trated nitric acid in slight excess, 28 g. of nitrate separated from which the base was liberated and converted to the picrate. The picrate after digestion with benzene was changed through the liberated base to the nitrate, a *selective* salt for this base. The nitrate crystallizes from acetone–ether in long slender needles melting with decomposition at 160.1°.

Anal. Calcd. for $C_{15}H_{19}N \cdot HNO_3$; C, 65.18; H, 7.23. Found: C, 64.99; H, 7.32.

Base.—This odorless base crystallizes from methyl alcohol in fine radiating needles and has the following constants: m. p. 69–70°; b. p. 330°; $n^{70}D$ 1.5618; $n^{44}D$ 1.5731.

Anal. Calcd. for $C_{15}H_{19}N$: C, 84.45; H, 8.98; N, 6.57. Found: C, 84.62; H, 9.12; N, 6.41.

Picrate.—This salt which, with the exception of glacial acetic acid, is difficultly soluble in ordinary solvents, crystallizes from 50% acetic acid in long lemon colored hexagonal needles melting undecomposed at 211–211.5°.

Anal. Calcd. for $C_{21}H_{22}O_7N_4$: C, 57.07; H, 5.01; N, 12.66. Found: C, 56.85; H, 5.08; N, 12.45.

Acid Sulfate.—On the addition of the calculated amount of concentrated sulfuric acid to the base in acetone, this salt precipitates. It crystallizes from *t*-butyl alcohol in small irregular platelets melting without decomposition at 230.5–231°.

Anal. Calcd. for $C_{15}H_{19}N \cdot H_2SO_4$: SO_4, 30.86. Found: SO_4, 30.91.

Hydrochloride.—This hygroscopic salt separates on passing dry hydrogen chloride into an ether solution of the base. No solvent was found for its recrystallization. It forms small lustrous ill-defined crystals melting undecomposed at 221–222°.

Anal. Calcd. for $C_{15}H_{19}N \cdot HCl$: Cl, 14.23. Found: Cl, 14.59.

2,3,4-Trimethylquinoline-8-carboxylic Acid.—The base (0.44 g.) is dissolved in a sufficient amount of 12 N sulfuric

acid to redissolve the initially precipitated acid sulfate and to the boiling solution 2.25 g. of potassium dichromate in 3 g. of concentrated sulfuric acid and 15 cc. of water is added dropwise over a period of forty minutes. The reaction mixture is made alkaline with ammonium hydroxide and then acidified with acetic acid. The chloroform extracted acid crystallizes from ethyl alcohol in long slender needles melting sharply and undecomposed at 234°; yield 0.090 g. A mixed melt of this product with an authentic sample of 2,3,4-trimethylquinoline-8-carboxylic acid[1] showed no depression.

Anal. Calcd. for $C_{13}H_{13}O_2N$: C, 72.53; H, 6.07; N, 6.51. Found: C, 72.23; H, 5.89; N, 6.48.

Synthesis of the Base.—In preparation of the intermediate, *o-n*-propylaniline from *n*-propylbenzene,[8] the procedure of Axe and Bailey[1] was followed. Molecular amounts of this base and methylacetylacetone are condensed in two steps,[5] with a yield of about 90%. The usual melting point comparison of the kero and synthetic bases established their identity.

Summary

This paper deals with multiple acid extraction in the isolation of a new $C_{15}H_{19}N$ kero base, 2,3,4-trimethyl-8-*n*-propylquinoline. Its structure has been established by chromic acid oxidation to a $C_{12}H_{12}NCOOH$ acid identical with the acid obtained by Axe and Bailey through a similar oxidation of 2,3,4,8 - tetramethylquinoline. This structure was confirmed through synthesis of the base from methylacetylacetone and *o-n*-propylaniline.

(8) *Cf.* Cohen, "Practical Organic Chemistry," The Macmillan Co., London, 1928, p. 155.

AUSTIN, TEXAS   RECEIVED MAY 19, 1939

The Chemistry of Vitamin E. XVIII. Condensation of Phenols and Hydroquinones with Allylic Alcohols, Allylic Halides, and Conjugated Dienes[1]

BY LEE IRVIN SMITH, HERBERT E. UNGNADE, J. R. STEVENS AND C. C. CHRISTMAN

In a previous paper[2] it was shown that isoprene could be condensed with 2,3,5-trimethylphenol to give the chroman I, and with trimethylhydroquinone to give the analogous chroman II. The same chroman, II, was obtained by condensing trimethylhydroquinone with γ,γ-dimethylallyl bromide.[3]
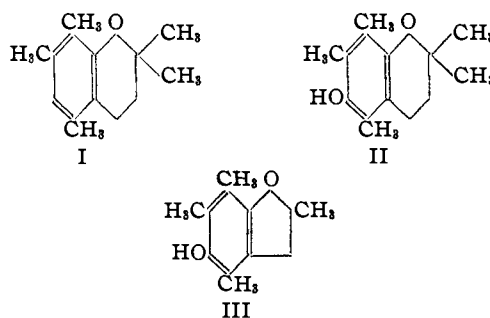
Several years ago Claisen[4] reported that allylic

(1) Paper XVII, THIS JOURNAL, 61, 2424 (1939). Presented at the 98th meeting of The American Chemical Society, Boston, Mass., September, 1939.

(2) Paper VI on Vitamin E, *J. Org. Chem.*, 4, 309 (1939).

(3) Paper V on Vitamin E, *ibid.*, 4, 305 (1939).

(4) German Patent 394,797 (1924).

carbinols as well as appropriate diols which gave dienes when catalytically dehydrated, would con-

dense with phenols to give chromans. This type of condensation has been modified for the preparation of α-tocopherol from trimethylhydroquinone and phytol by Bergel, Copping, Jacob, Todd and Work[5] and by us also.

Claisen implied that when allylic carbinols and diols condensed with phenols, the first step in the reaction involved formation of the diene which then condensed with the phenol, and when it was found that phytadiene could be condensed with trimethylhydroquinone to produce α-tocopherol,[2] Claisen's mechanism appeared to offer a common explanation for the formation of tocopherols from hydroquinones and phytyl bromide, phytol or phytadiene. In harmony with this conception was the formation of the chromans I and II when either γ,γ-dimethylallyl bromide or isoprene was used.

This mechanism, however, offers some difficulties when considered in the light of known facts regarding the addition of phenols to double bonds. In the first place, allyl alcohol, bromide and chloride all condense with 2,3,5-trimethylhydroquinone to give coumaran III and it is obvious that the diene-allene- cannot be an intermediate in this case unless an unusual mode of addition of the hydroquinone is postulated. Second, in some of the reactions between conjugated dienes and phenols, hydroquinones and their derivatives, allylic phenols or their HX addition products are formed and these may be cyclized in a separate operation, giving rise to the same cyclic compound whether the reaction is carried out in one step or in two.[2,4,6] With a substituted diene such as isoprene, therefore, it is again difficult to interpret the reaction as a direct addition of the phenol to the diene without assuming an unusual mode of addition, since the intermediate is known to contain a γ,γ-dimethylallyl group.

In order to reach a decision as to whether or not the diene is an intermediate, we have condensed ethylvinylcarbinol (IV) and pentadiene-1,3 (V) with trimethylhydroquinone under identical conditions. Since the diene to be expected

$$CH_3CH_2CHOHCH=CH_2 \quad (IV)$$
$$CH_3CH=CHCH=CH_2 \quad (V)$$

by dehydration of IV is V, these two substances should give identical products when condensed with the hydroquinone, providing that the diene

(5) Bergel, Copping, Jacob, Todd and Work, *J. Chem. Soc.*, 1382 (1938).

(6) Claisen, *Ann.*, **401**, 26 (1913); *ibid.*, **442**, 210 (1935); *Ber.*, **58**, 279 (1925).

is an intermediate. Actually, however, the two products are different. Although the structures of these products have not been proved definitely, tentatively we regard the products from ethylvinylcarbinol and pentadiene as the coumaran VI and the chroman VII, respectively.

VI

VII
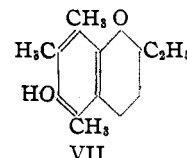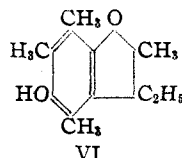
Thus, the diene cannot be an intermediate in the formation of VI, and it is therefore necessary to devise some other mechanism which will account for the known products obtained in these condensations when dienes, allylic alcohols and halides are used. While such a mechanism cannot at present be stated with certainty, the following is at least in harmony with present knowledge.

VIII

IX
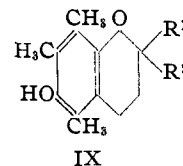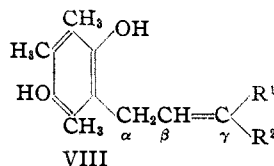
(a) In the case of the halides and alcohols, the first step involves nuclear "allylation" without rearrangement. Thus a primary allylic alcohol (or halide), such as allyl alcohol or phytol (or their halides), would give the intermediate allylic phenol VIII. The second step, the cyclization, may be regarded as an addition of the phenolic hydroxyl group to the double bond, in accordance with Markownikoff's rule and hence, when R[1] and R[2] are alkyl groups, the product would be a chroman (IX); when R[1] and R[2] are hydrogen, the


X

XIII
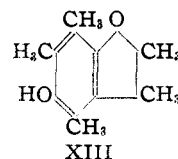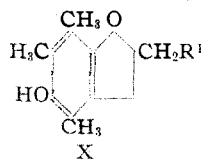
product would be a coumaran (III); while when R[1] is alkyl and R[2] is hydrogen, the product might be either the chroman (IX) or the coumaran (X) although the former is produced in all cases which have so far been investigated.

(b) When the diene is used, the first intermediate is the 1,4-addition product of the acidic catalyst (proton), (whether the addition is really 1,4 or is 1,2 followed by rearrangement). This intermediate then "allylates" the phenol directly,

and the cyclization proceeds in a second step as outlined under (a).

Thus pentadiene-1,3 (V), isoprene, 2,3-dimethylbutadiene, phytadiene, and other similarly constituted dienes with terminal CH_2 groups (XI, R^1, R^2, R^3 = H or alkyl) all give the same products as would be obtained by using the halide or

$$R^1CH=C(R^2)-C(R^3)=CH_2 \quad (XI)$$
$$R^1CH_2C(R^2)=C(R^3)CH_2X \quad (XII)$$
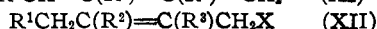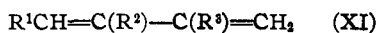
alcohol XII (R^1, R^2, R^3 = H or alkyl, X = OH or halogen). On the other hand, the secondary and probably also the tertiary allylic alcohols and halides give products different from those obtained from the related dienes and this regardless of whether the alcohols and halides are single substances or mixtures of allylic isomers, so long as one of the allylic isomers is not related to the diene as XII is to XI.

In accordance with this scheme, trimethylhydroquinone and methylvinylcarbinol give the coumaran XIII; crotyl bromide gives the chroman XIV, although the product is very difficult to purify and is probably contaminated with the isomeric coumaran (X, R = CH_3)[7] or with the coumaran XIII, derived from 3-chlorobutene-1, the allylic isomer of crotyl chloride.

XIV
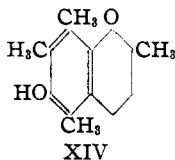
In connection with this work, certain improvements in procedure have been discovered which make it possible to use the cheaper allylic chlorides instead of the bromides, and also an improved procedure for condensing the allylic alcohols with phenols and hydroquinones has been devised. The latter, applied to the condensation of trimethylhydroquinone and phytol, constitutes, we believe, the best procedure so far developed for the preparation of α-tocopherol. The yield is not only better, but the product is more readily purified than that obtained by any method so far known to us. These details are given in the experimental section.

Experimental Part

Condensations with Allylic Alcohols

2,4,6,7 - Tetramethyl - 5 - hydroxycoumaran (II).—Trimethylhydroquinone (1 g.), allyl alcohol (1 cc.), zinc chloride (0.3 g.) and benzene (5 cc.) were sealed into a

Carius tube and the mixture was heated for three and one-half hours at 200°. The product was dissolved in petroleum ether and the solution was washed with water. The organic layer was allowed to stand for a day, and then filtered. The filtrate was evaporated and the residue was steam distilled. The distillate deposited a solid (200 mg.) on cooling. After crystallization from petroleum ether, the substance melted at 127–128° and did not depress the melting point (129–130°) of a specimen made by another method.[8]

2,3,4,6,7-Pentamethyl-5-hydroxycoumaran (XIII).—Trimethylhydroquinone (1 g.), methylvinylcarbinol (1 cc.), zinc chloride (0.3 g.) and benzene (5 cc.) were heated in a Carius tube for three hours at 200°. The product was crystallized directly from petroleum ether; yield 70 mg. After repeated crystallization first from dilute ethanol and then from petroleum ether, the white substance melted at 119.5–120.5°.

Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.73; H, 8.74. Found: C, 75.82; H, 8.68.

The coumaran is very soluble in 95% ethanol, somewhat soluble in aqueous ethanol, and soluble in ether and petroleum ether. It gives a positive phenol test (Folin), reduces alcoholic silver nitrate slowly, shows a positive Furter reaction, and gives a greenish-yellow color with cold concd. sulfuric acid. This color turns to orange-yellow when ferric chloride is added.

2,4,6,7-Tetramethyl-3-ethyl-5-hydroxycoumaran (VI).—Trimethylhydroquinone (2 g.), ethylvinylcarbinol (2 cc.), zinc chloride (0.6 g.) and benzene (5 cc.) were heated in a Carius tube for one hour at 150°, one hour at 150–200°, followed by one hour at 200°. The product was steam distilled and the solid in the distillate was crystallized first from petroleum ether and then from dilute methanol. The white solid melted at 88–89°; a mixture of VI and VII (m. p. 113–114°) melted at 77.5–81°.

Anal. Calcd. for $C_{14}H_{20}O_2$: C, 76.36; H, 9.09. Found: C, 76.54; H, 9.50.

The substance gives a positive phenol test (Folin) and a red color with nitric acid in absolute ethanol (Furter). It reduces alcoholic silver nitrate and gives a bright greenish-yellow color with cold concd. sulfuric acid.

2,5,7,8-Tetramethyl-2-isohexyl-6-hydroxy-chroman (?).—Trimethylhydroquinone (2 g.), geraniol (3 cc.), zinc chloride (0.6 g.) and benzene (5 cc.) were heated in a Carius tube for one hour at 150° and one hour at 200°. The product was diluted with ether and washed with water. The ether solution was filtered and the filtrate evaporated. The unsaturated chroman was extracted from the residue with petroleum ether; after removal of the petroleum ether, the chroman was taken up in methanol and reduced in the presence of a platinum oxide catalyst. The catalyst was filtered off, the solvent was evaporated, and the residue was distilled under high vacuum. The main fraction boiled at 110–115° (thermometer in the liquid) under 10^{-6} mm. Although the product was not obtained analytically pure, it showed the properties of a 6-hydroxychroman, *viz.*, positive Furter reaction, positive Folin test, yellow color with cold concd. sulfuric acid, and it reduced alcoholic silver nitrate.

2,4,6-Trimethyl-7-allyl-5-hydroxycoumaran and 2,4,6-Trimethyl-5-hydroxycoumaran.—*m*-Xylohydroquinone (5

(7) Karrer and Escher, *Helv. Chim. Acta*, **22**, 264 (1939).

g.), allyl alcohol (5 cc.), zinc chloride (1.5 g.) and benzene (10 cc.) were heated in a Carius tube at 150° for one hour and then at 200° for one hour. The product was steam distilled, but only traces of oil appeared in the distillate. The residue was an oil soluble in hot carbon tetrachloride. It brominated rapidly. It was considered to be mostly the trimethylallylcoumaran, although it was not obtained analytically pure.

α-Tocopherol.—Trimethylhydroquinone (200 g.) and fused zinc chloride (100 g.) were dissolved in acetic acid (800 cc.). The solution was refluxed gently (oil-bath temperature 125–130°) under an atmosphere of nitrogen, and with stirring phytol (400 g.) was added slowly (one hour). After refluxing for two hours longer, the mixture was poured over ice (several kilograms) and extracted with ether several times. The ether layer was washed with dilute potassium hydroxide several times, then with water, and dried over sodium sulfate. The ether was removed in an atmosphere of nitrogen, and the residue refluxed for an hour with a solution of potassium hydroxide (40 g.) in methanol (2000 cc.). The solution was poured over ice and worked up as before; then the treatment with alcoholic potassium hydroxide was repeated twice more. The concentrate (470 g.) finally was degassed and then distilled in a molecular still. A small amount (5–10%) of low boiling material came over first, followed by the tocopherol at 145–150°. The distillate was dissolved in petroleum ether (5 volumes) and stirred, in the presence of nitrogen, with an equal weight of aluminum oxide. The suspension was filtered and the filtrate distilled as before. The distillate had a pale yellow color and its absorption spectrum was identical with that of natural α-tocopherol.

Condensation with Dienes

2-Ethyl-5,7,8-trimethyl-6-hydroxychroman (VII).—Trimethylhydroquinone (2.74 g.), pentadiene-1,3 (1.23 g.), zinc chloride (0.3 g.) and sulfuric acid (1 drop) were refluxed in acetic acid (30 cc.) for an hour. The product was poured into water and the solid removed and crystallized several times from petroleum ether. It melted at 115–116°; mixed with VI. m. p. 77.5–81°.

Anal. Calcd. for $C_{14}H_{20}O_2$: C, 76.36; H, 9.1. Found: C, 76.06; H 9.11.

The substance gives a yellow color with cold concd. sulfuric acid, a positive Folin test, a positive Furter reaction, and reduces alcoholic silver nitrate.

Other examples of condensations between dienes and phenols or hydroquinones already have been reported.[2]

Condensations with Allylic Halides, Particularly Chlorides

Allyl chloride reacts with trimethylhydroquinone under the same condition as does the bromide, and the product in both cases is the known 2,4,6,7-tetramethyl-5-hydroxycoumaran. When crotyl chloride is used, the product is a mixture which consists predominantly of 2,3,4,6,7-pentamethyl-5-hydroxycoumaran (XIII), the same substance as is obtained when methylvinylcarbinol is used in the condensation. The crotyl chloride used in this experiment was obtained from the isomeric mixture of crotyl and methylvinylcarbinyl chloride by fractionation; the formation of XIII can be explained by an isomerization of the halide, which is known to occur at elevated temperatures

and in the presence of acidic catalysts, particularly hydrochloric acid.

$$CH_3CH=CHCH_2Cl \rightleftharpoons CH_3CHClCH=CH_2$$
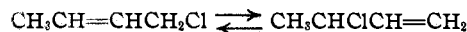
Crotyl chloride also will react with trimethylhydroquinone at atmospheric pressure, using benzene as a solvent, zinc chloride as the catalyst, and an inert atmosphere. The reaction with the chloride occurs as readily as it does with the bromide.

2,4,6,7-Tetramethyl-5-hydroxycoumaran (III).—Trimethylhydroquinone (1 g.), and allyl chloride (5 cc.) were heated in a tube at 150° for three hours. The product, isolated and purified as described above, weighed 600 mg. and had a melting point and mixed melting point of 130.6–131°.

2,3,4,6,7-Pentamethyl-5-hydroxycoumaran (XIII).—Trimethylhydroquinone (1 g.), and pure crotyl chloride (4 cc.) were heated in a tube at 150° for four hours. The product (400 mg.) was dissolved out with ether and crystallized from petroleum ether. After several crystallizations, the product melted at 117–117.5° and showed no depression in melting point when mixed with a specimen of XIII prepared from methylvinylcarbinol. It gave an acetate, melting point 70.5–71°. Using the procedure of Karrer, and substituting pure crotyl chloride for crotyl bromide, the product was the same. A repetition of Karrer's experiment,[8] using the isomeric mixture of crotyl bromide and methylvinylcarbinyl bromide, again gave predominantly this same substance, although the product was a mixture.

2,4,6-Trimethyl-7-allyl-5-hydroxycoumaran. — m-Xylohydroquinone (5 g.) and allyl bromide (10 cc.) were heated in a tube at 150° for three hours. The product was dissolved out with ether and steam distilled. Only traces of it came over into the distillate. The residue, when distilled under 10 mm. pressure from a sausage flask, gave a distillate consisting of a pale yellow, viscous oil, the properties of which corresponded with those of the product obtained from the hydroquinone and allyl alcohol (see above).

Summary

1. Allylic alcohols can be condensed directly with phenols and hydroquinones, thus avoiding the necessity of converting the alcohols into halides.

2. Although dienes also can be condensed with phenols and hydroquinones, the dienes are not always intermediates in the condensations when allylic alcohols and halides are used, for the products are not always the same.

3. A mechanism is proposed for these condensations, which, though not proved, correlates the facts well.

4. Allylic chlorides condense with phenols and hydroquinones as well as the bromides do.

5. An improved procedure is given for the preparation of α-tocopherol from trimethylhydroquinone and phytol.

(8) Karrer, Helv. Chim. Acta, 21, 946 (1938).