Preparation of the 15,6α-Lactone from 8β,13βH-Tetrahydroabietic Acid

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Photolysis of the amide (2) of the title acid in the presence of lead tetra-acetate and iodine gave 8β,13βH-tetrahydroabietan-15-yl isocyanate (3) and a compound identified as 8β,13βH-tetrahydroabietane-15,6α-carbolactone (11).

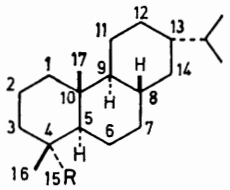
An *Alcaligenes* sp. capable of utilising abietic acid as its sole carbon source, when grown in the presence of abietic acid, produced *inter alia* a minor transformation product, $C_{20}H_{28}O_3$.[1] The latter, on the basis of the spectroscopic information then available, was tentatively assigned an epoxy-γ-lactone structure,[1] but lack of material prevented verification. Attempts to produce more of this transformation product were unsuccessful; however it seemed possible that the preparation of lactones derived from abietic acid derivatives might aid the elucidation of its structure.

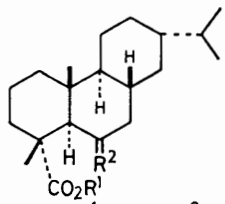
Barton's photolysis of *N*-iodoamides, which are generated *in situ* from the amide in the presence of lead tetra-acetate and iodine, provides a convenient route from carboxylic acids to the corresponding γ- and δ-lactones,[2] although the yields are often poor. It has been used to prepare a number of lactones[3] from diterpenoid acids in which the original carboxy-group was axial. In the photolysis of 16-carboxamides the formation of δ-lactones is usually favoured, by functionalisation of the 1,3-diaxially disposed 17-methyl group.[3]

RESULTS AND DISCUSSION

The photolysis of abietic acid leads to complex mixtures derived from the conjugated diene system;[4] consequently 8β,13βH-tetrahydroabietic acid (1) was chosen as a suitable and readily available starting material (*cf.* ref. 5). The photolysis of the amide derived from this acid is of additional interest since, unlike those acids described in ref. 3, it possesses an equatorial carboxy-function. However Drieding models show that photolysis of this amide could yield 15,1α-δ- or 15,2α-γ-lactones (with ring *A* in boat conformations) and/or 15,6α- or 15,6β-γ-lactones; in the latter ring *B* must adopt a boat conformation.

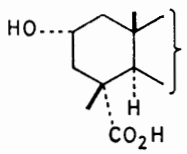
The amide (2) was irradiated in the presence of lead tetra-acetate and iodine, but, in contrast to the literature method,[2] an attempt was made to purify the neutral product by chromatography. The only identifiable compound was the isocyanate (3), $\nu_{max.}$ 2 250 cm^{-1}. Later fractions from the column showed i.r. bands at 1 780 and 1 740 cm^{-1}, but p.l.c. failed to yield pure lactones. Consequently the photolysis was repeated and the product worked-up by the usual base hydrolysis.[2,3] Acidification gave a hydroxy-acid, $C_{20}H_{34}O_3$, whose n.m.r. spectrum clearly distinguished structure (5) from the other possibilities (9) and (10). A one-proton signal at τ 6.02 (in pyridine) revealed the presence of >C*H*OH which, from the half-height width (17 Hz) of the resonance, possesses an equatorial proton as in structures (5) and (10), but not in structure (9). However a doublet at τ 7.52 (*J* 11 Hz) must be assigned to the 5-proton diaxially coupled to the 6β-proton in structure (5). This was confirmed when irradiation at the frequency of the signal at τ 6.02 caused the resonance at τ 7.52 to collapse to a singlet.



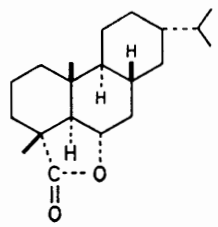


R	
(1)	CO_2H
(2)	$CONH_2$
(3)	NCO
(4)	CN

	R^1	R^2
(5)	H	α-OH, β-H
(6)	Me	α-OH, β-H
(7)	Me	O
(8)	H	O
(9)	H	α-H, β-OH



(10)



(11)

Acid-catalysed cyclisation of the hydroxy-acid (5) gave the γ-lactone (11), $\nu_{max.}$ 1 770 cm^{-1}, whose n.m.r. spectrum showed the 6β-proton resonance with a half-height width of 15.5 Hz, in agreement with its axial orientation, whereas cyclisation of the hydroxy-acid (10) would yield a lactone in which the 2β-hydrogen would be equatorial, since ring *A* must assume a boat conformation in this lactone. Hence structure (11) for the lactone was confirmed. The n.m.r. spectrum of the oxo-ester (7), prepared by oxidation of the methyl ester (6) with Jones reagent, contained a singlet at τ 7.09 attributable to the 5-proton, thus providing further evidence for structure (5) for the hydroxy-acid.

Reduction of the oxo-acid (8) with sodium borohydride unexpectedly gave mainly the 6α-hydroxy-acid (5)

(identical with the sample described above). The n.m.r. spectrum of the mother-liquors from the hydroxy-acid (5) revealed a resonance at τ 6.36 (m, $W_{\frac{1}{2}}$ 8 Hz) which was assigned to the 6α-H in the epimeric hydroxy-acid (9). The reduction may take place mainly from the apparently more-hindered β-face, because complex formation between the free carboxy-group and borohydride could block approach to the α-face of the molecule.

The poor yield of the γ-lactone (11) (*ca.* 20%) led to the abandonment of this approach to the structure of the epoxy-lactone.

EXPERIMENTAL

Details of chromatographic materials and conditions used for the determination of physical data *etc.*, have been reported.[5] Light petroleum had b.p. 60—80 °C.

Preparation of 8β,13βH-*Tetrahydroabietamide*.—Tetrahydroabietic acid (1) (5 g) (shown to contain 19% of its 13-epimer by g.l.c.) in dry benzene (12 ml) and dimethylformamide (3 drops) was treated with thionyl chloride (15 g) and the solution was refluxed for 2 h. The solvents were removed *in vacuo* to give the acid chloride as a gum (5.34 g), $\nu_{max.}$ 1 786 cm^{-1}.

Ammonia was bubbled through a solution of the acid chloride in dry benzene (30 ml) for 2 h. The solvent was removed *in vacuo*, the residue was added to water, and the products were recovered in ethyl acetate and chromatographed on silica gel (50 g). Elution with ethyl acetate–light petroleum (1 : 49) afforded 8β,13βH-*tetrahydroabietonitrile* (4bα,7βH,8aβ,10aα-*tetradecahydro*-1β,4aβ-*dimethyl*-7-*isopropylphenanthrene*-1α-*carbonitrile*) (4) as a pungent yellow oil (780 mg) which crystallised (Found: *m/z*, 287.2602. $C_{20}H_{33}N$ requires *M*, 287.2613); $\nu_{max.}$ (film) 2 213 cm^{-1}; τ 9.20 (3 H, s, 10-Me), 9.16 (6 H, d, *J* 6 Hz, CH*Me*$_2$), and 8.70 (3 H, s, 4-Me).

Further elution with ethyl acetate–light petroleum (1 : 49 and 1 : 9) gave starting material (700 mg) followed by 8β,13βH-*tetrahydroabietamide* (2) (3.02 g), which crystallised from ethyl acetate–light petroleum as felted needles, m.p. 198—198.5 °C (Found: C, 78.95; H, 11.3; N, 4.35%; *m/z*, 305. $C_{20}H_{35}NO$ requires C, 78.6; H, 11.55; N, 4.6%; *M*, 305); $\nu_{max.}$ 3 440, 3 340, 3 285, 1 681, and 1 628 cm^{-1}; τ 9.18 (6 H, d, *J* 6 Hz, CH*Me*$_2$), 9.15 (3 H, s, 10-Me), and 8.81 (3 H, s, 4-Me).

Photolysis of the Tetrahydroabietamide (2).—(a) *Attempted purification by chromatography*. Iodine (2.6 g) and lead tetra-acetate (5.2 g) were added to the amide (1 g) in dry benzene (200 ml) and the solution was irradiated with nitrogen agitation for 6 h at room temperature in an Engelhard Hanovia Photochemical Reactor, using a 125 W medium-pressure arc tube in a water-cooled quartz cell. The solution was filtered, the benzene was removed *in vacuo*, and the residue was extracted with ether. The extracts were washed with water, sodium sulphite solution, water, sodium hydroxide solution, dilute hydrochloric acid, and finally water. Recovery gave a semi-solid neutral fraction (1 g) which was chromatographed on Kieselgel (300 g).

Elution with chloroform–light petroleum (2 : 1) afforded a gum (75 mg) which sublimed at 110 °C (bath) and 0.02 mmHg to yield the crude isocyanate which partially crystallised. It was recrystallised from ethyl acetate–light petroleum to give 8β,13βH-*tetrahydroabietan*-15-*yl isocyanate* (4bα,7βH,8aβ,10aα-*tetradecahydro*-1β,4aβ-*dimethyl*-7-*isopropylphenanthren*-1α-*yl isocyanate*) (3) as needles, m.p. 168—172 °C (decomp.) (Found: *m/z*, 303.2551. $C_{20}H_{33}NO$ requires *M*, 303.2562); $\nu_{max.}$ 2 250 cm^{-1}.

Continued elution with chloroform–light petroleum (2 : 1) afforded a gum (239 mg) shown by i.r. spectroscopy ($\nu_{max.}$ 1 780 and 1 740 cm^{-1}) to contain both γ- and δ-lactones. However, attempts at further purification (p.l.c.) were unsuccessful.

Finally, elution with ethyl acetate–light petroleum (1 : 1) gave starting amide (439 mg).

(b) *Isolation of lactonic products using base hydrolysis*. The amide (2.0 g) was irradiated in benzene (150 ml) with iodine (5 g) and lead tetra-acetate (9.6 g) in a water-cooled Pyrex cell at 32 °C for 6 h with agitation by nitrogen bubbles and using the same lamp as in (a). Work-up as described in (a) afforded an oil (2.37 g), $\nu_{max.}$ 2 250 cm^{-1} (isocyanate) and a very broad C=O band centred at $\nu_{max.}$ 1 725 cm^{-1} (possibly lactones).

The oil in ethanol (60 ml) was heated under reflux with potassium hydroxide (3.7 g) and water (15 ml) for 2 h. The ethanol was removed *in vacuo*, and the residue was diluted with water. Recovery of the products in ethyl acetate afforded a neutral fraction (1.74 g).

The aqueous layer was acidified with dilute sulphuric acid and the precipitate (46 mg) was collected by filtration. The filtrate was extracted with ethyl acetate to yield more solid (53 mg). The two samples were combined and crystallized from ethyl acetate as fine needles of 6α-*hydroxy*-8β-13βH-*tetrahydroabietic acid* (5), m.p. 218—219 °C (Found: C, 70.4; H, 10.65. $C_{20}H_{34}O_3 \cdot C_2H_5OCOCH_3$ requires C, 70.2; H, 10.3%). Heating the needles *in vacuo* at 100 °C for 7 days, gave solvent-free material (78 mg), m.p. 219—220 °C (Found: C, 74.45; H, 10.65%; *m/z*, 322.2517. $C_{20}H_{34}O_3$ requires C, 74.5; H, 10.6%; *M*, 322.2508), $\nu_{max.}$ 3 375, 2 720, 1 702, and 1 688 cm^{-1}; τ (90 MHz in [$^2H_5$]-pyridine) 9.16 (6 H, d, *J* 7 Hz, CH*Me*$_2$), 9.10 (3 H, s, 10-Me), 8.29 (3 H, s, 4-Me), 7.52 (1 H, d, *J* 11 Hz, 5-H), 6.02 (1 H, m, $W_{\frac{1}{2}}$ 17 Hz, 6-H); *m/z* 322, 304, and 245. Irradiation at the frequency of the signal at τ 6.02 caused the doublet at τ 7.52 to collapse to a singlet.

Its *methyl ester* (6), prepared in the normal manner with diazomethane, was an oil (Found: *m/z*, 336.2658. $C_{21}H_{36}O_4$ requires *M*, 336.2664); $\nu_{max.}$ (film) 3 500 and 1 715br cm^{-1}; τ (90 MHz) 9.19 (6 H, d, *J* 7 Hz, CH*Me*$_2$), 9.18 (3 H, s, 10-Me), 8.71 (3 H, s, 4-Me), 8.07 (1 H, d, *J* 11 Hz, 5-H), 6.40 (3 H, s, OMe), and 6.35 (1 H, m, $W_{\frac{1}{2}}$ 16.5 Hz, 6-H); τ ([$^2H_5$]pyridine) 9.15 (6 H, d, *J* 7 Hz, CH*Me*$_2$), 9.14 (3 H, s, 10-Me), 8.37 (3 H, s, 4-Me), 7.70 (1 H, d, *J* 11 Hz, 5-H), 6.29 (3 H, s, OMe), and 6.05 (1 H, m, 6-H).

The neutral fraction from the photolysis reaction was chromatographed on Kieselgel (300 g); elution with methanol–chloroform (1 : 19) afforded a gum (469 mg) believed to be a δ-lactone, $\nu_{max.}$ 1 720 cm^{-1}. However attempts to isolate the pure lactone by p.l.c. failed. Further elution of the column with the same solvent system gave intractable mixtures. Elution with methanol–chloroform (1 : 9) furnished the hydroxy-acid (106 mg), identical (i.r. spectrum) with the sample described above.

Lactonization of the Hydroxy-acid (5).—The hydroxy-acid (29 mg) was added to toluene-*p*-sulphonyl chloride (12 mg) in benzene (15 ml) and the mixture was heated under reflux for 1 h in an atmosphere of nitrogen (*cf.* ref. 6). The benzene was removed *in vacuo* and the residue was extracted with ethyl acetate. The organic layer was washed with sodium hydrogen carbonate solution and water and dried.

Recovery afforded a gum (31 mg) which was purified by sublimation at 60 °C (bath) and 6×10^{-4} mmHg to yield 8β,13βH-*tetrahydroabietane*-15,6α-*carbolactone* (4bα,7βH,8aβ,10aα-*tetradecahydro*-1β,4aβ-*dimethyl*-7-*isopropylphenanthrene*-1α,10α-*carbolactone*) (11) as a semi-solid (Found: C, 79.0; H, 10.65%. $C_{20}H_{32}O_2$ requires C, 78.9; H, 10.6%); $\nu_{max.}$ ($CHCl_3$) 1 770 cm^{-1}; τ (90 MHz) 9.15 (6 H, d, *J* 7 Hz, $CHMe_2$), 9.13 (3 H, s, 10-Me), 8.78 (3 H, s, 4-Me), and 5.72 (1 H, m, $W_{\frac{1}{2}}$ 15.5 Hz, 6-H).

Preparation of the Oxo-acid (8).—The hydroxy-acid (5) (52 mg) in acetone (50 ml) was treated with an excess of Jones reagent, added in portions over 1 h, at room temperature and left for 2.5 h. Work-up in the usual manner gave 6-*oxo*-8β,13βH-*tetrahydroabietic acid* (8) (52 mg), which crystallised from ethyl acetate–light petroleum as prisms, m.p. 172—173 °C (Found: C, 74.95; H, 10.2%; *m/z*, 320. $C_{20}H_{32}O_3$ requires C, 75.0; H, 10.1%; *M*, 320); $\nu_{max.}$ 2 660 and 1 705br cm^{-1}; $\nu_{max.}$ (film) 2 660, 1 710, and 1 700 cm^{-1}; τ (90 MHz in [$^2H_5$]pyridine) 9.18 (3 H, s, 10-Me), 9.15 (6 H, d, *J* 7 Hz, $CHMe_2$), 8.11 (3 H, s, 4-Me), 7.75 (m, 7-H_2), and 6.75 (1 H, s, 5-H).

Its *methyl ester* (7), prepared by oxidation of the hydroxy-ester (6) in acetone with an excess of Jones reagent as in the previous experiment, was an oil (Found: *m/z*, 334.2492. $C_{21}H_{34}O_3$ requires *M*, 334.2508); $\nu_{max.}$ ($CHCl_3$) 1 725 and 1 710 cm^{-1}; τ (90 MHz) 9.20 (3 H, s, 10-Me), 9.16 (6 H, d, *J* 6 Hz, $CHMe_2$), 8.52 (3 H, s, 4-Me), 7.09 (1 H, s, 5-H), and 6.40 (3 H, s, OMe).

Reduction of the Oxo-acid (8).—Sodium borohydride was added to the oxo-acid (28 mg) in ethanol (10 ml) at 0 °C and the solution was left at room temperature for 18 h. The ethanol was removed *in vacuo*, and the products were recovered in ethyl acetate and crystallised from ethyl acetate to give the solvate of the hydroxy-acid (5), m.p. 218—219 °C, identical (i.r. spectrum) with the sample described above.

The mother liquors from the crystallisation were evaporated and the residue (81 mg) was purified by p.l.c. Development with ethanol–benzene–formic acid (11 : 88 : 1) gave a major band shown by n.m.r. spectroscopy to be a mixture of hydroxy-acids, epimeric at C-6, τ (90 MHz in [$^2H_5$]-pyridine) 9.12 (d, *J* 6.5 Hz, $CHMe_2$), 9.09 (s, 10-Me), 8.26 (s, 4-Me), 7.51 (d, *J* 11 Hz, 5-H), 6.36 [m, $W_{\frac{1}{2}}$ 8 Hz, 6α-H in (9)], and 6.00 [m, $W_{\frac{1}{2}}$ 16 Hz, 6β-H in (5)].

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