Studies Related to the Total Synthesis of Alkaloids in the Carpaine and Cassine Series. Part 6.† Total Synthesis of (±)-Azimic Acid ‡

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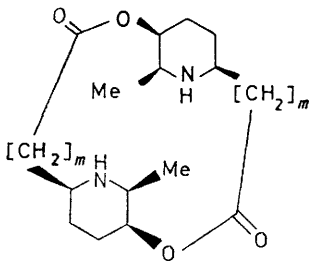
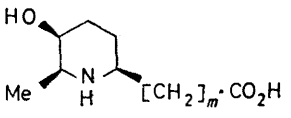
all-*cis*-6-(5-Hydroxy-6-methylpiperidin-2-yl)hexanoic acid [(±)-azimic acid] has been obtained in five steps from ethyl 7-methyl-3-oxo-oct-6-enoate.

AZIMINE (1a), an alkaloid extracted from the leaves of *Azima tetracantha* L.[1,2] can be considered as resulting from the double lactonization of azimic acid (2a). Azimine and azimic acid are analogues of carpaine (1b) and carpamic acid (2b), respectively. We report here a total synthesis of azimic acid.



(1) a ; m = 5
b ; m = 7

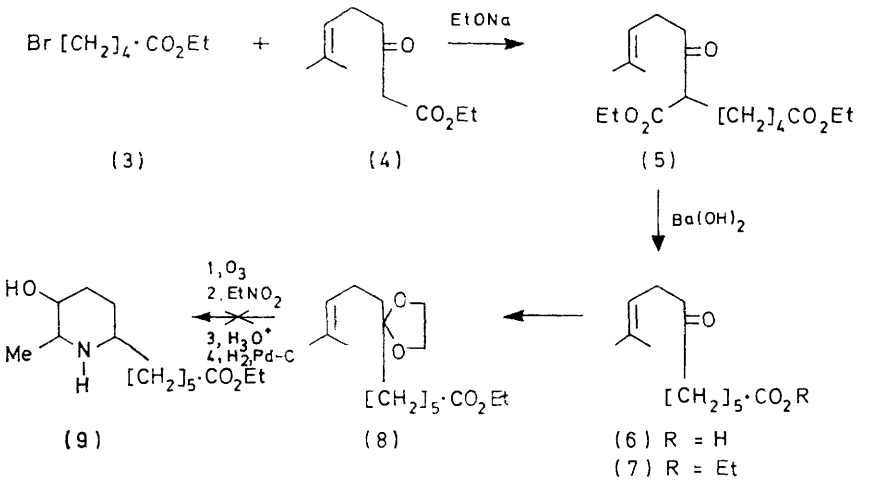


(2) a ; m = 5
b ; m = 7

We first investigated a route to ethyl azinate (9), following a general synthesis of 2,6-dialkylpiperidin-3-ols previously worked out in our laboratory with model compounds.[3,4] Ethyl 5-bromopentanoate (3), prepared in one stage from δ-valerolactone, was condensed with the β-oxo-ester (4) prepared through carboxylation of commercial 6-methylhept-5-en-2-one. The diester (5), obtained in quantitative yield, was treated in the crude state with aqueous barium hydroxide, and the acid (6) was isolated in crystalline state with an average yield of 60%. The ester (7) was obtained by the action of ethanol in benzene solution, in the presence of toluene-*p*-sulphonic acid. However it proved difficult to purify the derived acetal (8), and attempts to obtain ethyl azimate (9) from the crude product were unsuccessful.

Our second synthetic approach involved keeping the carboxy-function of compound (6) unprotected (in order to obtain crystalline intermediates), and also leaving the ketonic carbonyl group unprotected, expecting it not to participate in the reactions used. The acid (6) was treated with ozone in methanol and the ozonide was decomposed with aqueous sodium sulphite to give the aldehyde (10) (*ca.* 60%). This was condensed with nitroethane in ether in the presence of sodium ethoxide. Destruction of the sodium salt formed with acetic acid gave the β-nitro-alcohol (11), in high yield. The resulting mixture of *erythro*- and *threo*-isomers was subjected to catalytic hydrogenation (5% Pd–C) to afford a mixture of the epimeric piperidylhexanoic acids (2a) and (12), which was separated by preparative t.l.c.

5′-*epi*-Azimic acid (12), obtained in 35% yield, showed an axial C*H*OH signal in its n.m.r. spectrum (a broad multiplet). Since catalytic reduction of 2,6-dialkylpyridines is known to lead mainly to the corresponding *cis*-diequatorial piperidines,[5] the 5′-hydroxy-group must be *trans* with respect to the 2′- and 6′-substituents.



(3) (4) (5) (9) (8) (6) R = H (7) R = Et

† Part 5, E. Brown and A. Bourgouin, *Tetrahedron*, 1975, **31**, 1047.

‡ Preliminary report, E. Brown and R. Dhal, *Tetrahedron Letters*, 1974, 1029.

[1] G. J. H. Rall, T. M. Smalberger, and H. L. de Waal, *Tetrahedron Letters*, 1967, 3465.
[2] T. M. Smalberger, G. J. H. Rall, H. L. de Waal, and R. R. Arndt, *Tetrahedron*, 1968, **24**, 6417.
[3] E. Brown and R. Dhal, *Bull. Soc. chim. France*, 1972, 4292.
[4] E. Brown and R. Dhal, *Tetrahedron*, 1973, **29**, 455.
[5] M. Freifelder, R. M. Robinson, and G. R. Stone, *J. Org. Chem.*, 1962, **27**, 284.

(±)-Azimic acid (2a), obtained in 45% yield, showed a C*H*OH signal in its n.m.r. spectrum, with $W_{\frac{1}{2}}$ 5 Hz. According to Lyle,[6] this is only possible for an equatorial proton, which occurs only when the 2,6-dialkylpiperidin-3-ol is of the all-*cis*-pattern. *trans*-Alkyl groups in 2 and 6 positions could make ring inversion possible, resulting in a mixture of axial and equatorial C*H*OH forms for which a broader n.m.r. signal would be expected.

The all-*cis*-structure of compound (2a) was further confirmed by the i.r. spectrum (dilute CCl_4 solution) of (±)-methyl azimate. According to the work of Tichy and Sicher[7] and in conformity with our previous observations on various 2,6-dialkylpiperidin-3-ols,[8] such an all-*cis*-compound is not liable to ring inversion because of the presence of bulky equatorial 2- and 6-substituents.

(±)-carpamic acid (2b)[9] was achieved in our laboratory, by following the same reaction scheme. The ester hydrochloride corresponding to synthetic compound (2b) presented the same i.r. and mass spectra as natural methyl carpamate hydrochloride.

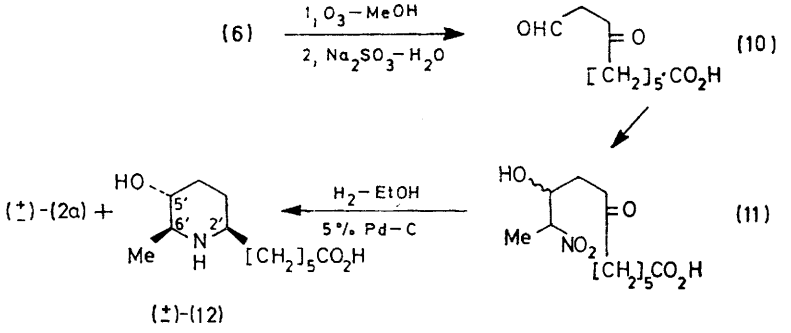
Attempts to bring about bis-lactonization of (±)-azimic acid (2a) by use of dicyclohexylcarbodi-imide, or by the method used by Narasimhan[10] to synthesize carpaine (1b) from carpamic acid (2b), have not yet been successful.

EXPERIMENTAL

Ethyl 5-Bromopentanoate (3).—Crude δ-valerolactone[11] (10 g, 0.1 mol), 62% hydrobromic acid (20 g, *ca.* 1.5 equiv.), ethanol (30 ml, *ca.* 6 equiv.), and benzene (100 ml) were refluxed with stirring, until elimination of the water formed (Dean–Stark head) was complete. After cooling, the solution was dried ($MgSO_4$) and evaporated and the residue (18.8 g) was distilled to give the bromide (3) (16 g, 78%), b.p. 105—106° at 12 mmHg.[12]

Diethyl 2-(5-Methylhex-4-enoyl)heptanedioate (5).—Schechter's method[13] was used. To a cooled solution of sodium (6.3 g, 0.273 mol) in anhydrous ethanol (135 ml) were added successively ethyl 7-methyl-3-oxo-oct-6-enoate (4) (54.2 g, 0.273 mol) in anhydrous ethanol (55 ml), ethyl 5-bromopentanoate (3) (57.1 g, 0.273 mol) in anhydrous ethanol (55 ml), and dry sodium iodide (2.7 g, 0.018 mol). The mixture was refluxed for 20 h with stirring. After cooling, the ethanol was evaporated off and the residue was treated with 0.5N-hydrochloric acid (60 ml) and extracted with ether. The extract was washed with water, dried ($MgSO_4$), and evaporated. The crude product, a yellow oil obtained in quantitative yield, was used without further purification. Molecular distillation gave a *sample*, b.p. 110—120° at 0.03 mmHg, $\nu_{max.}$ (film) 1 740 (ester CO), 1 720 (ketonic CO), and 1 640 cm^{-1} (C=C), δ(CCl_4) 5.0 (1 H, m), 4.15 and 4.05 (4 H, 2q), 3.3 (1 H, t), 2.0—2.5 (6 H), 1.6 (6 H), 1.4, and 1.25 and 1.20 (6 H, 2t) (Found: C, 66.3; H, 9.25; O, 24.3. $C_{18}H_{30}O_5$ requires C, 66.25; H, 9.25; O, 24.5%).

11-*Methyl*-7-*oxododec*-10-*enoic Acid* (6).—The procedure follows that reported[14] for the decarboxylation of β-oxo-esters. A stirred mixture of the diester (5) (27.2 g, 83.5 mmol) and a solution of barium hydroxide octahydrate



In the ester under consideration, the axial hydroxy-group can participate in hydrogen bonding with the electron pair of the ring nitrogen atom. In the i.r. spectrum of a dilute solution, this results in a broad band due to bonded OH and a narrower one due to the free OH, with $\varepsilon_{ass.}/\varepsilon_{free} > 1$, and Δν *ca.* 105 cm^{-1}. However in the case with the hydroxy-group equatorial, intramolecular bonding is impossible and the i.r. spectrum will show only a single band due to free OH. If the 2- and 6-substituents were *trans*, ring inversion would lead to a mixture of forms and the i.r. spectrum would then show two bands resulting from free and bonded OH with $\varepsilon_{ass.}/\varepsilon_{free} \leqslant 1$ and Δν *ca.* 80 cm^{-1}. A comparison of the i.r. spectra (dilute solutions in CCl_4) of synthetic (±)-methyl azimate, natural methyl azimate,[2] and natural methyl carpamate[7] is significant (see Table).

	ν_{OH}(free)/ cm^{-1}	ν_{OH}(bonded)/ cm^{-1}	Δν/ cm^{-1}	$\varepsilon_{ass.}/\varepsilon_{free}$
(±)-Methyl azimate	3 620	3 515	105	*ca.* 2.5
Methyl azimate	3 635	3 528	107	3.3
Methyl carpamate	3 628	3 522	106	3.6

Direct comparison of synthetic (±)-azimic acid (2a) with an authentic sample was not possible, because of the scarcity of azimine in nature, but in work parallel with the present investigation, the first total synthesis of

[6] R. E. Lyle, D. H. McMahon, W. E. Krueger, and C. K. Spicer, *J. Org. Chem.*, 1966, **31**, 4164.
[7] M. Tichy and J. Sicher, *Tetrahedron Letters*, 1962, 511.
[8] E. Brown and R. Dhal, *Tetrahedron*, 1972, **28**, 5607.
[9] E. Brown and A. Bourgouin, *Chem. Letters*, 1974, 109.
[10] N. S. Narasimhan, *Chem. and Ind.*, 1956, 1526.
[11] P. S. Starger and B. Phillips, *J. Amer. Chem. Soc.*, 1958, **80**, 4079.
[12] N. J. Leonard and W. E. Goode, *J. Amer. Chem. Soc.*, 1950, **72**, 5404.
[13] M. S. Schechter, N. Green, and F. B. Laforgue, *J. Amer. Chem. Soc.*, 1949, **71**, 3165.
[14] H. B. Wood, jun. and E. C. Horning, *J. Amer. Chem. Soc.*, 1953, **75**, 5511.

(40 g, 0.125 mol) in water (400 ml) was refluxed overnight. After cooling, the solution was acidified by slow addition of 6N-hydrochloric acid (50 ml) and then stirred until the barium salts formed had completely dissolved. The mixture was extracted with ether (4 × 100 ml) and the extracts were dried ($MgSO_4$) and evaporated. The semi-crystalline product (17.8 g, 94%) was treated with boiling pentane and the solution obtained was cooled in ice to give the crystalline *acid* (6) (12.5 g, 66%), m.p. 40—40.5° (from heptane), sufficiently pure for the following reactions; $\nu_{max.}$ (Nujol) 2 500—3 300br (acid OH), 1 720 (ketonic CO), and 1 700 cm^{-1} (acid CO), $\delta(CDCl_3)$ 11.0 (1 H), 5.05 (1 H, m), 2.35 (8 H), 1.65 (6 H, d), and 1.45 (6 H, m) (Found: C, 69.25; H, 9.65; O, 21.15. $C_{13}H_{22}O_3$ requires C, 69.0; H, 9.8; O, 21.2%).

Ethyl 11-*Methyl*-7-*oxododec*-10-*enoate* (7).—A stirred mixture of the acid (6) (9.25 g, 0.041 mol), absolute ethanol (19 g), and toluene-*p*-sulphonic acid (0.9 g, 0.1 equiv.) in dry benzene (200 ml) was refluxed until elimination of the water formed (Dean–Stark head) was complete. After cooling, the solution was washed with saturated aqueous sodium hydrogen carbonate, then water, dried ($MgSO_4$), and concentrated. The orange-yellow residue was treated with light petroleum and the solution obtained was filtered through basic alumina. Evaporation gave the *ester* (7) in 94% yield (9.8 g); it was homogeneous (t.l.c.) and could be distilled (b.p. 120—125° at 0.05 mmHg) but with a loss of 50%. Therefore it was purified by molecular distillation (105° and 0.1 mmHg) for analysis; $\nu_{max.}$ (film) 1 740 (ester CO), and 1 720 cm^{-1} (ketonic CO), $\delta(CCl_4)$ 5.05 (m), 4.05 (q), 2.10—2.50, 1.65 (d), 1.20—1.70, and 1.20 (t) (Found: C, 70.85; H, 10.05; O, 18.9. $C_{15}H_{26}O_3$ requires C, 70.85; H, 10.3; O, 18.85%).

Ethyl 11-*Methyl*-7-*oxododec*-10-*enoate Ethylene Acetal* (8).—The reaction was carried out according to the method of Salmy.[15] A stirred mixture of the ester (7) (7.8 g, 30.7 mmol) in distilled hexane (160 ml), toluene-*p*-sulphonic acid (0.4 g), and ethylene glycol (2.85 g, 1.5 equiv.) was refluxed overnight. The organic phase was washed successively with saturated aqueous sodium hydrogen carbonate and water, dried ($MgSO_4$), and evaporated. The crude *product* (8) (8.3 g, 91%) was contaminated with a scarcely separable by-product detected by t.l.c. A sample purified by molecular distillation (120° and 0.05 mmHg) showed $\nu_{max.}$ (film) 1 740 (ester CO), 1 050, and 950 cm^{-1} (C–O), $\delta(CCl_4)$ 5.1, 4.05 (q), 3.85 (s), 2.40—2.10, 1.60 (d), 2.0—1.20, and 1.20 (t) (Found: C, 68.8; H, 9.95; O, 21.55. $C_{17}H_{30}O_4$ requires C, 68.4; H, 10.15; O, 21.45%).

7,10-*Dioxodecanoic Acid* (10).—The acid (6) (2 g, 8.85 mmol) in dry methanol (150 ml) was treated with ozone in the presence of pyridine (1 ml, *ca.* 1.5 equiv.) at −60 °C (solid CO_2–acetone bath) until a characteristic blue colour appeared. The residual ozone was driven out with an oxygen stream (5 min). To the cold solution was added sodium sulphite (1.4 g, 1.2 equiv.) in water (7 ml); after stirring overnight the peroxide test was negative. After filtration, the solution was concentrated. The residue was treated with water (10 ml), brought to pH 4—5 with N-hydrochloric acid, and extracted with chloroform (3 × 20 ml). The organic phase was washed with distilled water, dried ($MgSO_4$), and evaporated, leaving a semicrystalline product (1.44 g, 81%). Recrystallization from hexane–ether gave the *aldehyde* (10) (1.10 g, 62%) of acceptable purity but with an ill-defined m.p. 40—50°, $\nu_{max.}$ (Nujol) 3 300—2 500br (acid OH), 2 750w (aldehyde CH), and 1 700s cm^{-1} (CO), $\delta(CDCl_3)$ 10.35 (1 H), 9.90 (1 H), 2.75 (4 H, s), 2.70—2.20 (4 H, m), and 1.90—1.30 (6 H) (Found: C, 60.2; H, 8.15; O, 32.05. $C_{10}H_{16}O_4$ requires C, 60.0; H, 8.05; O, 31.95%).

10-*Hydroxy*-11-*nitro*-7-*oxododecanoic Acid* (11) (erythro-*and* threo-*Isomers*).—The procedure follows that given in reference 16. To a solution of sodium (0.30 g, 13 mmol), anhydrous ethanol (3 ml), and dry ether (30 ml) was added, with stirring, a solution of nitroethane (1.22 g, 163 mmol) in dry ether (50 ml), followed slowly by the acid (10) (1.30 g, 6.5 mmol) in dry ether (15 ml). The mixture was then stirred overnight, and the sodium salt was destroyed by addition of acetic acid (0.975 g, 16.3 mmol) in water (2.5 ml) (complete disappearance of the precipitate). After further addition of water (10 ml), the ethereal layer was separated and the residual aqueous layer was saturated with sodium chloride and extracted with ether. The combined extracts were washed with saturated brine, dried ($MgSO_4$), and evaporated. The crude product (1.47 g, 82%), a viscous yellow liquid, was dissolved in ether and treated dropwise with hexane until cloudiness appeared. Overnight at 0 °C the solution deposited the *nitro-acid* (11) (0.41 g, 23%), which was recrystallized from ether–hexane; m.p. 81—84°, $\nu_{max.}$ (Nujol) 3 480 (strong and sharp) (alcohol OH), 3 300—2 500br (acid OH), 1 700s (CO), and 1 550s cm^{-1} (NO_2), $\delta(CDCl_3)$ 6.95, 4.55 (m), 3.95 (m), 2.90—2.20 (m), 2.30—1.10, and 1.55 (d) (Found: C, 52.35; H, 7.55; N, 5.05; O, 34.55. $C_{12}H_{21}NO_6$ requires C, 52.35; H, 7.7; N, 5.1; O, 34.85%).

(±)-*Azimic Acid* (2a) *and* (±)-5′-epi-*Azimic Acid* (12).—The recrystallized mixture of nitro-acids (11) (0.536 g, 1.95 mmol) in redistilled 95% ethanol (20 ml) containing 5% palladium–charcoal (0.2 g) was hydrogenated at 3 atm overnight at room temperature. Filtration and evaporation gave the crude product (400 mg, 90% in the most favourable cases). In most cases the product was a viscous oil which crystallized on trituration at *ca.* 40 °C in acetone–methanol. After recrystallization from acetone–ethanol, the mixture of *acids* (2a) and (12) melted at 210—212 °C (decomp.). T.l.c. [neutral silica (Merck); EtOH–NH_4OH (15N) (9 : 1 v/v)] showed two components, R_F 0.30 and 0.42; $\nu_{max.}$ (Nujol) 3 340 (alcohol OH), 2 800—2 200 (NH_2^+ str.), and 1 650 and 1 550 cm^{-1} (CO_2^- and NH_2^+) (Found: C, 63.1; H, 9.9; N, 6.0; O, 21.0. $C_{12}H_{23}NO_3$ requires C, 62.85; H, 10.1; N, 6.1; O, 20.95%).

The mixture of isomers (2a) and (12) (200 mg) was separated by preparative t.l.c. on Merck silica gel [four elutions with CH_2Cl_2–EtOH–NH_4OH (15N) (5 : 9 : 1 v/v)]. The appropriate bands (R_F *ca.* 0.60 and *ca.* 0.45) were extracted with methanol–15N-ammonia (9 : 1 v/v). The respective extracts were concentrated and the residues treated with methanol. Filtration and evaporation afforded the products (12) (70 mg; R_F *ca.* 0.60) and (2a) (90 mg; R_F *ca.* 0.45). (±)-5′-epi-*Azimic acid* (12) had m.p. 223—225° (decomp.) (from EtOH–Me_2CO), $\nu_{max.}$ (Nujol) 3 400 (alcohol OH), 2 700—2 200 (NH_2^+ str.), and 1 625 and 1 540 cm^{-1} (CO_2^- and NH_2^+), $\delta(D_2O)$ 3.50br (H-5′), 3.30—2.80 (m, H-2′ and 6′), 2.10 ($CH_2{\cdot}CO_2^-$), and 1.35 (d, 6′-Me). (±)-*Azimic acid* (2a) had m.p. 217—220° (decomp.) (from EtOH), $\nu_{max.}$ (Nujol) 2 800—2 200 (NH_2^+ str.) and 1 650 and 1 550 cm^{-1} (CO_2^- and NH_2^+), $\delta(D_2O)$ 3.90 ($W_{\frac{1}{2}}$ 5 Hz,

[15] E. Salmy, *Ber.*, 1936, **71**, 1803.
[16] H. J. Dauben, jun., H. J. Ringold, R. H. Wade, D. L. Pearson, and A. G. Anderson, jun., *Org. Synth.*, Coll. Vol. IV, 1963, p. 221.

H-5′), 3.5—2.8 (m, H-2′ and -6′), 2.05 ($CH_2 \cdot CO_2^-$), and 1.20 (d, 6′-Me).

Methyl (±)-*Azimate*.—The procedure was modelled on that used by Govindachari.[17]

(±)-Azimic acid (2a) (50 mg, 0.218 mmol) was added to anhydrous methanol (20 ml) previously saturated with dry hydrogen chloride. After 48 h at 0 °C the methanol was evaporated off and the residue, after drying under vacuum overnight, was treated hot with dry methanol (0.5 ml) and ether (1 ml). The solution was left overnight at room temperature to give (±)-*methyl azimate hydrochloride* (58 mg, 95%), m.p. 153—155° (lit.,[2] 164° for the optically active ester derived from the natural product), $\nu_{max.}$ (Nujol) 3 320 (OH), 1 735 (ester CO), and 1 560 and 1 540 cm^{-1} (NH_2^+), δ(D_2O) 3.90 ($W_{\frac{1}{2}}$ 5 Hz), 3.60 (s), 3.25 (m), 2.30, and 1.25 (d). The free base was obtained by shaking for 30 min a solution of the hydrochloride (45 mg, 0.161 mmol) in water (3 ml) in the presence of an excess of sodium carbonate. The aqueous phase was extracted with dichloromethane (5 × 3 ml) and, after decantation, the organic phase was drawn off with a pipette, dried ($MgSO_4$), centrifuged, and evaporated, leaving *methyl* (±)-*azimate*, a light yellow oil (29 mg, 74%), pure enough to be studied by i.r. spectroscopy (dilute CCl_4 solution).

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[17] T. R. Govindachari and N. S. Narasimhan, *J. Chem. Soc.*, 1955, 1563.