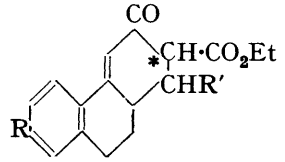
172. *Experiments on the Synthesis of Substances Related to the Sterols. Part X. Condensation of Furfurylidenetetralone with Ethyl Acetoacetate, and Analogous Studies.*

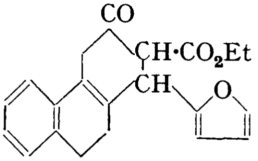
By D. A. Peak, Robert Robinson, and James Walker.

Knoevenagel's synthesis of *cyclo*hexenones from ethyl acetoacetate and unsaturated ketones can be applied to the preparation of potential intermediates for oestrone and analogous substances and the value of this route is being estimated in several directions in this laboratory.

Substances of the type (I) should be obtainable by one of two alternative methods: (a) by condensation of an alkylidene (or arylidene)-α-tetralone with ethyl acetoacetate, which is an adaptation of the normal known process, and (b) by the condensation of an α-tetralone with an alkylidene (or arylidene) derivative of ethyl acetoacetate.

(I.)





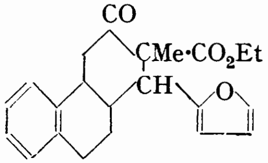
(II.)

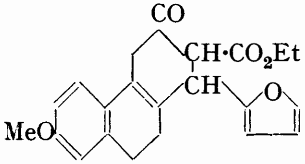
Suppose, for example, that R is MeO and R' is $\cdot CH_2CH_2\cdot CO_2Et$; then methylation at the asterisked carbon atom, reduction of the *cyclo*hexanone ring, and ketonisation should afford the methyl ether of a stereoisomeride of oestrone. This attractive scheme has not yet been realised because 6-methoxy-2-γ-carbethoxypropylidene-α-tetralone could not be obtained by the condensation of 6-methoxytetralone with ethyl β-formylpropionate and 6-methoxytetralone could not be condensed with *ethyl γ-carbethoxypropylideneacetoacetate*, $CH_3\cdot CO\cdot C(CO_2Et){:}CH\cdot CH_2\cdot CH_2\cdot CO_2Et$ (III). Further experiments in these directions are in progress, but in the meantime we have also examined simpler cases in which the group

R′ could be suitably modified at the appropriate stage. For example, the furyl radical has been employed because it could be oxidised to carboxyl or even form the source of a side chain terminated by a carboxyl group.

We have obtained (I; R = H, R′ = C_4H_3O) from ethyl furfurylideneacetoacetate and α-tetralone and, better, from *2-furfurylidene-α-tetralone* and ethyl acetoacetate. In the latter reaction sodium ethoxide is used as a catalyst in alcoholic solution and the first product is a bright yellow substance, which is gradually changed by the action of the reagent into an almost colourless isomeride. The yellow *α-form* is considered to be an αβ-unsaturated ketone (I) and the *β-form* is probably (II). Neither form can be directly *C*-methylated and the *β-form* is resistant to catalytic hydrogenation. The yellow α-variety affords, however, a *dihydro*-derivative and this has been methylated to the *keto-ester* (IV).

(IV.)



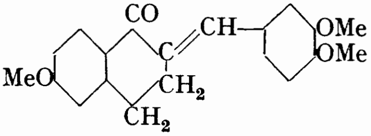


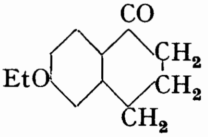
(V.)

The extension to the *6-methoxy-2-furfurylidene-α-tetralone* series has been commenced, but the product of condensation of this substance with ethyl sodioacetoacetate is probably (V) because it is not smoothly hydrogenated in the presence of a catalyst. The anticipated volume of the gas was slowly absorbed, but the unchanged ester was recovered in large relative amount. Evidently a portion of the product suffers hydrogenation of one or both of the aromatic nuclei. We shall return to this subject when further supplies of *γ-m*-methoxyphenylbutyric acid are available, the line of work adumbrated in Part IX (preceding paper) having priority.

We have also had occasion to prepare *6-methoxy-2-veratrylidene-α-tetralone* (VI) from 6-methoxytetralone and veratraldehyde by condensation in the usual manner in ethyl-alcoholic solution in the presence of sodium hydroxide. The apparently homogeneous product gave consistently high values for carbon content and many recrystallisations failed to remove the impurity.

(VI.)





(VII.)

The results suggested replacement of a methoxyl by an ethoxyl group and when methyl alcohol was used as solvent the analytical results were in perfect agreement with the anticipations of theory. Hence we prepared *6-ethoxy-α-tetralone* (VII) and condensed it with veratraldehyde in ethyl-alcoholic solution. The resulting *6-ethoxy-2-veratrylidene-α-tetralone* gave perfect analytical data, but was *not identical* with the abnormal compound mentioned above. The m. p.'s of these substances are grouped within a small range and mixtures show only small depressions; hence we conclude that exchange of alkoxyl does in fact occur in the reactive states of the molecules, but it is probably not confined to the 6-position in the tetralone nucleus.

EXPERIMENTAL.

Ethyl β-Formylpropionate.—Contrary to Wislicenus, Böklen, and Reuthe (*Annalen*, **1908**, **363**, 353) and in agreement with Sugasawa (*J. Pharm. Soc. Japan*, 1926, No. 534, 64; *Chem. Zentr.*, 1927, I, 1463) hydrolysis of ethyl hydroxymethylenesuccinate by means of water yields ethyl β-formylpropionate and not the free acid.

Ethyl hydroxymethylenesuccinate (100 g.) (Wislicenus, Böklen, and Reuthe, *loc. cit.*, p. 347) was heated with distilled water (250 c.c.) containing sodium acetate (1·0 g.) in an autoclave at 130—150° for 1½—2 hours. Care was taken to protect the liquid from contact with the walls and thermometer stem of the autoclave during the hydrolysis, as the yield was greatly diminished if this precaution was not observed. The product was taken up in ether after saturation of the aqueous layer with sodium chloride and the extract was dried over sodium sulphate and evaporated. The aldehydo-ester had b. p. 82—95°/10 mm. (practically all at 82—87°) (yield, 50 g.), $n_D^{14^\circ}$ 1·425, and was a colourless mobile oil having a characteristic odour.

Ethyl γ-Carbethoxypropylideneacetoacetate (III).—(A) A mixture of ethyl β-formylpropionate (1·7 g.), ethyl acetoacetate (1·8 g.), and acetic anhydride (1·9 g.) was maintained at 100° for 22 hours. The residue after removal of the acetic anhydride by distillation up to 140° at the ordinary pressure was fractionated under reduced pressure, *ethyl γ-carbethoxypropylideneacetoacetate* (1·4 g.) passing over as a faintly yellow, limpid oil at 160—168°/16 mm., $n_D^{14^\circ}$ 1·4640 (Found: C, 58·1; H, 7·2%). The product gave a faint but definite pure blue colour in alcoholic ferric chloride, and this fact and the analysis suggested contamination with the saturated acetylated aldol.

(B) A mixture of ethyl β-formylpropionate (11·2 g.) and ethyl acetoacetate (11·8 g.) was cooled to − 10° and saturated with dry hydrogen chloride. After 15 hours at room temperature the mixture was added to water and extracted with ether. The extract was dried (anhydrous sodium sulphate) and evaporated. On fractionation of the crude product under reduced pressure there were obtained: (i) b. p. up to 150°/10 mm. (0·9 g.), (ii) b. p. 150—180°/10 mm. (16·5 g.). On further fractionation of (ii) the pure product (14·2 g.; 69% yield) was obtained, b. p. 168—170°/10 mm., as a faintly yellow, limpid oil, $n_D^{14^\circ}$ 1·4645 (Found: C, 59·2; H, 7·2. $C_{12}H_{18}O_5$ requires C, 59·5; H, 7·4%). The product was halogen-free and gave no ferric reaction.

Attempted Condensation of Ethyl γ-Carbethoxypropylideneacetoacetate with 6-*Methoxy-α-tetralone*.—(A) The sodio-derivative of the ketone (8·8 g.) was prepared by means of sodamide (2·0 g.) and dry ether (100 c.c.) in the usual way, and the ester (12·1 g.) in ether (60 c.c.) was then slowly added with stirring. There was no evolution of heat nor any separation of a solid, but the reaction mixture became dark-greenish brown. After being stirred for 8 hours and kept at room temperature for 30 hours, the product was added to water and extracted with ether after acidification of the aqueous layer with acetic acid. The product isolated in the usual way was fractionated under reduced pressure, 6-methoxytetralone (7·2 g.) being recovered, possibly contaminated with some of the ester (the b. p.'s are practically coincident). On continued distillation decomposition set in and a very small fraction was collected at about 200°/0·2 mm. which, from the analysis, was not the desired product (Found: C, 64·2; H, 7·2. $C_{23}H_{28}O_6$ requires C, 69·0; H, 7·0%. Calc. for $C_{24}H_{32}O_8$: C, 64·3; H, 7·1%). This fraction gave a blue ferric reaction which gradually became violet.

(B) The ester (2·5 g.) and methoxytetralone (1·7 g.) were dissolved in absolute alcohol (25 c.c.) containing sodium ethoxide (0·3 g. of sodium). After being kept for 8 days at room temperature, the brown solution was added to water, acidified with acetic acid, extracted with ether, and worked up in the usual way. On distillation under reduced pressure a fraction (2·7 g.) consisting essentially of methoxytetralone was obtained, b. p. 160—175°/14 mm. There was a very small fraction distilling at *ca.* 210°/0·2 mm. which gave a red ferric reaction; it was not analysed or further examined.

Attempted Condensation of 6-*Methoxytetralone with Ethyl β-Formylpropionate*.—(A) The ketone (1·2 g.) and the aldehydo-ester (1·08 g.) were dissolved in absolute alcohol (15 c.c.) in which a trace of potassium had been dissolved. After 48 hours the ketone was recovered unchanged on passing into water.

(B) When a solution of the ketone (1·7 g.) and the aldehydo-ester (1·6 g.) in glacial acetic acid (2 c.c.) and acetic anhydride (0·5 c.c.) was saturated with dry hydrogen chloride at − 15°, a substance separated in prisms, the colour of which slowly deepened to reddish-orange and then red. After 15 hours the reddish-crimson prisms, which melted on access of moisture, gave a practically colourless oil on addition of water. This crystallised rapidly and on drying was found to consist of methoxytetralone (1·52 g.), m. p. 72—77°. The aqueous mother-liquor had a yellow colour and strong green fluorescence.

2-*Furfurylidene-α-tetralone*.—Aqueous sodium hydroxide (2 c.c. of 8%) was added to a solution of freshly distilled furfuraldehyde (11·2 g.) and α-tetralone (17 g.) in ethyl alcohol (50 c.c.). The liquid immediately darkened and after an hour had deposited a voluminous mass of pale yellow needles. After 12 hours the crystals were collected and washed with ethyl alcohol. The product (22·9 g.) had m. p. 75—76°, unaltered by recrystallisation (Found: C, 80·4; H, 5·3. $C_{15}H_{12}O_2$ requires C, 80·3; H, 5·3%). A further quantity (1·7 g.) was obtained by dilution of the mother-liquor with water. The *substance* was dimorphous, crystallising from alcohol in needles or in prisms, the latter being the stable form.

Condensation of Furfurylidenetetralone with Ethyl Sodioacetoacetate.—(A) Sodium (1·5 g.;

2 atoms) was dissolved in absolute alcohol (50 c.c.), ethyl acetoacetate (16·5 g.; 4 mols.) and furfurylidenetetralone (7 g.; 1 mol.) added, and the solution made up to 70 c.c. with absolute alcohol. The solution was then heated under reflux and 10 c.c. were withdrawn at periods of 15 mins., 30 mins., 1, 2, 3, and 4 hours from the commencement of heating. Each portion was made slightly acid with glacial acetic acid immediately after withdrawal, sufficient water added to redissolve the precipitated gelatinous sodium acetate, and the clear solution kept in the ice-chest for several hours. The crystalline products were then collected and washed with ethyl alcohol. Approximately the same quantity (0·2 g.) was obtained from each portion, but the initially formed substance (m. p. 117—118°) was golden-yellow and the final product was only faintly yellow (m. p. 118—119°, lowered by admixture with the former substance). Intermediate fractions showed a gradual decrease of colour intensity, the m. p. reaching a minimum (108—110°) in the 1-hour and 2-hour fractions and then rising again. They were, therefore, mixtures of the initial and the final product. Numerous experiments, in which the concentrations, temperature and time of reaction were varied and also in the presence of dehydrating agents such as aluminium ethoxide, have failed, as yet, to effect an increase in the yield of either substance (see below for an important by-product).

The first-formed product (*α-modification*) crystallised from ethyl alcohol and acetic acid in needles (labile form changing to plates) and prisms respectively, m. p. 119—120° (Found: C, 74·7; H, 6·1. $C_{21}H_{20}O_4$ requires C, 75·0; H, 6·0%). It was freely soluble in ether, moderately in ethyl acetate, and sparingly in cold ethyl alcohol and acetic acid. A green coloration developed on addition of ferric chloride to an alcoholic solution.

The end product (*β-modification*) crystallised from ethyl alcohol in faintly yellow needles, m. p. 120—121° (Found: C, 74·7; H, 6·1%). Its solubilities in most solvents were very similar to those of the α-modification, but it gave a violet ferric reaction. The faint colour, which could not be removed by repeated crystallisation, was evidently due to traces of the α-modification, since reduction with zinc and acetic acid or aluminium amalgam and absolute ethyl alcohol gave a colourless product, m. p. 121—122° alone or mixed with unreduced material (Found: C, 74·7; H, 6·1%). Further reduction either by catalytic or by other methods was not found possible.

(B) Ethyl sodioacetoacetate was prepared from powdered sodium (1·5 g.; 2 atoms) and ethyl acetoacetate (9 g.; > 2 mols.) in dry ether (80 c.c.) and a solution of furfurylidenetetralone (7 g.; 1 mol.) in dry ether (100 c.c.) was then added. The solution was refluxed for 18 hours; the sodio-derivative then disappeared and a clear yellow solution resulted. An equal volume of water was added and the ethereal layer was separated, dried, and concentrated to 20 c.c. Crystallisation soon commenced and the golden-yellow product (1·35 g.) melted at 115—116° alone or mixed with the α-modification. The ether was completely removed from the mother-liquor, and the residue taken up in a little alcohol. The solution first deposited unchanged furfurylidenetetralone (1·5 g.) and then further crops, all of which were mixtures of unidentified constituents.

(C) α-Tetralone (14·6 g.) was converted into its sodio-derivative in dry dioxan (nitrogen) by means of sodamide (3·9 g.). Ethyl furfurylideneacetoacetate (20·8 g.), b. p. 160—165°/1·5 mm., was added. Subsequently the α-modification (1·1 g.) of the above ester could be isolated, m. p. 116° alone or mixed with an authentic specimen.

3-*Keto*-1-*furyl*-1 : 2 : 3 : 4 : 9 : 10-*hexahydrophenanthrene*.—Furfurylidenetetralone and ethyl sodioacetoacetate were condensed in the same proportion as above (A) by heating for 30 minutes, yielding the α-modification (1·8 g.). The mother-liquor was diluted with water, and the resultant oil isolated by means of ether; it distilled as a pale yellow, viscous liquid (3·0 g.), b. p. 200—220°/3 mm. The *substance* crystallised in contact with ethyl alcohol and was recrystallised from this solvent, separating in almost colourless prisms, m. p. 113—114° (Found: C, 81·8; H, 6·0. $C_{18}H_{16}O_2$ requires C, 81·8; H, 6·0%). The same substance was produced on hydrolysis of the β-modification (above) with dilute aqueous-alcoholic sodium hydroxide. Obtained by this method, it was colourless, m. p. 114—115° alone or mixed with the above (Found: C, 82·0; H, 6·1%). It is therefore probably also a βγ-unsaturated ketone and it is important to note that this substance is the main product of the condensation reaction.

Ethyl 3-*Keto*-1-*furyl*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydrophenanthrene*-2-*carboxylate*.—A 2% palladised strontium carbonate catalyst (0·5 g.) was shaken with ethyl acetate (10 c.c.) in hydrogen at atmospheric pressure until it was completely reduced. A solution of ethyl ketofurylhexahydrophenanthrenecarboxylate (0·38 g.) in ethyl acetate (10 c.c.) was then added, and the shaking continued; absorption of hydrogen (1 mol.) rapidly took place. The filtered ethyl acetate solution was evaporated; the residue crystallised on cooling. Recrystallised from ethyl alcohol, the *substance* separated in colourless square plates, m. p. 134·5—135·5° (Found: C, 74·6; H, 6·5. $C_{21}H_{22}O_4$ requires C, 74·6; H, 6·5%). The ferric coloration in alcohol was pale brown.

Ethyl 3-*Keto*-1-*furyl*-2-*methyl*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydrophenanthrene*-2-*carboxylate* (IV).—The last-described ester (3·0 g.) in dry benzene (60 c.c.) was heated with finely powdered potassium (0·4 g.) for 3 hours; the metal gradually disappeared and a clear yellow solution was obtained. Methyl iodide (3 g.) was then added and refluxing continued until the solution was almost decolorised and exhibited a neutral reaction towards litmus (12 hours). The precipitated potassium iodide was washed out with water, the benzene removed, and the residue, which crystallised in contact with ethyl alcohol, taken up in this solvent (10 c.c.). The solution deposited first unchanged material (1·4 g.) and then a crop (1·0 g.) of a different *substance*. This was recrystallised from ethyl alcohol, separating in hexagonal prisms, m. p. 93—93·5° (Found: C, 75·4; H, 6·8; OEt, 12·4. $C_{22}H_{24}O_4$ requires C, 75·0; H, 6·8; OEt, 12·8%). Further small quantities of this substance were gradually deposited by the mother-liquors. The ester gave no coloration with ferric chloride in alcoholic solution.

6-*Methoxy*-2-α-*furfurylidene*-α-*tetralone*.—This derivative was prepared in the same manner as furfurylidenetetralone, 6-methoxy-α-tetralone being used. It crystallised from alcohol in pale yellow needles, m. p. 104·5° (Found: C, 75·7; H, 5·5. $C_{16}H_{14}O_3$ requires C, 75·6; H, 5·5%).

Ethyl 3-*Keto*-7-*methoxy*-1-α-*furyl*-1 : 2 : 3 : 4 : 9 : 10-*hexahydrophenanthrene*-2-*carboxylate* (V).—A mixture of furfurylidenemethoxytetralone (12·5 g.), ethyl acetoacetate (26 g.), and alcoholic (100 c.c.) sodium (4·6 g.) ethoxide was refluxed for 4 hours, kept for 12 hours, and again refluxed for 3 hours. The sticky product obtained after the addition of water and acetic acid was well washed with water to remove unchanged ethyl acetoacetate, dissolved in alcohol, and kept in the ice-chest. The crystals obtained (5·6 g.) were a mixture, the main constituent being a *substance*, m. p. 137—138° after many recrystallisations (Found: C, 72·6; H, 6·1; MeO, 15·3%). The mother-liquor was kept in the ice-chest and deposited soft colourless crystals (6·2 g.), which, unlike the compound first isolated, developed a brownish-violet coloration with ferric chloride in alcoholic solution. This *substance* separated from alcohol in colourless matted needles, m. p. 122° (Found: C, 72·2; H, 5·9. $C_{22}H_{22}O_5$ requires C, 72·1; H, 6·0%). When it was shaken in hydrogen with ethyl acetate and a good platinum catalyst, 2·32 g. absorbed 315 c.c. in 5 hours. The isolated product crystallised from methyl alcohol as aggregates of very small, colourless needles, m. p. 112° (Found: C, 72·6; H, 6·3%). The m. p. was very slowly raised by crystallisation to about 118° and it was raised by admixture with the original ester, m. p. 122°. About half the product remained in the mother-liquor as an uncrystallisable oil. It is probable that dehydrogenation accompanied hydrogenation in this experiment.

6-*Methoxy*-2-*veratrylidene*-α-*tetralone*.—The product of condensation of veratraldehyde and methoxytetralone in ethyl-alcoholic solution, with 5*N*-aqueous sodium hydroxide as the catalyst, crystallised from ethyl alcohol in yellow flat needles or leaflets, m. p. 110—111° (Found: C, 74·7, 74·3, 74·6; H, 6·6, 6·4, 6·5. $C_{20}H_{20}O_4$ requires C, 74·1; H, 6·2%. $C_{21}H_{22}O_4$ requires C, 74·6; H, 6·5%). Material of this type was condensed with ethyl sodioacetoacetate under conditions similar to those used in other cases and a ferric-negative product was isolated in soft, colourless, prismatic needles, m. p. 123—124° by crystallisation from alcohol. We are unable to interpret the analysis (Found: C, 72·3; H, 6·3; MeO, 28·2%).

When the preparation was performed in methyl-alcoholic solution (see p. 753), the *product* crystallised in better-defined and longer, paler yellow needles, m. p. 111—112°, giving excellent analytical data (Found: C, 74·1, 74·3; H, 6·2, 6·4. $C_{20}H_{20}O_4$ requires C, 74·1; H, 6·2%).

6-*Ethoxy*-α-*tetralone* (VII).—The preparation of this substance was carried out by Mr. J. Resuggan. *m*-Ethoxybenzaldehyde (105 g.) (Werner, *Ber.*, 1895, **28**, 2001) was condensed with malonic acid (190 g.) in pyridine (450 c.c.) and piperidine (6 c.c.) for 4 hours on the steam-bath. The acid crystallised from 90% alcohol in long prismatic needles (135 g.), m. p. 129—130° (Werner, *loc. cit.*, gives m. p. 122°). A mixture of this acid (130 g.), toluene (400 c.c.), and 10% ethyl-alcoholic sulphuric acid (300 c.c.) was refluxed for 5 hours. The resulting *ester* (125 g.) had b. p. 158°/1 mm. and $n_D^{10°}$ 1·558 (Found: C, 70·9; H, 7·2. $C_{13}H_{16}O_3$ requires C, 70·9; H, 7·3%). Reduction under the usual conditions with hydrogen and a 2% palladised strontium carbonate catalyst furnished *ethyl* β-m-*ethoxyphenylpropionate* (yield, quantitative), b. p. 148°/0·2 mm., $n_D^{10°}$ 1·502 (Found: C, 70·3; H, 8·1. $C_{13}H_{18}O_3$ requires C, 70·3; H, 8·1%). This ester (55 g.) in anhydrous alcohol (450 c.c.) was reduced by means of sodium (36·5 g.) at 160°. γ-m-*Ethoxyphenylpropyl alcohol* was obtained in 82% yield (Found: C, 73·4; H, 8·9. $C_{11}H_{16}O_2$ requires C, 73·3; H, 8·9%), b. p. 130°/3 mm., $n_D^{10°}$ 1·526. [It has been observed (J. R.) that there is no increase in the yield in the Bouveault–Blanc reductions in this series when the amount of sodium employed exceeds 4 atoms; in fact the optimum yields are obtainable with rather less than the theoretically required quantity of the metal.] On treatment with thionyl chloride and dimethylaniline in the usual manner this alcohol (68 g.) afforded γ-m-*ethoxyphenylpropyl chloride* (70 g.), b. p. 111°/1 mm., $n_D^{10^\circ}$ 1·525 (Found: C, 66·7; H, 7·7. $C_{11}H_{15}OCl$ requires C, 66·5; H, 7·6%). Again following the methoxy-series, the chloride (68 g.) was converted through the *nitrile* (60 g.), b. p. 127°/0·6 mm., $n_D^{10^\circ}$ 1·519 (Found: C, 76·5; H, 8·1. $C_{12}H_{15}ON$ requires C, 76·2; H, 7·9%), into γ-m-*ethoxyphenylbutyric acid* (61 g.), which formed leaflets, m. p. 65—66°, from light petroleum (Found: C, 69·2; H, 7·8. $C_{12}H_{16}O_3$ requires C, 69·2; H, 7·7%). The related amide (2 g.) was obtained by crystallisation of the residue from the distillation of the nitrile; m. p. 84—85° after deposition from benzene.

The ethoxyphenylbutyric acid (58 g.) was heated with a mixture of sulphuric acid (400 c.c.) and water (230 c.c.) for 20 minutes on the steam-bath. Purified in the usual manner, the product (37 g.) eventually crystallised from light petroleum in colourless prisms, m. p. 46—47° (Found: C, 75·8; H, 7·6. $C_{13}H_{14}O_2$ requires C, 75·8; H, 7·4%).

The *veratrylidene* derivative crystallised from alcohol in pale yellow plates, m. p. 119—120° (Found: C, 74·5; H, 6·6. $C_{21}H_{22}O_4$ requires C, 74·6; H, 6·5%). A mixture with pure veratrylidenemethoxytetralone had m. p. 110—112° and the same value was found for the mixture with presumed veratrylidenemethoxytetralone prepared in ethyl-alcoholic solution.

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