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The Chemistry of the Natural Order Cupressales

XXXIII *. The Structure of Procerin

JARL RUNEBERG

Organisk-kemiska Institutionen, Kungl. Tekniska Högskolan, Stockholm, Sweden

A new C_{15}-tropolone, procerin, has been isolated from *Juniperus procera* Hochst. The structure of procerin was shown to be I by catalytic hydrogenation of procerin to nootkatin (III) and by cleavage of procerin glycol (II) to yield acetone. The proton magnetic resonance spectra of procerin and nootkatin are discussed.

The tropolones commonly found in the heartwoods of species of the natural order Cupressales, are nootkatin and α-, β- and γ-thujaplicin [1]. Recently, however, a number of new tropolones have been found including β-thujaplicinol (7-hydroxy-4-*iso*propyltropolone) isolated by Gardner [2] from western red cedar (*Thuja plicata*) and β-dolabrin (4-*iso*propenyltropolone) isolated by Nozoe and coworkers [3] from the japanese Hiba tree (*Thujopsis dolabrata*). Both of these compounds have since been found in other species of the Cupressales [4,5]. A methoxy thujaplicin, pygmaein, has been reported by Zavarin [6] to occur in *Cupressus pygmaea* and some related species.

As described in the present series of papers [7] (*cf.* Ref.[4]), the heartwoods of several junipers also contain nootkatin and thujaplicins. *Juniperus procera* Hochst., however, yielded a new C_{15}-tropolone which will be described in this paper. Other constituents of *J. procera* will be dealt with in a forthcoming publication.

Extraction of the light petroleum-soluble part of the acetone extract of *J. procera* with sodium carbonate, gave a partly crystalline product from which a compound, $C_{15}H_{18}O_2$, m.p. 71–72°, was obtained. It gave a chloroform-soluble copper salt and was evidently a tropolone as shown by its ultraviolet spectrum which was identical with that of nootkatin [8](III). It had almost the same R_F value as nootkatin [9] but its colour reaction with *bis*-diazotised benzidine was darker brown. The name procerin is proposed for this tropolone.

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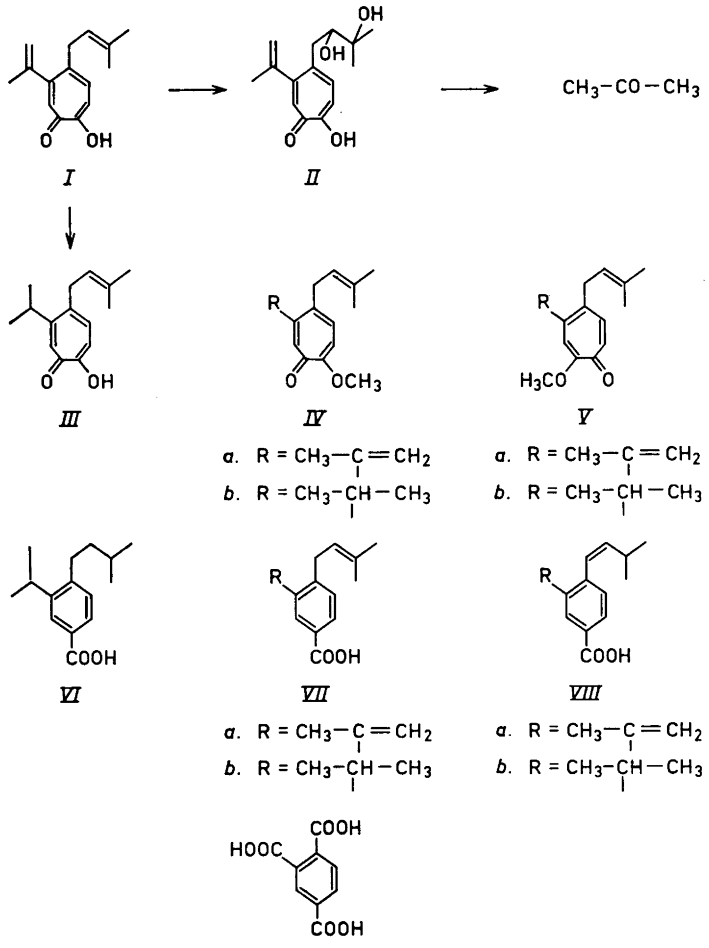

Fig. 1

Its infrared spectrum (*cf.* Fig 2) indicated that procerin differed from nootkatin in having an *iso*propenyl instead of an *iso*propyl group. On catalytic hydrogenation of procerin one mole of hydrogen was consumed and nootkatin (III) was obtained. The possibility of a diene system in the C_5-side chain undergoing 1,4-hydrogenation is very unlikely in view of the ultraviolet and infrared absorbtion of procerin.

During an attempt to determine the position of the side chain double bonds, procerin was treated with hydrogen peroxide in formic acid. Only one of the double bonds was attacked. The glycol monoformate obtained was readily hydrolysed to the corresponding glycol (II) which on treatment with periodic acid gave acetone in good yield. This proves the presence of an *iso*propylidene grouping in procerin and thus definitely eliminates the possibility that both

the double bonds are in the C_5-side chain. It follows that procerin must have the structure I.

Being unsymmetrically substituted, procerin on methylation gave two isomeric methyl ethers (IVa and Va). They could be separated into a crystalline and a liquid isomer. Both ethers on rearrangement with sodium methoxide [10] in methanol gave a mixture of the same two acids, the liquid isomer giving a much higher yield.

Oxidation of the acid mixture with dilute nitric acid afforded trimellitic acid (IX).

On catalytic hydrogenation the acid mixture absorbed two moles of hydrogen giving a single product, 4-*iso*pentyl-3-*iso*propyl-benzoic acid (VI) similarly obtained from nootkatin [10] (III).

The identity of the ultraviolet spectra of procerin and nootkatin appeared rather surprising in view of the distinct differences between the spectra of β-dolabrin [3] and β-thujaplicin (*cf.* Ref.[12]) which clearly indicate the effect of conjugation of the side chain double bond with the tropolone ring. A model of the procerin molecule shows, however, that the steric hindrance of the neighbouring *iso*pentenyl group forces the double bond of the *iso*propenyl group out of the plane of the tropolone ring, thus inhibiting conjugation. This is probably why only the C_5-side chain double bond reacted with performic acid.

A comparison of the proton magnetic resonance spectra of procerin and nootkatin indicated the presence in procerin of two protons of a $>C=CH_2$ group and the methyl protons of an *iso*propenyl group. Altogether three olefinic and three "aromatic" protons appeared to be present in this compound. The results are in full agreement with the proposed structure for procerin.

EXPERIMENTAL

Melting points were taken on a hot stage; melting and boiling points are uncorrected. Light petroleum refers to the fraction b.p. 40–60°.

Isolation of procerin. Air-dried heartwood of *Juniperus procera* Hochst. (24.4 kg, obtained from Kenya) was extracted with acetone for 24 h and the extract was fractionated as described in a previous paper in this series [13]. The fraction soluble in light petroleum and in sodium carbonate was an oil which, on standing for a month, yielded a crystalline precipitate (8.6 g). This was recrystallised from ligroin (b.p. 100–125°) and

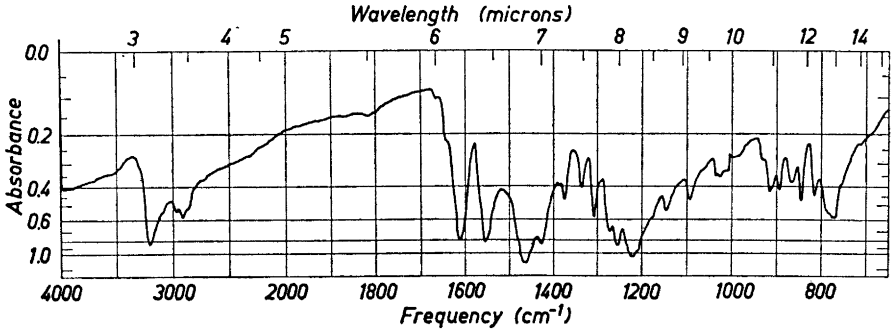

Fig. 2. Infrared spectrum of procerin in potassium bromide.

then from ethanol-water, m.p. 71—72°, $[\alpha]_D$ 0° (c, 3.4, $CHCl_3$). (Found: C 78.3; H 8.0; CH_3—(C) 9.7. $C_{15}H_{18}O_2$ requires C 78.2; H 7.9; CH_3—(C) (two) 12.9.) On further recrystallisation and sublimation in a high vacuum the melting point remained unchanged. A mixture of procerin and nootkatin melted at 67—91°. Infrared spectrum of procerin (in CCl_4): 3 075 w, 1 810 w, 1 640 m and 905 cm^{-1} s.

The copper complex, prepared by shaking a chloroform solution of procerin with a saturated aqueous solution of copper (II) acetate, was recrystallised from chloroform-ether, m.p. 203—204° (decomp.). (Found: C 68.9; H 6.5; ash 15.2. $C_{30}H_{34}O_4$ Cu requires C 69.0; H 6.6; ash (CuO) 15.2.)

Hydrogenation of procerin. Procerin (100 mg) was hydrogenated in ethanol (95 %) using a palladium (5 %)-charcoal catalyst. The reaction was interrupted after the absorption of one mole of hydrogen. The product was recrystallised from light petroleum and sublimed in a high vacuum, giving nootkatin [10] (III) m.p. 95—96° (mixed m.p., IR).

Procerin glycol monoformate. Procerin (900 mg) was treated with an ice-cooled solution of hydrogen peroxide (33 %, 860 mg) in formic acid (85 %, 9 ml). The mixture was kept at room temperature for 10 min and then heated at 40° for 2 h. Water (75 ml) and sulphuric acid (2 N, 5 drops) were then added and the solution was shaken vigorously. The product that crystallised out (720 mg) was recrystallised from ethanol (95 %), m.p. 181—183°. (Found: C 65.9; H 7.0; active H (Zerevitinoff) 0.72. $C_{16}H_{20}O_5$ requires C 65.7; H 6.9; active H (two) 0.69.) Infrared spectrum (in KBr): 1 810 w, 1 641 m, 905 cm^{-1} m.

Procerin glycol (II). Procerin glycol monoformate (400 mg) in aqueous potassium hydroxide (20 %, 16 ml) was heated in a nitrogen atmosphere on a boiling water bath for 2 h. The solution was cooled, diluted with water (40 ml), acidified with sulphuric acid (2 N) and extracted exhaustively with ether. The combined ether extracts were washed twice with a little water, dried and evaporated giving a glass which crystallised on treatment with light petroleum. The crystalline material was triturated with further amounts of light petroleum to remove traces of formic acid and repeatedly sublimed in a high vacuum, m.p. 120—121°. (Found: C 67.9; H 7.7; active H 1.22. $C_{15}H_{20}O_4$ requires C 68.2; H 7.6; active H (three) 1.14.) Infrared spectrum (in KBr): 1 815 w, 1 640 m and 904 cm^{-1} s.

Periodic acid oxidation of procerin glycol. An ice-cooled solution of procerin glycol (100 mg) in pure ethanol (95 %, 5 ml) was treated with sodium periodate (217 mg) in water (5 ml) at room temperature for 15 h. Water (20 ml) was then added and the solution was distilled (5 ml of distillate) into an excess of 2,4-dinitrophenylhydrazine in ethanolic phosphoric acid. The precipitate formed (48 mg, 53 %) was recrystallised from methanol-water, m.p. 124—125° and identified as acetone 2,4-dinitrophenylhydrazone (mixed m.p., IR). No acetone dinitrophenylhydrazone was obtained in a blank run.

Procerin methyl ethers (IVa and Va). Procerin (2.5 g) was treated with excess diazomethane in ether containing methanol (5 drops) and the mixture was kept over night in the refrigerator. The remaining diazomethane was then destroyed with acetic acid and the solution evaporated to dryness. The oily product (2.68 g) was chromatographed on silica gel (140 g). Ether-benzene (1:1) eluted a crystalline procerin methyl ether (1.31 g) which was recrystallised from light petroleum, m.p. 74—75°. (Found: C 78.3; H 8.0; CH_3O 12.7. $C_{15}H_{17}O$ (OCH_3) requires C 78.6; H 8.2; CH_3O 12.7.) Further elution with ether gave a liquid procerin methyl ether (1.08 g) which was distilled, b.p. 172—174°/0.3 mm. (Found: CH_3O 12.4. $C_{15}H_{17}O$ (OCH_3) requires CH_3O 12.7.)

Rearrangement of procerin methyl ethers. Liquid procerin methyl ether (880 mg) was dissolved in methanol (20 ml) containing sodium methoxide (from sodium, 1.8 g) and heated in a sealed tube for 15 h at 150°. The solvent was removed under reduced pressure and the residue dissolved in water. Extraction with ether gave an oil (36 mg) which was discarded. The aqueous solution was acidified and extracted with ether. The ether extract was washed with dilute sodium bicarbonate solution and then extracted with aqueous sodium carbonate. Acidification of the sodium carbonate solution, re-extraction with ether and evaporation gave a dark-brown resin (606 mg, 72 %). This was distilled in a high vacuum giving a product which crystallised immediately. On paper chromatography (dimethyl sulphoxide-impregnated paper, mobile phase: moist light petroleum [14]) the distillate gave two spots of about equal size (R_F 0.48 and 0.42), different from those of VIIb (R_F 0.56, λ_{max} 242 mμ) and VIIIb (R_F 0.45, λ_{max} 270 mμ) obtained by rearrangement of the nootkatin methyl ethers IVb and Vb [10]. The ultraviolet spectrum of the mixture of acids obtained from procerin showed maxima at 236 and 278 mμ. This mixture obviously consists of the acids VIIa and VIIIa.

Crystalline procerin methyl ether, when treated with sodium methoxide as described above, gave the same mixture of acids but in much lower yield (17 % of sodium carbonate-soluble material).

Oxidation of the acid mixture VIIa + VIIIa. The acids VIIa + VIIIa (100 mg) were heated with nitric acid (30 %, 12 ml) at 170° for 20 h in a sealed tube. The reaction mixture was concentrated to a small volume and the product that crystallised (IX, 54 mg) was heated briefly to 220° and then sublimed in a vacuum giving trimellitic acid anhydride, m.p. 164—165°, identified by mixed m.p. and IR.

Hydrogenation of the acid mixture VIIa + VIIIa. On hydrogenation in ethanol (95 %) over a palladium (5 %)-charcoal catalyst, the acid mixture VIIa + VIIIa rapidly absorbed two moles of hydrogen and then absorption ceased. The product, which was paperchromatographically homogeneous, was recrystallised from light petroleum and sublimed in a high vacuum, m.p. 124.5—126°, and identified as 4-*iso*pentyl-3-*iso*propylbenzoic acid (VI) obtained from nootkatin [10] (mixed m.p., IR).

Proton magnetic resonance measurements. The PMR spectra of procerin and nootkatin were run in dilute carbon tetrachloride solutions (mole fractions 0.04—0.12) with a Varian V-4 300 Spectrometer operating at 40 Mc/s. Measurements were made against an internal benzene standard.

The spectrum of procerin (I) showed a strong signal at 221 c/s and another of half its intensity at 208.5 c/s. The signal at 221 c/s can be assigned to the two equivalent methyl groups on the *iso*propylidene double bond. In the spectrum of nootkatin (III) the corresponding methyl peak occurred at 222 c/s. The signal at 208.5 c/s in the spectrum of procerin was assigned to the methyl protons of the *iso*propenyl group attached to the tropolone ring. (The signal from the methyl protons in α-methyl styrene occurs at 205 c/s.) In addition the spectrum of procerin showed peaks at 94 c/s and 84 c/s, respectively. In this region signals from olefinic hydrogens are expected. The peaks were rather broad and showed no fine structure. The total area of the olefinic signal group suggested that it was due to three protons.

In the spectrum of nootkatin the proton on the *iso*propylidene double bond appeared as a broad triplet with the central maximum at 88.5 c/s. A corresponding proton in procerin should absorb at about the same frequency and the two protons of the $\rangle C=CH_2$ group could also be expected to absorb in the 80—100 c/s region. By analogy with other compounds containing *iso*propenyl and vinyl groups the two protons of the $\rangle C=CH_2$ group in procerin should have slightly different chemical shifts and a comparatively small mutual spin-spin coupling constant (1—3 c/s) (*cf.* Ref.[15]). The combined effects of overlapping of the signals from two different olefinic proton groups and a small spin-spin coupling constant may explain the broadness and the lack of fine structure of the signals at 94 and 84 c/s in the spectrum of procerin.

This spectrum also contained another doublet with peaks at 153.7 and 161 c/s. These were assigned to the methylene group linking the tropolone ring with the *iso*propylidene double bond. The methylene protons should be spin-coupled with the neighbouring olefinic proton and the observed doublet was regarded as the A_2-part of an A_2X-spectrum (for nomenclature *cf.* Ref.[16]). The X-part evidently overlapped the signals from the olefinic protons of the *iso*propenyl group as was mentioned above. The spin-spin coupling constant J_{AX} was calculated to be 7.3 ± 0.2 c/s. (In the spectrum of nootkatin the corresponding methylene signals were found at 152 and 159.5 c/s, thus J_{AX} 7.5 ± 0.2 c/s.)

The spectrum of procerin showed additional peaks at 9 c/s and 5 c/s, respectively. The latter was apparently made up from two overlapping signals. These signals were assigned to the protons on the tropolone ring. The total area of the peaks at 9 and 5 c/s corresponded to three protons.

The procerin spectrum also showed a signal at −65 c/s which was assigned to the proton of the OH-group. The corresponding signal in the spectrum of nootkatin was found at −56 c/s.

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