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The Chemistry of the Natural Order Cupressales

XVI.* Heartwood Constituents of *Chamaecyparis nootkatensis* (Lamb.) Spach. The Structure of Chamic and Chaminic Acids

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Chamic acid, $C_{10}H_{14}O_2$, has been shown to be a monoterpene acid of structure (I). The presence of the dimethyl*cyclo*propyl grouping (IX) was demonstrated by the formation of *trans*-caronic acid (VIII) on permanganate oxidation and the relative positions of the carboxyl group and the *cyclo*propane ring were deduced from the transformation of chamic acid into *m*- and *p-iso*propylbenzoic acids (IV, VI) and further into *iso*- and *tere*phthalic acids (V, VII). The position of the double bond followed from a study of the ultra-violet and infra-red absorption spectra of chamic acid and its alkali isomerisation product, *iso*chamic acid (III).

Another acid, chaminic acid, has also been isolated in very small quantities from the heartwood and has been shown to be the optical antipode of *iso*chamic acid.

The isolation of chamic acid from the heartwood of *Chamaecyparis nootkatensis* and its characterisation as the *p*-bromophenacyl ester and the *cyclo*hexylamine and *S*-benzylthiuronium salts has been described in a previous communication [1]. The present communication describes the degradative experiments which have led to the elucidation of the structure of chamic acid and the probable structure of chaminic acid.

Permanganate oxidation of chamic acid under alkaline conditions resulted in extensive decomposition but from the mixture of oxidation products a small quantity of *dl-trans*-caronic acid (VIII) and acetone (as the 2,4-dinitrophenylhydrazone) were isolated and evidence for the presence of dimethylmalonic acid was also obtained. This establishes the presence of the grouping (IX) in chamic acid **. Moreover these results are reminiscent of the results obtained

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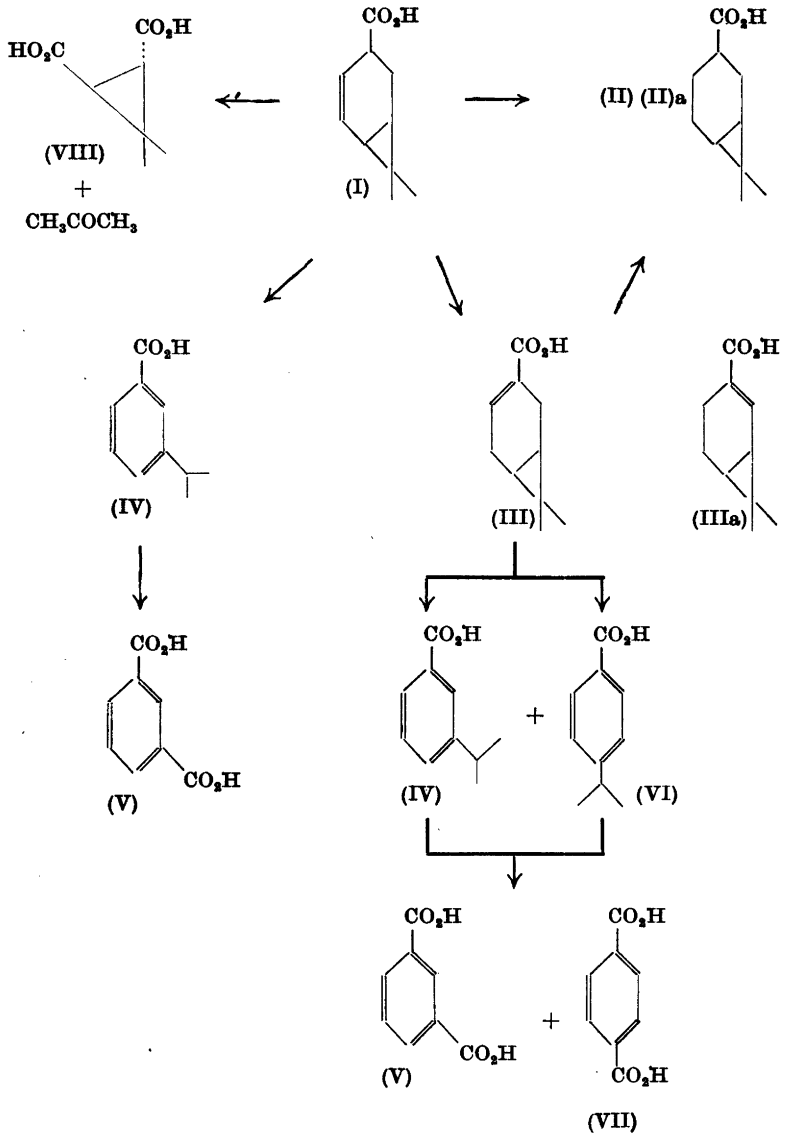
** The weak infra-red bands at 1 007 cm^{-1}, 998 cm^{-1} and 1 011 cm^{-1} for chamic, *iso*chamic and dihydrochamic acids, respectively, provide additional evidence for the presence of the *cyclo*-propane ring system in these compounds.



on oxidation of Δ^3-carene under similar conditions [2] and suggest that chamic acid may possess a close structural resemblance to the carenes.

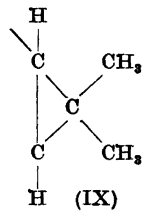
The catalytic reduction of chamic acid in alcoholic solution in the presence of Adams' catalyst resulted in the rapid uptake of one mole of hydrogen affording dihydrochamic acid (II), obtained as an oil but readily characterised by its *p*-bromophenacyl ester m. p. 79—80°. Hence chamic acid has one double bond and therefore could possess a fused *cyclo*propane-*cyclo*hexene ring system.

On hydrogenation of dihydrochamic acid in acetic acid solution with Adams' catalyst one mole of hydrogen was very slowly absorbed and this clearly corresponds to fission of the *cyclo*propane ring.

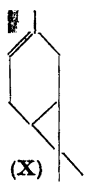
The ultra-violet absorption spectrum of chamic acid contains no strong bands thus indicating that the double bond is not conjugated with the carboxyl group. This deduction is supported by infra-red measurements, the medium intensity band at 1 644 cm^{-1} present in the spectrum of chamic acid but absent in the case of the dihydro-compound corresponding to the isolated double bond in the former substance.

When chamic acid is treated with hot aqueous alkali, crystalline *iso*chamic acid is obtained. The ultra-violet absorption spectrum of *iso*chamic acid has a maximum at *ca.* 218 mμ (ε 7 250), and the infra-red spectrum shows strong bands at 1 684 cm^{-1} and 1 647 cm^{-1} clearly demonstrating that the double bond has moved into conjugation with the carboxyl group.

*Iso*chamic acid when reduced catalytically gave a dihydro-compound (IIa) as an oil which afforded a single *p*-bromophenacyl ester not identical with that prepared from dihydrochamic acid (II) obtained by catalytic reduction of chamic acid. The two dihydro-compounds (II) and (IIa) are presumably diastereoisomers differing according to the *cis* or *trans* relationship of the carboxyl group to the *cyclo*propane ring.



(IX)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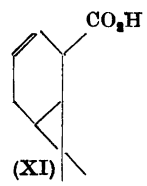
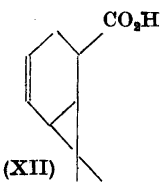


(XI)



(XII)

At this stage structures (I), (XI) and (XII) were probable for chamic acid and clearly the next step was to determine the relative positions of the carboxyl group and the *cyclo*propane ring in the molecule.

Treatment of chamic acid in chloroform solution with an equimolar quantity of bromine in the same solvent resulted in a rapid reaction with no significant formation of hydrogen bromide. Further bromine could be absorbed but at a greatly reduced rate. The crude dibromo-compound was dehydrobrominated directly by heating with dimethylaniline to give a liquid acid mixture in which the presence of a considerable quantity of aromatic material was indicated by ultra-violet and infra-red spectra measurements. In fact the ultra-violet absorption spectrum of the mixture resembled rather closely that of *m-iso*propylbenzoic acid which was therefore probably the main component of the mixture, a deduction subsequently verified. Separation of the acids by partition chromatography or by fractional crystallisation of the *p*-bromophenacyl esters was not successful, but after catalytic hydrogenation of the mixture (palladium, room temperature and pressure) and conversion of the product to the amide *via* the acid chloride, pure *m-iso*propylbenzamide could be isolated by careful chromatography of the amide mixture on alumina. In

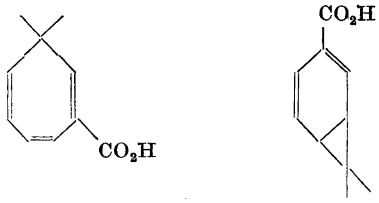
addition, oxidation of the crude acid mixture with dilute nitric acid afforded *iso*phthalic acid, identified as its dimethyl ester.

The addition of a unimolecular quantity of bromine to *iso*chamic acid proceeded at a much slower rate than in the case of chamic acid owing to the conjugation of the double bond with the carboxyl group. Dehydrobromination of the resulting dibromo-compound was accomplished by heating with pyridine to yield a liquid acid mixture which, from its ultra-violet absorption spectrum appeared to consist largely of non-aromatic material. Hydrogenation of the acid mixture, conversion to the amides and chromatography of the latter on alumina gave a small quantity of *m-iso*propylbenzamide as the only recognisable product. The addition of *cyclo*hexylamine to a petroleum ether solution of the acid mixture gave a considerable quantity of insoluble *cyclo*hexylamine salts which after crystallisation from acetone furnished what had every appearance of being a pure salt, not identical with, but according to analysis isomeric with, *iso*chamic acid *cyclo*hexylamine salt. Decomposition of the salt afforded the free acid as a crystalline solid of rather indefinite melting point. The acid (A), which was not optically active, had an ultra-violet absorption spectrum with a maximum at 260 mμ (ε 8 750), and it thus appeared that the acid possessed a conjugated system of two double bonds and a carboxyl group and had arisen by ring opening of the *cyclo*propane ring of *iso*chamic acid probably as a result of the presence of hydrogen bromide in the bromine. However, if the unpurified mixture of *cyclo*hexylamine salts obtained from the acid degradation products was refluxed with an acetic acid-hydrochloric acid mixture, distillation of the acid products gave a small quantity of material boiling at the same temperature as the original acid degradation product and a main fraction which boiled considerably higher. The lower boiling product, which partially crystallised, had an ultra-violet absorption spectrum distinctly resembling that of *p-iso*propylbenzoic acid. The higher boiling main fraction also deposited a crystalline solid, insoluble in petroleum ether, of m. p. 156—160°. The ultra-violet absorption spectrum of this compound showed a maximum at 280 mμ (ε *ca.* 30 000), and it seems very likely that it is a dicarboxylic acid formed by dimerisation of the acid (A) isolated by purification of the *cyclo*hexylamine salt as previously described, or a similar compound. The lower boiling distillate was converted to the amide and by fractional evaporative distillation followed by crystallisation a very small quantity of pure *p-iso*propylbenzamide was isolated. Also oxidation with dilute nitric acid of the acid mixture as obtained directly from the dehydrobromination gave a mixture of *iso-* and *tere*phthalic acids which were separated by fractional crystallisation of their dimethyl esters. Thus these degradations establish conclusively the relative positions of the carboxyl group and the *cyclo*propane ring in chamic acid which must therefore possess structure (I). *Iso*chamic acid consequently must be formulated as (III) or (IIIa), (III) being the most probable since the addition of bromine to, followed by the dehydrobromination of (IIIa), would be expected to give a considerable quantity of *p-iso*propylbenzoic acid (by analogy with the similar degradation of chamic acid in which a bromine atom is situated in an adjacent position to the *cyclo*propane ring) whereas in actual fact, as already described, a complex mixture of acids is formed containing very little aromatic material. However, a con-

clusive distinction between the possible structures (III) and (IIIa) for *iso*-chamic acid cannot be made on the present evidence. Further investigations on this point have been hampered by lack of material.

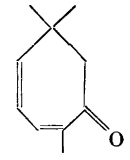
In an earlier paper [1] describing the isolation of chamic acid the presence of small quantities of other acids in the mother liquors from the precipitation of the *cyclo*hexylamine salt of chamic acid was reported. One of these acids, chaminic acid, m. p. 104—105°, $[\alpha]_D$ 6 (± 1)° has now been obtained in the pure state. The infra-red spectrum of chaminic acid is identical with that of *iso*chamic acid, m. p. 105—106°, $[\alpha]_D$ —6 (± 1)°, and chaminic acid is therefore the optical antipode of *iso*chamic acid. The fact that chaminic acid is the *d*-form whereas *iso*-chamic acid formed by isomerisation of chamic acid is the *l*-form eliminates the possibility that chaminic acid is an artefact formed from chamic acid during the isolation process which necessarily involves alkaline treatments.

Although it is clear that *m-iso*propylbenzoic acid is formed directly by the addition of bromine to, followed by dehydrobromination of, *iso*chamic acid, this cannot be stated with certainty in the case of *p-iso*propylbenzoic owing to its method of isolation. *p-Iso*propylbenzoic acid *cyclo*hexylamine salt is insoluble in petroleum ether whereas the *cyclo*hexylamine salt of *m-iso*propylbenzoic acid is soluble. Hence if *p-iso*propylbenzoic acid is a direct product of the degradation then it is possible that its separation from *m-iso*propylbenzoic acid occurred at this stage and that the treatment with acetic acid-hydrochloric acid served only to dimerise acid (A) and thus make possible a separation of *p-iso*propylbenzoic acid on account of its widely different volatility from the dimer of (A). On the other hand if either thujic acid (XIII) or "dehydrochamic acid" (XIV) are the direct products of the degradation then these, after separation as their petroleum ether insoluble salts, would be rearranged by the acetic acid-hydrochloric acid reagent to *p-iso*propylbenzoic acid [3].



(XIII)

(XIV)



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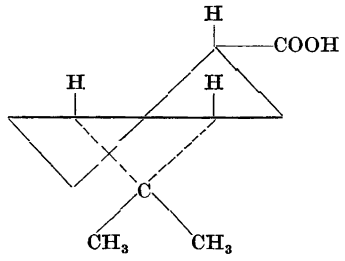

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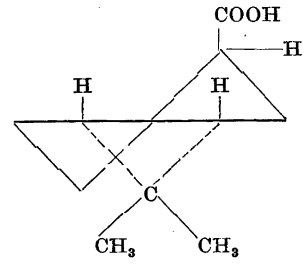

(XVII)

The relationship between chamic acid (I), chaminic acid (III), dehydrochamic acid (XIV) and thujic acid (XIII) is of interest particularly in view of their possible common biogenetic origin from carene-like precursors [4]. In this connection it would be desirable to effect the interconversion of chamic acid or chaminic acid and dehydrochamic acid or thujic acid. At this juncture it should be pointed out that dehydrochamic acid and thujic acid may be regarded as valence tautomers and in fact Gripenberg [5] considered the possibility that thujic acid might possess structure (XIV). Similar problems arose in the study of the structures of certain compounds prepared from eucarvone [6] (XV) and were resolved with certainty by the use of nuclear magnetic resonance measurements [7]. This method has been used very recently to distinguish between structures (XIII) and (XIV) for thujic acid [8], the results clearly pointing to structure (XIII). Moreover although one can consider an equilibrium between the *cyclo*heptatriene and *bicyclo*heptadiene structures for these compounds it seems that in all cases so far known one form is so much more stable that it is formed to the exclusion of the other form. Hence the possibility that dehydrochamic acid (XIV) exists as such is remote. The possible formation of thujic acid (in small quantity) as an intermediate product in the degradation of *iso*chamic acid to *p-iso*propylbenzoic acid has already been discussed but no direct evidence for its presence could be obtained. An alternative degradation of *iso*chamic acid involving bromination using N-bromosuccinimide followed by dehydrobromination by heating with base was briefly examined but also gave a complex mixture of acids, none of which predominated.

The formation of *dl-trans*-caronic acid rather than the *cis*-isomer on permanganate oxidation of chamic acid is presumably the result of a *cis-trans* rearrangement and racemisation at some stage in the oxidation as a *trans* ring junction in (I) is unlikely. *l-* and *dl-trans* and *cis*-Caronic acids have all been obtained from the oxidation of Δ^3-carene under different conditions [2,9,10].

The fact that stereoisomeric dihydrochamic acids (II) (IIa) are obtained depending on whether chamic acid or *iso*chamic acid is reduced enables certain deductions to be made concerning the probable stereochemistry of chamic acid. The catalytic reduction of *iso*chamic acid would be expected to give the dihydrochamic acid with an equatorially placed carboxyl group and a *cis* relationship between the carboxyl group and the *cyclo*propane ring (XVI) (*cis*-dihydrochamic acid) (*cf.* Ref.[11]). Thus the dihydrochamic acid obtained from chamic acid should have an axial carboxyl group (XVII; *trans*-dihydrochamic acid) and hence in chamic acid itself the carboxyl group and the *cyclo*propane ring can be assigned a *trans* relationship.

Since oxidation of the methyl group in Δ^3-carene would lead to *iso*chamic acid the selenium dioxide oxidation of Δ^3-carene was investigated with a view to effecting this change *via* the corresponding aldehyde. A similar oxidation of α-pinene is known to give myrtenal [12] but in the case of Δ^3-carene the oxidation apparently took place at the methylene groups adjacent to the double bond and not at the methyl group.

It is hoped to confirm the structure of chamic acid and establish with certainty the structure of chaminic acid by synthetic studies.

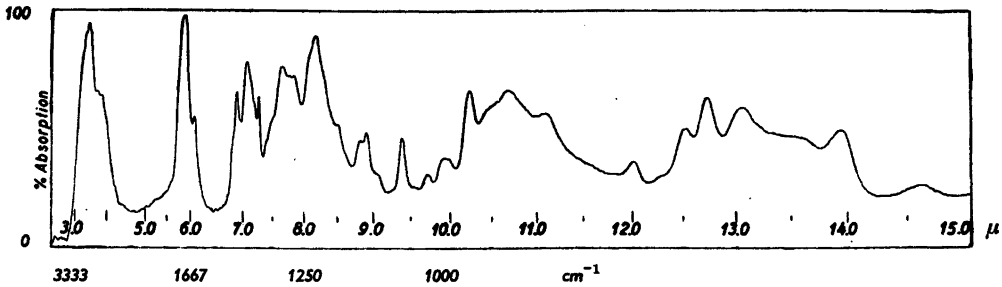

Fig. 1. Infra-red absorption spectrum of chamic acid.

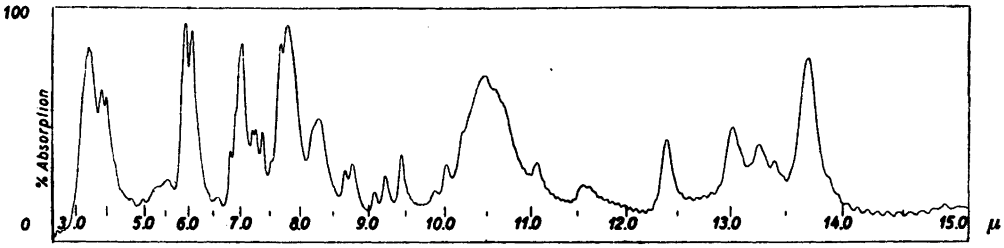

Fig. 2. Infra-red absorption spectrum of isochamic acid.

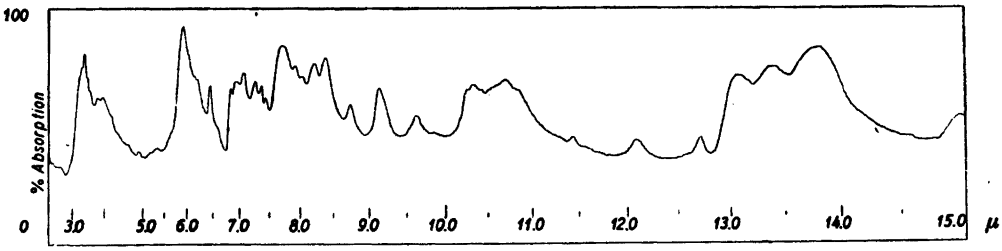

Fig. 3. Infra-red absorption spectrum of thujic acid.

EXPERIMENTAL

Isolation of chamic acid. Wood samples employed included some from large trees grown near Vancouver, Canada, which constituted the major source and some from a small Scandinavian grown tree. The latter sample gave much greater yields of chamic acid. The acetone extraction procedure described previously [1] (with omission of the preliminary ether extraction) was found to be the most convenient method for the extraction of chamic acid. The yields of crude steam volatile acid varied between 3 g and 6 g per 10 kg batch of heartwood. The crude acid normally afforded 60—80 % yields of the crude acetone insoluble *cyclo*hexylamine salt of chamic acid which after recrystallisation gave 40—50 % yields (based on the crude salt) of pure chamic acid *cyclo*hexylamine salt. Hence 0.75—2.0 g of pure chamic acid could usually be obtained from 10 kg of heartwood. In some extractions, however, the yield was much below these average values.

The ultra-violet absorption spectrum of chamic acid showed no strong bands. Infra-red spectrum: (Fig. 1.) Medium intensity band at 1 644 cm^{-1} (isolated double bond), weak band at 1 007 cm^{-1} (*cyclo*propane ring).

Isolation of chaminic acid. The mother liquors from which the *cyclo*hexylamine salt of chamic acid had been precipitated were concentrated to small volume, filtered, and the remaining solvent evaporated under reduced pressure. The free acids were recovered by acidification and ether extraction and were obtained as a faintly coloured viscous oil which slowly deposited a crystalline solid on storage in the refrigerator. The solid material was collected by filtration and recrystallised from petroleum ether yielding pure *chaminic acid*, m. p. 104—105°, $[\alpha]_D$ 6 (± 1)° (*c* 3.9 in methanol). (Found: C 72.6; H 8.56. $C_{10}H_{14}O_2$ requires C 72.3; H 8.49). The infra-red spectrum was identical with that of *iso*chamic acid, m. p. 105—106°, $[\alpha]_D$ −6 (± 1)°. A mixture of approximately equal parts of the *d*- and *l*-isomers melted at the same temperature as either of them, but if the two were mixed in non-equivalent amounts depressions in the melting point of up to 10—12° were obtained. The p-*bromophenacyl ester* was prepared in the usual manner and after recrystallisation from aqueous ethanol formed flat plates, m. p. 72.5—73,° $[\alpha]_D$ −2.6° (methanol).

Oxidation of chamic acid. Chamic acid (1.09 g) was dissolved in a solution of sodium carbonate (0.5 g anhydrous) in water (100 ml) and finely powdered potassium permanganate was added with cooling and shaking until no further reaction occurred. Further potassium permanganate (1 g) was added and the solution was warmed on the water bath, decolourisation rapidly taking place. This process was repeated until no further reaction took place at 100° by which time a total of 10 g of permanganate had been added. The solution was finally heated on the boiling water bath for 1 ½ hours. The resulting solution was cooled to room temperature, acidified with dilute sulphuric acid, treated with sulphur dioxide and steam distilled. The distillate was made alkaline by the addition of sodium hydroxide and steam distilled once more. The second distillate was treated with an aqueous solution of 2:4-dinitrophenylhydrazine hydrochloride and the yellow precipitate which formed in the cold was collected and recrystallised from ethanol giving yellow needles of acetone 2:4-dinitrophenylhydrazone, m. p. 123—124°, undepressed on admixture with an authentic specimen. The residual liquid from the first distillation was diluted with water to dissolve the salts which had separated and extracted with ether (4 × ½ volume). The ether extracts were combined, washed with a little water, dried (Na_2SO_4) and evaporated giving a semi-solid residue. This material gave a strong fluorescein reaction and paper chromatography showed that at least four substances were present although two of these apparently occurred only in small amount. The mixture was triturated with a little chloroform and the insoluble matter was collected and washed with a few drops of chloroform. It melted over a very wide range, gave a strong fluorescein reaction and on paper chromatography gave two well defined spots. The faster moving substance moved at about the same speed as pimelic acid and is in fact caronic acid whilst the slower moving substance travelled at about the same speed as succinic acid or a little faster and is probably dimethylmalonic acid. The mixture of acids was recrystallised repeatedly from water finally yielding a small amount of *dl-trans*-caronic acid, m. p. 212—213°, undepressed on admixture with an authentic specimen of *dl-trans*-caronic acid and behaving identically on paper chromatography.

Hydrogenation of chamic acid. Chamic acid, in ethanol, was shaken in an atmosphere of hydrogen at room temperature and pressure, in the presence of Adams' catalyst until one mole of hydrogen had been absorbed, at which stage the rate of uptake of hydrogen decreased sharply. The catalyst was removed by filtration and the ethanol evaporated under reduced pressure giving an almost colourless oil which was distilled in high vacuum affording *dihydrochamic acid* as a colourless viscous oil, d_{20}^{20} 1.0445, n_D^{20} 1.4835, $[\alpha]_D$ −47° (methanol). (Found: C 71.6; H 9.66. $C_{10}H_{16}O_2$ requires C 71.4; H 9.59.) Infra-red spectrum: No band corresponding to the band at 1 644 cm^{-1} (isolated double bond) found in the spectrum of chamic acid. Weak band at 1 011 cm^{-1} (*cyclo*propane ring). The same product was obtained if the hydrogenation was carried out in ethanol solution using a palladised charcoal catalyst.

Dihydrochamic acid p-*bromophenacyl ester* was prepared in the usual manner and crystallised from aqueous ethanol as long thin plates, m. p. 79—80°. (Found: C 59.45; H 5.74. $C_{18}H_{21}O_3Br$ requires C 59.2; H 5.80.)

In the presence of Adams' catalyst either in alcoholic or, preferably in acetic acid solution, a second mole of hydrogen was very slowly absorbed. The product obtained on removing the catalyst and evaporating the solvent partially solidified but has not been investigated in detail.

Iso*chamic acid*. Chamic acid (1.30 g), in aqueous sodium hydroxide (25 ml 25 %), was heated gently under reflux for 2 h. The solution was cooled and acidified with hydrochloric acid and the precipitate which formed collected by filtration and dried affording almost pure *iso*chamic acid in practically quantitative yield. Recrystallisation was effected from petroleum ether giving *iso*chamic acid as colourless prisms, m. p. 105—106°, $[\alpha]_D$ −6 (± 1)°. (Found: C 72.7; H 8.59. $C_{10}H_{14}O_2$ requires C 72.3; H 8.49). Ultra-violet absorption spectrum: max. *ca.* 218 mμ (ε 7 250). Infra-red spectrum: (Fig. 2.) Strong bands at 1 684 cm^{-1} (conjugated C=O) and 1 647 cm^{-1} (conjugated double bond). Weak band at 998 cm^{-1} (*cyclo*propane ring).

Iso*chamic acid* cyclo*hexylamine salt* was prepared by the addition of *cyclo*hexylamine to an acetone solution of *iso*chamic acid and recrystallised from acetone-ethanol forming fine needles, m. p. 166—167°, subliming readily *in vacuo* below 100°. (Found: C 72.5; H 10.28. $C_{16}H_{27}O_2N$ requires C 72.4; H 10.25).

Iso*chamic acid* p-*bromophenacyl ester* was prepared from the acid and *p*-bromophenacyl bromide by the standard procedure and recrystallised from aqueous ethanol giving colourless plates, m. p. 73.5—74°, $[\alpha]_D$ + 2.3° (methanol). (Found: C 59.6; H 5.36. $C_{18}H_{19}O_3Br$ requires C 59.5; H 5.27).

Hydrogenation of iso*chamic acid*. *Iso*chamic acid, in ethanol, was hydrogenated in the presence of Adams' catalyst until one mole of hydrogen had been absorbed, at which stage the rate of uptake of hydrogen ceased or became very slow. The catalyst was removed by filtration and the solvent evaporated under reduced pressure yielding an oil which was converted directly into the p-*bromophenacyl ester*. The crude ester melted at 53—54° and repeated recrystallisation raised the melting point only to 55.5—56.5° and no evidence was obtained for the presence of more than one component. (Found: C 59.0; H 5.70. $C_{18}H_{21}O_3Br$ requires C 59.2; H 5.80).

Dehydrobromination of dibromochamic acid. To a solution of chamic acid (1.35 g), in chloroform (25 ml) was added dropwise, with shaking, a solution of bromine (1.30 g, 1 mole) in chloroform (10 ml). Immediate decolourisation of the bromine solution took place and no evolution of hydrogen bromide was detected. The chloroform was evaporated and the residue refluxed with freshly distilled dimethylaniline for 1 h. Most of the dimethylaniline was removed by heating on a water bath under reduced pressure. The residue was shaken with ether and dilute hydrochloric acid and the ether layer removed. The acid layer was extracted with fresh ether and the combined ethereal solutions washed with dilute hydrochloric acid followed by water and dried (Na_2SO_4). The ether was removed and the residue distilled *in vacuo* to give 0.66 g of nearly colourless product (A), b. p. *ca* 120—170° (bath temperature) / 0.15 mm. Ultra-violet absorption: max. 230 mμ (ε 7 500); 277 mμ (ε 1 000); *m-iso*propylbenzoic acid: max. 230 mμ (ε 7 500); 277 mμ (ε 1 050). The infra-red spectrum showed bands at 1 652, 1 606 and 1 582 cm^{-1}, indicative of an aromatic carboxylic acid. On paper chromatography using propanol-ammonia-water (80 : 4 : 16) or *t*-butanol-ammonia-water (80 : 4 : 16) as solvents a single spot was obtained. No *cyclo*hexylamine salt was precipitated in acetone or petroleum ether solution. Conversion to the *p*-bromophenacyl esters gave a product m. p. 83—87° (corr.), clearly a mixture, which could not be purified by fractional crystallisation or by chromatography on alumina. The distilled product (A) (0.65 g), in ethanol (15 ml), was hydrogenated in the presence of 10 % palladium charcoal (0.1 g) as catalyst at room temperature and atmospheric pressure. The uptake of hydrogen after 2 h was 45 ml when the hydrogenation had practically ceased. The catalyst was removed by filtration, the alcohol evaporated and the residual acid refluxed for 15—20 min with freshly distilled thionyl chloride. The excess of thionyl chloride was removed by distillation and the residual acid chloride dissolved in dry ether (25 ml). Ammonia gas was passed into the ether solution for 15—20 min. and water was then added. The ether layer was separated and the aqueous layer extracted with fresh ether. The combined ether solutions were washed with a little 2 N sodium hydroxide solution followed by water, dried (Na_2SO_4) and the ether removed to give 0.40 g of brown semi-solid amide. Sublimation of a small portion of this material followed by crystallisation of the solid part of the sublimate from petroleum ether gave needles, m. p. 81—82.5°. This material was undoubtedly impure *m-iso*propylbenzamide (m. p. of the pure compound 93—94° (corr.) since its melting point was not depressed on admixture with the authentic compound and the ultra-violet absorption spectra of the two samples were amost identical. However, the impure sample could not be purified by repeated recrystallisations. The remainder of the semi-

solid amide preparation (0.380 g) was chromatographed on alumina (40 g), (column 22.5 cm × 1.7 cm), in benzene solution and eluted successively with ether-benzene mixtures and finally ether. The ether-benzene eluates yielded small quantities of oily material (total 0.035 g). A total of 18 fractions were obtained from the elution with ether and of these, 12 (total 0.250 g) consisted of substantially pure *m-iso*propylbenzamide judged by mixed melting point and ultra-violet absorption spectra determinations. Recrystallisation of the combined fractions from petroleum ether gave pure *m-iso*propylbenzamide as fine needles, m. p. 93—94° (corr.), (Found: C 73.2; H 8.0; N 8.5. $C_{10}H_{13}ON$ requires C 73.6; H 8.0; N 8.6) undepressed on admixture with authentic *m-iso*propylbenzamide. When this work was carried out *m-iso*propylbenzamide had not been reported in the literature. *m-Iso*propylbenzoic acid[13] was converted into its acid chloride by the action of thionyl chloride and an ethereal solution of the acid chloride treated with ammonia gas. The resulting amide crystallised from petroleum ether in fine needles, m. p. 93—94° (corr.), (Found: C 73.5; H 7.8; N 8.5. $C_{10}H_{13}ON$ requires C 73.6; H 8.0; N 8.6).

Distilled product (A) (0.150 g) from the dehydrobromination was heated overnight at 170—180° in a sealed tube with a mixture of concentrated nitric acid (4 ml) and water (8 ml). The crystalline precipitate which formed was collected and washed with water. It melted above 300°, gave no fluorescein reaction and was readily and completely soluble in barium hydroxide solution (distinction from *tere*phthalic acid). The methyl ester, prepared in ethereal solution with diazomethane, was recrystallised from aqueous methanol giving dimethyl *iso*phthalate as fine needles, m. p. 63—64°, undepressed on admixture with an authentic specimen.

*The dehydrobromination of dibromo*isochamic acid. To *iso*chamic acid (3.45 g, 1 mole) in chloroform (75 ml) was added portionwise over 2 ½ hours, a solution of bromine (3.33 g, 1 mole) in chloroform (50 ml). The reaction was complete 1—2 h after the addition of the last portion of bromine. No detectable amount of hydrogen bromide was evolved. The chloroform was removed and the gummy, pale yellow residue was refluxed in pyridine for 30 min. The reaction mixture was poured into 15 % hydrochloric acid (300 ml), the product extracted with ether (2 × 100 ml) and the ether solution washed with 15 % hydrochloric acid followed by water and then extracted with 2 N sodium hydroxide solution (2 × 50 ml). The alkaline extracts were acidified (hydrochloric acid), the liberated acids, isolated with ether, amounting to 1.70 g. Distillation of the product *in vacuo* gave a practically colourless distillate (B) (1.16 g), b. p. 120—140° / 0.02 mm (bath temp.). The ultra-violet absorption spectrum of this material showed no maxima above 220 mμ. A small higher boiling fraction was also obtained from the distillation. On keeping it partially solidified and was crystallised from aqueous acetic acid (small prisms) m. p. 95—100° (corr.). Recrystallisation from the same solvent increased the melting point to 115—116° (corr.), which was strongly depressed on admixture with *p-iso*propylbenzoic acid, m. p. 117—118° (corr.). The ultra-violet absorption spectrum showed no maxima above 220 mμ and the substance was not further investigated.

Distillate (B) (0.36 g) was hydrogenated in ethanol solution (20 ml) with a 10 % palladium charcoal catalyst (0.50 g), 35 ml of hydrogen (N.T.P.) being absorbed. The hydrogenation product was converted to the acid chloride by refluxing with thionyl chloride (3 ml) for 30 min. and after removal of excess of thionyl chloride ammonia gas was bubbled through a solution of the acid chloride in dry ether (25 ml) for 15 min. The ether solution was washed with water, dilute sodium hydroxide solution and water again, dried (Na_2SO_4) and the ether removed yielding the crude amide as a brown gum (0.235 g). The amide, in benzene solution, was placed on a column of alumina (40 g) and eluted with ether, 30 fractions being taken. The ultra-violet absorption spectra of fractions 11—13 indicated the presence of *m-iso*propylbenzamide. These fractions were combined and recrystallised from petroleum ether affording a small quantity of pure *m-iso*propylbenzamide, m. p. and mixed m. p. 93—94°. Examination of the other fractions yielded only small quantities of impure crystalline material which did not give any characteristic absorption in the ultra-violet and was not further investigated.

To distillate (B) (0.58 g), in petroleum ether (5 ml) was added a solution of *cyclo*hexylamine (0.39 g), in petroleum ether (5 ml). There was a considerable heat of reaction and the *cyclo*hexylamine salt began to separate almost immediately. After 30 min. in the refrigerator the *cyclo*hexylamine salt (C) was filtered off (0.54 g, m. p. 135—140°). The crude salt (0.250 g) was refluxed for 5 h with concentrated hydrochloric acid (5 ml) containing enough glacial acetic acid to produce a homogeneous solution at the boiling

point. The reaction mixture was diluted with water and extracted with ether (2 × 75 ml). The ethereal solution was washed with water, dried (Na_2SO_4) and the ether evaporated. The residue was evaporatively distilled and separated into two fractions. The more volatile fraction (0.035 g) was refluxed with thionyl chloride (2 ml) for 30 min. and the excess of thionyl chloride then removed by distillation. The resulting acid chloride was dissolved in dry ether (25 ml) and ammonia gas bubbled through the solution for 30 min. The ether solution was washed with 2 N sodium hydroxide solution followed by water, dried (Na_2SO_4) and the ether evaporated. Evaporative distillation of the residue gave a small crystalline fraction which, after two recrystallisations from petroleum ether (fine needles), had m. p. 148.5—149.5° (corr.), undepressed on admixture with an authentic specimen of *p-iso*propylbenzamide.

Crude *cyclo*hexylamine salt (C) (0.360 g), repeatedly recrystallised from acetone gave what was apparently a single, pure *cyclo*hexylamine salt (0.07 g), m. p. 170—171° (depresses the melting point of the *cyclo*hexylamine salt of *iso*chamic acid). (Found: C 72.3; H 10.1. $C_{16}H_{27}O_2N$ requires C 72.4; H 10.25). Treatment of this salt with dilute hydrochloric acid followed by ether extraction afforded the free acid which crystallised from aqueous methanol as thin plates of rather indefinite melting point (115—130°). The melting point behaviour was unchanged after further recrystallisation. $[\alpha]_D$ 0° (chloroform). Ultra-violet absorption: max. 260 mμ (ε 8 750).

Distillate (B) (0.200 g) was oxidised with nitric acid (4 ml) and water (8 ml) in a sealed tube at 170—180° overnight and the crystalline product formed was collected and washed with water. This material was not completely soluble in barium hydroxide solution. It was converted to the methyl ester by treatment with phosphorus pentachloride followed by methanol and the crystalline product obtained was recrystallised from methanol forming long flat needles of dimethyl *tere*phthalate, m. p. 139—140°, undepressed on admixture with an authentic specimen. The methanol mother liquors were diluted with water and the crystalline material which precipitated was recrystallised from aqueous methanol yielding fine needles of dimethyl *iso*phthalate, m. p. 63.5—64°, undepressed on admixture with an authentic specimen.

The oxidation of Δ^3-Carene with selenium dioxide. To a stirred refluxing solution of Δ^3-carene (20 g, 1 mole), in ethanol (40 ml), was added over 30 min. a solution of selenium dioxide (18 g, 1. 1 mole) in ethanol (40 ml). The formation of red selenium metal was soon noticed. The reaction mixture was refluxed for 5 h, filtered to remove selenium, and the filtrate concentrated and steam distilled. The steam volatile product was extracted with ether and the ether extract washed with 2 N sodium hydroxide solution. Acidification of the alkali washings revealed the absence of steam volatile acidic material. The ether solution was washed with water, dried (Na_2SO_4) and the ether removed giving 6.67 g of crude product. Distillation *in vacuo* afforded the following fractions as pale yellow oils: (1) b. p. 65—73°/7 mm, 1.07 g (2) b. p. 80—97° (mainly 92—97°)/10 mm, 3.1 g (3) b. p. 115—120°/10 mm, 1.0 g. Ultra-violet absorption: fraction (1) max. 245 mμ; fraction (2) max. 242 mμ.

Fraction (2) (1.0 g), in ethanol (100 ml), containing a trace of sodium hydroxide, was refluxed with freshly precipitated silver oxide (2.32 g, 1.5 mole) for 4 h. The silver and unchanged silver oxide were removed by filtration and most of the solvent was evaporated from the filtrate (A). The inorganic material was treated with dilute nitric acid and the ether washings were added to the concentrated filtrate (A). The ether solution was washed with water and dried (Na_2SO_4). Removal of the ether yielded only a trace of acidic material. A similar treatment of fraction (1) gave the same result.

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