[Contribution from the School of Chemistry of the University of Minnesota]

3-Acetoxy-6-hydroxy-2,4,5-trimethylbenzylacetoacetic Ester, and its Transformation into Chromene and Chroman Derivatives[1]

By Lee Irvin Smith and Robert B. Carlin[2]

In another paper[3] structure I was established for the product resulting from chloromethylation of trimethylhydroquinone diacetate. Substance I was used to alkylate malonic ester, and the trans-

formations of the alkylated malonic ester were all in accord with those of a benzylmalonic ester derived from I. The benzyl chloride (I) has now been used to alkylate acetoacetic ester. This reaction proved to be quite analogous in its limitations to the reaction in the malonic ester series. Under the proper conditions, it led to the mono-acetoxybenzylacetoacetic ester (II), and not the dihydroxybenzyl compound, as previously reported.[4] The acetoxybenzyl compound (II) was smoothly converted into the known 3-acetyl-6-acetoxy-5,7,8-trimethyldihydrocoumarin (III)[5] by action of sodium hydroxide or sodioacetoacetic ester in ether. Sodium acetate was without any effect upon II, and until the researches were well advanced all the evidence indicated that there was a strict analogy between the compounds of the malonic ester series and those of acetoacetic ester.

The benzylacetoacetic ester (II) was smoothly converted into a pyrazolone by action of phenylhydrazine, a reaction which showed that the acetoacetic ester residue in the side chain had not been modified or attacked during the alkylation. On acetylation, however, II behaved quite differently

from its malonic ester analog. The product was not the diacetate corresponding to II, but was a substance derived from II by loss of water. The new substance did not give the Folin phenol test. From the method of formation, the composition and behavior of this material, structure IV, that of a γ-chromene, was indicated.

γ-Chromenes, unsubstituted in the 4-position, are represented in the literature by only one member, the 2-methyl-γ-chromene (IX) of Baker and Walker.[6] These authors found that 2-hydroxybenzylacetone, when allowed to stand in ether over sodium sulfate, lost water to form the chromene IX. Further, the ketone, when treated

IV R=Ac; R¹=COOC₂H₅
V   R=R¹=H
VI R=H; R¹=COOH
VII R=Ac; R¹=COOH
VIII R=H; R¹=COOC₂H₅

X R = C₂H₅
XI R = H

with ethanolic hydrogen chloride, gave the cyclic acetal (X). The acetal X was readily hydrolyzed to the ketone by aqueous hydrochloric acid, and the action of acetic anhydride upon X led to the chromene IX. Because of the ease with which the elements of water and of alcohol were eliminated from the ketone and acetal, respectively, Baker and Walker believed that the ketone could be represented, at least in part, by structure XI. John and Schmeil[7] prepared the ketone (XII), but the behavior of this ketone was

XII R = H
XIII R = CH₃

XIV

XV

(1) The Chemistry of Vitamin E. XXXII; Paper XXXI, This Journal, 64, 433 (1942).

(2) Abstracted from a thesis by Robert B. Carlin, presented to the Graduate Faculty of the University of Minnesota, in partial fulfillment of the requirements for the Ph.D. degree, June, 1941.

(3) Smith and Carlin, This Journal, 64, March (1942).

(4) Smith, Ungnade, Opie, Prichard, Carlin and Kaiser, J. Org. Chem., 4, 327 (1939).

(5) Smith and Tenenbaum, This Journal, 59, 667 (1937).

(6) Baker and Walker, J. Chem. Soc., 646 (1935).

(7) John and Schmeil, Ber., 72, 1652 (1939).

so peculiar that the authors believed it was represented better by structure XIV than by XII.

Since II, when treated with acetic anhydride, did not form an acetyl derivative, but rather lost the elements of water to form IV, it is quite probable that, in analogy with the other known cases, II exists at least partly in the form of XV. When IV was refluxed with 60% sulfuric acid, a white solid appeared in the condenser. This solid proved to be the known 2,5,7,8-tetramethyl-6-hydroxychroman (XVI).

XVI

XVII

XVIII

XIX R = Ac; R' = COOC₂H₅
XX R = H; R' = COOH
XXI R = Ac; R' = COOH
XXII R = H; R' = COOC₂H₅
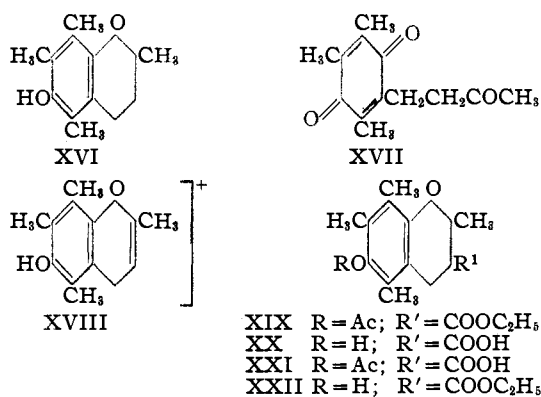
If the ketone II does exist in part as the cyclic structure XV, it follows that II, as well as IV, should give the chroman XVI with sulfuric acid. This was in fact the case; when boiled with 60% sulfuric acid, II gave XVI in 20% yield. These reactions involved not only hydrolysis and decarboxylation, but reduction or disproportionation as well. The best yield of XVI obtained was 28% (from IV), and while John and Günther[8] obtained much better yields of XVI by demethylation of the dimethoxy ketone (XIII) with hydrobromic acid in acetic acid, their reaction, as well as ours, was accompanied by a reduction.

Two mechanisms may be considered for the conversion of II and IV into XVI. The first mechanism would begin with hydrolysis and loss of carbon dioxide from IV to form 2,5,7,8-tetramethyl-6-hydroxychromene (V), the ring of which might then be opened by sulfuric acid to give the hydroquinone (XII). This hydroquinone could then disproportionate into the chroman XVI and the corresponding quinone XVII or its decomposition products. The second mechanism would also involve the same chromene V but the chromene would disproportionate directly into the chroman XVI and a benzopyrylium salt such as XVIII. In the first mechanism, two hydrogen

(8) John and Günther. Ber., **72**, 1649 (1939).

atoms are transferred from one molecule of XII, or 2V → 2XII → XVI + XVII. According to this mechanism, the maximum yield of XVI would be 50%. In the second mechanism, only one hydrogen atom is transferred, or 3V → XVI + 2XVIII and in this case the maximum yield of XVI would be 33%. The best yield actually obtained was 28%, from IV.

When the ester (IV) was hydrolyzed by alcoholic alkali, there resulted the rather intractable acid (VI) which gave a positive phenol test (Folin) and was acetylated readily to the acetoxy acid (VII). The acetoxy acid (VII) could not be esterified by the usual means, because of loss of the acetoxy group, and although the silver salt of VII was difficult to prepare, it was possible to use it to convert VII into IV. The phenolic acid (VI) was converted into the phenolic ester (VIII) by action of ethanol and hydrogen chloride. The reaction was extremely sensitive to slight changes in conditions and frequently gave low-melting, complex mixtures together with dark blue solids which exhibited a reddish-green fluorescence in ether solution. The phenolic ester (VIII) was readily acetylated to IV in good yield. All these changes showed quite clearly the nature of the groups joined to the chroman system in IV and related compounds.

The phenolic acid (VI) was next subjected to the action of boiling quinoline in the presence of a copper chromite catalyst. The solid product was very difficult to purify, and even after repeated crystallization it was still somewhat brownish in color. It melted at 122-124°, gave a strong phenol test (Folin), and it had the composition of the expected decarboxylation product plus one molecule of water. This substance was obviously not the chromene V, and it strongly resembled the product XII or XIV obtained by John and Schmeil[7] by an entirely different sequence of reactions, and reported by them to melt at 122°. Although a diacetate and a dimethyl ether (XIII) of XII were known, these substances were not obtained from XII. Attempts to methylate this decarboxylation product of VI did not lead to XIII, but only to tarry materials which could not be crystallized. Likewise acetylation produced only tars. Reduction of this substance in the presence of Raney nickel produced the chroman XVI. It followed, therefore, that the decarboxylation of the acid VI did not give V as the product, but gave the compound of John and Schmeil,

XII or XIV. These results not only support the conclusions of John and Schmeil that XII is a peculiar substance and is much more accurately represented by structure XIV, but they also support the first of the proposed mechanisms for the transformation of II (and IV) into XVI. In favor of the second mechanism for the transformation of II into XVI via benzopyrylium salts were the deep colors always developed in the reaction mixtures. Attempts were made to isolate these colored substances, but only purple, tarry materials could be obtained.

The transformation of IV and XVI by two methods, together with the formation of the derivatives of IV, namely, VI, VII, VIII, leave no doubt as to the structure of IV. When hydrogenated in the presence of Raney nickel, IV gave the corresponding chroman XIX. The acetoxy-chroman ester (XIX) was hydrolyzed readily to the phenolic acid (XX) by alcoholic alkali. Unlike the chromene phenolic acid (VI), the chroman acid XX was easily handled and was readily soluble in warm organic solvents, as well as in aqueous alkali, carbonate or bicarbonate. The acid XX gave a strong phenol test (Folin) and it smoothly formed an acetate, XXI. Acid XX was also readily esterified by action of ethanol and hydrochloric acid. The resulting phenolic ester (XXII) was acetylated easily, and the product was XIX. All these transformations of the chroman occurred smoothly and in good yields, in contrast with the corresponding transformations in the chromene series. Attempts were made to decarboxylate the phenolic acid XX and so arrive at the chroman XVI, but these were unsuccessful. Although XX melted at 212° with decomposition, it was recovered in yields as high as 70% after it was boiled in quinoline containing copper chromite. No trace of XVI could be found.

Experimental[9]

Ethyl-3-acetoxy-6-hydroxy-2,4,5-trimethylbenzyl Acetoacetate (II).—A solution of ethyl acetoacetate (8.46 g.) in dry ether (50 cc.) was slowly (one hour) dropped into a stirred suspension of powdered sodium (1.50 g.) in ether (250 cc.). Stirring was continued overnight and the enolate suspension was then added, with vigorous stirring, to a solution of the chloromethyl compound I (15 g.) in ether (75 cc.). The mixture was stirred for ninety minutes longer and then shaken with water (300 cc.) containing sulfuric acid (1 cc.). The water layer was removed and

(9) Microanalyses by E. E. Renfrew, E. B. Hardy, and C. H. Stratton.

the solid (5 g., m. p., 131–135°) suspended in the ether was filtered off. The ethereal filtrate was dried (sodium sulfate), concentrated to 75 cc. and diluted with petroleum ether (75 cc., b. p. 60–68°). The cooled solution deposited 10 g. of material which melted at 128–134°. Concentration of the filtrate gave an additional 2.5 g. of product which melted at 125–130°. The total yield of 17.5 g. represented 84% of the theoretical amount. Although white and nicely crystalline, the crude product was contaminated with acetoacetic ester and several crystallizations, alternately from alcohol and ether–petroleum ether, were required to produce a pure specimen melting at 136–137°. The substance formed no precipitate when its ethereal solution was shaken with aqueous copper acetate, but it gave a strongly positive Folin phenol test. *Anal.* Calcd. for $C_{18}H_{24}O_6$: C, 64.28; H, 7.14. Found: C, 64.26; H, 7.23.

Pyrazolone.—The ester II (100 mg.) was dissolved in hot alcohol (10 cc.) and the solution was refluxed for twenty minutes with phenylhydrazine (10 drops) and acetic acid (3 drops). After the mixture had stood overnight, the solid was removed and crystallized several times from alcohol. The pyrazolone crystallized in soft, fine white needles which melted at 208–209° with some decomposition. *Anal.* Calcd. for $C_{22}H_{24}O_4N_2$: C, 69.44; H, 6.37; N, 7.36. Found: C, 69.71; H, 6.55; N, 7.35.

3-Acetyl-6-acetoxy-5,7,8-trimethyl-3,4-dihydrocoumarin (III) (A). Using Sodioacetoacetic Ester.—To a suspension of sodioacetoacetic ester (sodium, 10 mg., acetoacetic ester, 7 drops) in ether was added the ester II (1 g.). After standing for four weeks at room temperature, the suspended solid was removed, washed with very dilute sulfuric acid, and at once crystallized from alcohol. It then formed long, silky white threads which melted at 128–129°. When mixed with a specimen prepared in a different manner[5] (m. p. 124–125°), the substance melted at 126–128°. It gave a pronounced melting point depression when mixed with the starting material II (m. p. 136–137°) or with the chromene ester IV (m. p. 131–132°). After the solid enolates had been removed from the reaction mixture, the ethereal filtrate was evaporated and the residue was crystallized from alcohol. It melted at 134–135° and was the starting material, ester II.

(B) Using Sodium Hydroxide.—The keto ester II (662 mg.) was suspended in dry ether (20 cc.) and sodium hydroxide (90 mg., 1.1 moles, powdered under petroleum ether) was added. Immediately the suspended solid became gelatinous. After standing for three weeks at room temperature, the suspended solid (271 mg.) was removed and washed with very dilute sulfuric acid (1%). After crystallization from alcohol, the substance melted at 126–127° alone or when mixed with an authentic sample of III.

2,5,7,8-Tetramethyl-3-carbethoxy-6-acetoxy-γ-chromene (IV).—The keto ester II (15.2 g.) was suspended in acetic anhydride (100 cc.), sulfuric acid (3 drops) was added and the mixture was carefully heated to the boiling point. It was immediately thereafter poured into water (500 cc.) containing cracked ice (100 g.). After standing until decomposition of the acetic anhydride was complete, the mixture was filtered and the bright yellow solid was dissolved in boiling alcohol (100 cc.). A little Raney nickel catalyst was added and the mixture was refluxed overnight. The

catalyst was removed and the solution, when cooled, deposited long, faintly yellow threads (12.5 g.) which melted at 132–133° to a bright yellow liquid. Concentration of the filtrate almost to dryness gave an additional 0.7 g. of product. The total yield was 95%. This substance, IV, was always yellow when first prepared. The yellow color could not be removed with Norit; only Raney nickel was found to be effective. Frequently the initial reaction mixture turned a brilliant green just before the boiling point was reached, and though in such cases the crude product was yellowish-green, this made no difference in the yield or final quality of the product. The compound IV gave a bright yellow solution in sulfuric acid; it decolorized cold, dilute neutral aqueous permanganate; and the Folin phenol test was negative. For analysis, a specimen was refluxed for the second time in alcohol over Raney nickel and then crystallized. It was perfectly white and melted at 132–133° to a yellow liquid. The white substance when dissolved in alcohol gave a colorless solution which, however, turned yellow when boiled. *Anal.* Calcd. for $C_{18}H_{22}O_5$: C, 67.88; H, 6.98. Found: C, 67.67; H, 6.99.

2,5,7,8-Tetramethyl-6-hydroxychroman (XVI) (A). From IV.—The ester IV (1.0 g.) was covered with sulfuric acid (20 cc., 60%) and the mixture was refluxed. A gas was evolved, and a white solid appeared in the condenser. This solid was periodically washed into a separate container. Refluxing was continued until no more solid appeared. The solid weighed 0.18 g. (28%) and, after crystallization from petroleum ether containing a little methanol, it melted at 142–143°, alone or when mixed with a specimen of XVI prepared by the method of John and Günther,[8] *Anal.* Calcd. for $C_{13}H_{18}O_2$: C, 75.65; H, 8.82. Found: C, 75.29; H, 8.57.

(B) From II.—The β-keto ester II (1.048 g.) was refluxed with sulfuric acid (22 cc., 60%) and the reaction mixture was processed as described above. The chroman XVI weighed 0.129 g. (20%) and melted at 140–141° after recrystallization.

The acid solutions from which XVI was obtained were diluted to 150 cc. with water and filtered. A solution of ferric chloride (2 parts to 1 of water) was added to the clear red filtrate until a flocculent precipitate appeared, but an excess of ferric chloride was avoided. The orange-red precipitate was removed and washed with water. Attempts to crystallize the material (benzopyrylium salts?) from any of the usual organic solvents produced only red and purple tars. The solid, when ignited, gave first a black coke and finally a red solid.

2,5,7,8-Tetramethyl-3-carboxy-6-hydroxy-γ-chromene (VI).—The acetoxychromene ester (IV) (12.5 g.) was refluxed with alcoholic alkali (sodium, 2.0 g., ethanol, 90 cc., water, 35 cc.) for three and one-half hours. The dark solution was poured into dilute sulfuric acid (600 cc., 3%). The precipitate was removed and washed with a little water. It melted at 209–215° with effervescence, to a black liquid. This acid (VI) proved to be difficult to handle. It was only sparingly soluble in the usual organic solvents, and the dried acid was insoluble in aqueous carbonate, bicarbonate, or alkali, or even in Claisen's alkali. The insolubility in alkalies was more likely due to insolubility of the salts than to failure to form the salts,

for suspensions of the solid acid in alkaline solutions changed considerably in appearance on standing and, moreover, the acid was extracted from its ether solution by saturated aqueous bicarbonate. The acid was best crystallized from a 1:1 mixture (1000–1500 cc.) of alcohol and acetone, from which it separated in very fine white threads. After several crystallizations, it melted at 230–231° with decomposition. It weighed 8.3 g. (86%).

Anal. Calcd. for $C_{14}H_{16}O_4$: C, 67.71; H, 6.53. Found: C, 67.77; H, 6.55.

2,5,7,8-Tetramethyl-3-carboxy-6-acetoxy-γ-chromene (VII).—The phenolic acid (VI) (1.0 g.) was suspended in acetic anhydride, a drop of sulfuric acid was added, and the mixture was brought to the boiling point. The hot solution was poured into water (100 cc.) and ice (50 g.) and allowed to stand until the excess acetic anhydride decomposed. The yellow solid was removed and crystallized from alcohol (50 cc.). It then melted at 242–243° and weighed 1.0 g. (86%). For analysis, a sample was crystallized twice from alcohol and once from alcohol–ethyl acetate. This specimen melted at 244–245° to a brown liquid which appeared to undergo slow decomposition.

Anal. Calcd. for $C_{16}H_{18}O_5$: C, 66.16; H, 6.27. Found: C, 66.14; H, 6.26.

The acetoxy acid (VII) (345 mg.) was suspended in alcohol and brought into solution by addition of concentrated ammonium hydroxide (10 drops). The solution was evaporated to dryness on the steam-bath, a drop of ammonia being added from time to time during the process. The residue was dissolved in hot alcohol (50 cc.) and to the cooled solution alcoholic silver nitrate (10 cc., 4%) was added. Sodium acetate (a few mg.) was added and the precipitate was removed and dried in a vacuum desiccator. The dark silver salt was then refluxed overnight with ethyl iodide (20 cc.). Alcohol (20 cc.) was added and the liquid was then evaporated almost to dryness on the steam-bath. This process was repeated twice more, and finally the residue was boiled with alcohol (20 cc.), the hot mixture was filtered and the filtrate was concentrated to 5 cc. and cooled. The product (50 mg.) was the acetoxy ester (IV), melting point and mixed melting point 128–130°.

2,5,7,8-Tetramethyl-3-carbethoxy-6-hydroxy-γ-chromene (VIII).—The phenolic acid (VI) (50 mg.) was suspended in absolute ethanol (20 cc.) and the mixture was saturated with dry hydrogen chloride. The solid gradually dissolved, and after standing for three days, the bright red solution was poured into water (100 cc.). The pale blue solid was removed and warmed with a little alcohol, when the blue color disappeared. More alcohol was added and the solid was brought into solution. On cooling, the solution deposited 35 mg. of product which melted at 171–175° with some decomposition. After two more crystallizations from alcohol, the substance melted at 173–175°.

Anal. Calcd. for $C_{16}H_{20}O_4$: C, 69.52; H, 7.48. Found: C, 69.31; H, 7.32. When acetylated in the usual way, the ester VIII (8 mg.) gave IV (9.7 mg.), m. p. and mixed m. p., 128–130°.

3,6-Dihydroxy-2,4,5-trimethylbenzylacetone, XII or XIV. —The phenolic acid (VI) (1.0 g.) was heated to 200° (metal bath) with quinoline (7 cc.) and a little copper chromite

catalyst. A vigorous evolution of gas occurred. The temperature was gradually raised until after two hours it had reached 220° and evolution of gas had practically ceased. The cooled reaction mixture was poured into water (50 cc.) containing cracked ice (10 g.) and hydrochloric acid (10 cc.). The aqueous solution was extracted five times with 25-cc. portions of ether. The combined ether extracts were washed with hydrochloric acid (5%), then twice with saturated bicarbonate solution, and finally with water. The ether solution was dried (sodium sulfate) and decolorized (Norit). Removal of the ether under reduced pressure left a dark, viscous oil which was taken up in benzene (5 cc.). Petroleum ether (5 cc., b. p. 60-68°) was added and the solution was cooled. The light brown solid (330 mg.) was removed and crystallized several times from benzene, when it was obtained as a granular, buff-colored solid which melted at 122-124°. John and Schmeil[7] reported that the compound melted at 122°.

Anal. Calcd. for $C_{18}H_{18}O_3$: C, 70.21; H, 8.19. Found: C, 69.93; H, 7.92.

Substance XII (400 mg.) was dissolved in alcohol (25 cc.) and subjected to the action of hydrogen at 150° under 1600 lb. pressure in the presence of Raney nickel catalyst. After five hours, reduction was incomplete as shown by the darkening of the solution on standing. The solution was returned to the bomb, fresh catalyst was added, and hydrogenation was repeated under the conditions described above. The catalyst was removed and the solution was concentrated to 10 cc.; water (10 cc.) was added and the white, granular solid (150 mg.) was removed. After crystallization from petroleum ether–methanol, it melted at 139-141° alone or when mixed with an authentic sample of XVI.

2,5,7,8-Tetramethyl-3-carbethoxy-6-acetoxychroman, XIX.—The acetoxy ester (IV) must be absolutely colorless, and must give a colorless solution in hot alcohol, or it will be unaffected by hydrogen in the presence of Raney nickel catalyst. Apparently the yellow impurities usually present in IV poison the catalyst, these yellow specimens must be warmed (not boiled) in alcohol in the presence of Raney nickel, repeating the process, if necessary, until all of the yellow color has been removed. The purified ester (IV) (3.0 g.) was dissolved in boiling alcohol (25 cc.) and the hot, colorless solution was transferred to the bomb. Raney nickel was added and the mixture was subjected to the action of hydrogen at 125° under 1300 lb. pressure for six hours. The catalyst was removed and the solution was concentrated under reduced pressure until solid began to deposit. Water and alcohol were then added alternately in small portions until crystallization was complete. Any other means employed for the crystallization of XIX produced mostly oils and very poor yields of solid material. The dry solid weighed 3.0 g. and melted at 68-72°. Once the solid material was obtained, it could be readily crystallized from dilute alcohol; it then melted at 76-77°.

Anal. Calcd. for $C_{18}H_{24}O_5$: C, 67.46; H, 7.56. Found: C, 67.77; H, 7.57.

2,5,7,8-Tetramethyl-3-carboxy-6-hydroxychroman, XX.—The acetoxy ester XIX (2.1 g.) was added to alcoholic alkali (sodium 0.5 g., ethanol 25 cc., water 10 cc.) and the mixture was refluxed for three and one-half hours. The dark brown solution was poured into water (200 cc.) and

ice (100 g.) containing sulfuric acid (10 cc.). The white solid (1.7 g., 97%) was removed. It melted at 198-201° with decomposition. After crystallization from methanol, the acid formed white, fine needles which blackened at 205° and melted at 210-212° to a black liquid. The acid was soluble in the usual organic solvents when warmed, and it was soluble in aqueous alkali, carbonate or bicarbonate. It gave a positive Folin phenol test.

Anal. Calcd. for $C_{14}H_{18}O_4$: C, 67.15; H, 7.27. Found: C, 67.09; H, 7.11.

2,5,7,8-Tetramethyl-3-carboxy-6-acetoxychroman, XXI.—The acid XX (250 mg.) was suspended in acetic anhydride (5 cc.), a drop of sulfuric acid was added and the mixture brought to the boiling point. The product (250 mg., 87%, m. p. 186-192°) was crystallized repeatedly from methanol containing a little petroleum ether (b. p. 60-68°). It was then white and melted at 199° to a slightly brown liquid. This acetate was soluble in the usual organic solvents, and in aqueous alkali, carbonate or bicarbonate.

Anal. Calcd. for $C_{16}H_{20}O_5$: C, 65.71; H, 6.92. Found: C, 65.50; H, 7.20.

2,5,7,8-Tetramethyl-3-carbethoxy-6-hydroxychroman, XXII.—The phenolic acid XX (1.1 g.) was suspended in absolute ethanol (25 cc.) and the mixture was saturated with hydrogen chloride. After standing for twenty-four hours, the bright red solution was poured into ice water (100 cc.) and extracted three times with 50-cc. portions of ether. The combined ether extracts were washed twice with saturated bicarbonate and once with water. No solid material was obtained when the bicarbonate extracts were acidified. The ether solution was dried (sodium sulfate) and the solvent was removed under reduced pressure. The brownish residue (1.1 g., 92%) was crystallized several times from dilute alcohol. It was then white and melted sharply at 99°.

Anal. Calcd. for $C_{16}H_{22}O_4$: C, 69.02; H, 7.98. Found: C, 69.13; H, 8.27.

Acetylation of XXII (0.4 g.) by the process described for preparation of XXI gave 0.4 g. of the acetoxy ester XIX which, after crystallization from dilute alcohol, melted at 74-75° alone or when mixed with a specimen prepared by reduction of IV.

Summary

1. Alkylation of acetoacetic ester by 3-acetoxy-6-hydroxy-2,4,5-trimethylbenzyl chloride I gives the normal product II, which may be cyclized to the known 3-acetyl-6-acetoxy-5,7,8-trimethyldihydrocoumarin, III.

2. Action of acetic anhydride upon II, however, does not give a diacetate but instead transforms II into a derivative of γ-chromene, IV. The transformations of this γ-chromene and its reduction product, a chroman, have been studied.

3. Decarboxylation of the chromene IV does not give a chromene, but rather a chroman, and the mechanism of this reaction has been discussed.

4. Another example has been added to the

list of the derivatives of o-hydroxybenzylacetone, and the peculiar behavior of these compounds has been discussed.

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

# The Chemistry of Vitamin E. XXXIII. A New Synthesis of 6-Hydroxychromans, Including α-Tocopherol[1]

BY LEE IRVIN SMITH AND HENRY C. MILLER[2]

By degradative methods, several workers have shown that α-tocopherol, the most active vitamin E factor, possesses structure I, $R^1 = CH_3$; $R^2 = C_{16}H_{33}$.[3] However, the only methods so far available for synthesis of α-tocopherol—namely, condensation of phytol or its derivatives with trimethylhydroquinone—do not require, in themselves, that α-tocopherol should possess a chroman structure. Model researches have shown[1] that when condensed with hydroquinones, simple γ,γ-disubstituted allylic alcohols or halides give chromans exclusively while the γ-monosubstituted analogs give both chromans and coumarans, and the unsubstituted allyl alcohols or halides give only coumarans. From the synthetic point of view, structure I for α-tocopherol rests entirely upon the assumption that phytol and its derivatives, which are γ,γ-disubstituted allylic compounds of rather high molecular weight, will behave in the condensation reaction as the simpler analogs do.

It was the aim of this research to synthesize α-tocopherol by a method which did not involve condensation of a phytol derivative with trimethylhydroquinone, and to utilize for this purpose a series of known reactions leading via intermediates of unambiguous structure to the final product (I). Synthesis of chromans such as I in which the two alkyl groups attached to the hetero ring are different is a matter of some difficulty, and although John and his collaborators[5] have recently made considerable progress in this direction, their methods did not lead them to α-toco-

pherol. Moreover, their methods require 100–200% excess of a Grignard reagent derived from a long chain halide—often the most difficult of the intermediates to obtain—and the excess of the reagent is lost as a saturated hydrocarbon.

Our synthesis started with the carbinol (II)

II R = OH
III R = Br or Cl
IV R = MgBr or MgCl
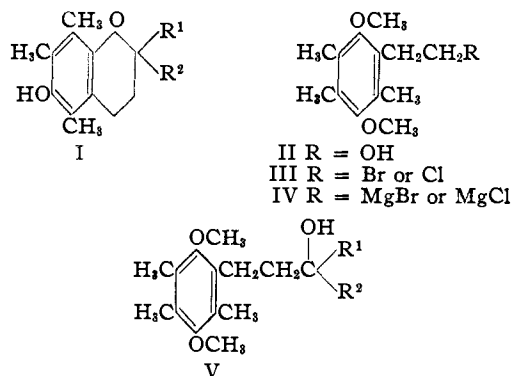
which was prepared from trimethyldimethoxyphenylmagnesium bromide and ethylene oxide.[6]

This carbinol was transformed into the bromide (III) and then into the Grignard reagent (IV). The Grignard reagent was then converted into the carbinol (V) by reaction with a ketone. By proper selection of the ketone, the two groups R^1 and R^2 may be varied within wide limits. These carbinols were viscous oils of low vapor pressure, and, while the pure carbinols were not isolated, it was possible to remove most of the impurities present by steam distillation. The carbinol derived from acetone was converted into the 3,5-dinitrobenzoate which proved to be identical with a specimen of this ester prepared by another method.[7]

The carbinols (V), when subjected to the action of hydrobromic acid in acetic acid, were smoothly demethylated and cyclized to the chromans (I). By varying the nature of the ketone, five 2,5,7,8-tetramethyl-2-alkyl-6-hydroxychromans were prepared: those in which R^2 was methyl, ethyl, n-

(1) Paper XXXII, THIS JOURNAL, 64, 435 (1942).

(2) Abstracted from a thesis by Henry C. Miller, presented to the Graduate Faculty of the University of Minnesota, in partial fulfillment of the requirements for the Ph.D. degree, July, 1941.

(3) (a) Fernholz, THIS JOURNAL, 60, 700 (1938); (b) John, Z. physiol. Chem., 252, 222 (1938); (c) John, Dietzel and Emte, ibid., 257, 173 (1939); (d) Tishler and Wendler, THIS JOURNAL, 63, 1532 (1941).

(4) (a) Smith, Ungnade, Hoehn and Wawzonek, J. Org. Chem., 4, 305 (1939); (b) Karrer, Escher and Rentschler, Helv. Chim. Acta, 22, 1287 (1939).

(5) (a) John and Günther, Ber., 74, 879 (1941); (b) John and Rathmann, ibid., 74, 890 (1941).

(6) Smith, Wawzonek and Miller, J. Org. Chem., 6, 230 (1941).

(7) Smith, Ungnade and Irwin, THIS JOURNAL, 62, 143 (1940).