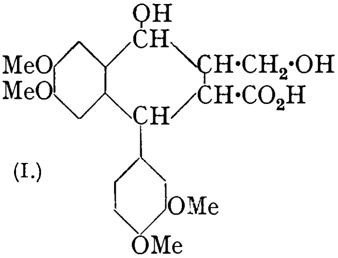
53. *The Constituents of Natural Phenolic Resins. Part XIX. The Action of Formalin on* 4-*Keto*-6 : 7-*dimethoxy*-1-*veratryl*-1 : 2 : 3 : 4-*tetrahydronaphthalene*-2-*carboxylic Acid.*

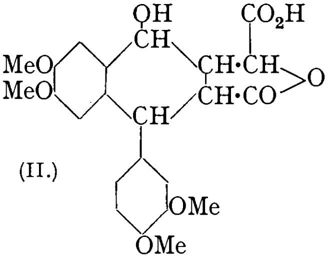
By Robert D. Haworth and George Sheldrick.

Formalin reacts almost quantitatively with cold alkaline solutions of 4-keto-6 : 7-dimethoxy-1-veratryl-1 : 2 : 3 : 4-tetrahydronaphthalene-2-carboxylic acid, yielding a substance with ketonic, alcoholic, and lactonic properties. The reactions of the product indicate that it has structure (V).

In the work described in Part II (J., 1935, 636) the compounds (I) and (II) were synthesised and converted by the action of heat into the α- and the β-form respectively of the lactone (III; R = H). Attempts to isolate the expected lactone (III; R = OH) or the dihydronaphthalene dehydration product were unsuccessful, and, as lactones of type (III; R = OH) are of interest in connection with the chemistry of picropodophyllin (see J., 1935, 1576; 1938, 348), an alternative route involving the action of formalin on 4-keto-6 : 7-dimethoxy-1-veratryl-1 : 2 : 3 : 4-tetrahydronaphthalene-2-carboxylic acid (IV) was examined. Most of the experimental work described in this communication was carried out in 1935 and a structural interpretation of the reaction, based on some new analytical results and also on the additional knowledge emerging in the meantime from other investigations in this series, is now possible.



(I.)



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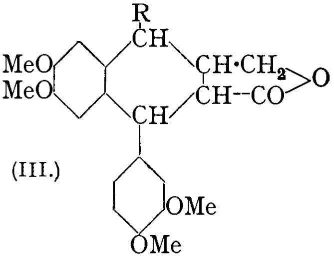
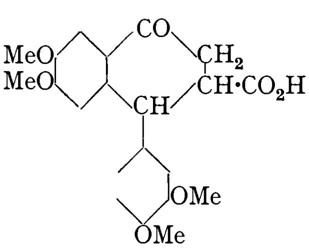
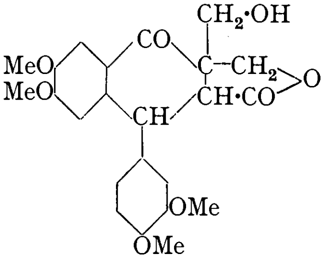


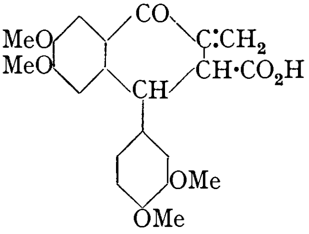
(III.)



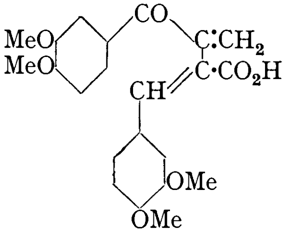
(IV.)



(V.)



(VI.)



(VII.)

An alkaline solution of the acid (IV) reacts at room temperature with excess of formalin, yielding a *substance* (A) which separates from methyl alcohol in a form, m. p. 174°, from acetone in a form, m. p. 120°, and from benzene in a form, m. p. 103—104°, containing two molecules of solvent of crystallisation. Further work is required to determine the relationship between the two unsolvated forms, m. p. 174° and 120°, but they are closely related and the reactions and derivatives described below are given by either modification. The analytical data of the unsolvated forms agree with the formula $C_{23}H_{24}O_8$, and suggest the elimination of water from a primary condensation product of two molecules of formaldehyde with one molecule of acid (IV). Zerewitinoff determinations and the formation of a crystalline *monoacetyl* derivative, m. p. 160—162°, show the presence of one hydroxyl group in the substance (A), which also possesses feeble ketonic properties, prolonged treatment yielding a *semicarbazone*, m. p. 242—244° (decomp.). The insolubility in sodium carbonate solution and the recovery after attempted esterification with methyl-alcoholic hydrogen chloride show that (A) is not a carboxylic acid. It dissolved very slowly in cold dilute sodium hydroxide solution, but more rapidly on warming with the evolution of formaldehyde, which was isolated as the dimedon derivative, m. p. 183°. Acidification of the alkaline residue liberated a *carboxylic acid* (B), m. p. 175—177°, which slowly crystallised from benzene–light petroleum and has the composition $C_{22}H_{22}O_7$.

The properties of (A) are consistent with structure (V), and the ready elimination of formaldehyde is analogous to the reversed aldol reactions discussed by Kenner and collaborators (J., 1928, 2698; 1930, 919. See also Welch, J., 1930, 257). The presence of at least one hydroxymethyl group, at position 3, was established by the reduction of (V) with amalgamated zinc and hydrochloric acid; an oily product was obtained which yielded 6 : 7-dimethoxy-1-veratryl-3-methylnaphthalene (J., 1938, 810) on heating with selenium. The absence of the readily detectable dehydroguaiaretic acid dimethyl ether (6 : 7-dimethoxy-1-veratryl-2 : 3-dimethylnaphthalene) in the dehydrogenation products is consistent with structure (V) and excludes an alternative structure in which the second hydroxymethyl group is associated with position 2 of the naphthalene nucleus.

The acid (B), obtained from (A) by elimination of formaldehyde and represented by structure (VI), lacks ketonic properties and resists lactonisation. A similar inhibition of ketonic and ethylenic functions is observed with many αβ-unsaturated ketones, including the open-chain analogues of type (VII). In the latter case lactonisation occurs when the ketonic group is destroyed during conversion into a naphthalene derivative (J., 1935, 1576), and it has been found that reduction of the ketonic group in (VI) may be accompanied by lactonisation. Reduction of the acid (VI) by Clemmensen's method yielded a complex mixture, from which a lactone, m. p. 209°, identical with the β-form of (III; R = H) was isolated in small yield, together with an acid, m. p. 220—222°, which has been identified by comparison with an authentic specimen of 6 : 7-dimethoxy-1-veratryl-3-methyl-1 : 2 : 3 : 4-tetrahydronaphthalene-2-carboxylic acid (J., 1938, 812).

The direct conversion of (IV) and (VI), or its hydration product, has not been realised in spite of numerous variations of the experimental conditions.

EXPERIMENTAL.

Lactone of 4-Keto-6 : 7-dimethoxy-1-veratryl-3 : 3-bishydroxymethyl-1 : 2 : 3 : 4-tetrahydronaphthalene-2-carboxylic Acid (V).—A solution of the acid (IV) (10 g.) (J., 1935, 641) in 8% sodium hydroxide solution (20 c.c.) and 40% formalin (20 c.c.) was kept for 12 hours at room temperature. After dilution with water (40 c.c.) the solution was acidified with concentrated hydrochloric acid, and the turbid solution extracted twice with ether and twice with chloroform. The combined extracts were dried with sodium sulphate, the solvents removed, and the semi-solid residue crystallised from methyl alcohol, giving colourless prisms (9·8 g.), m. p. 174° (Found : C, 64·2, 64·4; H, 5·8, 6·0; OH, 4·4. $C_{23}H_{24}O_8$ requires C, 64·5; H, 5·7; OH, 4·0%). Crystallisation of the crude product or the form, m. p. 174°, from acetone yielded colourless prisms, m. p. 120° (Found : C, 64·3; H, 5·9; OH, 4·3%), which were converted into the form, m. p. 174°, on crystallisation from methyl alcohol. Either of these forms separated from benzene in prisms, which softened at 75° and melted at 103—104° (Found : C, 71·8, 71·8; H, 6·3, 6·2; loss at 80° in a vacuum, 26·2. $C_{23}H_{24}O_8,2C_6H_6$ requires C, 71·9; H, 6·2; loss, 26·7%). The *monoacetyl* derivative, prepared in 95% yields by boiling any of the three forms of (V) with acetic anhydride for 2 hours, crystallised from methyl alcohol in colourless prisms, m. p. 160—162° [Found : C, 63·6, 63·9; H, 5·6, 5·9; acetyl (Freudenberg), 8·5, 8·9. $C_{25}H_{26}O_9$ requires C, 63·8; H, 5·6; acetyl, 9·1%], which yielded the lactone (V) on hydrolysis with toluene-*p*-sulphonic acid during the acetyl estimation. The *semicarbazone*, obtained by refluxing with semicarbazide hydrochloride and potassium acetate in alcohol for 48 hours, separated from methyl alcohol in micro-crystals, m. p. 242—244° (decomp.) (Found : N, 9·0. $C_{24}H_{27}O_8N_3$ requires N, 8·7%).

4-*Keto*-6 : 7-*dimethoxy*-1-*veratryl*-2-*methylene*-1 : 2 : 3 : 4-*tetrahydronaphthalene*-2-*carboxylic Acid* (VI).—After the lactone (V) (2 g.) and 5% sodium hydroxide solution (50 c.c.) had been warmed on the water-bath for 1 hour, the mixture was concentrated to about half bulk, and the distillate warmed for 15 minutes with an alcoholic solution of dimedon. The formaldehyde dimedon compound, m. p. 183°, was collected after standing overnight. The alkaline residue was acidified with concentrated hydrochloric acid, and the gummy product extracted three times with ether. The acid was removed from the extract by washing with sodium bicarbonate solution, recovered, taken up in ether, and dried with sodium sulphate. Removal of the ether left an oil, which crystallised very slowly from benzene–light petroleum (b. p. 60—80°). A second crystallisation (carbon) yielded colourless prisms (0·6 g.), m. p. 175—177° (Found : C, 66·5, 66·4; H, 5·3, 5·3. $C_{22}H_{22}O_7$ requires C, 66·3; H, 5·5%).

Conversion of (V) *into* 6 : 7-*Dimethoxy*-1-*veratryl*-3-*methylnaphthalene*.—The lactone (V) (2 g.), amalgamated zinc (10 g.), and concentrated hydrochloric acid (10 c.c.) were refluxed for 24 hours. After dilution with water the mixture was extracted with ether, washed several times with 1% sodium hydroxide solution, dried, and distilled. The fraction (1 g.), b. p. 240—270°/0·4 mm., was heated with selenium (1 g.) at 280—300° for 24 hours. The product was isolated with chloroform, the solvent removed, and the residue taken up in ether, filtered from impurities, and purified by sublimation at 0·2 mm. and finally by crystallisation from light petroleum (b. p. 60—80°). 6 : 7-Dimethoxy-1-veratryl-3-methylnaphthalene was obtained in stout prisms (0·1 g.), m. p. 140—141°, identical with the specimen obtained previously (J., 1937, 1646; 1938, 812). The picrate, red needles, m. p. 133°, was also prepared.

Conversion of (VI) *into* (II; R = H) *and* 6 : 7-*Dimethoxy*-1-*veratryl*-3-*methyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene*-2-*carboxylic Acid*.—The acid (VI) (4 g.), amalgamated zinc (20 g.), and concentrated hydrochloric acid (20 c.c.) were refluxed for 36 hours. The product, isolated with chloroform, was a brown oil, which was dissolved in warm 8% sodium hydroxide solution (20 c.c.). The neutral impurities, removed in ether, were not investigated. The alkaline layer was acidified with concentrated hydrochloric acid and heated on the water-bath for 1 hour, and the product extracted with chloroform. After removal of carboxylic acids and phenols by shaking with dilute sodium hydroxide solution, the lactonic product was recovered from the chloroform and purified by sublimation at 0·4 mm. The sublimate crystallised from methyl alcohol–chloroform in stout prisms (0·02 g.), m. p. 209—210°, which did not depress the m. p. of a specimen of the β-form of (III; R = H) (J., 1935, 643). The sodium hydroxide solution containing carboxylic acids and phenolic impurities was acidified, and the product (1·5 g.), isolated with chloroform, was refluxed with methyl-alcoholic hydrogen chloride (30 c.c.) for 12 hours, diluted with water, and extracted with ether. The extract was washed several times with 2% sodium hydroxide solution, which removed a considerable quantity of dark-coloured impurity, and evaporated. The residual oil was hydrolysed with 10% methyl-alcoholic potassium hydroxide (10 c.c.), most of the alcohol was removed, and after the addition of water the mixture was acidified and extracted with ether. The extract yielded a crude brown acid, which was taken up in sodium bicarbonate solution, filtered from impurities, recovered from the filtrate, dried, and crystallised three times from benzene (carbon); 6 : 7-dimethoxy-1-veratryl-3-methyl-1 : 2 : 3 : 4-tetrahydronaphthalene-2-carboxylic acid was obtained in colourless nodules (0·2 g.), m. p. 220—222°, which gave no depression in m. p. when mixed with the specimen synthesised previously (J., 1938, 813).

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