variably checked well either for the anhydrous hydrochloride or for the hemihydrate.

Anal. Calcd. for $C_{29}H_{52}ONCl \cdot {}^1/_2H_2O$: C, 73.28; H, 11.24. Found: C, 72.73, 73.63, 73.13; H, 11.43, 11.06, 10.83.

Conversion of α-Tocopheramine to α-Tocopherol.—A suspension of the amine hydrochloride (0.95 g.) in water (25 cc.), methanol (10 cc.), hydrochloric acid (1 cc.) and ferric chloride hexahydrate (1.62 g.) was heated to 70° and stirred for thirty minutes. The mixture was cooled and extracted with ether. The ether solution was dried (Drierite) and evaporated, and the residue of viscous oil was stirred for two and one-half hours with methanol (20 cc.) to which had been added a solution of sodium hydrosulfite (1 g.) in water (2 cc.). The mixture was poured into a separatory funnel containing water (70 cc.) and petroleum ether (10 cc.) and was shaken thoroughly. The petroleum ether layer was removed and chilled in an ice-bath. The voluminous white precipitate of tocopherylhydroquinone (VI) was separated by centrifuging and washed twice with a little cold petroleum ether. The solid was refluxed for four hours with dioxane (10 cc.), hydrochloric acid (1.7 cc.) and stannous chloride dihydrate (2.3 g.). This mixture was poured into water and extracted with petroleum ether. The extract was washed with water, dried (Drierite) and the solvent was evaporated. There remained 0.37 g. (43%) of faintly straw-colored α-tocopherol.

Summary

1. α-Tocopheramine, the amino analog of α-tocopherol, has been prepared by condensation of 2,3,5-trimethyl-4-formylaminophenol with phytol.

2. The hydrochloride of this amine has been converted into α-tocopherol by the procedure of Tishler and Wendler.

3. The amine hydrochloride exhibits vitamin E activity in approximately the same degree as does α-tocopherol.

4. Although tocopherylquinone possesses no vitamin E activity, it cannot be eliminated as a possible factor in producing biological activity, in view of its close relationship to both α-tocopherol and α-tocopheramine.

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[JOINT CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA AND THE RESEARCH LABORATORIES OF MERCK & CO., INC.]

The Chemistry of Vitamin E. XXXIX. Calcium α-Tocopheryl Succinate[1]

BY LEE IRVIN SMITH, W. B. RENFROW, JR., AND J. W. OPIE

The rather large number of simple esters of α-tocopherol which have been prepared[2] include many which have a high biological activity, but all of these are liquids. It appeared likely that the metallic salts of the acid esters of α-tocopherol and dibasic acids would be stable, solid substances with a high degree of biological activity. This paper reports the results of experiments along these lines, and includes a description of the preparation and properties of calcium α-tocopheryl succinate.

2,2,5,7,8-Pentamethyl-6-hydroxychroman was used in the model experiments, and it was found that this chroman failed to give an ester with ethyl chlorocarbonate, alone or in the presence of alcoholic potassium hydroxide or sodium methoxide in methanol. However, the bromomagnesium derivative of the chroman reacted readily with ethyl chlorocarbonate to give the mixed carbonate ester, a solid melting at 50–52°. This ester was extremely sensitive to alkali, hydrolyzing completely in a minute or two when in contact with dilute alkali.

Using the bromomagnesium derivative of the chroman, the acid succinate and the chloroacetate were prepared by action of succinic anhydride and chloroacetyl chloride, respectively. These esters, like the carbonate, were hydrolyzed with extreme ease. The succinate dissolved in 2% sodium hydroxide to give a clear solution, but within thirty seconds this solution became cloudy and the chroman began to precipitate. It had been planned to use the chloroacetate as an intermediate in the preparation of the glycine ester of the chroman, but action of ammonia upon a solution of the chloroacetate in methanol gave only the chroman, and no glycine ester.

Succinic, maleic and phthalic anhydrides reacted with the bromomagnesium derivative of α-tocopherol to give the corresponding acid esters. The acid succinate formed a pasty solid which was converted into potassium, calcium and barium

(1) Presented at the 103rd meeting of The American Chemical Society, Memphis, April, 1942; Paper XXXVIII, THIS JOURNAL, **64**, 1082 (1942).

(2) Demole, Isler, Ringier, Salomon and Karrer, *Helv. Chim. Acta*, **22**, 65 (1939).

salts. Of these, the calcium salt formed a white solid, soluble in ether and petroleum ether, moderately soluble in alcohol, soluble in hot dioxane, sparingly soluble in cold dioxane, slightly soluble in acetone and insoluble in water. The melting point of the salt from different preparations varied somewhat between the limits of about 200–225°.

The calcium salt was tested for vitamin E activity by Dr. H. M. Evans of the University of California[3] with the following results. The salt was dissolved in ethyl laurate and fed to each of 8 rats at a level of 8 mg. There resulted 5 good litters with an average of 9+ living young (average weight, 5.8 g.), one fair litter of 3 living young (average weight 5.2 g.) and 2 dead young, and one poor litter of 4 dead young. When fed to each of 6 rats at a level of 4 mg., there resulted 4 fair to good litters with an average of 6.5 living young (average weight 4.7 g.), 1 poor litter of 1 dead young, and one case in which loss of weight and autopsy findings indicated that a litter was cast but eaten. On a molecular basis, therefore, this calcium α-tocopheryl succinate is as active as α-tocopherol itself.

Experimental[4]

Experiments with 2,2,5,7,8-Pentamethyl-6-hydroxychroman. The O-Carbethoxy Derivative.—The hydroxychroman (1 g.) was dissolved in dry ether (5 cc.) and to this solution was added a 2 *N* solution of ethylmagnesium bromide (2.5 cc., standardized by titration against hydrochloric acid) and the mixture was allowed to stand for five minutes. A solution of ethyl chlorocarbonate (0.7 cc.) in ether (3 cc.) was added and the mixture was allowed to stand at room temperature for one hour. The solution was washed with water, dried (calcium chloride), and the solvent evaporated. The residue of light yellow, viscous oil crystallized on standing. After recrystallization from dilute ethanol, the substance melted at 50–52°. When this material was warmed gently with dilute alcoholic potassium hydroxide, the chroman, m. p. and mixed m. p. 94°, was obtained.

The chroman (0.5 g.) in methanol (1.5 cc.) was cooled in an ice-bath and a solution of potassium hydroxide (0.5 g.) in methanol (2 cc.) was added. Dry ether (25 cc.) was added, followed by ethyl chlorocarbonate (1 cc.). The mixture was washed with water, dried (calcium chloride), and the solvent evaporated. The residue was unchanged chroman; m. p. 94.5°. The same result was obtained when the chroman was dissolved in the calculated amount of sodium methoxide in methanol and subjected to the action of ethyl chlorocarbonate.

Acid Succinate.—Ethylmagnesium bromide (2.5 cc., approximately 2 *N*) was added to a solution of the chroman (1 g.) in dry ether (8 cc.) and the solution was allowed to stand for five minutes. A solution of succinic anhydride (0.5 g.) in dry dioxane (5 cc.) was added, and the cloudy mixture was allowed to stand overnight. More dioxane (5 cc.) was added, and the mixture was heated for two hours on the steam-bath. The mixture was poured into excess dilute hydrochloric acid and extracted with ether. The ether layer was washed with water, dried (calcium chloride) and the solvent evaporated. The residue (1.47 g., m. p. 120–130°), when crystallized from xylene, gave 1.13 g. of the acid succinate which melted at 138–139.5°.

Anal. Calcd. for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55. Found: C, 67.59; H, 7.29.

The acid succinate dissolved in dilute sodium hydroxide (2%), forming a clear solution, but in about thirty seconds precipitation of the chroman, m. p. 93–94.5°, began. The whole of the chroman precipitated within a few minutes.

Chloroacetate.—*n*-Propylmagnesium chloride (2.3 cc., 2.03 *N*) was added to a solution of the chroman (1 g.) in ether (15 cc.) and the solution was shaken thoroughly and added slowly to a solution of chloroacetyl chloride (0.51 g.) in ether (10 cc.). After standing overnight, the solution was washed with dilute hydrochloric acid, then with water, and was dried (Drierite). The ether was evaporated and the residue was crystallized from petroleum ether (b. p. 60–68°). The product weighed 1.2 g. and melted at 112–114°. When 1 g. of the above chloroacetate was dissolved in 20 g. of a methanol solution of ammonia (19.5%), a gradual cleavage occurred as was shown by examination of aliquots withdrawn at intervals. No material soluble in dilute hydrochloric acid was formed, and after forty-eight hours at room temperature, hydrolysis to the chroman (m. p. and mixed m. p. 92–94°) was complete.

Calcium α-Tocopheryl Succinate.—A solution of α-tocopherol (17.2 g., 0.04 mole) in dry ether (150 cc.) was placed in a three-necked flask equipped with a dropping funnel, mechanical stirrer, and reflux condenser protected by a drying tube. Ethylmagnesium bromide in ether (12 cc., 3.44 *N*, 0.041 mole) was slowly added from the dropping funnel. The solution became cloudy, but no precipitate formed. Succinic anhydride (4.5 g., freshly distilled) in dry dioxane (40 cc.) was added, and the mixture was then set aside in a refrigerator for twelve hours, after which it was refluxed for four hours. The mixture was poured into water, and hydrochloric acid was added until the *p*H was about 3. The ether layer was removed, and the aqueous layer was extracted once with ether (100 cc.). The combined ether solutions were washed until the washings were neutral, and then the organic layer was dried (Drierite) and the ether was evaporated. The residue was dissolved in methanol (100 cc.) and the solution was stirred while ammonium hydroxide (4 cc.) and calcium chloride (52 cc., 10%) were successively added. A viscous oil separated; this was stirred for thirty minutes with a heavy glass rod, and then more ammonium hydroxide (12 cc.) was stirred into the mixture. The oil solidified,

(3) We wish to thank Dr. Evans for his aid in this investigation.

(4) Microanalyses by D. Hayman and E. E. Renfrew. The authors are particularly indebted to Mr. Hayman, who performed the analyses cited in this paper in which the compounds were weighed out of contact with the air ("pig"), and who found that many compounds, such as the calcium tocopheryl succinate described here, which give low carbon values when analyzed in the usual way, give the proper values when the sample is mixed with vanadium pentoxide before burning it.

the supernatant liquid was decanted, and the solid was washed four times with acetone (50 cc. each time) and was dried *in vacuo* at 100° for thirty minutes. The dried solid was dissolved in hot, dry dioxane (100 cc.), the hot solution was filtered, and the filtrate was poured slowly into vigorously stirred, cold acetone (500 cc.). The white, flocculent precipitate was collected on a filter, washed with cold acetone, and dried at room temperature for twelve hours under high vacuum. The product weighed 8 g. (36%), and melted at 210–212°. A sample was dried for two hours at 100° under high vacuum, and was weighed out of contact with the air ("pig") and then analyzed.[4]

Anal. Calcd. for $C_{66}H_{106}O_{10}Ca$: C, 72.10; H, 9.75. Found: C, 71.83; H, 9.70.

The above process was repeated, with proportionate amounts of all materials, except for the time of refluxing, standing, etc., which was the same. The results were as follows.

α-Tocopherol, 94.3 g. (0.218 mole) gave a product (65 g., 55%) melting at 194–199°. *Anal.* Found: C, 72.39; H, 10.09.

α-Tocopherol, 100 g., gave a product (86 g., 67%) melting at 194–198°. *Anal.* Found: C, 72.27; H, 9.70; Ca, 3.37. Calcd.: Ca, 3.64.

α-Tocopherol, 4.91 (*n*-propylmagnesium chloride used in place of ethylmagnesium bromide) gave a product (4.4 g., 71%) which softened at 220°, and melted at 225°. *Anal.* (E. E. R.). Found: C, 71.36; H, 9.65. This sample was used for the biological assays.

The above procedure gave pasty acid esters when either maleic or phthalic anhydride was substituted for succinic anhydride. These compounds, however, were not characterized further.

Summary

1. Several esters of 2,2,5,7,8-pentamethyl-6-hydroxychroman have been prepared by reaction between the appropriate acid derivative and a halo-magnesium derivative of the chroman. These esters include the O-carbethoxy derivative, the acid succinate, and the chloroacetate. All of these esters are hydrolyzed with extreme ease, and it was not possible to prepare the glycine ester of the chroman by ammonolysis of the chloroacetate.

2. Calcium α-tocopheryl succinate has been prepared and characterized. This substance, a solid soluble in organic solvents and insoluble in water, exhibited a vitamin E activity approximately equal, on a molecular basis, to that of α-tocopherol itself.

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The Action of Grignard Reagents on Benzoylformanilides[1]

BY R. F. REEVES[2] AND H. G. LINDWALL

An investigation[3] of the reactions of N-alkyl isatin derivatives with phenylmagnesium bromide showed that N-ethylisatin reacts with two moles of the Grignard reagent to form two isomeric compounds: one, 2,3-diphenyl-1-ethylindole oxide-2,3 (I), undergoes rearrangement to give the other (3,3-diphenyl-1-ethyloxindole) (II). These reactions suggested that analogous products might be obtained through the substitution of N-ethylbenzoylformanilide for N-ethylisatin.

However, in the case of N-ethylbenzoylformanilide, only one mole of phenylmagnesium bromide reacted, producing N-ethylbenzilanilide (III), which was found, incidentally, to be very stable toward alkaline hydrolytic agents. In an attempt to synthesize III by another method acetylbenzilyl chloride was allowed to react with ethylaniline in the hope of obtaining the acetyl derivative of III; the product, however, was found to have the empirical formula $C_{22}H_{19}ON$ instead of the $C_{24}H_{23}O_3N$ which would be required by the acetyl derivative of III, and was found to be identical with authentic samples of II. Thus, acetylbenzilyl chloride and ethylaniline had reacted with the loss of acetic acid and hydrogen chloride to form 3,3-diphenyl-1-ethyloxindole (II).

It was then found that treatment of III with reagents such as acetic anhydride, aqueous or alcoholic hydrogen chloride, or cold concentrated sulfuric acid gave rise also to the formation of II. The most rapid conversion of III to II was obtained through the use of sulfuric acid.

In an entirely similar manner N-methylbenzilanilide (IV) was prepared by the action of an excess of phenylmagnesium bromide upon N-methyl benzoylformanilide. Compound IV yielded 3,3-diphenyl-1-methyloxindole (V) upon beingt reated with acids or dehydrating agents. Also, acetylbenzilyl chloride reacted with methylaniline to give V.

(1) Presented at the Detroit meeting of the American Chemical Society, September, 1940.

(2) Present address: Calco Chemical Division, American Cyanamid Corp., Bound Brook, N. J.

(3) Myers and Lindwall, THIS JOURNAL, 60, 2153 (1938).