719. *The Structure of Alphitonin.*

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Reduction of alphitonin pentamethyl ether with sodium in liquid ammonia removes a methoxyl group and gives the benzylcoumaranone (I) with potassamide in ammonia; this product affords the chalcone (II) but the alphitonin ether affords the amide (VI). Alphitonin therefore has the structure (V; R = H), a deduction confirmed by the synthesis of the ether (V; R = Me). The wood of *Alphitonia excelsa* also contains the triterpene emmolic acid.

A substance, now named alphitonin, was extracted by Read and Smith [1] from the heartwood of the Australian " red ash " (*Alphitonia excelsa*). Industrially, advantage has been taken of its presence to stain the wood brown by painting it with alkali.

The substance was reported [1] to be optically inactive, to crystallise from water, to give a purple ferric test, to form crystalline potassium and ammonium salts, and thus to be a phenol. It was thought to be a glycoside since an " osazone " was obtained after acid-treatment.

We had at first some difficulty in purifying alphitonin but satisfactory modifications of the original method were found. The state of purity is difficult to determine in view of the indefinite m. p. and we were unable to obtain the crystalline acetyl derivative reported.[1] A gummy product obtained by acetylation gave infrared bands corresponding to both aliphatic and aromatic ester groups. No sugar could be detected after acid-treatment, and the substance itself gave with phenylhydrazine a rather indefinite yellow product that could have been mistaken for an osazone. Degradation with 50% aqueous potassium hydroxide gave protocatechuic acid, detected by paper chromatography. No further information could be obtained directly from alphitonin itself, so we turned to the more stable and highly crystalline pentamethyl ether.

Alphitonin could not be fully methylated with diazomethane, but gave a good yield of a pentamethyl ether, $C_{20}H_{22}O_7$, under the action of dimethyl sulphate and potassium carbonate in acetone at room temperature. The formula was confirmed by bromine analysis of the dibromo-derivative, $C_{20}H_{20}O_7Br_2$. Alphitonin should therefore have the formula $C_{15}H_{12}O_7$, in reasonable agreement with direct analyses on the thoroughly

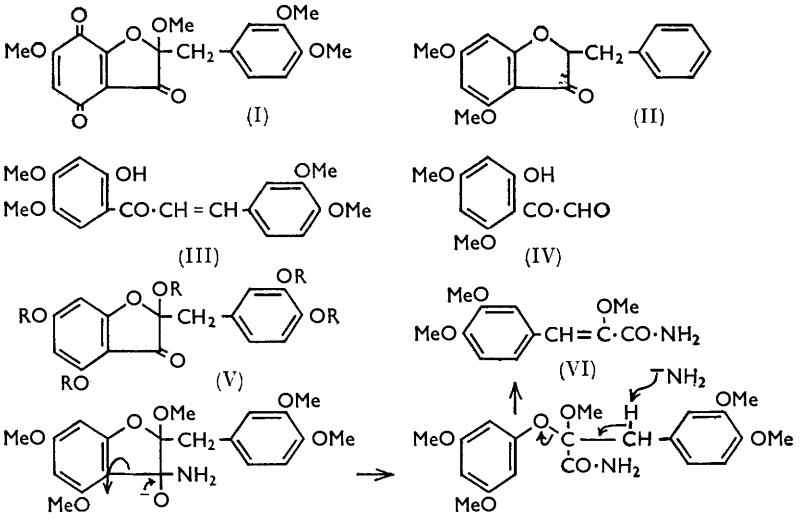
[1] Read and Smith, *J. Proc. Roy. Soc. New South Wales*, 1922, **56**, 253.

dehydrated substance.[1] The pentamethyl ether gave no infrared hydroxyl band but an intense carbonyl peak at 1710 cm.$^{-1}$. The oxygen atom unaccounted for is, therefore, probably in a cyclic ether linkage to account for the analysis and the absence of methoxyl groups from alphitonin. The pentamethyl ether does not give a hydroxymethylene derivative, and therefore probably lacks a methylene group adjacent to the carbonyl group; the carbonyl group is also sterically hindered since the pentamethyl ether reacts with hydroxylamine only under vigorous conditions to form an oxime and is reduced only slowly by sodium borohydride.

Ultraviolet spectra suggest the presence of an acylphenol or related group; and, since the pentamethyl ether has a carbonyl band at $\nu_{max.}$ 1710 cm.$^{-1}$, the carbonyl group is probably in a five-membered ring and adjacent to the aromatic ring. Alphitonin showed none of the colour reactions characteristic of flavanones.

Alphitonin pentamethyl ether was only slowly oxidised by potassium permanganate, then giving veratric acid. Oxidation with chromic acid in acetic acid gave a small yield of a quinone $C_{19}H_{18}O_8$ containing four methoxyl groups, probably of structure (I) although this could not be assigned initially. No other useful products were obtained by oxidation.

Reduction of alphitonin pentamethyl ether with about three equivalents of sodium in liquid ammonia gave a good yield of a substance $C_{19}H_{20}O_6$ containing four methoxyl groups. The infrared spectrum was very similar to that of the starting material, and the reaction clearly involved the reductive removal of methoxyl. This substance was shown to be the benzylcoumaranone (II) by treatment with potassamide in liquid ammonia, which resulted in the chalcone (III), $C_{19}H_{20}O_6$, recognised by its spectrum and general properties. Synthesis by standard routes and direct comparison confirmed the structure (III). The structure (II) was confirmed by direct comparison with an authentic specimen obtained by the sequence: 2′-hydroxy-3,4,4′,6′-tetramethoxychalcone (+ alkaline



hydrogen peroxide) ⟶ 3′,4′,4,6-tetramethoxyaurone (+ hydrogenation) ⟶ (II). Before the structure of the chalcone (III) had been established ozonisation had been found to give veratric aldehyde and, as 2,4-dinitrophenylhydrazone, a substance $C_{10}H_{10}O_5$; on the above allocations the latter can be represented by formula (IV).

There remained only to determine the position of the last oxygen atom, present in alphitonin as aliphatic hydroxyl and in the pentamethyl ether as methoxyl. The ready methylation indicated the 2-position (cf. V; R = H or Me), but then alphitonin pentamethyl ether would be a ketal, and no evidence could be found for this by acid-treatment.

As noted above, however, alphitonin itself gives what seems to be an osazone. The course of the sodium–ammonia reduction could be explained by the presence of a 2- or an α-methoxyl group, although again the former is more likely since its removal would be greatly facilitated by the adjacent carbonyl group. Neither alphitonin nor its methyl ether is optically active, which also favours the 2-position, the biogenetic precursor probably being an inactive α-diketone.

The correctness of the 2-position was confirmed by an interesting reaction which may have wider applications. With potassamide in liquid ammonia alphitonin pentamethyl ether gave a neutral substance, $C_{12}H_{15}O_4N$, in good yield. This was shown to be an amide by means of its infrared spectrum and by hydrolysis to an acid, $C_{12}H_{14}O_5$, reconverted into the amide by diazomethane followed by ammonia. Reduction of the acid with sodium in liquid ammonia yielded β-3,4-dimethoxyphenylpropionic acid. The structure of the amide is, therefore, probably (VI), which is supported also by the ultraviolet spectrum, by the ready hydrogenation, and by ozonolysis to veratraldehyde and methyl oxamate. A surprising feature is the stability of the enol-ether grouping in the amide and in the acid to 4N-hydrochloric acid.

There is little doubt, therefore, that alphitonin is correctly represented as (V; R = H). The only other possibility would have been that alphitonin is (±)-taxifolin, which has rearranged during methylation, but this is ruled out by the failure of alphitonin to give flavanone colour reactions, by a melting-point depression with (±)-taxifolin, and by non-identity of infrared spectra of the two. Alphitonin pentamethyl ether has, in fact, been obtained as a by-product during methylation of (±)-taxifolin but only under more drastic conditions than were used in the present methylation.

The fission of alphitonin pentamethyl ether to give the amide (VI) is related to the Haller–Bauer reaction [3] in which a non-enolisable ketone is converted into an amide and a hydrocarbon by the action of sodamide in boiling benzene or toluene. The reaction has apparently not been observed before in liquid ammonia at −33°. The mechanism is as shown in the formulæ. In a model reaction, 2′,3,4,4′,6′-pentamethoxychalcone was found to give 3,4-dimethoxycinnamamide. The presence of ether-oxygen atoms adjacent to the carbon developing the anionic charge is a favourable feature [4] which probably explains the ease of the reaction.

The action of only about two equivalents of potassamide in ammonia on alphitonin pentamethyl ether produced a neutral crystalline substance, $C_{20}H_{25}O_7N$, which formally represents the addition of a molecule of ammonia. It was not further investigated.

The structure of alphitonin pentamethyl ether was finally confirmed by its synthesis, the method used being that developed by Enebäck and Gripenberg.[5] Veratraldehyde was condensed with 2-hydroxy-ω,4,6-trimethoxyacetophenone [6,7] to give 2′-hydroxy-α,3,4,4′,6′-pentamethoxychalcone. This was cyclised by alkali [5] to alphitonin pentamethyl ether, shown to be identical with the substance obtained from alphitonin by a mixed melting point and infrared spectra. Cyclisation with acid produced, not only the pentamethyl ether, but also the tetramethyl ether previously described [7] as 3-hydroxy-5,7,3′,4′-tetramethoxyflavanone.

Another substance isolated from the wood of *A. excelsa* was identified as emmolic acid (a triterpene dicarboxylic acid first obtained [8] from the wood of *Emmenospermum alphitonioides* F. v. Muell.) by the melting points, mixed melting points, rotations, and infrared spectra (in Nujol) of the acid and its methyl ester and methyl ester acetate. The comparisons were made by Dr. J. J. H. Simes.

[2] Hergert, Coad, and Logan, *J. Org. Chem.*, 1956, **21**, 304.
[3] Haller and Bauer, *Ann. Chim.* (*France*), 1914, **1**, 5.
[4] Cf. Birch, *Quart. Rev.*, 1950, **4**, 74.
[5] Enebeck and Gripenberg, *Acta Chem. Scand.*, 1957, **11**, 866.
[6] Row and Seshadri, *Proc. Indian Acad. Sci.*, 1946, **23**, *A*, 23.
[7] Kimura, *J. Pharm. Soc. Japan*, 1938, **58**, 415.
[8] Boyer, Eade, Locksley, and Simes, *Austral. J. Chem.*, 1958, **11**, 236.

Experimental

Isolation of Alphitonin.—Shavings of the wood of *Alphitonia excelsa* (2·7 kg.) were covered with ethanol at room temperature for several days and then the extract was run off. Evaporation at room temperature gave a reddish-brown friable solid (135 g.). Repetition of the process afforded an additional amount (31 g.). The total powdered solid was extracted with boiling ether (5 × 1500 c.c.), yielding extract " E " and residue " R " (105 g.).

The extract " E " was concentrated to about 2 l. and shaken with 5% aqueous sodium hydrogen carbonate (5 × 200 c.c.), each aqueous extract being washed once with ether which was returned to the original ether solution. The final ether solution contained triterpene acids and was reserved. The combined dark aqueous extracts were acidified, but no precipitate appeared. After saturation with salt, the solution was extracted with ether, and the extracts were dried and evaporated to yield crude alphitonin as dark reddish-brown crystals (35 g.) which tenaciously retained ether.

This material was difficult to purify. It was dissolved in hot water (250 c.c.), salt (80 g.) was added, and the dark cloudy solution was kept overnight. After filtration from a black tar, the solution was extracted with ether (3 × 100 c.c.), and the combined extracts were re-extracted with 5% aqueous sodium hydrogen carbonate (5 × 100 c.c.). The product (25 g.) recovered from the aqueous extracts by acidification, saturation with salt, and extraction with ether was reddish-brown and was purified further by either of two procedures. Repeated crystallisation from concentrated aqueous solution at 0°, a slow process not appreciably hastened by seeding and scratching, eventually gave nearly colourless crystals, m. p. 221—223° (11 g.). Alternatively the crude material was dried at 110°, ground, and shaken with dry ether (4 × 150 c.c.), the dark ethereal extract being discarded. The residue then crystallised fairly readily from concentrated aqueous solution. Two further recrystallisations from water gave colourless crystals, m. p. 222—223° (10·5 g.). Although alphitonin is readily extracted from aqueous solution by ether, the dried material is almost insoluble, or at least very slowly soluble, in dry ether.

Purification of the crude material by precipitation of its potassium salt from ethanolic solution could also be accomplished, but with much loss.

The residue " R " was exhaustively extracted with ethyl acetate. The insoluble material (41 g.) appeared to consist largely of tannins and no pure substance was isolated. Evaporation of the ethyl acetate extract yielded reddish-brown crystals (62 g.) which were dissolved in water (500 c.c.). After being nearly saturated with salt, the solution was kept overnight, then filtered from tar, and the product was extracted with ether and recrystallised three times from water. By re-working of mother-liquors this fraction yielded alphitonin as nearly colourless crystals (42·5 g.), m. p. 225—226°. The total yield of alphitonin was 2%.

When its aqueous solution was left to evaporate at room temperature, alphitonin was obtained as colourless plates.

Isolation of Emmolic Acid.—The ether extract (see above), after being washed with sodium hydrogen carbonate solution to remove alphitonin, was extracted with 5% aqueous sodium carbonate (5 × 200 c.c.), each extract being washed with ether as above. The reddish-brown aqueous solution was acidified and the precipitate removed with ether. On evaporation of the solvent a mixture (about 12 g.) of crystals and jelly was obtained which was difficult to dry.

The material was dissolved in warm 2% aqueous potassium carbonate, the solution treated with charcoal, filtered, washed with ether, and acidified, and the product extracted with ether. The residue obtained on evaporation of the ether was dissolved in hot acetic acid (400 c.c.), and hot water (400 c.c.) was added. After cooling, the crystalline precipitate was collected and dried. Recrystallisation from methanol (charcoal) gave colourless needles (3·3 g.), m. p. 337—339° (decomp.), $[\alpha]_D^{18}$ +37° (*c* 1·78 in EtOH) (Found: C, 74·3; H, 9·5. Calc. for $C_{30}H_{46}O_5$: C, 74·0; H, 9·5%). It was undepressed in m. p. by authentic emmolic acid, m. p. 337—339°, $[\alpha]_D$ +38°.

Much material remained in the methanolic mother-liquors, but was difficult to purify by direct crystallisation. The pure dimethyl ester was readily obtained from it or from the original crude acid. The crude acid (as first obtained; 12 g.), in methanol–ether, was treated with an excess of ethereal diazomethane, and the mixture was evaporated. The residue was taken up in benzene, washed with aqueous sodium carbonate and water, dried, and passed through a

short column of alumina. The eluates were evaporated. The residue crystallised from methanol, yielding colourless plates (8·5 g.), m. p. 216—218° raised by further purification to 218—220°, $[\alpha]_D^{18}$ +45° (*c* 1·36 in $CHCl_3$) (Found: C, 74·7; H, 9·9; OMe, 12·0. Calc. for $C_{32}H_{50}O_5$: C, 74·7; H, 9·8; 3OMe, 12·1%). It was undepressed in m. p. by an authentic specimen, m. p. 223—224°, $[\alpha]_D$ +44·5°. The same substance was obtained from the purified acid.

The dimethyl ester acetate was obtained by heating the ester with acetic anhydride and pyridine on the water-bath for 4 hr. It crystallised from methanol in needles, m. p. 159°, $[\alpha]_D^{18}$ +29° (*c* 0·79 in $CHCl_3$) (Found: C, 73·4; H, 9·6. Calc. for $C_{34}H_{52}O_6$: C, 73·3; H, 9·4%). It was undepressed in m. p. by an authentic specimen, m. p. 167—168°, $[\alpha]_D$ +28°, which is a second crystalline form.

Reactions of Alphitonin.—(i) *Acetylation.* The compound, crystallised from hot water, had m. p. 219—220° (darkens 200°), α 0 in concentrated acetone solution. Various acetylation techniques were tried, but gums resulted. One product had $\nu_{max.}$ 1765 and 1715 cm.$^{-1}$ (liquid film).

(ii) *Alkaline fission.* A solution of alphitonin (2 mg.) in 60% aqeous potassium hydroxide (1 c.c.) was refluxed for 5 min., acidified with 10N-hydrochloric acid, and extracted with ether. A few drops of ether solution were applied to Whatman No. 1 paper; development with butan-1-ol–water showed protocatechuic acid, detected by spraying with diazotised *p*-nitroaniline and overspraying with aqueous sodium carbonate.

Alphitonin Pentamethyl Ether.—Alphitonin (100 mg.), dimethyl sulphate (0·6 c.c.), and potassium carbonate (1 g.) were left in acetone (5 c.c.) at about 20° for 10 days with occasional shaking. After evaporation the organic material was extracted with ethyl acetate, and the product chromatographed on deactivated alumina, to give a pale green gum which crystallised from ethanol as colourless prisms (95 mg.), m. p. 119—120° (Found: C, 64·3; H, 6·05; OMe, 41·15. Calc. for $C_{20}H_{22}O_7$: C, 64·2; H, 5·9; 5OMe, 41·4%), $\lambda_{min.}$ 248 (log ε 3·08), $\lambda_{max.}$ 290 mμ (log ε 4·31).

A 10% solution of bromine in carbon tetrachloride was slowly added to the ether (100 mg.) in carbon tetrachloride (4 c.c.) until the colour persisted for about a minute. Worked up as usual, *dibromoalphitonin pentamethyl ether* formed colourless crystals (105 mg.), m. p. 187° (from methanol). Recrystallisation from methanol–chloroform raised the m. p. to 193—194° (Found: C, 44·75; H, 3·5; Br, 30·6; OMe, 28·5. $C_{20}H_{20}O_7Br_2$ requires C, 45·1; H, 3·75; Br, 30·1; 5OMe, 29·1%).

Alphitonin pentamethyl ether (50 mg.) in acetic acid (2 c.c.) containing 10% of concentrated nitric acid was left overnight. Worked up as usual, *nitroalphitonin pentamethyl ether* crystallised from methanol–benzene as pale yellow prisms (38 mg.), m. p. 167° (Found: C, 57·7; H, 5·2; N, 3·75; OMe, 34·1. $C_{20}H_{21}O_9N$ requires C, 57·3; H, 5·05; N, 3·3; 5OMe, 36·9%).

Alphitonin pentamethyl ether was heated on the steam-bath with an equal weight of hydroxylamine hydrochloride in pyridine for 10 hr. Isolated as usual and crystallised from ethyl acetate–methanol, *alphitonin pentamethyl ether oxime* had m. p. 224° (Found: C, 61·3; H, 6·1; N, 3·5. $C_{20}H_{23}O_7N$ requires C, 61·7; H, 5·95; N, 3·6%).

Oxidation of Alphitonin Pentamethyl Ether.—(i) *With chromic acid.* To alphitonin pentamethyl ether (400 mg.) in acetic acid (10 c.c.), powdered chromium trioxide (1 g.) was added with stirring during 30 min. After 3 hr. the mixture was added to water and extracted with ether, and the ether washed with sodium carbonate solution. Evaporation, and addition of methanol, gave pale yellow (?) 4,7-*dihydro*-2-(3,4-*dimethoxybenzyl*)-2,6-*dimethoxycoumaran*-3,4,7-*trione*, m. p. 200° (decomp.) (Found: C, 60·1; H, 5·35; OMe, 32·8. $C_{19}H_{18}O_8$ requires C, 61·0; H, 4·85; 4OMe, 33·1%).

(ii) *With potassium permanganate.* Finely powdered alphitonin pentamethyl ether (100 mg.) and excess of potassium permanganate in 1% aqueous sodium carbonate were refluxed for 2 hr. From the aqueous solution a small amount of veratric acid was obtained; purified by sublimation and crystallisation from benzene, it had m. p. and mixed m. p. 182°.

Reduction of Alphitonin Pentamethyl Ether.—The pentamethyl ether (500 mg.) in ethylene glycol dimethyl ether (8 c.c.) was added to liquid ammonia (30 c.c.). Sodium (80 mg.) was added in small pieces. After 5 min., water (1 c.c.) was added and the ammonia evaporated. The organic product was taken up in ethyl acetate and washed with 2% aqueous sodium hydroxide to remove phenolic material. The 2-benzyl-3′,4′,4,6-tetramethoxycoumaran-3-one crystallised from methanol as colourless needles (350 mg.), m. p. 125—127°, raised by

recrystallisation from ethanol to 127—128° (Found: C, 65·8; H, 5·85; OMe, 35·6. Calc. for $C_{19}H_{20}O_6$: C, 66·3; H, 5·85; 4OMe, 35·95%), $\lambda_{min.}$ 248 (log ε 3·36), $\lambda_{max.}$ 282 mμ (log ε 4·38).

This coumaranone (100 mg.) in ethylene glycol dimethyl ether (10 c.c.) was added to a solution of potassamide (from 250 mg. of potassium) in liquid ammonia. After 10 min., ethanol (9·5 c.c.) and water (2 c.c.) were added, and the mixture was evaporated, acidified, and extracted with ethyl acetate. Crystallisation from methanol gave 2′-hydroxy-3,4,4′,6′-tetramethoxychalcone as yellow plates (60 mg.), m. p. 150° (Found: C, 65·8; H, 5·9; OMe, 35·7. Calc. for $C_{19}H_{20}O_6$: C, 66·3; H, 5·85; 4OMe, 35·9%).

Ozonolysis of the chalcone in ethyl acetate at 0° until the yellow colour had disappeared, reduction of the ozonide with zinc dust, and addition of the solution to Brady's reagent gave mixed 2,4-dinitrophenylhydrazones. The more soluble derivative was extracted with boiling benzene, chromatographed in chloroform on deactivated alumina, and crystallised from chloroform–ethyl acetate. It proved to be veratraldehyde 2,4-dinitrophenylhydrazone, m. p. and mixed m. p. 264°, with the correct infrared spectrum.

The benzene-insoluble derivative was soluble in sodium hydroxide solution and was purified by crystallisation from acetone as bright red needles, m. p. 232°. It is probably *2-hydroxy-4,6-dimethoxyphenylglyoxal 2,4-dinitrophenylhydrazone* (Found: C, 48·9; H, 3·85; N, 14·65. $C_{16}H_{14}O_8N_4$ requires C, 49·23; H, 3·6; N, 14·4%).

The above chalcone was synthesised in the usual manner [9] from phloracetophenone 2,4-dimethyl ether and veratraldehyde, m. p. 156°, undepressed by the substance above and identical in infrared spectrum. It was converted in the usual way by 1% ethanolic hydrochloric acid [9] into 3′,4′,5,7-tetramethoxyflavanone,[10] m. p. 161°, which gave the characteristic red colour with magnesium and hydrochloric acid in ethanol,[11] unlike the isomeric compound obtained above by the reduction of alphitonin pentamethyl ether.

2-Benzyl-3′,4′,4,6-tetramethoxycoumaran-3-one.—This was synthesised (cf. Gripenberg [12]) by preparing the benzylidenecoumaronone from the chalcone above and hydrogenating it with hydrogen in the presence of Adams catalyst. The product, m. p. 127—128°, was identified as the reduction product of alphitonin pentamethyl ether above by mixed m. p. and identity of infrared spectra.

Action of Potassamide in Liquid Ammonia on Alphitonin Pentamethyl Ether.—(i) A solution of alphitonin pentamethyl ether (500 mg.) in ethylene glycol dimethyl ether (8 c.c.) was added to potassamide (from 100 mg. of potassium) in liquid ammonia. After 15 min. ethanol (1 c.c.) and water (2 c.c.) were added and the ammonia was evaporated off. Extraction with ethyl acetate gave a pale yellow oil which crystallised from ethanol as colourless needles (330 mg.), m. p. 148°; this *substance* had $\nu_{max.}$ 3420, 3180, and 1685 cm.$^{-1}$ (in Nujol) (Found: C, 61·25; H, 6·55; N, 3·6; OMe, 39·05. $C_{20}H_{25}O_7N$ requires C, 61·4; H, 6·4; N, 3·6; 5OMe, 39·55%).

(ii) When more potassamide (from 500 mg. of potassium) was used, the product (240 mg.) crystallised from ethyl acetate as colourless prisms, m. p. 169°. The reactions below show it to be *α,3,4-trimethoxycinnamamide* (Found: C, 61·1; H, 6·4; N, 6·9; OMe, 38·45. $C_{12}H_{15}O_4N$ requires C, 60·75; H, 6·4; N, 5·9; 3OMe, 39·15%); it had $\nu_{max.}$ 3330, 3170, and 1607 cm.$^{-1}$ (in Nujol) and $\lambda_{max.}$ 291 (log ε 4·34) and 313 mμ (log ε 4·34).

The amide (100 mg.) was refluxed in 10% ethanolic potassium hydroxide (5 c.c.) for 2 hr. Acidification and extraction with ethyl acetate gave *α,3,4-trimethoxycinnamic* acid (65 mg.), m. p. 156—158° (from benzene) (Found: C, 60·35; H, 5·85; OMe, 38·15%; equiv., 232. $C_{12}H_{14}O_5$ requires C, 60·5; H, 5·9; 3OMe, 39·0%; equiv., 238). Esterification with diazomethane and reaction with aqueous ammonia regenerated the amide, m. p. and mixed m. p. 169°.

α,3,4-Trimethoxycinnamic acid (60 mg.) in ethylene glycol dimethyl ether (6 c.c.) was added to liquid ammonia (20 c.c.), and sodium (30 mg.) added, followed by solid ammonium chloride. Evaporation of the ammonia, acidification, and extraction with ether gave an oil that crystallised with some difficulty from benzene–light petroleum (b. p. 60—80°) to give needles of β-(3,4-dimethoxyphenyl)propionic acid (15 mg.), m. p. and mixed m. p. 98—99°, with the correct infrared spectrum.

α,3,4-Trimethoxycinnamamide (50 mg.) in ethyl acetate (5 c.c.) was hydrogenated in the

[9] Cf. Geissman and Clinton, *J. Amer. Chem. Soc.*, 1946, **68**, 697.
[10] Geissman and Fukushima, *J. Amer. Chem. Soc.*, 1948, **70**, 1686.
[11] Pew, *J. Amer. Chem. Soc.*, 1948, **70**, 3031.
[12] Gripenberg, *Acta Chem. Scand.*, 1953, **11**, 1323.

presence of palladium–charcoal. Worked up as usual, the product was β-3,4-*dimethoxyphenyl*-α-*methoxypropionic acid*, m. p. 112° [from benzene–light petroleum (b. p. 60—80°)] (Found: C, 60·1; H, 6·8. $C_{12}H_{17}O_4N$ requires C, 60·2; H, 7·2%).

Ozonolysis of α,3,4-*Trimethoxycinnamamide.*—The amide (50 mg.) in ethyl acetate (3 c.c.) and chloroform (3 c.c.) was ozonised at 0° for 10 min.; zinc dust (100 mg.), water (0·5 c.c.), and acetic acid (0·5 c.c.) were added, and the whole was shaken at room temperature for 15 min. and left for a further 30 min. After filtration and evaporation, the residue was extracted with ether and with acetone, and the combined extracts were evaporated. The semisolid residue was divided into fraction (A) soluble in light petroleum (b. p. 60—80°) and (B) an insoluble residue. Fraction B was repeatedly crystallised from benzene, to give colourless needles, m. p. 122—123°, identified as methyl oxamate by mixed m. p. and by means of its infrared spectrum. Fraction A gave a dark red 2,4-dinitrophenylhydrazone (purified by chromatography on deactivated alumina and crystallisation from ethyl acetate–chloroform), m. p. 264°, identified by its mixed m. p. and infrared spectrum as the derivative of veratraldehyde.

Amide Fission of 2′,3,4,4′,6′-*Pentamethoxychalcone.*—The chalcone (250 mg.) in ethylene glycol dimethyl ether (5 c.c.) was added to potassamide (from potassium, 400 mg.) in liquid ammonia (20 c.c.). After 25 min. water (2 c.c.) was added, the ammonia evaporated off, and the residue extracted with ethyl acetate. The extract gave 3,4-dimethoxycinnamamide (40 mg.) [purified by crystallisation from benzene–light petroleum (b. p. 60—80°)], m. p. and mixed m. p. 168°.

Synthesis of Alphitonin Pentamethyl Ether (2-*Benzyl*-3′,4′,4,6-*pentamethoxycoumaran*-3-*one*).—2′-Hydroxy-α,3,4,4′,6′-pentamethoxychalcone was prepared by condensing 2-hydroxy-ω,4,6-trimethoxyacetophenone [6] with veratraldehyde by Kimura's method.[7] Cyclisation was by two procedures:

(i) *Cyclisation with alkali.* The chalcone (1·5 g.) in warm ethanol (3·2 c.c.) was added to sodium hydroxide (0·3 g.) in water (17·5 c.c.). After 40 hr. at room temperature the dark red solution was refluxed for 5 hr.; an oil began to separate after 3 hr. On cooling, the product was extracted with ether and the gum chromatographed on alumina in benzene. The resulting gum crystallised on contact with methanol; recrystallisation from methanol gave 2-benzyl-2,3′,4′,4,6-pentamethoxycoumaran-3-one (0·4 g.), m. p. 118—119° (Found: C, 64·0; H, 5·8. Calc. for $C_{20}H_{22}O_7$: C, 64·2; H, 5·9%). Mixed m. p. and infrared spectra showed it had to be identical with alphitonin pentamethyl ether. Acidification of the aqueous alkaline layer gave recovered chalcone (0·8 g.).

(ii) *Cyclisation with acid.* The chalcone (1·5 g.) in ethanol (225 c.c.), water (22 c.c.), and 10N-hydrochloric acid (9 c.c.) was refluxed for 6 hr., the yellow colour almost disappearing. After evaporation under reduced pressure, water was added to the residue, and the product extracted with ether. After being washed with alkali, the neutral gum (0·75 g.) was dissolved in methanol; crude pentamethyl ether (0·3 g.) was deposited on seeding. Further crystallisation raised the m. p. to 118—119°, alone or on admixture with the above compounds.

Acidification of the alkaline washings and extraction with ether yielded a pale brown gum (0·55 g.), which crystallised from chloroform–light petroleum (b. p. 60—90°) as plates (0·3 g.), m. p. 85—120°. When shaken with a little benzene this material dissolved but crystallised again almost immediately as colourless prisms, m. p. 176—177°. Recrystallised from methanol, it had m. p. 177—178°; it is almost certainly 2-hydroxy-3′,4′,4,6-tetramethoxy-2-benzylcoumaranone (Found: C, 63·1; H, 5·6. Calc. for $C_{19}H_{20}O_7$: C, 63·6; H, 5·6%). Kimura [7] described this substance (his m. p. 176°) as 3-hydroxy-3′,4′,5,7-tetramethoxyflavanone, but Gripenberg [12] and Kubota [13] both favour the benzylidenecoumaranone structure.

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[13] Kubota, *J. Chem. Soc. Japan*, 1952, **73**, 571.