ACTA CHEMICA SCANDINAVICA 8 (1954) 1073—1082

# The Chemistry of the Natural Order Cupressales

## XI. Heartwood Constituents of *Chamaecyparis nootkatensis* (Lamb.) Spach. Nootkatin

S. R. DUFF, H. ERDTMAN and W. E. HARVEY

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

The tropolone nootkatin, $C_{15}H_{20}O_2$, has been shown to have structure (I). Nootkatin yields a glycol (XI) which on oxidation with periodic acid gives acetone; in addition *iso*butyric acid is obtained on oxidation with chromic acid. Rearrangement of either of the two nootkatin methyl ethers (II) with sodium methoxide yields a mixture of two isomeric acids, 3-*iso*propyl-4-(3′-methylbut-2′-enyl)-benzoic acid (III), and 3-*iso*propyl-4-(3′-methylbut-1′-enyl)-benzoic acid (IV), which are reduced to the same dihydrocompound, 4-*iso*amyl-3-*iso*-propyl-benzoic acid (V). On nitric acid oxidation all three acids yield 3,3-dimethylphthalide-5-carboxylic acid (VI), which has been synthesised by oxidation of *iso*propyl-*p*-xylene (V), obtained by Friedel-Crafts' reaction between *p*-xylene and *iso*propyl chloride. Further oxidation of (VI) yields trimellitic acid (VIII). Decarboxylation of (V) with copper chromite and quinoline affords *o*-*iso*amyl-cumene (IX) which was not isolated, but was oxidised to phthalic acid (X). It follows from this series of reactions that nootkatin is β-*iso*propyl-γ--(3-methylbut-2-enyl)-tropolone (I). Preliminary accounts of the investigation have been published [8,10].

The isolation of the tropolone nootkatin (I), $C_{15}H_{20}O_2$, from the heartwood of *Chamaecyparis nootkatensis* has been described [1] and a preliminary note on its chemistry has appeared [8] together with a report of an X-ray examination of its copper complex, $C_{30}H_{38}O_4Cu$, kindly carried out by Campbell and Robertson [2]. Recently the isolation of nootkatin from the heartwood of *Cupressus macrocarpa* Hart. has been reported [3] *.

The tropolone nature of nootkatin is clearly shown by the U.V. [4] and I.R. [5] spectra, and the X-ray studies favour structure (I) for nootkatin.

The molecular formula, the tropolone nature of nootkatin and the fact that on complete hydrogenation it absorbs five moles of hydrogen, indicate that

* The genera *Chamaecyparis* and *Cupressus* are botanically very closely related and nootkatin may be expected to have a more widespread occurence in this group of the N. O. Cupressales.

nootkatin contains an exocyclic double bond, and hence is monocyclic. The U.V. spectrum shows that this double bond is not conjugated with the nucleus. It might be expected that it would be possible to hydrogenate this exocyclic double bond without at the same time reducing the ring system. Such however is not the case, and even when a mild palladised charcoal catalyst in ethanol is used, continuous absorption of hydrogen takes place, four moles being absorbed rapidly, and the fifth, probably reducing the carbonyl group, slightly less quickly. Even when the reaction is stopped after four moles have been absorbed it is not possible to obtain the ketonic octahydro-derivatives uncontaminated with the decahydronootkatins. That the tropolone ring is approximately equally reactive as the exocyclic double bond to catalytic hydrogenation is an interesting indication of the lability of this system, and demonstrates the relatively low reactivity of the double bond.

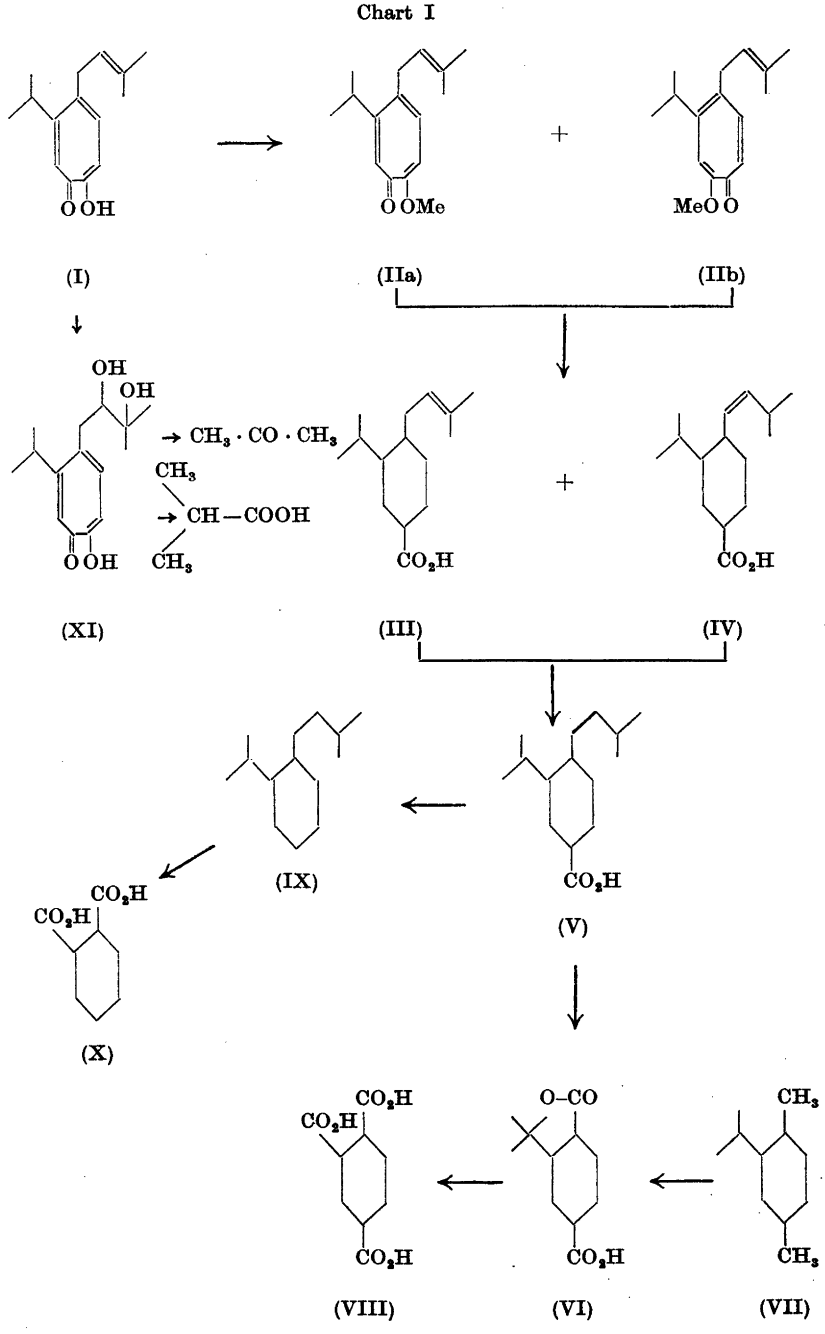
The presence of the double bond is also indicated by the ready formation of a glycol monoformate when nootkatin is treated with hydrogen peroxide in formic acid. The monoformate is readily hydrolysed to the parent glycol (XI), which is cleaved by periodic acid, affording acetone in good yield as the only identified oxidation product. Permanganate oxidation of the decahydronootkatin mixture and subsequent ring closure of the acid product yields ketonic material, possibly a mixture of diastereoisomeric *iso*propyl*iso*amyl-*cyclo*hexanones. Oxidation of the glycol with chromic acid yields *iso*butyric acid in addition to acetone.

The above evidence indicates that nootkatin is a tropolone containing one or two side-chain substituents, but does not indicate which of the possible formulae is the most likely. An *iso*propyl-3-methylbut-2-enyl tropolone structure seemed most satisfactory, and Campbell and Robertson suggested that formula (I) is probably the correct representation of nootkatin. This X-ray work was of considerable practical assistance in the chemical investigation, in indicating the best manner in which to employ the limited amounts of nootkatin available. A rigorous proof of this structure, by chemical methods, has now been obtained, and is summarized in Chart I. For the sake of brevity the argument will be developed on the basis of formula (I) for nootkatin.

The chemical approach used in the elucidation of the structure of the thujaplicins; oxidation of the fully saturated derivative, an $\alpha$-glycol, to the corresponding pimelic acid, is unpromising in the case of a disubstituted tropolone, as it would involve the purification of complex mixtures of isomeric acids. Attention was therefore turned to the possibility of rearranging the tropolone to the corresponding benzoic acid, a type of reaction frequently observed in this field, and preliminary studies carried out with very small amounts of nootkatin, indicated that nootkatin methyl ether may be rearranged to a benzoic acid derivative containing two side chains, and also showed that nootkatin itself is unusually stable against alkaline rearrangement. This is in agreement with the observation that tropolone methyl ethers generally rearrange more readily than the parent compounds [6].

Unsymmetrically substituted tropolones will be expected to yield two isomeric methyl ethers, and this was found to be the case with nootkatin. The methylation product previously described as an oil has been separated into a crystalline and an oily methyl ether (II). The latter is probably not a pure

Chart I



compound, but in the case of nootkatin glycol both isomeric ethers were obtained pure, in the crystalline state.

Both the crystalline and oily nootkatin methyl ethers (II) could be rearranged by treatment with a methanolic solution of sodium methoxide, to give a mixture of two isomeric acids, $C_{15}H_{20}O_2$, acid A (III) and acid B (IV), in which the former greatly preponderated. The isomerism is obviously due to a migration of the side chain double bond since acid A has a maximum in the U.V. spectrum at 242 m$\mu$ whereas in acid B the maximum is at 270 m$\mu$. This conclusion was confirmed by treating acid A with sodium methoxide, whereupon a good yield of acid B was obtained. Moreover both acids yield the same dihydro-compound (V) on catalytic hydrogenation.

That acid A, the less stable isomer, is the chief rearrangement product is significant as proof that the double bond in nootkatin occupies a similar position and is unconjugated with the ring system, in agreement with the spectral evidence. It is also of interest that rearrangement of the tropolone to the benzene ring takes place more readily than that of the unconjugated double bond to the conjugated position.

In the rearrangement reaction a quantity of oily material was obtained together with the pure acids. It could not be purified by crystallisation but yielded further quantities of acid B on treatment with alkali. Alternatively it could be oxidised to the oxidation product described below. It is obviously a mixture of the two acids.

Oxidation with dilute nitric acid of acid A (III), acid B (IV), the dihydro-acid (V), or the oily residues resulted in the production of only one identified product, an acid lactone, $C_{11}H_{10}O_4$, m.p. 265—266° (VI). Evidence of the structure of this oxidation product was obtained by synthesis from *p*-xylene which on Friedel-Crafts' reaction with *iso*propylchloride gave *iso*propyl-*p*-xylene (VII) oxidised by dilute nitric acid chiefly to the above acid lactone. The presence of the lactone ring in the oxidation product from the natural material was demonstrated by hydrolytic titration, and in view of its great stability the ring may be formulated as a $\gamma$-lactone system. It appears therefore that oxidation has been accompanied by hydroxylation, which is readily explained by the presence of an *iso*propyl substituent in nootkatin, as indicated also by the production of *iso*butyric acid on oxidation of nootkatin glycol. It is well-known that this group is easily hydroxylated, and the production of 3,3-dimethylphthalide by oxidation of *o-iso*propyl toluene affords a ready parallel with the above reaction [12].

Nitric acid oxidation of (VI) under more severe conditions yields trimellitic acid (VIII) as the sole product. The acid was characterised by the preparation of its anhydride and anhydride methyl ester, which were identical with authentic specimens obtained from $\beta$-naphthoic acid [7].

That this compound (VI) produced by the loss of four carbon atoms, is obtained from all three pure acids is proof of the occurrence of a five-carbon side chain in these acids, and hence in nootkatin. Moreover the presence of the double-bond unconjugated with the ring system in acid A, and the production of acetone on oxidation of nootkatin glycol, indicating branching of the chain, are conclusive proof that nootkatin contains a 3-methylbut-2-enyl substituent. The proof of structure of (VI) shows that the rearrangement acids,

and nootkatin also, must contain an *iso*propyl substituent. Moreover it proves that the five-carbon substituent in the rearrangement acids, and the dihydroacid, is *para* to the carboxyl group, and hence the 3-methylbut-2-enyl side chain in nootkatin is in the $\gamma$-position in the tropolone ring. But the *iso*propyl group can be in the $\alpha$- or $\beta$-position as either of these compounds would, on rearrangement and oxidation, yield (VI) and trimellitic acid.

This point was settled by decarboxylation of dihydroacid A (V), whereby the carboxyl group obtained by rearrangement of the tropolone ring was removed. The resulting hydrocarbon (IX) was not isolated, but on oxidation yielded phthalic acid showing that the two alkyl substituents are adjacent to one another in the acid, and hence in nootkatin. With this additional evidence acid A may be formulated as 3-*iso*propyl-4-(3'-methylbut-2'-enyl)-benzoic acid (III), acid B as, 3-*iso*propyl-4-(3'-methylbut-1'-enyl)-benzoic acid (IV), and dihydroacid A as 3-*iso*propyl-4-*iso*amylbenzoic acid (V), and it follows, therefore, that nootkatin is $\beta$-*iso*propyl-$\gamma$-(3-methylbut-2-enyl)-tropolone (I).

## EXPERIMENTAL

M. p.'s are uncorrected. "Petrol" refers to the fraction having b. p. 40—60°.

*Nootkatin* was isolated by essentially the same procedures as previously described [1]. It could also be obtained from the preliminary ethereal extract, by working up in the manner described for the acetone extract.

The *copper complex*, m. p. 234—235°. (Found: C 68.5; H 7.16; ash 15.1. $C_{30}H_{38}O_4Cu$ requires: C 68.5; H 7.28; ash (CuO) 15.1) has been submitted to X-ray crystallographic analysis by Prof. J. M. Robertson [2].

*Nootkatin glycol.* A solution of hydrogen peroxide (43.5 mg, 1 mole) in formic acid (85 %, 3 ml) made by dilution of a standardised solution was added to nootkatin (0.3 g). Heat was evolved on mixing and the solution darkened slightly in colour. The mixture was cooled until the reaction moderated, then heated at 40° for two hours, with intermittent shaking. Water (25 ml) was added followed by a few drops of dilute sulphuric acid, and the solution was shaken vigorously and set aside until precipitation was complete. The crystalline material was collected by filtration (250 mg, m. p. 160—165°) and after crystallisation from methanol formed colourless needles of *nootkatin glycol monoformate* m. p. 170—171°. (Found: C 65.4; H 7.43. $C_{16}H_{22}O_5$ requires: C 65.3; H 7.53). Light absorption: $\lambda_{max}$ 241, 322 m$\mu$; log$\varepsilon_{max}$ 4.52, 3.97. $\lambda_{min}$. 274 m$\mu$; log$\varepsilon_{min}$ 3.14. This substance gave an intense ferric chloride reaction, did not respond to the periodate spray test [3], and reacted with sodium periodate solution only very slowly (0.17 mole/mole after 41 hrs., 0.275 mole/mole after 90 hrs).

The monoformate (1 g) was added to a solution of potassium hydroxide (20 ml, 20 %). The solid did not dissolve completely in the cold but did so on slight warming and the resulting solution was heated in a boiling water bath for 2 hours and then cooled. No precipitate formed, so the mixture was diluted with water (50 ml), acidified with hydrochloric acid (some oil separated) and extracted with ether (4 × half volume). The ethereal extracts were combined, washed twice with a little water, dried ($Na_2SO_4$) and evaporated, giving a solid product which was triturated with petrol several times to remove traces of formic acid: m. p. 114—117°: yield 750 mg. Crystallisation from acetonitrile gave large needles which, however, melted at approximately 82—84° the actual melting point depending on the rate of heating and never being very sharp, and clearly contained some solvent of crystallisation. (Found: C 63.9; H 7.87.) If this material is dried at 70° in a high vacuum it gives *nootkatin glycol* m. p. 118—119°. (Found: C 68.1; H 8.29. $C_{15}H_{22}O_4$ requires: C 67.6; H 8.33.) This substance gives an intense ferric chloride reaction, and a positive result in the periodate spray test. It is soluble in polar organic solvents, and sparingly soluble in hot water. It is soluble to some extent in sodium bicarbonate solution and can be extracted from ethereal solution by this reagent. The sodium salt is very sparingly soluble in dilute sodium hydroxide solution, and if the potassium

hydroxide used in the hydrolysis of the monoformate is replaced by sodium hydroxide, a precipitate forms during the reaction and it is more difficult to work up the product.

*Nootkatin glycol methyl ether.* Nootkatin glycol (200 mg) was dissolved in ether (30 ml), and an excess of diazomethane in ether (10 ml) added. After standing for 2 days in the refrigerator white crystalline material was found to have separated and was collected. Yield, 174 mg. (Found: OMe 11.8. $C_{16}H_{24}O_4$ req.: OMe 11.1.) Evaporation of the ethereal solution afforded an oil which solidified on rubbing with petrol, and was crystallised from ethyl acetate-ether. Yield, 21 mg. M. p. 113—126°.

Examination of the main fraction under the microscope showed that it consisted of two crystalline species, large prisms and smaller less well defined crystals. They were separated by hand, and the former were crystallised from ether in prisms, m. p. 129—130°. (Found: C 68.9; H 8.68. $C_{16}H_{24}O_4$ req.: C 68.6; H 8.57). The other material crystallised from ethyl acetate in prisms, m. p. 161—2°. (Found: C 68.7; H 8.63). When mixed the substances melted at 124—129°.

*Oxidation of nootkatin glycol with chromic acid.* Sodium dichromate (1.8 g) in water (4 ml) was added slowly with vigorous stirring and cooling to a solution of nootkatin glycol (250 mg) in 50% sulphuric acid (15 ml). A vigorous reaction took place with the evolution of a heat and a brisk evolution of gas. When the reaction moderated the mixture was set aside at room temperature for 2.5 hours after which time excess chromic acid was still present. The solution was diluted with water (40 ml) and distilled in steam in a steamed out apparatus until the distillate was no longer acid (total vol. *ca.* 250 ml). The residual solution was continuously extracted with ether for 16 hrs. but no acidic material was present in the ether extract. The above steam distillate was neutralised with standard sodium hydroxide (required 8.3 ml 0.1083 *N* NaOH, corresponding to 0.96 moles acid per mole of nootkatin glycol) and the solution was concentrated to half volume, the distillate being allowed to run into a solution of 2,4-dinitrophenylhydrazine hydrochloride in water. The orange precipitate that formed was collected by filtration and crystallised from alcohol forming long needles of *acetone 2,4-dinitrophenylhydrazone*, m. p. 124—125° undepressed in admixture with an authentic specimen. The yield of crude hydrazone (m. p. 121—122°) was 73 mg (0.32 mole/mole glycol). The neutral solution from which the acetone had been distilled was evaporated to dryness on a water bath. Paper chromatography using propanol-ammonia-water (80 : 4 : 16) as solvent and ninhydrin as spraying reagent revealed the presence of at least two acids with $R_F$-values corresponding to acetic (or formic) and butyric (or *iso*butyric) acids.

The mixed sodium salts were dissolved in the minimum amount of the same solvent mixture and transferred to the top of a column of powdered cellulose (15 × 1.5 cm) which had been packed in the dry state and then washed thoroughly with the solvent. The column was run with the same solvent and the effluent was collected in fractions of *ca.* 2 ml. These fractions were spotted on filter paper and treated with the ninhydrin reagent and those which gave a positive reaction were treated with 0.5 ml of 0.1 *N* NaOH and evaporated to dryness in a stream of air, and then samples were run on paper chromatograms in the usual way. The elution of the column was continued only until the faster moving component of the original mixture had been eluted and this appeared to be recovered in a pure state. The fractions containing this material were combined, dissolved in a little water, and passed through a column of Amberlite IR 120 ion exchange resin to remove the sodium ions. The eluate from this column was neutralised with standard alkali and evaporated to dryness on the water bath. Paper chromatography showed that it contained only one component and that this travelled at the same rate as *iso*butyric acid. The sodium salt was converted into the *p*-bromophenacyl ester using the calculated amount of *p*-bromophenacyl bromide and the ester isolated in the usual way and crystallised from aqueous alcohol giving the *p-bromophenacyl ester of isobutyric acid*, m. p. 76° undepressed in admixture with an authentic specimen.

*Periodate oxidation of nootkatin glycol.* Sodium periodate solution (5 ml, 0.1 *M*) was added to a solution of nootkatin glycol (100 mg) in pure methanol (5 ml) and the mixture was set aside at room temperature overnight, during which time some inorganic material separated. Water was added and the solution was distilled, the distillate being run into excess 2 : 4-dinitrophenylhydrazine hydrochloride solution. Distillation was continued until no further reaction occurred and the crystalline material was collected and crystallised from methanol giving yellow needles of acetone 2 : 4-dinitrophenyl hydrazone (53 mg, 60 %) m. p. 124—125°, undepressed on admixture with an authentic specimen.

The residue in the distilling flask was acidified with dilute sulphuric acid, and the gummy material collected by extraction with ether (4 × equal vol.). Evaporation of the dried ethereal solution gave a gum which solidified on trituration with petrol. This material reacted with Brady's reagent, and after crystallisation from acetonitrile melted at 128—129°.

*Oxidation of decahydronootkatin.* A solution of sodium periodate (60 ml 0.0967 *M*, 1 mole) was added to a solution of decahydronootkatin (1.38 g) in methanol (75 ml), shaken at room temperature for 4 hours, and then set aside for 2 days. Solid inorganic material which formed was removed and the solution concentrated under reduced pressure. The oil which separated was collected with the aid of ether and the ethereal extracts were combined, washed with water, dried ($Na_2SO_4$) and evaporated to a colourless oil which was suspended in water (50 ml). Sodium carbonate (1 g) and potassium permanganate (1.4 g) were added and the mixture was shaken overnight (unreacted permanganate was still present). The solution was treated with sulphur dioxide in the usual manner, a little dilute sulphuric acid was added and the mixture was extracted with ether (2 × equal volume). The ether extracts were extracted with sodium bicarbonate and the acidic material recovered by acidification and extraction with ether. Evaporation of the dried ethereal solution gave a colourless oil which was distilled in a high vacuum giving a very viscous gum (0.69 g) which did not crystallise even on long standing, and is presumably a mixture of isomers.

The barium salt of this acid mixture (2 g) was dry distilled in a stream of nitrogen at 300—320° and the pale yellow oily distillate was taken up in ether. The ethereal solution was washed once with a little sodium bicarbonate, then with water, dried ($Na_2SO_4$) and evaporated and the residue was distilled *in vacuo* giving a pale yellow liquid, $n_D^{19}$ 1.4688 (223 mg).

A sample of the ketonic material was treated with an ethanolic solution of 2,4-dinitrophenylhydrazine hydrochloride in the usual way and the dinitrophenylhydrazone which precipitated was collected and crystallised from a large volume of alcohol forming yellow plates, m.p. 171—172° the analysis of which was in reasonable agreement with that expected for an *iso*propyl*iso*amyl*cyclo*hexanone dinitrophenylhydrazone. (Found: C 58.75; H 7.38; N 13.6. $C_{30}H_{30}O_4 . H_2O$ requires: C 58.8; H 7.90; N 13.7.)

*Nootkatin methyl ether* previously described as a gum was prepared on a larger scale, and the product distilled in high vacuum. The resultant pale yellow oil (Found: OMe 12.3. Calc. for $C_{16}H_{22}O_2$: OMe 12.6) was chromatographed on an alumina column using the method of fractional elution. Coloured end fractions were obtained but the compound came off the column over a wide range, and no crystalline material was obtained. The end fractions were rejected and the others were combined and distilled. The resultant oil was allowed to stand for some weeks whereupon long needle-shaped crystals appeared. They were collected and crystallised from petrol in needles, m.p. 72°. (Found: C 78.0; H 8.88; OMe 12.6. $C_{16}H_{22}O_2$ req.: C 78.0; H 8.94; OMe 12.6). The residual oily methyl ether could not be obtained crystalline.

*Action of sodium methoxide on nootkatin methyl ether.* Pure crystalline nootkatin methyl ether (600 mg) was dissolved in a solution of sodium methoxide (from sodium (1.2 g) in pure methanol (20 ml)), giving a dark red solution, and was heated in a sealed tube at 145° for 14 hours. The solvent was removed under reduced pressure and water added until the residue was completely in solution. The solution was extracted with ether, and the ethereal extract washed with water, dried ($NaSO_4$), and the solvent removed to give a dark oil (115 mg) from which it was not found possible to obtain an identifiable product.

The aqueous solution was acidified with sulphuric acid and extracted exhaustively with ether. The ethereal solution was extracted with sodium bicarbonate solution, and then with sodium carbonate solution.

The aqueous sodium bicarbonate extract was acidified, extracted with ether, the ethereal extract washed, dried ($Na_2SO_4$), and the solvent removed to yield a dark oil (61 mg) which was distilled to give a pale yellow gum. No pure material could be obtained from the gum, but it appeared to be a mixture of the acids described below.

The aqueous sodium carbonate extract was worked up in the same way to yield a dark oil (357 mg) which on distillation *in vacuo* gave an oil which crystallised on standing. The solid was crystallised from petrol to give *acid A* (III) (207 mg) in thick plates, m.p.

114—116°. Concentration of the petrol mother liquour gave a small quantity of impure *acid B* (IV) in needles, m.p. 84—92°. An oily acid residue from which pure material could not be obtained except by conversion to acid B, or by oxidation (see below) was obtained from the mother liquors.

Treatment of the oily nootkatin methyl ether in the manner described above afforded the same products:

*Acid A*, 3-*iso*propyl-4-(3′-methylbut-2′-enyl)-benzoic acid (III) m.p. 114—116°; $\lambda_{max}$ 242 m$\mu$; log $\varepsilon_{max}$ 4.1; inflection 275 m$\mu$; log $\varepsilon$ 3.4. (Found: C 77.9; H 8.58. $C_{15}H_{20}O_2$ req.: C 77.55; H 8.68).

*Acid B*, 3-*iso*propyl-4-(3′-methylbut-1′-enyl)-benzoic acid (IV), was obtained from the mother liquors from the rearrangement of nootkatin methyl ether (10 g). It crystallised in needles, m.p. 108—109°; $\lambda_{max}$ 270 m$\mu$; log $\varepsilon_{max}$ 4.0. (Found: C 77.8; H 8.50; Eq. wt. 238. $C_{15}H_{20}O_2$ req.: C 77.55; H 8.68.)

On admixture the acids melted at 96—106°, with softening at 80°.

*Dihydro-acid A*, 4-isoamyl-3-*iso*propyl-benzoic acid (V). On hydrogenation in ethyl acetate, using a palladium charcoal catalyst, both acid A and acid B absorbed one mole of hydrogen rapidly, after which no further absorption took place. Both acids gave the same product, *dihydro-acid A*, which crystallised from petrol in fine needles, m.p. 126—127.5°. (Found: C 77.35; H 9.40. $C_{15}H_{22}O_2$ req.: C 76.9; H 9.40.)

*Conversion of acid A to acid B.* Acid A (45 mg) was dissolved in a solution of sodium methoxide, (from sodium (100 mg) in methanol (2 ml)) and heated in a sealed tube at 145° for 15 hours. On cooling sodium salts separated but were dissolved by the addition of water, and the solution was acidified and extracted with ether. The ethereal extract was washed with water and dried ($CaCl_2$,) the solvent removed and the product crystallised from petrol to give acid A (3 mg) and acid B (28 mg), identified by melting point and mixed melting point with an authentic specimen.

Acid B could be obtained by treatment, as above, of the impure residues from the rearrangement of nootkatin methyl ether.

*Oxidation of acid A, acid B, and dihydro-acid A.* Acid B (100 mg) was added to a solution of conc. nitric acid (3.5 ml) in water (6.5 ml) and heated in a sealed tube at 146° for 16 hours. The resultant solution on cooling to 0° deposited crystalline material (32 mg) which was collected, and purified by sublimation at 196—205°/4 mm, yielding white clusters of plates, m.p. 265—266°; equivalent weight 209; equiv. wt. by hyrolytic titration 98; $\lambda_{max}$ 240, 285 m$\mu$; log $\varepsilon_{max}$ 4.2, 3.43. (Found: C 63.9; H 5.3. $C_{11}H_{10}O_4$ req.: C 64.08; H 5.3. Equiv. wt. 206; Equiv. wt. by hydrolytic titration 103.) On concentrating the mother liquors a solid residue was obtained from which pure compounds could not be obtained.

Oxidation of acid A (110 mg) in the same manner gave the same acid lactone (40 mg) m.p. and mixed m.p. 262°: methyl ester, m.p. 141°.

Oxidation of dihydro-acid A (85 mg) gave the same acid lactone (30 mg), m.p. and mixed m.p. 263°, equiv. wt. 213; methyl ester, m.p. 143°.

The acid lactone could also be obtained by oxidation of the oily residues from the oxidation of nootkatin methyl ether, and the bicarbonate soluble fraction.

*Methyl ester of the acid lactone.* The acid lactone dissolved or suspended in ether was treated with excess of diazomethane in ether, the volatile compounds removed, and the residue sublimed at 120°/4 mm. The crystalline sublimate was crystallised from ether in needles, m.p. 143°. (Found: C 65.35; H 5.61; OMe 14.14. $C_{12}H_{12}O_4$ req.: C 65.5; H 5.48; OMe 14.09.)

The acid lactone was shown to be 3 : 3-dimethylphthalide-5-carboxylic acid, and will be referred to as such below.

*Isopropyl-p-xylene: cf.* Nightingale and Carton [12]. *Iso*propyl chloride (40 g) was added with stirring over 1 hr., to a mixture of *p*-xylene (106 g) and finely powdered aluminium chloride (30 g). Stirring was continued for a further 3 hrs and the product worked up in the usual manner, and roughly fractionated by distillation through a 30 cm column packed with glass cylinders. The fraction (33 g), b.p. 190—200° was distilled through a Vigreux column, yielding *iso*propyl-*p*-xylene (18.4 g) b.p. 207—214°, $n_D^{22}$ ,1.4964. (Found: C 89.02; H 10.70. $C_{11}H_{16}$ requires: C 89.12; H 10.88.)

*3,3-dimethylphthalide-5-carboxylic acid. Iso*propyl-*p*-xylene (0.5 ml) was heated with dilute nitric acid (10 ml, 1 : 2) for 15 hrs, at 145°. The reaction mixture was cooled and the crystalline material (200 mg) collected, treated with charcoal, and crystallised from

water, yielding 3,3-dimethylphthalide-5-carboxylic acid, m.p. 263—265°, undepressed on admixture with the acid lactone obtained from nootkatin as described above. Treatment with diazomethane afforded the methyl ester, m.p. 140—142°, undepressed on admixture with a specimen obtained from nootkatin.

The mother liquors from the oxidation were concentrated to *ca.* 2 ml volume, cooled, and the crystalline material (136 mg) collected, and crystallised from water in needles, which did not melt but sublimed above 300°. Treatment with diazomethane afforded an ester, m.p. 107—108°. The identity of this compound was not established.

*Oxidation of 3,3-dimethylphthalide-5-carboxylic acid.* The above acid (73 mg) was heated with a solution of conc. nitric acid (4 ml) in water (8 ml) at 172° for 12 hours, in a sealed tube. On concentrating the solution to a small volume trimellitic acid (63 mg) crystallised and was collected. It had m.p. 210—216°, and equiv. wt. 80. (Required equiv. wt. 70.)

The acid was sublimed at 170—220°/4 mm yielding the anhydride m.p. 162° undepressed on admixture with an authentic specimen.

The acid anhydride was treated with diazomethane in the usual way, yielding the anhydride methyl ester, m.p. 104—105° after sublimation and crystallisation from ether. The melting point was undepressed on admixture with an authentic sample.

*Trimellitic acid.*(*cf.* Ekstrand[7]). β-Naphthoic acid (10 g) was dissolved in a solution of sodium hydroxide (2.5 g) in water (160 ml). The solution was heated on the waterbath and a warm saturated aqueous solution of potassium permanganate was added in portions, with shaking, until a permanent red colour was obtained. Excess reagent was destroyed by the addition of ethanol, and the manganese sludge was separated by filtration. The filtrate was made acid ($H_2SO_4$) and concentrated until salts began to separate. It was extracted continuously with ether, and the ethereal solution was evaporated to dryness. The residue was heated at 200°/2 mm until no more phthalic anhydride sublimed. The residue was dissolved in water, treated with charcoal, the charcoal separated, and the solution evaporated to dryness. The residue was sublimed at 2 mm pressure by heating gently with a free flame, giving trimellitic anhydride, which crystallised from ether-petrol in needles, m.p. 162—164°.

Treatment of the anhydride with diazomethane in the usual way gave trimellitic anhydride methyl ether, which crystallised from ether-petrol in needles, m.p. 100—103°.

*Decarboxylation of dihydro-acid A:* Dihydro-acid A (581 mg), copper chromite (200 mg) and quinoline were heated at 230°. Evolution of carbon dioxide commenced about 200°, and became vigorous at 230°. After 1 1/4 hrs evolution had slowed up appreciably, and after a further 1/2 hr appeared to have ceased. The reaction mixture was cooled, diluted with ether (100 ml), filtered, and the ethereal solution washed with 5 *N* hydrochloric acid (5 × 1/2 vol.), then with sodium bicarbonate solution (3 × 1/2 vol.) and finally with water. The solvent was removed yielding a dark oil with an aromatic hydrocarbon odour, which was not further purified, but was oxidised as described below.

*Oxidation of decarboxylation product:* The above oil was heated with dilute nitric acid (10 ml 1 : 2) at 145° for 15 hrs. The resulting solution was freed from traces of gummy material, concentrated to small volume (*ca.* 1 ml), and final traces of solvent removed under reduced pressure. The gummy solid residue was distilled in four portions at 1 mm pressure. An oil was obtained which crystallised on standing. The crystalline material was freed from oil (probably impure 3,3-dimethylphthalide) on a porous plate, and sublimed by heating on the waterbath, at water-pump pressure. Phthalic anhydride was obtained in long needles, m.p. and mixed m.p. 129—130°. The identity of the phthalic anhydride was checked by the preparation of fluorescein, and of phthalanil, m.p. 204—204.5°, mixed m.p. 204—205° with an authentic specimen of m.p. 205°.

The authors are indebted to *Statens Naturvetenskapliga Forskningsråd* for financial support, and Crown Zellerbach Co., Camas, Washington, for generous gifts of wood.

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Received March 31, 1954.