Anal. Calcd. for $C_{29}H_{46}O_6$: C, 70.96; H, 9.46. Found: C, 71.08; H, 9.56.

A mixture with gitogenic acid dimethyl ester, m. p. 146–147°, melted at 146–147°.

Summary

Chlorogenonic acid is not identical with either digitogenic or digitoic acid. Wolff–Kishner reduction yields gitogenic acid showing that oxidation of chlorogenin has taken place between C-2 and C-3. On the basis of our present knowledge, these facts are in conflict with the location of the hydroxyl groups of chlorogenin at the 3- and 6-positions.

STANFORD UNIV., CALIF. RECEIVED MAY 23, 1941

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

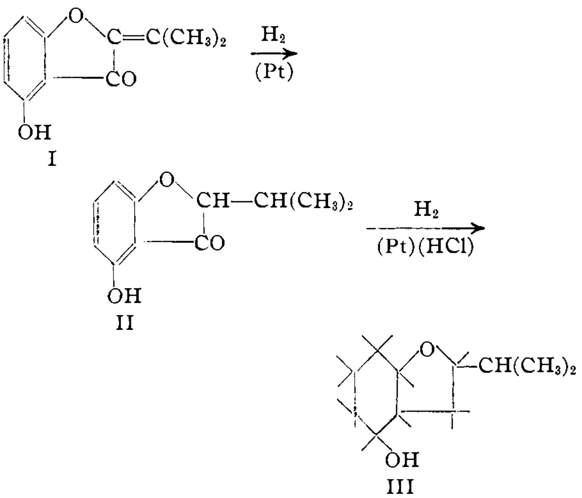
Derivatives of Coumaran. VIII. Reductions in the Coumaranone Series. A New Synthesis of Dihydrotubanol

BY R. L. SHRINER AND MICHAEL WITTE

Although most hydroxycoumaranones have been readily reduced by catalytic methods,[1] difficulty has been encountered in the reduction of the carbonyl group in the 4-hydroxycoumaran-3-one series. Since the physical properties of 4-hydroxycoumaranones differ markedly from those of other hydroxycoumaranones, it has been suggested that, in these compounds, the hydroxyl group is chelated with the carbonyl.[2] This would explain the unusual stability which 4-hydroxycoumaranones exhibit toward catalytic hydrogenation.

Although 4-hydroxycoumaranones are stable to hydrogen, 4-hydroxycoumarans are not. Thus LaForge and Haller found that tubaic acid was cleaved by hydrogen to give tetrahydrotubaic acid.[3] Goodhue and Haller[4] reduced rotenone in butyl acetate solution in the presence of Raney nickel and found that considerable amounts of rotenic acid and tetrahydrorotenone were formed. The present communication describes the catalytic reduction products of 2-isopropylidene-4-hydroxycoumaran-3-one (I) and its benzoate. Although a considerable number of reductions were carried out with platinum and nickel at various temperatures and pressures only those procedures leading to definite compounds with the heterocyclic ring intact will be described.

Catalytic reduction of I in ethanol with platinum and hydrogen at 3 atmospheres yielded the dihydro derivative (II). In the presence of a trace of hydrochloric acid further reduction occurred to give chiefly 2-isopropyl-4-hydroxyhexahydrocoumaran or octahydrotubanol (III). Compound II was characterized by the preparation and analyses of its ketazine, monoacetate, diacetate, dibenzoate and a *bis*-phenylurethan. The latter derivatives are enol esters similar to that previously established for the enol acetate[5] of 6-methoxycoumaran-3-one.



A high pressure reduction of I in absolute ethanol at 60° with Raney nickel yielded a compound whose analysis indicated that it was the diethyl ether of 2-isopropyl-3,4-dihydroxydihydrobenzofuran. With dioxane as the solvent high pressure hydrogenation yielded 2-isopropyl-3,4-dihydroxyoctahydrobenzofuran characterized by its analysis, non-phenolic properties and formation of a diphenylurethan.

In the presence of a trace of hydrochloric acid an absolute ethanol solution of the benzoate (IV) absorbed six moles of hydrogen in the presence of

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[1] Shriner and Anderson, THIS JOURNAL, **61**, 2705 (1939).

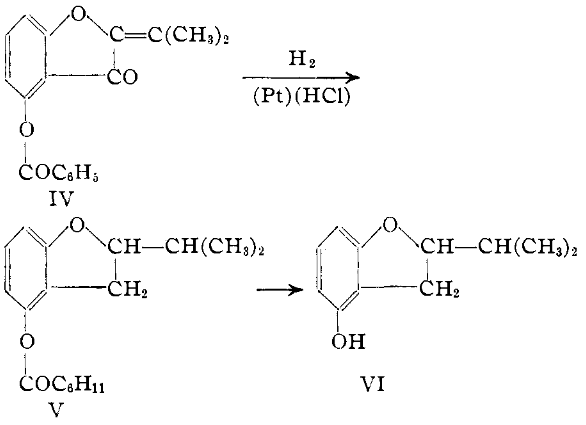
[2] Shriner and Witte, *ibid.*, **61**, 2328 (1939).

[3] Haller and LaForge, *ibid.*, **53**, 4460 (1931).

[4] Goodhue and Haller, *Ind. Eng. Chem.*, *Anal. Ed.*, **12**, 652 (1940).

[5] Shriner and Anderson, THIS JOURNAL, **60**, 1418 (1938).

platinum with a hydrogen pressure of about 4 atmospheres. The product was dihydrotubanol hexahydrobenzoate (V) which was hydrolyzed to hexahydrobenzoic acid and dihydrotubanol (VI).



The latter is a liquid whose properties agreed with those reported by Takei,[6] who prepared it by reduction of isotubanol obtained from rotenone. In the present work a solid crystalline phenylurethan was prepared as a derivative.

The most interesting point in connection with the above reductions is the remarkable effect of the presence of a trace of hydrochloric acid. It not only promoted the reduction of the aromatic benzene ring as previously demonstrated[7] but also seemed to stabilize the oxygen containing heterocyclic ring. When reductions were carried out under conditions more drastic than those described above without hydrochloric acid, complex mixtures were obtained containing products in which the heterocyclic ring had been opened.

Experimental

2-Isopropyl-4-hydroxycoumaran-3-one (II).—A mixture of 13 g. of 2-isopropylidine-4-hydroxycoumaran-3-one,[8] 200 cc. of absolute ethanol and 0.2 g. of platinum oxide catalyst was shaken with hydrogen under a pressure of 45 lb. at room temperature for thirty minutes. Six pounds of hydrogen corresponding to one mole was taken up. The reaction mixture was then filtered and the ethanol was removed by distillation under a reduced pressure of 30 mm. until approximately 25 cc. of a residual oil remained in the distillation flask. This liquid was then treated with distilled water, added dropwise until the solution became cloudy. When shaken, a white crystalline precipitate slowly formed. The yield of white glistening plates melting at 92° was 13 g., which was 98.5% of the theoretical.

Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68.71; H, 6.30. Found: C, 68.79; H, 6.50.

Ketazine of 2-Isopropyl-4-hydroxycoumaran-3-one.—A mixture of 4 g. of 2-isopropyl-4-hydroxycoumaran-3-one, 8 cc. of 95% ethanol and 3 cc. of 85% hydrazine hydrate was refluxed for one hour. A yellow precipitate formed at the end of this time. The reaction mixture was cooled and filtered. The yellow product was washed with water and then with high-boiling petroleum ether. The ketazine was recrystallized from 95% ethanol to give yellow prisms which melted at 220°. The yield of pure compound was 3.7 g. (94% of the theoretical).

Anal. Calcd. for $C_{22}H_{24}O_4N_2$: N, 7.37. Found: N, 7.58.

4-Acetoxy-2-isopropylcoumaran-3-one and 3,4-Diacetoxy-2-isopropylbenzofuran.—Ten grams of 4-hydroxy-2-isopropylcoumaran-3-one was refluxed with 30 g. of acetic anhydride for six hours. The reaction mixture was cooled and fractionally distilled. The low-boiling fraction consisting of acetic acid and acetic anhydride was distilled under a pressure of 20 mm. using a water pump. The residual yellow oil was then distilled under a pressure of 3 mm. The first fraction consisted of 3 g. of a colorless oil boiling at 147° under 3 mm. It was shown to be the monoacetyl derivative: d^{20}_{20} 1.1970; n^{20}_{D} 1.5320; M_D calcd. 59.75; found 60.50.

Anal. Calcd. for $C_{13}H_{14}O_4$: C, 66.63; H, 6.02. Found: C, 66.57; H, 6.18.

A second fraction was collected at 175° at 3 mm. which was dissolved in a little ethanol and the solution cooled in an acetone-dry-ice mixture. The crystals which separated were again recrystallized from 95% ethanol and 7.5 g. of white prisms of the diacetate melting at 72–74° obtained.

Anal. Calcd. for $C_{15}H_{16}O_5$: C, 65.19; H, 5.83. Found: C, 65.27; H, 5.75.

***bis*-Phenylurethan of 4-Hydroxy-2-isopropylcoumaran-3-one.**—A mixture of 100 mg. of 4-hydroxy-2-isopropylcoumaran-3-one and 1 cc. of phenyl isocyanate was heated in a sealed Pyrex test-tube in a steam cone for twenty hours. At the end of the reaction time, the tube was cooled and broken. The contents were washed out with 20 cc. of a solution containing equal amounts of benzene and high boiling petroleum ether. This mixture was filtered and allowed to evaporate slowly in the hood. White needles precipitated when most of the solvent was gone. Three recrystallizations from a benzene-high-boiling petroleum ether mixture gave 0.19 g. of white needles melting at 220°. This was 89% of the theoretical.

Anal. Calcd. for $C_{25}H_{22}O_5N_2$: N, 6.50. Found: N, 6.59.

The above analysis points to the formation of a *bis*-urethan, the reaction taking place with the enol form of the coumaranone as well as with the phenolic hydroxyl.

2-Isopropyl-3,4-dibenzoxybenzofuran.—A mixture of 5 g. of 2-isopropyl-4-hydroxycoumaran-3-one, 9 cc. of benzoyl chloride, 10 g. of sodium carbonate, 25 cc. of acetone and 25 cc. of water was refluxed for two hours. The acetone was removed by distillation and the aqueous solution was neutralized by the addition of dilute sulfuric acid. The mixture was extracted five times with 25-cc. portions of diethyl ether. The combined ether extracts were dried over anhydrous sodium sulfate. The ether was removed

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(6) Takei, *Ber.*, **61**, 1003 (1928).

(7) Brown, Durand and Marvel, THIS JOURNAL, **58**, 1544 (1936).

(8) Shriner and Witte, *ibid.*, **63**, 1108 (1941).

by distillation to leave a yellow oil which was distilled under reduced pressure. A colorless oil came over at 130° and 3 mm. This was characterized as starting material. At 215° and 3 mm. a viscous orange oil distilled which hardened to a yellow solid mass. Two recrystallizations from ethanol gave 3.5 g. of white prisms melting at 132°. The amount of recovered starting material was 2.5 g. None of the mono benzoxy derivative was isolated.

Anal. Calcd. for $C_{25}H_{20}O_5$: C, 74.99; H, 5.05. Found: C, 75.35; H, 5.21.

2-Isopropyl-4-hydroxyhexahydrocoumaran (III).—A mixture of 3 g. of 2-isopropyl-4-hydroxycoumaran-3-one, 0.25 g. of platinum oxide, 55 cc. of absolute ethanol and 3 drops of concentrated hydrochloric acid was shaken with hydrogen at an initial pressure of 42 pounds. An amount of hydrogen equivalent to 5 moles was taken up in three hours. The mixture was filtered and the ethanol was distilled under reduced pressure. The resulting yellow oil was then distilled at 4 mm. At 60° and 4 mm. a colorless terpene smelling oil came over. About 0.2 cc. of this oil was collected but nothing further was done with it. At 130° and 4 mm. a colorless viscous oil was collected. Attempts to effect crystallization failed and the product was redistilled for analysis. About 1.6 g. of a colorless oil boiling at 130° at 4 mm. was obtained.

Anal. Calcd. for $C_{11}H_{20}O_2$: C, 72.05; H, 10.45. Found: C, 71.78; H, 10.30.

Phenylurethan of 2-Isopropyl-4-hydroxyhexahydrocoumaran.—The 4-hydroxycoumarans and coumaranones fail to react with isocyanates under the usual conditions employed to form urethans.[9] The following procedure gave a 43% yield.

A mixture of 30 mg. of 2-isopropyl-4-hydroxyhexahydrocoumaran and 0.25 cc. of phenyl isocyanate was placed in a dry Pyrex test-tube. The tube was sealed and placed on the steam cone for twelve hours. At the end of this time white crystals were visible on the bottom of the tube. The tube was then cooled and the contents were washed out with 20 cc. of a 5% benzene solution in high-boiling petroleum ether. Evaporation of the solvent left pink crystals which were washed with 10 cc. of high-boiling petroleum ether. They were placed into 20 cc. of 95% ethanol, 0.1 g. of Norit was added and the solution boiled until about 10 cc. of alcohol remained. The solution was filtered and 20 mg. of white granular crystals was obtained by cooling. These were filtered, washed with high-boiling petroleum ether, and found to melt at 181–182°.

Anal. Calcd. for $C_{18}H_{25}O_3N$: C, 71.47; H, 8.61; N, 4.60. Found: C, 70.72; H, 8.33; N, 4.71.

Diethyl Ether of 2-Isopropyl-3,4-dihydroxydihydrobenzofuran.—A mixture of 1.4 g. of 2-isopropylidine-4-hydroxycoumaran-3-one, 25 cc. of absolute ethanol and 1 g. of Raney nickel was shaken with hydrogen at an initial pressure of 1300 pounds and at 60°. The reaction was stopped at the end of six hours, when an amount of hydrogen equivalent to two moles was absorbed. The reaction mixture was cooled, filtered and the ethanol removed by distillation to leave an oily residue. Vacuum distillation yielded a colorless oil boiling at 115° and 3 mm. This compound gave no ferric chloride test for phenols. Of all the probable compounds which could be obtained in this reaction, the analysis as well as the negative test for phenols points to the diethyl ether of 2-isopropyl-3,4-dihydroxy-2,3-dihydrobenzofuran. A nearly quantitative yield was obtained.

Anal. Calcd. for $C_{15}H_{22}O_3$: C, 71.94; H, 8.97. Found: C, 72.08; H, 8.93; C, 72.09; H, 8.75.

3,4-Dihydroxy-2-isopropyloctahydrobenzofuran.—A mixture of 4 g. of 2-isopropyl-4-hydroxycoumaran-3-one, 23 cc. of dry dioxane and 2 g. of Raney nickel was shaken with hydrogen for six hours. The initial pressure of the hydrogen was 2700 pounds and the temperature was 100°. After the absorption of 4 moles of hydrogen the bomb was cooled and the reduction mixture was filtered. The dioxane was then distilled at 40° and 20 mm. to leave a yellow oil which soon crystallized on standing. Two recrystallizations from high-boiling petroleum ether gave 3.5 g. of white prisms melting at 134°. This was 84% of the theoretical.

Anal. Calcd. for $C_{11}H_{20}O_3$: C, 65.93; H, 10.09. Found: C, 66.02; H, 10.11.

Phenylurethan of 3,4-Dihydroxy-2-isopropyloctahydrobenzofuran.—A mixture of 100 mg. of the above reduced furan and 1 cc. of phenyl isocyanate was placed in a clean dry Pyrex test-tube. The tube was sealed and placed in the steam cone. At the end of seventeen hours, a mass of crystals had formed in the tube. The tube was broken and the contents washed out with 25 cc. of chloroform. The chloroform solution was allowed to evaporate slowly to leave white needles. These were filtered and washed with ice-cold chloroform. They were then recrystallized twice from 95% ethanol to give lustrous plates melting at 192°. The yield was 150 mg., which was 69% of the theoretical.

Anal. Calcd. for $C_{25}H_{30}O_5N_2$: N, 6.39. Found: N, 6.44.

Dihydrotubanol Hexahydrobenzoate (V).—A mixture of 4.5 g. of 2-isopropylidine-4-benzoxycoumaran-3-one,[8] 0.25 g. of platinum oxide, 4 drops of concentrated hydrochloric acid and 100 cc. of absolute ethanol was shaken with hydrogen at 42 pounds pressure and 25°. The shaking was continued until no more hydrogen was taken up, which corresponded to 6 moles. The reaction mixture was filtered The ethanol was removed by distillation at 30° and 30 mm. to leave a yellow oil. This was distilled at 2 mm. pressure. A few drops of a colorless oil came over at 72°. This was not characterized. At 170° a colorless oil was obtained. The yield was 3 g. (68% of the theoretical).

Anal. Calcd. for $C_{18}H_{24}O_3$: C, 74.94; H, 8.36. Found: C, 74.89, 75.02; H, 8.22, 8.10.

Dihydrotubanol (VI).—A mixture of 2 g. of the hexahydrobenzoic ester, 25 cc. of ethanol, 10 cc. of water and 10 cc. of 10% aqueous sodium hydroxide was refluxed one and a half hours. The mixture was cooled, then treated with an excess of dry carbon dioxide. The resulting solution was then extracted four times with 25-cc. portions of diethyl ether. The ether extracts were combined and dried over anhydrous sodium sulfate. After filtration the ether was evaporated, leaving an oily residue. This was distilled. A colorless oil came over at 134° and 4 mm.

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[9] Shriner and Fuson, "Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 2nd Ed., 1940, p. 136.

This checks with the reported boiling point in the literature.[6] The yield was 0.5 g. (40.5%). There was not enough to purify further.

Anal. Calcd. for $C_{11}H_{14}O_2$: C, 74.08; H, 7.96. Found: C, 73.71; H, 8.09.

The aqueous solution which was extracted with ether contained the hexahydrobenzoic acid. This solution was acidified with dilute sulfuric acid, then extracted three times with 15-cc. portions of ether. The ether extracts were combined and dried over anhydrous sodium sulfate. The ether mixture was then filtered and the ether was evaporated to leave an unpleasant smelling oil. This oil was dried in a vacuum desiccator at 3 mm. pressure overnight. It was then treated with 1 cc. of thionyl chloride and heated under reflux for thirty minutes. The reaction mixture was cooled and a solution of 1 g. of aniline in 25 cc. of dry benzene was added. The mixture was then warmed on the steam cone for fifteen minutes. The mixture was cooled and filtered. The filtrate was washed successively with 2 cc. of water, 5 cc. of 5% hydrochloric acid, 5 cc. of 5% sodium hydroxide and finally 2 cc. of water. The benzene solution after drying over calcium chloride was evaporated to leave white plates melting at 137°. These were recrystallized twice from benzene to give a melting point of 142°. This checks with the melting point of the anilide of hexahydrobenzoic acid as given in the literature.[10]

Phenylurethan of Dihydrotubanol.—A mixture of 0.1 g. of dihydrotubanol and 0.5 cc. of phenylisocyanate was heated in a sealed Pyrex glass tube for seventeen hours. At the end of this time, a small crystalline precipitate had formed in the bottom of the tube. The reaction tube was then broken and the reaction mixture was washed out with a 1:1 mixture of benzene and ligroin. Upon slow evaporation of the benzene high-boiling petroleum ether solution, white prisms of the urethan precipitated. These were filtered, washed with cold ligroin and recrystallized from the benzene ligroin mixture. The yield of urethan was 0.12 g. The melting point was 137°.

Anal. Calcd. for $C_{18}H_{19}O_3N$: N, 4.72. Found: N, 4.93.

Summary

Catalytic reduction of 2-isopropylidine-4-hydroxycoumaran-3-one with platinum and hydrogen yields the 2-isopropyl derivative but in the presence of a trace of hydrochloric acid complete reduction to the substituted hexahydrocoumaran took place.

Dihydrotubanol has been synthesized by reducing the benzoate of 2-isopropylidine-4-hydroxycoumaran-3-one to the hexahydrobenzoate of dihydrotubanol followed by hydrolysis.

URBANA, ILLINOIS RECEIVED MAY 23, 1941

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[10] Ref. 9, p. 182.

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF HEALTH, UNITED STATES PUBLIC HEALTH SERVICE]

Preparation of 4-Aminobenzenephosphonic Acid (Phosphanilic Acid)*

BY HUGO BAUER

The chemotherapeutic properties of organic phosphorus compounds hitherto have not been investigated. Preliminary studies[1] indicated that active phosphorus compounds with comparatively low toxicity can be obtained. Bis-(4-dimethylaminophenyl)-hydroxyphosphine,[2] $[(CH_3)_2NC_6H_4]_2POH$, showed activity against streptococcal infections in mice equal to that of sulfanilamide. In the course of chemotherapeutic studies an attempt has been made to obtain benzene phosphorus derivatives containing a free primary amino group in the para position. The present report deals with the preparation of 4-aminobenzenephosphonic acid for which the name phosphanilic acid is suggested by analogy with sulfanilic and arsanilic acids.

D. R. Nijk[3] made an unsuccessful attempt to prepare phosphanilic acid by the reaction of ammonium hydroxide with 4-chlorobenzenephosphonic acid[4] in the presence of copper powder at 150°. H. Erlenmeyer and E. Berger,[5] who followed the procedure of Nijk, determined the quantity of phosphanilic acid present in the mixture of acids by titration with nitrite, but did not report the yield.

In the present investigation the maximum yield of phosphanilic acid that could be obtained with the use of copper powder was 5–15%. However, the substitution of freshly precipitated cuprous oxide for copper powder increased the yield to 60–63%. The action of cuprous oxide apparently is not exclusively catalytic. To secure a good yield, it was necessary to use one mole of cuprous

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[1] H. Bauer and S. M. Rosenthal, *Pub. Health Repts.*, **54**, 2093 (1939).

[2] Bourneuf, *Bull. soc. chim. Mém.*, [4] **33**, 1808 (1923); H. Raudnitz, *Ber.*, **60**, 743 (1927).

[3] D. R. Nijk, *Rec. trav. chim.*, **41**, 461 (1922).

[4] A. Michaelis, *Ann.*, **293**, 193 (1897).

[5] H. Erlenmeyer and E. Berger, *Biochem. Z.*, **255**, 429 (1932).