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Azacineole (1,3,3-Trimethyl-2-azabicyclo[2.2.2]octane)

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The title compound (5) has been synthesized and its presence sought in various eucalypt leaf oils. Aspects of the chemistry of the precursor aziridine (14) are discussed.

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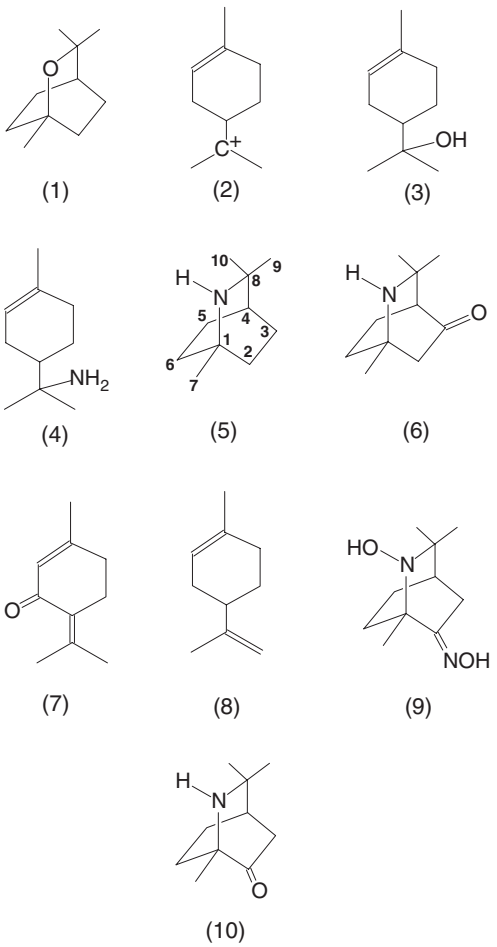
Introduction

Cineole (1,8-cineole, eucalyptol, 1,3,3-trimethyl-2-oxabicyclo[2.2.2]octane) (1) (see Diagram 1) is the most abundant and most widespread component of the eucalypt leaf oils.[1] Its biosynthesis in the tree has been postulated[2] to occur through cation (2) (or its equivalent), which is trapped by water to provide α-terpineol (3), and this is then cyclized with enzymatic assistance to cineole (1).

We now consider the possibility that cation (2) might also be trapped by ammonia (or its equivalent) to provide amine (4), which may then be enzymatically cyclized within the tree to provide 'azacineole' (5). While eucalypts are widely reported to be notably sparse in alkaloid content, we nevertheless resolved to synthesize compound (5) and to then seek its presence in various trees, especially those that abundantly synthesize cineole (1).



(1) (2) (3) (4) (5) (6) (7) (8) (9) (10)

Diagram 1

Results and Discussion

Syntheses for azacineole (5) have been previously reported. Rassat and Rey[3] produced the compound in 1971 in a three-step synthesis from 1,8-diamino-*p*-menthane (as a *cis*/*trans* mixture) through azacineole *N*-oxide in less than 16% overall yield. Greene and Gilbert[4] subsequently repeated this work but achieved significantly lower yields in the first step and thereby an overall yield of approximately 5%.

Nelson et al.[5] reported the Wolff–Kishner reduction of the 3-keto compound (6). This synthesis was based on earlier work[6] where ketone (6) was made through the double Michael addition of ammonia to piperitenone (7), which in turn was synthesized by condensation of mesityl oxide with methyl vinyl ketone. Nelson et al. reported a low yield for the Wolff–Kishner step with significant reversion to piperitenone (7) and its subsequent reduction under the alkaline conditions. The overall yield of azacineole (5) from methyl vinyl ketone was 4%.

The brief experimental section of the Nelson[5] paper employs incorrect numbering for the described compounds, and the data published is for azacineole (5) and not the claimed 3-keto derivative (6). The authors report three singlet peaks in the ^{1}H NMR spectrum for compound (5), at δ 0.98, 1.22, and 1.50. On the NMR timescale, we expect rapid inversion about the nitrogen atom, leading to a molecule containing a symmetry plane through C1, N, C8, and C4. Thus only two types of methyl singlets, of 2 : 1 integrated area, would be

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expected. Clarification of this point provided further reason to synthesize structure (5) in this current study.

After this work had commenced, work was published[7,8] claiming considerably higher yields of compound (5). Hydroxylamine attack on the nitrosochloride of limonene (8) provided oxime (9), which then required two steps to remove the oxygen atoms, including a Wolff–Kishner reduction of ketone (10). The mechanism of cyclization in this synthesis was modified by Coogan and Knight,[9] who proposed a reverse Cope-like process. Coogan managed to get through to compound (9), although his experimental methodology has not been reported. The experimental section of ref. [7] seriously misreports the work in some places, for instance implying that compound (9) is insoluble in ether. Considerable modification of this synthesis led us to compound (10) in 18% yield, but we then had serious trouble with the Wolff–Kishner reduction to compound (5) (5% yield versus 90% claimed yield[8]). At this stage we had obtained a sample of the required compound (5), but the overall yield (about 1%) was so poor that we sought an improved synthetic route.

We now report a direct two-step synthesis of azacineole (5) from 8-amino-*p*-menthene (4), which is available from limonene (8) (Scheme 1). Addition of mercuric azide, cautiously generated in situ, to limonene followed by borohydride reduction of the organomercurial yields azide (11).[10] The crude azide, contaminated with unreacted limonene, need not be purified at this stage as lithium aluminium hydride reduction of the mixture affords amine (4),[11] and separation of this amine from limonene (8) using acid extraction is then trivial.

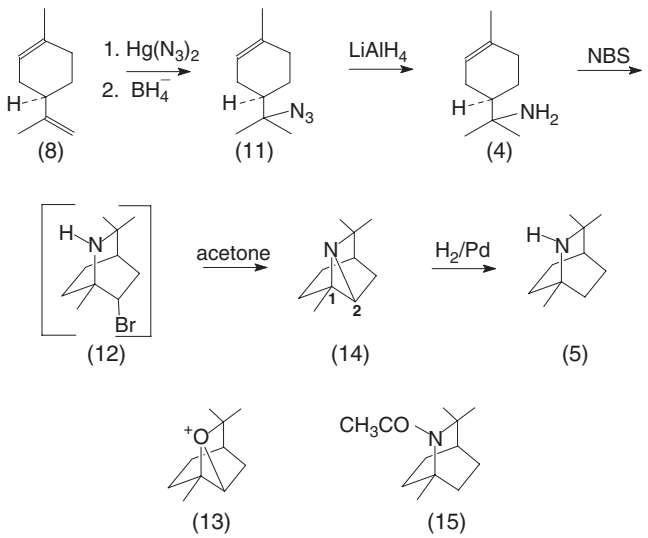
Ring closure of amine (4) with *N*-bromosuccinimide might be expected to provide bromide (12). However, the corresponding bromide in the oxa-cineole series is unstable due to the presence of the neighbouring oxygen atom, and in polar solvents yields breakdown products derived from the oxonium ion (13).[12] The nitrogen in compound (12) is obviously more nucleophilic than oxygen and in acetone spontaneously displaces the bromine to provide isolable aziridine (14). The structure of compound (14), a volatile oil, was supported by NMR evidence especially in light of the one-bond coupling (J_{C2H2} 176 Hz), which is characteristic of a carbon in a three-membered ring.[13]

Hydrogenation of aziridine (14) occurred quantitatively at the less-hindered C2—N bond to afford azacineole (5). This compound, also a volatile oil, provided NMR data consistent with the proposed structure, showing only two methyl peaks (ratio 2 : 1) and providing only seven types of carbon atoms as expected from symmetry arguments. The yield from limonene (8) ranged between 25% and 33%. A crystalline derivative, acetamide (15), was prepared for characterization purposes.

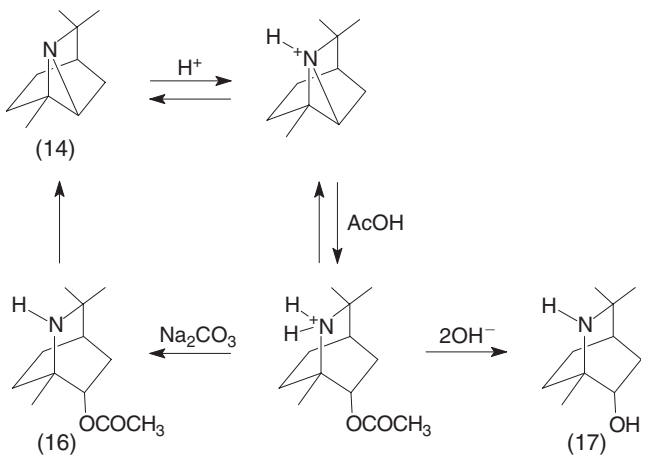
The chemistry of the interesting aziridine (14) was briefly explored. The compound was stable towards nucleophilic attack and in alkaline solution but was reactive when protonated. In acetic acid compound (14) equilibrated with the acetate (16), which could be isolated by sodium carbonate workup (Scheme 2). However, unprotonated compound (16) slowly reverted back to aziridine (14), again showing the effective participation of the nitrogen atom in the solvolysis of a suitably placed C2 leaving group in structures such as (12) and (16). When the reaction of aziridine (14) in acetic acid was quenched with sodium hydroxide the product was the stable alcohol (17). In strong base acetate hydrolysis occurs faster than the nitrogen displacement of the leaving group, while in weaker base the displacement reaction is faster.

The NMR data for these compounds supported the structures. The H2 signal for compound (16) and (17) appears as a ddd, which shows the characteristic long-range W-coupling (J 2.0 Hz) to H6β, and thus defines the stereochemistry at C2.

The availability of synthetic azacineole (5) simplified the search for the natural presence of this compound in eucalypt species by GC and GCMS examination of leaf extracts. However, a preliminary survey of six locally available trees (*E. citriodora*, *E. curtisii*, *E. grandis*, *E. microcorys*, *E. tereticornis*, and *E. ptychocarpa*) provided no sign of compound (5) from neutral leaf extracts, and indeed, no alkaloids were detected at all from the acid extracts. Wider examination of the plant kingdom, possibly outside the eucalypts, will be required.



Scheme 1



Scheme 2

Experimental

NMR spectra were recorded in $CDCl_3$ solution unless otherwise stated, using either a Bruker AMX400 or AV400 spectrometer. ^{13}C NMR multiplicities were assigned by the distortionless enhancement by polarization transfer (DEPT) pulse sequence. Mass spectra were recorded upon a Hewlett–Packard MSD5970 spectrometer using a GC inlet and BP5 column. High-resolution mass spectra (HRMS) were recorded on both Finnigan 2001 FT-MS and Kratos MS25RFA instruments. Infrared spectra were measured using a Perkin–Elmer 1600 series FT-IR with NaCl disks. GC analyses were performed upon a BP5 capillary column with flame ionization detection in a Varian 3300 instrument. Flash column chromatography was performed using Merck silica, grade 60, and distilled solvents.

The numbering of skeletons in compounds (5) and (14)–(17) is based on cineole numbering; see structure (5).

*(4*R*)-8-Azido-*p*-menth-1-ene (11)*

Caution: Explosions may result if this reaction is sealed, or if a higher ratio of water to tetrahydrofuran is used.

A mixture of tetrahydrofuran (20 mL) and water (25 mL) was chilled (0°C) while separate solutions of sodium azide (3.25 g, 50 mmol) in water (10 mL), and (*R*)-(+)-limonene (8) (1.36 g, 10 mmol) in tetrahydrofuran (5 mL), were prepared. Aqueous tetrafluoroboric acid (50%, 3.51 g, 20 mmol) and yellow mercuric oxide (2.16 g, 10 mmol) were mixed in a 300 mL flat-bottomed flask containing a magnetic stirrer bar. The mixture was sonicated in an ultrasound cleaning bath until all the solid mercuric oxide had reacted to give a pale yellow solution. The flask was immediately transferred to an ice–salt bath and stirred while the previously prepared chilled tetrahydrofuran–water solution was added. Without delay the sodium azide solution was added dropwise with rapid stirring, and then the limonene solution in tetrahydrofuran was added. The reaction was stirred (−5°C, 2 h), allowed to warm to room temperature and then stirred a further 24 h.

The flask was then cooled to −5°C and a pre-chilled solution of sodium borohydride (0.76 g, 20 mmol) in sodium hydroxide solution (5 M, 5 mL) was added. After 2 h at −5°C the flask was allowed to warm to room temperature and was then stirred (24 h) to allow mercury to collect. The upper layer was decanted into a separatory funnel and the mercury rinsed with diethyl ether, which was also transferred to the funnel along with brine (20 mL). The organic layer was collected and the aqueous layer further extracted with diethyl ether. The combined ether layers were washed with brine and dried (sodium sulfate). These extracts contained azide (11) and limonene (8) (ca. 55 : 45 by GC analysis; over many attempts under identical conditions the amount of azide (11) varied between 55% and 70%). This mixture of azide (11) and limonene (8), obtained by removal of solvent from the dried ether extracts, was used for further reaction. A pure sample of the title azide (11) [(4*R*)-4-(1-azido-1-methylethyl)-1-methylcyclohexene] as a clear oil (lit.[14] bp 212°C/690 mmHg) was obtained by flash chromatography (silica, hexane). NMR spectra were consistent with the literature[14,15] and provided extra information. ν_{max} (neat)/cm^{-1} 2966, 2924, 2099 (s, azide stretch), 1388, 1369, 1260, 1220, 1159, 1133, 799. δ_H ([D$_6$]benzene) 5.28 (1 H, m, $W_{h/2}$ 10, H2), 1.88–1.71 (3 H, m, H3, H6), 1.70–1.60 (2 H, m, H5eq, H6), 1.56 (3 H, br s, H7), 1.34 (1 H, dddd, *J* 11.9, 11.4, 4.9, 2.5, H4), 1.09 (1 H, dddd, *J* 12.4, 12.3, 11.4, 5.9, H5ax), 0.94 and 0.92 (6 H, 2 × s, 2 × Me). δ_C ([D$_6$]benzene] 133.6 (C1), 120.7 (C2), 63.8 (C8), 43.6 (C4), 31.0 (C3), 27.0 (C6), 24.3 (C5), 23.4 (C7), 22.8 and 23.6 (C9, C10). Mass spectrum (GCMS) *m*/*z* 150 (1%, $[M-29]^{+\bullet}$), 138 (1), 137 (12), 136 (23), 123 (3), 122 (6), 121 (33), 119 (4), 110 (22), 109 (5), 108 (38), 107 (6), 105 (5), 94 (84), 79 (100).

*(4*R*)-8-Amino-*p*-menth-1-ene (4)*

The mixture (1.6 g) of dry azide (11) (5.5 mmol) and limonene (8) (4.5 mmol) was stirred in dry tetrahydrofuran (80 mL, distilled from sodium) while lithium aluminium hydride (0.5 g, 14 mmol) was added in small portions. A reflux condenser was connected and, after the initial vigorous bubbling had ceased, the mixture was refluxed (4 h). Undried diethyl ether (40 mL) and then sodium sulfate decahydrate (7 g) were carefully added and the mixture stirred (10 h). The organic layer was decanted and the precipitate washed with diethyl ether with the assistance of ultrasound. The organic layers were combined and extracted with hydrochloric acid (0.4 M). The combined acid extracts were washed with diethyl ether and were then basified (2 M sodium hydroxide). The cloudy alkaline layer was back-extracted into diethyl ether, and the ether washed with brine and dried over sodium sulfate. Removal of solvent gave the title amine (4) [(4*R*)-4-(1-amino-1-methylethyl)-1-methylcyclohexene (766 mg, 5.0 mmol) as a colourless oil (lit.[16] colourless oil) (>95% pure by GCMS). NMR spectra were consistent with the literature[14] and provided extra information. ν_{max} (neat)/cm^{-1} 3354, 2961, 2922, 1595, 1437, 1381, 1363, 914, 799, 668. δ_H 5.33 (1 H, m, $W_{h/2}$ 13, H$_2$), 2.04–1.86 (3 H, m, H3, H6eq), 1.79 (1 H, dm, width 28 Hz, H5eq), 1.70 (1 H, m, width ca. 40 Hz, H6ax), 1.59 (3 H, br s, H7), 1.32 (2 H, br s, NH$_2$), 1.30 (1 H, dddd, *J* 12.3, 11.2, 4.7, 2.3, H4), 1.16 (1 H, dddd, *J* 12.3, 12.3, 11.2, 5.9, H5ax), 1.00 and 0.99 (6 H, 2 × s, 2 × Me). δ_C 133.8 (C1), 120.7 (C2), 51.0 (C8), 45.2 (C4), 31.2 (C3), 28.3 and 27.6 (C9, C10), 26.7 (C6), 24.0 (C5), 23.2 (C7). Mass spectrum (GCMS) *m*/*z* 154 (1%, $[M+1]^{+\bullet}$), 153 (1, $M^{+\bullet}$), 139 (2), 138 (27), 137 (8), 136 (87), 122 (15), 121 (95), 110 (9), 108 (11), 107 (15), 105 (12), 93 (100), 79 (72), 77 (59).

Aziridine (14)

Amine (4) (1.1 g, 7.15 mmol) in acetone (100 mL, previously dried over anhydrous sodium sulfate) was stirred (16 h) with *N*-bromosuccinimide (1.27 g, 7.15 mmol). The solvent was carefully reduced to ca. 3 mL by rotary evaporation (**caution**: aziridine (14) is highly volatile) and diethyl ether (30 mL) was added. The mixture was sonicated and filtered to remove precipitated succinimide, which was afterwards washed with ether. The combined filtered ether layers were carefully taken to dryness to give crude aziridine (14) (1.03 g, 77% pure by GCMS). Flash chromatography (silica, dichloromethane/methanol, 19 : 1) afforded pure aziridine (14) [(2*S*,5*R*,7*R*)-2,8,8-trimethyl-1-azatricyclo[3.2.1.0^{2,7}]octane] (582 mg, 3.85 mmol) as a hygroscopic colourless oil (Found: C, 77.4; H, 11.9; N, 9.0%; $M^{+\bullet}$, 151.1357. $C_{10}H_{17}N$ + (0.2 H_2O) requires C, 77.6; H, 11.3; N, 9.0%; $M^{+\bullet}$, 151.1361). ν_{max} (neat)/cm^{-1} 3307 (NH and OH), 2930, 1648, 1457, 1372, 1301, 1213, 1131, 1072, 1008, 878, 814, 778, 737. δ_H 2.07 (1 H, br d, H2), 2.02 (1 H, dddd, $J_{3\alpha,3\beta}$ −12.6, $J_{3\beta,4}$ 7.0, $J_{2,3\beta}$ 4.4, $J_{3\beta,5\beta}$ 2.6, H3β), 1.78 (1 H, ddd, $J_{6\alpha,6\beta}$ −15.3, $J_{5\alpha,6\alpha}$ 11.6, $J_{5\beta,6\alpha}$ 4.6, H6α), 1.72 (1 H, dddd, $J_{5\beta,6\beta}$ 9.7, $J_{5\alpha,6\beta}$ 5.9, $J_{2,6\beta}$ 1.1, H6β), 1.67 (1 H, br d, H3α), 1.61 (1 H, dddd, $J_{5\alpha,5\beta}$ −13.0, $J_{4,5\beta}$ 3.0, H5β), 1.44 (1 H, ddd, $J_{4,5\alpha}$ 3.0, H4), 1.30 (1 H, dddd, H5α), 1.20 and 1.00 (6 H, 2 × s, H9,10), 0.97 (3 H, s, H7). δ_C 60.9 (C8), 45.6 (C2,J_{C2H2} 177 Hz), 38.3 (C1), 36.9 (C4), 31.1 (C3), 28.8, 25.5, 22.9 (3 × Me), 23.0 (C5), 20.7 (C6); with remaining $^1J_{CH}$ couplings between 140 and 160 Hz. Mass spectrum (GCMS) *m*/*z* 152 (3%, $[M+1]^{+\bullet}$), 151 (32), 137 (5), 136 (35), 122 (9), 111 (9), 110 (100), 108 (22), 96 (14), 95 (99), 94 (47), 93 (20), 91 (17), 83 (78), 82 (26), 79 (59), 77 (32).

Azacineole (5)

Aziridine (14) (140 mg, 0.926 mmol) in ethyl acetate (10 mL) was hydrogenated (atmospheric pressure, 20 h) over palladium (10% on carbon, 14 mg). The solution was filtered (celite) and the solvent removed to give pure azacineole (5) [1,3,3-trimethyl-2-azabicyclo[2.2.2]octane] as a colourless oil (121 mg, 0.787 mmol) (lit.[3,5–8] colourless oil, bp 90°C at 3–4 Torr) (Found: $M^{+\bullet}$, 153.1519; $[M-CH_3]^{+\bullet}$, 138.1291. $C_{10}H_{19}N$ requires $M^{+\bullet}$, 153.1517; $[M-CH_3]^{+\bullet}$, 138.1283). ν_{max} (neat)/cm^{-1} 3384, 2937, 2803, 2725, 2501, 1712, 1660, 1622, 1590, 1469, 1395, 1381, 1287, 1230, 1174, 1091, 1061, 916, 732. δ_H 8.80 (1 H, s, NH), 2.18 (2 H, m), 2.04 (2 H, m), 1.60 (6 H, 2 × s, H9,10), 1.57 (3 H, s, H7), 1.64–1.48 (5 H, m). The spectrum was overlapped and second order, therefore no reliable coupling constants were available. δ_C 58.1 and 55.0 (C1, C8), 33.4 (C4), 28.4 (C2,6), 27.8 (C9, C10), 24.4 (C7), 21.5 (C3, C5). Mass spectrum (GCMS) *m*/*z* 154 (3%, $[M+1]^{+\bullet}$), 153 (27, $M^{+\bullet}$), 139 (11), 138 (100, $[M-CH_3]^{+\bullet}$), 125 (9), 124 (49), 111 (8), 110 (87), 108 (15), 98 (26), 96 (26), 94 (11), 93 (9), 82 (23), 81 (13), 70 (81).

N-*Acetyl-azacineole (15)*

Azacineole (5) (50 mg, 0.326 mmol) was stored (16 h) with acetic anhydride (5 mL) and triethylamine (1 mL). Normal workup, including ether extraction and washing with sodium carbonate solution and with dilute aqueous acid, gave a residue which comprised >98% purity (by GCMS) the *N*-acetyl derivative (15). Flash chromatography (silica, diethyl ether/pentane, 50 : 50, R_F 0.3) gave analytically pure title compound (15) [2-acetyl-1,3,3-trimethyl-2-azabicyclo[2.2.2]octane] (38 mg, 0.195 mmol) as small colourless prisms, mp 74–75°C (Found: C, 73.7; H, 11.0; N, 7.0%. $C_{12}H_{21}NO$ requires C, 73.8; H, 10.8; N, 7.2%). ν_{max} (nujol)/cm^{-1} 1654, 1632, 1324, 1278, 1163, 1098, 1030, 723. δ_H 2.10 (3 H, s, H12), 2.01 (2 H, m), 1.89 (2 H, m), 1.52 (6 H, 2 × s, H9,10), 1.39 (3 H, s, H7), 1.50–1.38 (5 H, m). The spectrum was overlapped and second order, therefore no reliable coupling constants were available. δ_C 171.6 (C11), 59.1 and 54.5 (C1, C8), 40.1 (C4), 34.0 (C2, C6), 29.2 and 28.5 (C7, C12), 27.7 (C9, C10), 22.3 (C3, C5). Mass spectrum (GCMS) *m*/*z* 196 (5%, $[M + 1]^{+\bullet}$), 195 (37, $M^{+\bullet}$), 181 (6), 180 (51, $[M - CH_3]^{+\bullet}$), 166 (7), 153 (6), 152 (18, $[M - CH_3]^{+\bullet}$), 139 (10), 138 (100), 124 (21), 110 (26), 99 (8), 98 (8), 96 (8), 93 (8), 82 (13), 81 (9).

Acid Treatment of Aziridine (14)

Aziridine (14) (100 mg) was refluxed in glacial acetic acid (20 mL). After 1 h an aliquot was worked up by adding excess sodium carbonate solution followed by extraction into diethyl ether. Analysis of this aliquot showed starting aziridine (14) and acetate (16) (40 : 60 by GCMS). Further aliquots taken after additional periods of reflux showed increasing amounts of acetate (16). When these worked up aliquots were examined (GCMS) several days later the mixtures had reverted to aziridine (14) (100%).

Workup (sodium carbonate) of the acetic acid mixture followed by rapid extraction into cold dichloromethane gave an oil which was rapidly flash-chromatographed over silica using dichloromethane/methanol (87 : 13) as eluent. Aziridine (14) eluted first, followed by (1*S*,2*S*,4*R*)-1,8-azacineole-2-acetate (16) [(1*S*,4*R*,6*S*)-1,3,3-trimethyl-2-azabicyclo [2.2.2]octan-6-yl acetate] (30 mg), which was an unstable, colourless and viscous oil (Found: $M^{+\bullet}$, 211.1569. $C_{12}H_{21}NO_2$ requires $M^{+\bullet}$, 211.1572). ν_{max} (neat)/cm^{-1} 3314, 2965, 1736, 1654, 1560, 1458, 1371, 1244, 1169, 1066, 1027. δ_H 4.67 (1 H, ddd, $J_{2\beta,3\beta}$ 9.6, $J_{2\beta,3\alpha}$ 3.6, $J_{2\beta,6\beta}$ 2.0, H2β), 2.54 (1 H, dddd, $J_{3\alpha,3\beta}$ −15.0, $J_{3\beta,4}$ 3.6, $J_{3\beta,5\beta}$ 3.5, H3β), 2.02 (3 H, s, OAc), 1.93 (1 H, ddddd, $J_{5\alpha,5\beta}$ −14.0, $J_{5\beta,6\beta}$ ca. 12, $J_{5\beta,6\alpha}$ 5.3, $J_{4,5\beta}$ 4.0, H5β), 1.83 (1 H, ddd, $J_{6\alpha,6\beta}$ −13.4, $J_{5\alpha,6\alpha}$ 13.3, H6α), 1.52 (1 H, dddd, $J_{5\alpha,6\beta}$ 7.0, $J_{4,5\alpha}$ 3.0, H5α), 1.44 (1 H, dddd, H4), 1.25 (1 H, dddd, H6β), 1.22 (1 H, ddd, H3α), 1.26 and 1.21 (6 H, 2 × s, H9, H10), 1.01 (3 H, s, H 7). δ_C 170.5 (C11), 73.5 (C2), 52.8 and 52.0 (C1, C8), 34.6 (C4), 32.6 (C3), 29.8 and 29.7 (C9, C10), 25.5 (C6), 21.9 (C5), 23.6 and 21.2 (C7, C12). Mass spectrum (GCMS) *m*/*z* 213 (1%), 212 (7, $[M + 1]^{+\bullet}$), 211 (55, $M^{+\bullet}$), 197 (10), 196 (83, $[M - CH_3]^{+\bullet}$), 169 (29), 168 (78), 154 (6), 153 (8), 152 (73), 151 (10), 138 (8), 136 (33), 125 (32), 124 (62), 123 (10), 111 (10), 110 (100), 109 (13), 108 (44), 107 (19), 98 (16), 96 (23), 95 (26), 94 (17), 93 (22), 83 (27), 82 (33), 81 (13), 79 (19), 77 (15).

A further aliquot from the acetic acid reaction was worked up by addition to sodium hydroxide solution (5 M) and extraction into diethyl ether. Analysis showed aziridine (14) and alcohol (17) (15 : 85 by GCMS). After 2 h, a similar acetic acid reaction was added dropwise to a stirred sodium hydroxide solution (5 M, 100 mL). After 30 min, the solution was extracted with diethyl ether, the ether extract was washed with brine and dried over sodium sulfate. Analysis (GCMS) showed alcohol (17) (96%). The solvent was removed to give a crystalline solid (93 mg) which was sublimed (50°C/0.05 mmHg) to give (1*S*,2*S*,4*R*)-2-hydroxy-1,8-azacineole (17) [(1*S*,4*R*,6*S*)-1,3,3-trimethyl-2-azabicyclo[2.2.2]octan-6-ol] as colourless chunks, mp 108–110°C (Found: C, 70.8; H, 11.6; N, 8.0%. $C_{10}H_{19}NO$ requires C, 71.0; H, 11.3; N, 8.3%). ν_{max} (nujol)/cm^{-1} 3141 br, 1338, 1233, 1199, 1145, 1131, 1100, 1079, 1069, 1036, 989, 973, 925, 908, 802, 722. δ_H 3.57 (1 H, ddd, $J_{2\beta,3\beta}$ 9.6, $J_{2\beta,3\alpha}$ 3.7, $J_{2\beta,6\beta}$ 2.0, H2β), 2.44 (1 H, dddd, $J_{3\alpha,3\beta}$ −14.1, $J_{3\beta,4} = J_{3\beta,5\beta}$ 3.3, H3β), 1.91 (1 H, ddddd, $J_{5\alpha,5\beta}$ −14.0, $J_{5\beta,6\beta}$ 12.0, $J_{4,5\beta}$ 4.0, $J_{5\beta,6\alpha}$ 3.0, H5β), 1.83 (1 H, ddd, $J_{6\alpha,6\beta}$ −14.0, $J_{5\alpha,6\alpha}$ 11.5, H6α), 1.48 (1 H, dddd, $J_{5\alpha,6\beta}$ 7.0, $J_{4,5\alpha}$ 2.5, H5α), 1.39 (1 H, dddd (app. pentuplet), $J_{3\alpha,4}$ 3.0, H4), 1.30 (1 H, dddd, H6β), 1.25 (1 H, ddd, H3α), 1.18 and 1.09 (6 H, 2 × s, H9,10), 0.94 (3 H, s, H7); all couplings were supported by 2D spectra. δ_C 73.0 (C2), 52.2 and 51.3 (C1, C8), 35.1 (C4), 35.0 (C3), 30.9 and 30.8 (C9, C10), 25.7 (C6), 24.7 (C7), 22.5 (C5). Mass spectrum (GCMS) *m*/*z* 169 (20%, $M^{+\bullet}$), 155 (5), 154 (35), 152 (3), 138 (4), 136 (5), 125 (25), 124 (19), 111 (9), 110 (100), 108 (16), 107 (6), 98 (7), 97 (9), 96 (17), 95 (15), 94 (10), 93 (10), 91 (5), 83 (12), 82 (22), 81 (6), 80 (5), 79 (10), 77 (7), 70 (20).

Eucalyptus Leaf Extraction

Fresh eucalypt leaves (10 g) were finely cut with scissors into a round-bottomed flask. A mixture of acetone (40 mL) and hexane (40 mL) was added and the flask was sonicated (10 min). The mixture was then refluxed (4 h) and the solvent was decanted. The remaining leaf matter was subjected to a further round of sonication and reflux with a fresh portion of solvent. The combined extracts were taken to dryness and the green residue was weighed and taken into diethyl ether (140 mL), which was separated into two equal portions. The solvent was removed from one of the portions and the residue was taken up into ethyl acetate (2 mL) and centrifuged. The supernatant was filtered and analyzed by GCMS (total extract). The other portion was extracted with hydrochloric acid (0.4 M, 5 × 20 mL). The acid extracts were basified (dilute sodium hydroxide) and re-extracted back into ether. These ether extracts were dried, the solvent was removed, and the residue was taken up into ethyl acetate (2 mL) and centrifuged. The supernatant was filtered and analyzed by GCMS (acid extract). Standard terpenoid compounds[1] were observed, but no peaks corresponding to compound (5) were observed in either the total or acid extracts.

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