The Chemistry of the Compositae. Part XXXI.[1] Absolute Configuration of the Sesquiterpene Lactones Centaurepensin (Chlorohyssopifolin A), Acroptilin (Chlorohyssopifolin C), and Repin

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Direct comparison of the sesquiterpene lactones chlorohyssopifolin A (6c), from *Centaurea hyssopifolia*, and centaurepensin, from *Centaurea repens* showed them to be identical. The former was converted, by dehalogenation (zinc–copper couple) and subsequent saponification, into the deacyldihydrocynaropicrin (10a), a derivative of cynaropicrin (11j), the absolute stereochemistry of which for the centres of asymmetry C-1 (α-H), C-5 (α-H), C-6 (β-H), and C-7 (α-H) has been rigorously established. This stereochemistry is the same as has been found to date in all the guaianolides for which absolute configurations are known, and is the opposite of that previously assigned to centaurepensin. Correlation between structure (6c) and the lactones acroptilin and repin, reported to have structures (4c and d) (C-1 β-H), suggests that in these substances the fusion of rings A and B is also *cis* C-1 α-H and not *trans*.

In previous papers on *Centaurea hyssopifolia* Vahl,[2] we reported the isolation of five sesquiterpene lactones containing chlorine, which we called chlorohyssopifolins A—E. Their structures, determined from spectroscopic data and chemical transformations, were assigned as (1b and a), (2b), and (1h and i), respectively.

At the same time, two lactones new to the literature were described. One of them, centaurepensin,[3] isolated from *C. repens* L., was assigned the structure and absolute configuration (3c), on the basis of *X*-ray diffraction analysis, and the other, acroptilin, isolated from *Acroptilon repens* (*Centaurea picris*) and from *C. hyrcanica* Borm,[4] was assigned the structure (4c). The former proved to be identical with our chlorohyssopifolin A on the basis of i.r. and n.m.r. spectra, m.p., mixed m.p. and chromatographic behaviour. The physical constants of the latter [4] agree with those of chlorohyssopifolin C, suggesting that these two compounds are also identical.† Another sesquiterpene lactone, repin,[5] was also isolated from *C. hyrcanica* and assigned the structure and absolute configuration (4d). The *trans*-fusion of rings A and B (1β*H*, 5α*H*) was assigned from a detailed analysis of its n.m.r. spectrum. Acroptilin and repin can be converted into the same derivative (5a). The stereochemistry at C-1, -5, -6, and -8 must therefore be the same in both lactones, since these centres are not affected in the chemical transformation.

† Acroptilin:[4] m.p. 197—199°, $[\alpha]_D$ 92.3°; chlorohyssopifolin C:[2b] m.p. 197—199, $[\alpha]_D$ 100°. The ^{1}H n.m.r. spectrum of the diacetate of acroptilin is identical with that of the diacetate of chlorohyssopifolin C. We were unable to obtain an authentic sample of acroptilin for comparison.

‡ The footnote on p. 158 of vol. 3 of the Chem. Soc. Specialist Periodical Reports 'Terpenes and Steroids,' which states that centaurepensin and chlorohyssopifolin A are not identical, was based on the results of a study of ours, subsequently disproved, which we forwarded to the author prematurely.

Centaurepensin is widespread in the genus *Centaurea*. Recently, it has been found in *C. nigra*,[6] *C. solstitialis*,[7] and *C. linifolia* (in the last together with acroptilin [8]).

From the fact that chlorohyssopifolin A and centaurepensin are identical ‡ and that chlorohyssopifolin C can be converted into chlorohyssopifolin A,[2b] we deduced that both chlorohyssopifolins have a secondary hydroxy-group on C-3 and a β-chloro-α-hydroxyisobutyryl group, rather than an OH on C-2 and an α-chloro-β-hydroxyisobutyryl group, as we had erroneously assumed. Consequently, chlorohyssopifolins A, B, D, E, and C have the structures (6c, a, h, and i) and (4c; with 1α*H*) and not those previously reported.

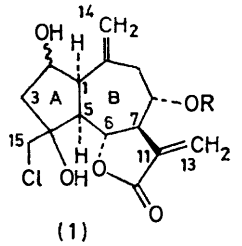
The absolute configuration indicated for centaurepensin is worthy of comment. Its main feature is the α-orientation of the C(7)—C(11) bond, which is the reverse of that found so far in all sesquiterpene lactones with absolute configurations rigorously established [9] and which might originate biogenetically from some of the various possible conformations [10] of the cation (7). The β-orientation of the 7,11-bond, assigned on the basis of chemical considerations and conformational analysis, has been confirmed in many sesquiterpene lactones by *X*-ray diffraction analysis.[11]

In the case of the centres C-1, -5, -6, and (probably) -11 (when there is an asymmetric centre), the absolute configuration ascribed to centaurepensin is the opposite of that in all the guaianolides found in the *Centaurea* with a

[1] Part XXX, A. G. González, J. Bermejo, G. M. Massanet, J. M. Amaro, and B. Domínguez, in the press.
[2] A. G. González, J. Bermejo, J. L. Breton, G. M. Massanet, and J. Triana, *Phytochemistry*, 1974, **13**, 1193.
[3] J. Harley-Mason, A. T. Hewson, O. Kennard, and R. C. Pettersen, *J.C.S. Chem. Comm.*, 1972, 460.
[4] R. I. Evstratova, V. I. Sheichenko, and K. S. Rybalko, *Khim. prirod. Soedinenii*, 1973, **9**, 161.
[5] R. I. Evstratova, K. S. Rybalko, and V. I. Sheichenko, *Khim. prirod. Soedinenii*, 1972, **8**, 451.
[6] A. G. González, J. Bermejo, I. Cabrera, and G. M. Massanet, *Anales de Quím.*, 1974, **70**, 74.
[7] J. Sakakibara, personal communication.
[8] A. G. González, J. M. Amaro, J. Bermejo, and G. M. Massanet, unpublished results.
[9] S. M. Kupchan and J. E. Kelsey, *Tetrahedron Letters*, 1967, 2863, and references quoted therein.
[10] J. B. Hendrickson, *Tetrahedron*, (*a*) 1959, **7**, 82; (*b*) 1963, **19**, 1837; (*c*) W. Parker and J. S. Roberts, *Quart. Rev.*, 1967, **21**, 331.
[11] W. Klyne and J. Buckingham, 'Atlas of Stereochemistry,' Chapman and Hall, London, 1974, pp. 97—100.

definitely established stereochemistry.[12] Consequently, the lactone (8) derived from centaurepensin must be the mirror image of the corresponding lactone obtained from cynaropicrin (11j), the absolute configuration of which at the above-mentioned centres has also been rigorously established.[13]

In order to prepare the lactone (8), chlorohyssopifolin A was dehalogenated with zinc–copper couple, a reagent widely used in halogen elimination reactions.[14] Depending on the reaction time, six different compounds, separable by column chromatography after interrupting the reaction at the most convenient moment (after 24 h), were obtained. In all these compounds, saturation of the 11,13-double bond had taken place. This is reflected in their ^{1}H n.m.r. spectra (Table) by the absence of the characteristic signals due to the olefinic protons of the α-methylene-γ-lactone grouping and the appearance of a doublet (J 7 Hz) at δ *ca.* 1.25 due to the methyl group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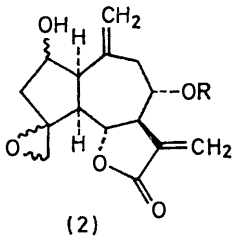
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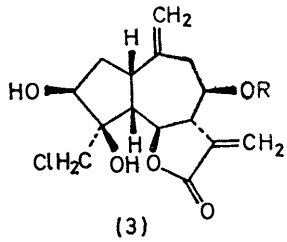
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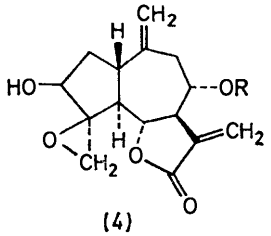
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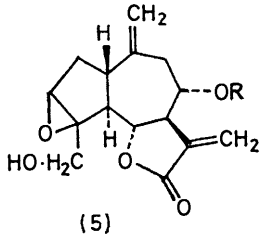
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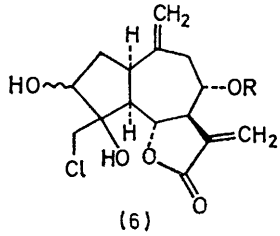
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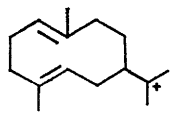
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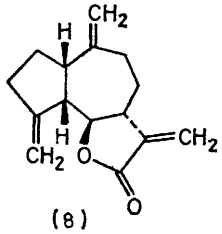
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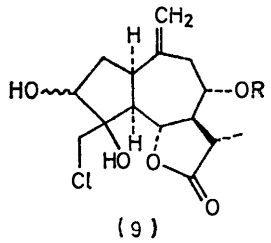
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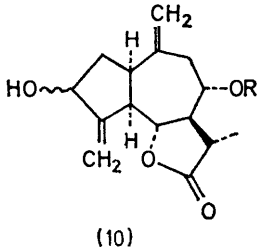
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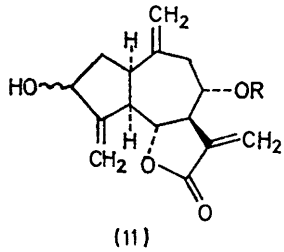
(11)

a; R = H
b; R = CO·CClMe·CH$_2$·OH
c; R = CO·CMe(OH)·CH$_2$Cl
d; R = CO·CMe·CH$_2$·O
e; R = CO·CMe:CH$_2$
f; R = CO·CMe(OH)·CH$_3$
g; R = COPr^i
h; R = CO·CMe(OEt)·CH$_2$·OH
i; R = CO·CMe(OH)·CH$_2$·OH
j; R = CO·C(:CH$_2$)·CH$_2$·OH

[12] (*a*) A. G. González, B. García, and J. L. Bretón, *Anales de Quím.*, 1971, **66**, 1245; (*b*) Z. Samek, M. Holub, K. Vokak, B. Drodz, G. Jommi, A. Gariboldi, and A. Corbella, *Coll. Czech. Chem. Comm.*, 1972, **37**, 2611; (*c*) A. G. Gonzalez, J. Bermejo, and G. M. Massanet, *Anales de Quím.*, 1973, **69**, 1333; (*d*) A. G. González, J. Bermejo, and M. Rodríguez, *ibid.*, 1972, **68**, 333; (*e*) W. E. Thiessen and A. Hope, *Acta Cryst.*, 1970, **266**, 554.

[13] A. Corbella, P. Gariboldi, J. Jommi, Z. Samek, M. Holub, D. Drodz, and E. Bolszyk, *J.C.S. Chem. Comm.*, 1972, 386.

[14] S. M. Kupchan and M. Maruyama, *J. Org. Chem.*, 1971, **36**, 1187, and references quoted therein.

α to the lactone carbonyl group. The first compound formed is identical with dihydrochlorohyssopifolin A (9c), obtained by hydrogenation ($NaBH_4$) of (6c). The reduction (Zn–Cu) of the conjugated methylenic double bond is, therefore, stereoselective, giving rise to an apart from confirming the position of the secondary hydroxy-group on C-3, suggests that the absolute configuration of the previously mentioned centres in chlorohyssopifolin A is the same as in cynaropicrin and not the opposite, as it should be if the absolute configuration

^{1}H N.m.r. data (δ values; solvent $CDCl_3$; 60 MHz; J/Hz in parentheses)

Compd.	H-3	H-6 [a]	H-8 [b]	H-13 [c]	H-14	H-15	3′-H_2 [d]	2′-Me [d]
(4c) †	3.90	4.80	5.22	5.70 (3.5) 6.05 (3.5)	5.03, 5.21	3.05d (5), 3.15d (5)	3.76d (11.5), 3.96d (11.5)	1.54s
(4d) ‡	4.02q (4.5, 6.5)	4.68	5.16	5.62 (4), 6.24 (3.5)	5.02, 5.24	3.14d (4.5), 3.34d (4.5)	2.87d (6), 3.22d (6)	1.66s
(6c) †	4.20	4.90	5.3	5.70 (3.5), 6.07 (3.5)	4.99, 5.15	3.87d (12), 4.30d (12)	3.78d (12), 3.99d (12)	1.60s
(9c)	4.20	4.70	5.20	1.25 (7)	5.02, 5.17	3.88 (12), 4.23 (12)	3.63d (11.5), 3.88d (11.5)	1.50s
(9e)	4.20	4.65	5.20	1.20 (7)	4.90, 5.12	3.87 (12), 4.25d (12)	5.65 (2), 6.16	1.96d (2)
(10a) †		4.50		1.32 (7)	4.95, 5.05	5.25		
(10c)	4.55	4.20	5.20	1.25 (7)	5.10, 5.15	5.35, 5.43	3.59d (12), 3.86d (12)	1.50s
(10e)	4.55	4.20	5.20	1.25 (7)	5.05, 5.15	5.35, 5.42	5.65 (2), 6.15s	1.95d (2)
(10f)	4.55	4.18	5.20	1.28 (7)	5.00, 5.15	5.37, 5.42	1.45s	1.45s
(10g)	4.55	4.15	5.20	1.25 (7)	5.00, 5.12	5.32, 5.40	1.17d (6.5)	1.17d (6.5)

† Solvent $(CD_3)_2CO$; 100 MHz. ‡ Data from ref. 5 (100 MHz).

[a] q (10.5, 9). [b] m. [c] d. [d] Acyl group designated C(1′)–C(2′)Me–C(3′).

α-oriented methyl group, as in the reduction with $NaBH_4$.[15] The n.m.r. and mass spectra of the second lactone formed (9e) clearly show that it is an ester of methacrylic acid {prominent mass spectral peaks at $M^+ - C_4H_6O_2$ and *m/e* 69 [CO·C(:CH_2)·CH_3]; n.m.r. signals for a vinylic methyl group (δ 1.95, d) and a conjugated methylene group (δ 5.65 and 6.15)}. In the succeeding four lactones the C(4) (OH)·CH_2Cl group has been converted into an exocyclic methylene group, C(4):CH_2, which is reflected in their n.m.r. spectra by the absence of the quartet (AB system) centred at δ *ca.* 4.05 and the presence of two new signals between δ 5.3 and 5.5. These four lactones differ from each other solely in the acyl group, since saponification of each yields the same lactone (10a). The n.m.r. and mass spectra indicate the presence of an α-hydroxy-β-chloroisobutyryl group in (10c) {δ 1.50 [s, CH_3·C(OH)] and 3.59 and 3.86 (AB system, CH_2Cl); $M^+ - C_4H_7ClO_3$}, an α-hydroxyisobutyryl group in (10f) {δ 1.45 [6 H, s $(CH_3)_2C(OH)$]; $M^+ - C_4H_8O_3$ and *m/e* 59 (C_3H_7O)}, a methacryloyl group in (10e), and an isobutyryl group in (10g) {δ 1.20 [6 H, d, $(CH_3)_2CH$]; $M^+ - C_4H_8O_2$ and *m/e* 71 (C_4H_7O)}. After a sufficiently long reaction time, all the other five lactones were converted into compound (10g).

The lactone (10a), obtained by the saponification of lactones (10c, e, f, and g), turned out to be identical with the deacyldihydrocynaropicrin prepared from deacylcynaropicrin (11a) by stereoselective reduction of the conjugated methylene group. This surprising result, assigned to centaurepensin were correct. We feel, therefore, that a reconsideration of the latter might well be interesting.

In the light of the transformation of chlorohyssopifolin A into chlorohyssopifolin C (acroptilin) and the conversion of acroptilin and repin into the derivative (5a), it may be assumed that the absolute configuration of these two lactones at C-1 is the same as that of (10a) and, hence, that the fusion of rings A and B is *cis* (1α*H*, 5α*H*), and not *trans* as reported.[5]

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. I.r. spectra were taken for solutions in chloroform, u.v. spectra in ethanol, and 60 MHz ^{1}H n.m.r. spectra in $CDCl_3$ (Me_4Si as internal reference). Optical rotations were measured for solutions in chloroform. Silica gel (0.05—0.2 mm) was used for column chromatography.

Reduction of Chlorohyssopifolin A with Zinc–Copper Couple.—A mixture of chlorohyssopifolin A (1.6 g), zinc–copper couple (40 g), and ethanol (250 ml) was refluxed for 5 days. The reaction was monitored by t.l.c. After 24 h, six different compounds had been formed. Most of the mixture was filtered through Celite and concentrated under vacuum; the residue (600 mg) was chromatographed on a column of silica gel. The rest of the mixture was left to

[15] S. B. Mathur, S. V. Hiremath, G. H. Kulkarni, G. R. Kelkar, S. C. Bhattacharyya, D. Simonovic, and A. S. Rao, *Tetrahedron*, 1972, **21**, 3556.

react for another 4 days, after which all six compounds had been converted into compound (10g).

Elution with benzene–ethyl acetate (1 : 1) produced first a mixture of two lactones, which could be separated by preparative t.l.c. with benzene–ethyl acetate (8 : 2) (two elutions). The compound of higher R_F value was recrystallized from acetone–petroleum to give *15-chloro-3,4-dihydroxy-8-methacryloyloxyguai-10(14)-en-12,6-olactone* (9e); m.p. 163—167°; $[\alpha]_D$ 32.7 (*c* 1.1); $\nu_{max.}$ 3 540 (OH), 1 770 (γ-lactone), 1 710 (ester), and 1 635 cm^{-1} (C=C); *m/e* (no M^+) 298 (M^+ − 86, 5%) and 69 (100%) (Found: C, 59.7; H, 6.45; Cl, 9.0. $C_{19}H_{25}ClO_6$ requires C, 59.3; H, 6.5; Cl, 9.25%).

The compound of lower R_F value (an oil) (10e) could not be crystallized; $[\alpha]_D$ 38.4; $\nu_{max.}$ 3 490, 1 760, 1 720, and 1 620 cm^{-1}; *m/e* 332 (M^+, 5%), 246 (M^+ − 86, 27), and 69 (100). Acetylation with acetic anhydride–pyridine produced a liquid monoacetate.

Two more compounds eluted from the column were separated by fractional crystallization from acetone–petroleum. One of them was identical with 11,13-dihydrochlorohyssopifolin A (9c) (m.p., mixed m.p. and i.r. spectra); m.p. 167—170°; $[\alpha]_D$ 9.8 (*c* 1.0 in MeOH); $\nu_{max.}$ 3 530, 1 770, and 1 730 cm^{-1}; *m/e* (no M^+) 298 (M^+ − 138, 41%) and 93 (100) (Found: C, 52.45; H, 6.1; Cl, 16.35. Calc. for $C_{19}H_{26}Cl_2O_7$: C, 52.3; H, 5.95; Cl, 16.05%).

The other was the final product, *3-hydroxy-8-isobutyryloxyguaia-4(15),10(14)-dien-12,6-olactone* (10g); m.p. 203—208°; $[\alpha]_D$ 61.8 (*c* 3.56); $\nu_{max.}$ (KBr) 3 240, 1 780, 1 715, and 1 630 cm^{-1}; *m/e* 334 (M^+, 22%), 246 (M^+ − 88, 75), and 71 (100) (Found: C, 67.9; H, 7.85. $C_{19}H_{26}O_5$ requires C, 68.3; H, 7.85%).

After this, a mixture of (9c) and the *β-chloro-α-hydroxyisobutyryl compound* (10c) was eluted and separated by fractional crystallization from ethyl acetate–petroleum; (10c) is a liquid, $[\alpha]_D$ 90° (*c* 1.3) (Found: C, 59.5; H, 6.65; Cl, 9.1. $C_{19}H_{25}ClO_6$ requires C, 59.3; H, 6.5; Cl, 9.25%); $\nu_{max.}$ 3 520, 1 765, 1 730, and 1 630 cm^{-1}; *m/e* 384 (M^+, 21%), 246 (M^+ − 138, 66), and 93 (100).

Finally, an oily compound, the *α-hydroxyisobutyryl derivative* (10f), was eluted. T.l.c. showed it to be homogeneous; $[\alpha]_D$ 45.5 (*c* 1.56); $\nu_{max.}$ 3 580, 1 765, 1 720, and 1 635 cm^{-1}; *m/e* 350 (M^+, 7%), 246 (M^+ − 104, 18), and 59 (100) (Found: C, 64.9; H, 7.55. $C_{19}H_{26}O_6$ requires: C, 65.15; H, 7.5%).

Dihydrochlorohyssopifolin A (9c).—Sodium borohydride (300 mg) was added to compound (6c) (50 mg) dissolved in methanol (40 ml) and the solution was stirred for 10 min at 0 °C. The solution was evaporated and the residue acidified with aqueous 5% hydrochloric acid and continuously extracted with ethyl acetate. The resulting solid was chromatographed on silica gel, yielding the product (9c), m.p. 168—170°.

Dihydrodeacylcynaropicrin from Compounds (10g) *and* (11a).—A solution of compound (10g) (100 mg) in methanol (6 ml) was treated overnight with aqueous 5% potassium carbonate (10 ml) at room temperature. The methanol was evaporated off under vacuum and the residue acidified with 5% sulphuric acid (10 ml) and extracted with ethyl acetate. The crude product was eluted from a column of silica gel with benzene–ethyl acetate (3 : 2). Crystallization from ethyl acetate–petroleum gave a *solid*, m.p. 135—137°; $[\alpha]_D$ 72.8 (*c* 1.34 in MeOH); $\nu_{max.}$ (KBr), 3 330, 1 730, and 1 630 cm^{-1}; *m/e* 264 (M^+, 13%), 246 (9), 218 (9), and 200 (11) (Found: C, 68.4; H, 7.7. $C_{15}H_{20}O_4$ requires C, 68.15; H, 7.65%), identical with that obtained by saponifying a mixture of (10c, e, f, and g) under the same conditions.

A solution of compound (11a) (80 mg) in methanol (50 ml) was treated with sodium borohydride (480 mg). Under the same conditions as above, a solid (60 mg) [m.p. 135—137°; $[\alpha]_D$ 74.8 (*c* 1.02 in MeOH)], was obtained, identical with that produced from (10g) (mixed m.p., i.r. and n.m.r. spectra, and chromatographic behaviour).

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