treated with a PhMgBr soln, prepared from 250 mg (10·4 mg atom) Mg, 2·5 g (15·9 mmole) bromobenzene, and 10 ml anhyd ether, as described above. In this case the product was isolated as the oily hydroxy acid- XXXVIII, 739 mg, ν_{max}^{liquid} 3400, 3300–2400, 1700, 1600, 1495, 785, 760, 700 cm^{-1}, which was immediately dehydrated with 30 ml of 70 % (v/v) H_2SO_4. The unsaturated acid XXXVIb was obtained as colourless prisms 300 mg (33·8 %), m.p. 136–138° and recrystallized from pentane : ether, m.p. 139–140°, λ_{max}^{EtOH} 253 mμ (log ε: 4·21), ν_{max}^{Nujol} 3300–2400, 1695, 1600, 1500, 950, 890, 773, 705 cm^{-1}, τ^{CCl_4} 8·94 (doublet, $J = 6$, 3H), 3·78 (doublet, $J = 10$, 1H). (Found: C, 82·11, 82·32; H, 7·27, 7·39. $C_{21}H_{22}O_2$ requires: C, 82·32; H, 7·24 %.)

cis,cis-*Nepetic acid* (XXXVIIb). Esterification of 317 mg of XXXVIb with ethereal diazomethane gave the methyl ester as a colourless viscous liquid, ν_{max}^{liquid} 1730 cm^{-1}, τ^{CCl_4} 9·05 (doublet, $J = 6$, 3H), 3·92 (doublet, $J = 10$, 1H).

A soln of the ester in 15 ml CCl_4 was ozonized at −20° for 2 hr. The acidic product (51 mg) was heated under reflux with 3 ml 8N HCl for 2 hr. The soln was evaporated to dryness under vacuum and the residual oil was chromatographed on 300 mg silicagel with $CHCl_3$. Recrystallization of a crude solid from pentane : ether gave 3 mg of *cis-cis*-XXXVIIb as a colourless crystals. m.p. 137–138°. The IR spectrum of its dimethyl ester was identical with that of dimethyl DL-*cis,cis*-nepetate reported by McElvain.[25]

Acknowledgement The authors are indebted to Professor H. Inoue, Kyoto University, Professor L. H. Briggs, University of Auckland, and Professor T. Kaneko, Osaka University, for supplying their valuable samples, and to Doctor Y. Hirose, The Institut of Food Chemistry, Osaka, for measurement and analyses of the mass spectra.