TMS), 10 (broad OH), 7.60 (CH=), 7.16 (C_6H_4), 4.39 (CH_2 quadruplet), 2.38 (CH_3), 1.41 (CH_3 triplet); $\lambda_{max}^{CH_3OH}$ 270, 313, and 455 mμ (log ε 3.72, 3.60, and 3.99).

Anal. Calcd for $C_{15}H_{14}O_3S_2$: C, 58.81; H, 4.61; S, 20.9. Found: C, 58.15; H, 4.65; S, 20.8.

Treatment of IV with acetyl chloride and pyridine yielded an acetate that crystallized as yellow needles from benzene–hexane: mp 96–97.5°; infrared (mull), 5.75, 5.85, and 6.02 μ (C=O); nmr (carbon tetrachloride) (parts per million from TMS), 7.93 (CH=), 7.06 (C_6H_4), 4.20 (CH_2 quadruplet), 2.35 (CH_3C=O), 2.25 (CH_3), 1.35 (CH_3 triplet). The acetate was unstable in methanol solution when exposed to ultraviolet radiation, and rapidly hydrolyzed to IV in the presence of alcohol and pyridine.

Anal. Calcd for $C_{17}H_{16}O_4S_2$: C, 58.60; H, 4.63; S, 18.4. Found: C, 58.22; H, 4.70; S, 18.2.

2-Imino-3-carbethoxy-4-mercapto-5-(*p*-tolyl)-2H-thiapyran (V).—Ethyl cyanoacetate, 1.80 g (0.015 mole), was added to a solution of 0.015 mole of sodium ethoxide in 10 ml of ethanol and the resulting mixture was treated with 1.70 g (0.0076 mole) of 4-(*p*-tolyl)-1,2-dithiole-3-thione dissolved in 15 ml of benzene. Reaction was immediate and the orange-yellow solid that formed was collected and washed with water, benzene, and ether. The yield of crude 2-imino-3-carbethoxy-4-mercapto-5-(*p*-tolyl)-2H-thiapyran, mp 240–245° dec, was 2.0 g (86%). A purified sample, mp 246–248° dec, was obtained by crystallization from methyl ethyl ketone: infrared (mull), 3.02 (NH), 5.91 (C=O), and 8.90 μ (C=S); $\lambda_{max}^{CH_3OH}$ 334 and 390 mμ (log ε 3.95 and 3.34).

Anal. Calcd for $C_{16}H_{15}NO_2S_2$: C, 58.99; H, 4.95; N, 4.59; S, 21.0. Found: C, 59.59; H, 4.91; N, 4.29; S, 21.5.

The acetate, prepared with acetyl chloride in pyridine solution, was isolated as dark red crystals from ethyl acetate: mp 193–196°; infrared (mull), 5.85 (C=O), 6.00 (C=O), and 8.88 μ (C=S).

Anal. Calcd for $C_{17}H_{17}NO_3S_2$: N, 4.03. Found: N, 3.98.

2-Imino-3-cyano-4-mercapto-5-(*p*-tolyl)-2H-thiapyran (VI).—A solution of 24.6 g (0.110 mole) of 4-(*p*-tolyl)-1,2-dithiole-3-thione and 9.1 g (0.14 mole) of malononitrile in 330 ml of benzene was added to 8.9 g (0.165 mole) of sodium methoxide in 500 ml of methanol. After standing for 1 hr the reaction mixture was added to an excess of dilute hydrochloric acid and the red solid was collected and washed with water and benzene. The yield of crude product, mp 245–250° dec, was quantitative. Samples of VI were purified in 77% yield, by crystallization from acetone–benzene, without any change in the melting point: infrared (fluorolube), 3.06 and 3.23 μ (NH_2); (mull), 4.50 (C≡N), 6.03 (C=N), and 8.92 (C=S); nmr (deuterated DMSO) (ppm from TMS), 9.09 (NH_2), 7.34 (CH=), 6.85 (C_6H_4), 2.30 (CH_3) (all singlets); $\lambda_{max}^{CH_3OH}$ 248, 331, and 472 mμ (log ε 4.08, 4.36, and 4.30).

Anal. Calcd for $C_{13}H_{10}N_2S_2$: C, 60.43; H, 3.90; N, 10.85; S, 24.8. Found: C, 60.55; H, 3.90; N, 10.73; S, 24.9.

With ammonium hydroxide the thiapyran gives a yellow solution from which the starting material can be recovered upon acidification. The amino hydrogens, observed *via* nmr spectroscopy, readily exchange with deuterium oxide in deuterated dimethyl sulfoxide. Acetylation with acetyl chloride–pyridine gives a purple-red monoamide that was crystallized from acetone–benzene: mp 245–248°; infrared (mull), 3.08 (NH), 4.50 (C≡N), 5.82 (C=O), and 8.95 μ (C=S). The amide is soluble in aqueous ammonium hydroxide giving an orange-red solution. Acidification with hydrochloric acid precipitates the amide.

Anal. Calcd for $C_{15}H_{12}N_2OS_2$: C, 59.98; H, 4.03; N, 9.33; S, 21.4. Found: C, 60.47; H, 4.35; N, 9.33; S, 21.6.

A Rational Synthesis of 4-Hydroxy-2,5-dimethyl-3(2H)-furanone, a Flavor Component of Pineapple

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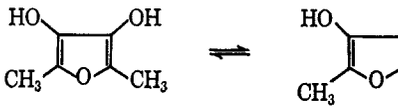
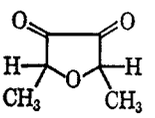
The title compound (I), recently isolated from pineapple flavor concentrate by Rodin, *et al.*,[1] was identified on the basis of its spectral characteristics. It was known also from the work of Hodge, *et al.*, to be produced by a complex reaction between piperidine acetate and the deoxy sugar, rhamnose.[2,3] The product of this reaction was identified on the basis of its spectral properties and on a degradative sequence.[3,4] This Note presents a rational synthesis of furanone I, which confirms the previous structural assignments.

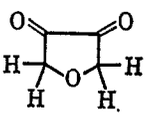
4-Hydroxy-2,5-dimethyl-3(2H)-furanone may be considered as one of three possible tautomers (I, Ia, and Ib). Dienolic tautomer Ia is formally a furan, and a synthetic approach utilizing intermediates containing this relatively stable heteroaromatic ring could be



Ia I



Ib



II

expected to avoid some of the well-documented instability problems associated with the monoenolic final product.[1,5,6] Almost all α- or β-hydroxyfurans tend to assume the carbonyl tautomeric form[7]; thus, the lower homolog of I, tetrahydrofuran-3,4-dione (II), is reported to exist solely in the diketo form.[8] In the special case where carbalkoxy groups are present in the 2 and 5 positions, however, 3,4-dihydroxyfurans exist as such, and several examples of this class of compound are known.[9] The behavior of these hydroxyl groups parallels that of phenols and they may be alkylated or acylated in the normal manner.[9]

In the present work, dimethyl 3,4-dihydroxyfuran-2,5-dicarboxylate (III), prepared by base-catalyzed condensation of dimethyl oxalate and dimethyl diglycolate,[10] was readily converted to dibenzyl derivative IV by treatment with excess benzyl chloride in the presence of base. Reduction of IV with lithium aluminum hydride gave a viscous diol (V), which was transformed directly to dibenzoate ester VI with benzoyl chloride and pyridine (see Scheme I). Catalytic hydrogenolysis of a tetrahydrofuran solution of the dibenzoate,

(1) J. O. Rodin, C. M. Himel, R. M. Silverstein, R. W. Leeper, and W. A. Gortner, *J. Food Sci.*, **30**, 280 (1965).

(2) J. E. Hodge, B. E. Fisher, and E. C. Nelson, *Proc. Am. Soc. Brewing Chemists*, **84** (1963).

(3) J. E. Hodge and B. E. Fisher, Abstracts, 145th National Meeting of the American Chemical Society, New York, N. Y., Sept 1963, p 3D.

(4) B. E. Fisher and J. E. Hodge, Abstracts, 150th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept. 1965, p 4D.

(5) J. E. Hodge, personal communication.

(6) B. Willhalm, M. Stoll, and A. F. Thomas, *Chem. Ind.* (London), **38**, 1629 1965.

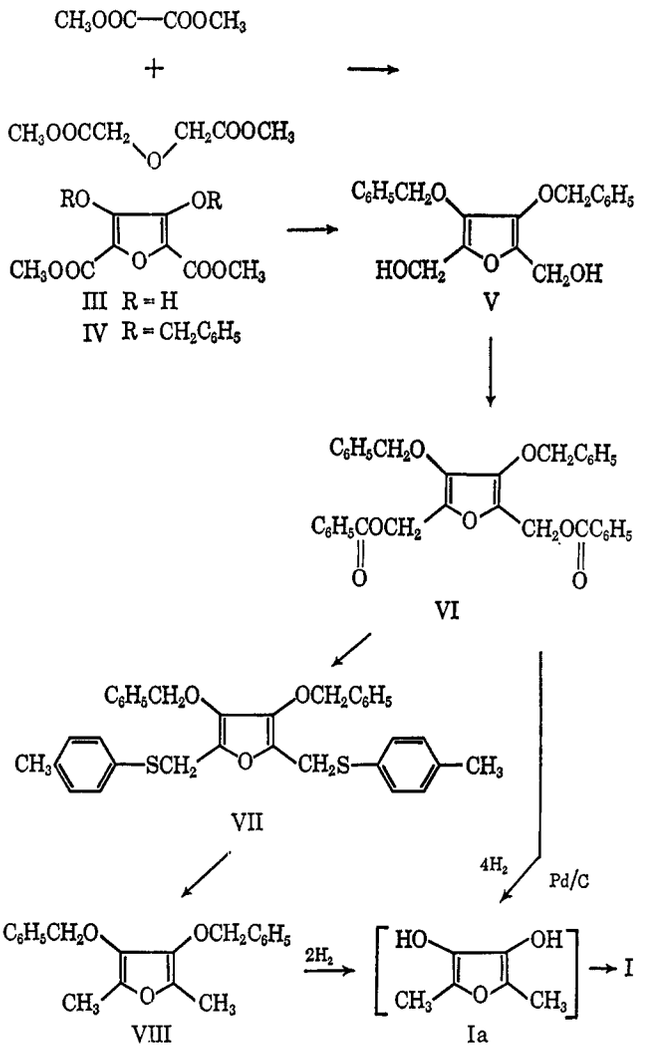
(7) R. Rosenkranz, K. Allner, R. Good, W. V. Philipsborn, and C. Eugster, *Helv. Chim. Acta*, **46**, 1259 (1963), and references therein.

(8) E. C. Kendall and Z. G. Hajos, *J. Am. Chem. Soc.*, **82**, 3219 (1960).

(9) A. P. Dunlop and F. N. Peters, "The Furans," Reinhold Publishing Corp., New York, N. Y., 1953, pp 180–183.

(10) O. Hinsberg, *Chem. Ber.*, **45**, 2413 (1912).

SCHEME I



in the presence of palladium on charcoal and anhydrous potassium carbonate, resulted in rapid uptake of 4 moles of hydrogen to give the desired furanone I. The use of potassium carbonate in the reaction gave improved yields due to removal, as the potassium salt, of the benzoic acid formed during the hydrogenolysis. Isolation of I from the reaction mixture by conventional means proved to be quite difficult. Although gas phase chromatography indicated that good yields (*ca.* 70%) were obtained in the reaction, much of the product was lost during the work-up. The best method for obtaining pure samples was gas phase chromatography. Samples thus prepared gave excellent analyses and had nmr, mass, and infrared spectra in agreement with those obtained by the previous workers.[1,5] The ultraviolet spectrum of the synthetic product [λ_{max}^{MeOH} 291 mμ, (ϵ_{max} 8700)] differed slightly from the spectrum obtained by Rodin, *et al.*[1] [λ_{max}^{MeOH} 289 mμ, (ϵ_{max} 6700)], but their sample had had the opportunity to partially decompose. Hodge[5] reported $\lambda_{max}^{H_2O}$ 286 mμ, (ϵ_{max} 9100) for his compound, which is in substantial agreement with the synthetic product reported here [$\lambda_{max}^{H_2O}$ 289.5 mμ (ϵ 9500)].

A fully satisfactory melting point was not obtained, and the best samples melted at 75–78°. These samples were obtained when the collection tube on the gas chromatograph was seeded with previously crystallized product, thus causing the effluent to crystallize directly from the gas stream. Without seeding, a liquid was obtained that crystallized on scratching and, subsequently, melted at 50–70°. Correct combustion analyses were obtained on samples collected under both conditions, however. Hodge[3,5] reported a melting point of 82–84° for freshly crystallized (ether) or sublimed samples. Crystalline samples, as reported previously,[1,5,6] changed to viscous liquids of altered odor within 1 or 2 days if stored at room temperature in the presence of air. Storage under nitrogen at subzero temperatures improved stability markedly, and samples have been stored in such a manner for several months with only slight decomposition. Larger samples prepared by Hodge's method[2] were appreciably easier to handle and, as a preparative method, his procedure is clearly the one of choice.

A variation on the above synthetic scheme also led to furanone I. Dibenzoate VI, when treated with the sodium salt of *p*-toluenethiol, underwent displacement of the benzoate groups to give bissulfide VII. Careful treatment of this thio compound with Raney nickel resulted in desulfurization to 3,4-dibenzyloxy-2,5-dimethylfuran (VIII). This compound absorbed 2 moles of hydrogen to yield I. It was necessary to add the Raney nickel in small portions while following the progress of the desulfurization by thin layer chromatography. Excess nickel caused debenzylation as indicated by the characteristic odor of I. No furanone could be isolated from such over-treated reaction mixtures, however.

An attempt to reduce diol V directly to I with hydrogen and palladium on charcoal resulted in rapid uptake of only 2 moles of hydrogen and slow uptake of the remaining two. Although the aroma of the product was obvious, gas phase chromatography showed only traces to be present.

Experimental Section[11]

Dimethyl Diglycolate.—A solution of 203.4 g (1.52 moles) of diglycolic acid in 760 ml of methanol, 354 g (3.4 moles) of acetone dimethyl acetal, and 15 ml of concentrated sulfuric acid was held for 2 hr at room temperature. Most of the solvent was removed *in vacuo* and the residue was taken up in *ca.* 2 l. of water. Threefold extraction of the aqueous solution with ether, followed by drying of the combined extracts with sodium sulfate and removal of solvent *in vacuo*, left a crystalline residue of 126.2 g. Distillation *in vacuo* (10 mm) gave 119.3 g (48.5%) of product boiling at 116–119°, which crystallized in the receiver. Material prepared in a similar manner showed a single peak on gas phase chromatography (0.25 in. × 5.5 ft column, 15% DC 550 on Chromosorb W, 171°, 70 cc of He/min, retention time 4.0 min); a sample collected by this method melted at 37.5–39°, lit.[12] mp 36°, bp 130° (12 mm).

Dimethyl 3,4-Dihydroxyfuran-2,5-dicarboxylate (III).—A stirred solution of 27.6 g (0.17 mole) of dimethyl diglycolate and 20.4 g (0.17 mole) of dimethyl oxalate in dimethylformamide (400 ml) was treated in portions with 8.6 g (0.36 mole) of sodium hydride. After addition of methanol (0.5 ml), the mixture was warmed to *ca.* 50° when a mild exothermic reaction began, accompanied by hydrogen evolution. The temperature was held

(11) Melting points were taken in capillary tubes on a Mel-Temp apparatus and are corrected. Nmr spectra were obtained on either Varian HR-60, A-60, or HA-100 instruments and were taken in carbon tetrachloride solution with tetramethylsilane as the internal reference. Infrared spectra were taken on a Perkin-Elmer Model 137 Infracord. Ultraviolet spectra were obtained on a Perkin-Elmer Model 202 recording spectrophotometer. The mass spectrum was provided by a CEC 21-103C instrument.

(12) R. Anschutz and S. Jaeger, *Chem. Ber.*, **55**, 676 (1922).

at 50–55° by occasional cooling with an ice bath. When the temperature had dropped spontaneously to 40°, the thickened mixture was poured into water (1500 ml) containing 60 ml of 3*N* HCl. Thorough chilling in an ice bath caused precipitation of 15.3 g (41.5%) of tan crystals melting at 216–220° after oven drying at 120°, lit.[10] mp 220°.

On one occasion out of three, the spontaneous reaction failed to occur, and the mixture required heating at 85–95° for 1.5 hr to conclude the slow hydrogen evolution. The same work-up gave a 34% yield in this instance.

Dimethyl 3,4-Dibenzyloxyfuran-2,5-dicarboxylate (IV).—A stirred solution of 21.6 g (0.10 mole) of dimethyl 3,4-dihydroxyfuran-2,5-dicarboxylate and 50 ml (0.44 mole) of benzyl chloride in dimethylformamide (175 ml) was treated slowly and in small portions with 52% sodium hydride in oil (9.8 g, 0.21 mole). The mixture was heated at 100° for 1 hr, poured into water (*ca.* 1.5 l.), and the partially crystalline precipitate was removed by extraction with ether. The ether solution was dried over Na_2SO_4, the ether was removed by boiling, and the residue was treated with 30–60° petroleum ether (*ca.* 100 ml). Swirling the mixture caused crystallization and, after cooling, the product was filtered off and washed with petroleum ether. Recrystallization from methanol gave 31.2 g (79%) melting at 95–97°. This product was analyzed after drying *in vacuo*.

Anal. Calcd for $C_{22}H_{20}O_7$: C, 66.66; H, 5.09. Found: C, 66.83; H, 5.12.

3,4-Dibenzyloxy-2,5-dihydroxymethylfuran (V).—A solution of dimethyl 3,4-dibenzyloxyfuran-2,5-dicarboxylate (14.0 g, 0.035 mole) in anhydrous ether (500 ml) was added dropwise over 0.5 hr to a stirred mixture of 5.0 g (0.13 mole) of lithium aluminum hydride in anhydrous ether (150 ml). Stirring was continued for an additional 0.5 hr. Water (*ca.* 15–20 ml) was then added carefully dropwise until the gray color of the inorganic salts had changed to white. The mixture was gravity-filtered and the precipitate was washed several times with ether. The solvent was removed from the combined filtrate and washings *in vacuo* to leave 9.7 g of viscous, pale-yellow, crude diol. Thin layer chromatography (silica gel, ether) showed a major component at R_f 0.3 (presumably the diol) and two very minor impurities with R_f 0.05 and 0.15. The infrared spectrum of this material showed a strong, broad hydroxyl band at 3.0 μ. This unstable product was immediately converted to the dibenzoate without further purification.

2,5-Dibenzoyloxymethyl-3,4-dibenzyloxyfuran (VI).—Crude 3,4-dibenzyloxy-2,5-dihydroxymethylfuran (9.7 g, 0.0285 mole) in 25 ml of dry pyridine was treated in small portions with 10 ml (12 g, 0.085 mole) of benzoyl chloride with swirling and intermittent cooling. After 1 hr at room temperature, the mixture was poured into dilute aqueous sodium bicarbonate (*ca.* 250 ml, excess). The oily precipitate crystallized almost immediately and was filtered off. Recrystallization of the wet product from methanol gave 9.3 g (48%, based on dimethyl 3,4-dibenzyloxyfuran-2,5-dicarboxylate) of product, mp 82–83.5°. Infrared spectrum: λ (Nujol mull) 5.79 (C=O), 6.23 (C=C), 7.68, 7.95, 9.15, 9,36, 9.75, 13.5, 14.2, and 14.4 μ. Nmr spectrum: τ 4.97 (singlet, 8 protons, α to phenyl and furyl rings), 2.04 (ill-defined doublet, 4 protons α to aromatic carbonyls), 2.5–2.9 (multiplet, 16 protons, aromatic).

Anal. Calcd for $C_{34}H_{28}O_7$: C, 74.44; H, 5.14. Found: C, 74.18; H, 5.17.

4-Hydroxy-2,5-dimethyl-3(2H)-furanone (I).[13]—A stirred solution of 1.10 g (2.0 mmoles) of 3,4-dibenzyloxy-2,5-dibenzoyloxymethylfuran in tetrahydrofuran (33 ml) was hydrogenated at atmospheric pressure and room temperature in the presence of 10% palladium on charcoal (160 mg) and powdered anhydrous potassium carbonate (0.63 g, 4.6 mmoles). During 2 hr, 175 ml of hydrogen (91% of theoretical) was taken up and absorption then ceased. Vapor phase chromatography (3/8 in. × 6 ft column, Chromosorb W, 50/60 mesh, 143°, 150 cc of He/min) of an aliquot of the reaction mixture indicated a yield of 73% by comparison with a standard solution prepared from rhamnose-derived furanone.[2] Retention times for the hydrogenolysis product and the reference compound were 10.5 and 10.4 min, respectively. The catalyst and inorganic salts were removed by centrifugation and the supernatant was reduced to a volume of *ca.* 2 ml, without heating, by a stream of nitrogen. Vapor phase chromatography was used to isolate samples from this concentrate for the various analytical procedures. Fresh individual samples were collected immediately before use in uncooled glass tubes seeded with traces of crystalline product. A 220-μl. aliquot of the concentrate gave 17 mg of crystalline product melting at 75–78°. Without seeding, a liquid product was obtained. The infrared spectrum was taken on such a sample in order to compare it with the liquid film spectrum of Rodin, *et al.*[1] Infrared spectrum: λ (liquid film) 3.1 (OH, broad), 5.90 (C=O), 6.16, 7.66, 8.33, 9.97, 10.71, and 13.15 μ. Nmr spectrum: τ 2.76 (1 proton, broad singlet), 5.67 (1 proton, quartet, J = 7 cps), 7.81 (3 protons, singlet), 8.60 (3 protons, doublet, J = 7 cps). Ultraviolet spectrum: λ_{max}^{MeOH} 291 mμ (ϵ_{max} 8700); $\lambda_{max}^{H_2O}$ 289.5 mμ (ϵ_{max} 9500). The mass spectrum gave a molecular ion of m/e 128 and fragment peaks in agreement with those previously obtained.[1] A small, long-range coupling effect (0.75 cps) was noted in the nmr spectrum between the C-2 proton and the C-5 methyl protons.

Anal. Calcd for $C_6H_8O_3$: C, 56.24; H, 6.29. Found: C, 56.25; H, 6.40.

3,4-Dibenzyloxy-2,5-di(*p*-tolylthiomethyl)furan (VII).—A solution of sodium *p*-toluenethiolate was prepared by adding 54 mg of 52% sodium hydride in oil (1.2 mmoles) to 135 mg (1.1 mmoles) of *p*-toluenethiol in dimethylformamide (2 ml). To this solution was added 3,4-dibenzyloxy-2,5-dibenzoyloxymethylfuran (266 mg, 0.49 mmole) and the mixture was heated *ca.* 5 min on the steam bath. The gelled reaction mixture was diluted with 8 ml of water and the oily precipitate was isolated by ether extraction. The 248-mg residue, obtained after drying the ether extracts over Na_2SO_4 and removal of the solvent *in vacuo*, was chromatographed over Merck basic alumina (8.7 g). Petroleum ether (lys 30–60°) and 10% ether in petroleum eluted a total of 8 mg of low-polarity impurities. Elution with 25–50% ether gave 165 mg (61%) of colorless, oily product, which displayed only a single spot on thin layer chromatography (alumina, 5% ether in petroleum ether, R_f 0.7). This material gave a very clean nmr spectrum: τ 2.6–3.1 (18 aromatic protons, multiplet), 5.36 (4 protons, singlet, benzyloxy methylenes), 6.25 (4 protons, singlet, furyl methylenes), 7.72 (6 protons, singlet, aromatic methyls).

Anal. Calcd for $C_{34}H_{32}O_3S_2$: C, 73.88; H, 5.84. Found: C, 73.77; H, 5.95.

3,4-Dibenzyloxy-2,5-dimethylfuran (VIII).—A stirred solution of 2.0 g (3.7 mmoles) of 3,4-dibenzyloxy-2,5-di(*p*-tolylthiomethyl)-furan in 60 ml of 1:1 absolute alcohol–benzene was treated at room temperature with small portions of Raney nickel. After each portion was added (the desulfurization was very rapid), the progress of the reaction was monitored by thin layer chromatography (alumina, 5% ether in 30–60° petroleum ether). The R_f values of the bissulfide and the product were 0.7 and 0.85, respectively. During the reaction, a third spot (R_f 0.78), presumed to be the monodesulfurized intermediate, was also present in low concentration. When essentially all of the starting material was gone, the catalyst was removed by filtration and the solution was evaporated to an oily residue (1.0 g). Chromatography over Merck basic alumina (20 g) using 30–60° petroleum ether intially, then 30% ether in petroleum ether to elute the product, gave a colorless oil (487 mg), which was estimated to be >99% pure by thin layer chromatography. A trace of starting bissulfide could be detected, however. Nmr spectrum: τ 2.67 (10 aromatic protons, singlet), 5.08 (4 benzyloxy protons, singlet), 8.06 (6 methyl protons, singlet).

Before this product could be catalytically hydrogenated, it was necessary to treat it with a small amount of Raney nickel to remove the sulfur-containing residual starting material. Apparently this impurity was enough to poison the catalyst and no hydrogen uptake occured.

Catalytic hydrogenolysis of 3,4-Dibenzyloxy-2,5-dimethylfuran (VIII).—A solution of 96 mg (0.31 mmole) of 3,4-dibenzyloxy-2,5-dimethylfuran in tetrahydrofuran (5 ml) was hydrogenated at atmospheric pressure and room temperature in the presence of 31 mg of 10% palladium on charcoal. Hydrogen uptake slowed markedly but did not stop after 2 moles had been absorbed. The reaction was stopped after 16.4 ml (theoretical 15.4 ml) had been taken up, and, after removal of the catalyst by centrifugation, the mixture was concentrated under a nitrogen stream to 2.3 ml. Vapor phase chromatography of an aliquot (previous conditions) indicated a yield of 57%. A sample isolated by vapor phase chromatography had an infrared spectrum identical with that of 4-hydroxy-2,5-dimethyl-3(2H)-furanone obtained previously.

(13) NOTE ADDED IN PROOF.—The title compound was recently isolated from the hydrogenolysis products of acetylformoin: A. Hofman and C. Eugster, *Helv. Chim. Acta*, **49**, 53 (1966).

Acknowledgment.—The nuclear magnetic resonance spectra were performed by Mr. W. R. Anderson, Jr. The mass spectrum was obtained by Mr. F. M. Church. Microanalyses were carried out by the Stanford Research Institute analytical department.

Stereochemistry of the Palladium-Catalyzed Hydrogenation of 3-Oxo-4-ene Steroids[1]

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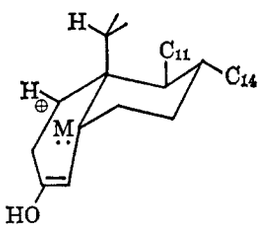
Received December 16, 1965

Recently, the effect of solvents on the stereochemistry of the catalytic hydrogenation of α,β-unsaturated ketones has been reported with two series of ketones.[3,4] Augustine has shown that under acidic conditions $\Delta^{1,9}$-2-octalone and 2-benzoyl-1,2,3,4,8,8a-hexahydro-6-isoquinolone give the corresponding saturated *cis* ketones predominantly in the hydrogenation with a 10% palladium–charcoal as a catalyst.[3] On the other hand, McQuillin, Ord, and Simpson have reported that the use of less polar solvents or the presence of acid causes the decrease of the formation of 5β ketones, the ring A/B-*cis* isomers, in the hydrogenation of cholest-4-en-3-one and testosterone with a palladium–charcoal catalyst.[4] Thus, the effect of acid on the stereochemistry of the hydrogenation led to completely different results with the two series of ketones. Apparently the main difference in these studies seems to come from the fact that the former deals with the ketones having no angular methyl group, while the latter with those having such a group at C-10 position. In order to obtain more comparable data and to clarify the cause of this difference in results, three steroid ketones with and without the C-19 angular methyl group, cholest-4-en-3-one (I), testosterone (II), and 19-nortestosterone (III), have been hydrogenated using prereduced palladium oxide and palladium hydroxide as catalysts. Unsupported catalysts were used in this study, because supported catalysts seemed to be more difficult to be prepared in a state free from alkaline or acidic substances. The acetates of II and III have also been subjected to hydrogenation in order to know the effect of the 17-hydroxyl group on the stereochemistry of the hydrogenation.

Table I summarizes the ratio of saturated 5β to 5α ketone formed in the hydrogenation of I, II, III, and the acetates of II and III with palladium black catalysts at 25° and atmospheric pressure of hydrogen. The hydrogenation in ethanol was complicated by an unexpected reaction: the resulting saturated ketones are easily liable to further reduction to give the corresponding ethoxy compounds along with slight amounts of saturated alcohols.[5] This reaction is strongly depressed with addition of alkali or hydrochloric acid. Because of an extensive occurrence of this reaction, the results obtained in ethanol will not be reliable ones, although the hydrogenations were carried out under the conditions to minimize the formation of the ethoxy compounds by using a smaller ratio of catalyst to substrate and a shorter reaction time. Palladium hydroxide was used preferentially in the hydrogenations in neutral alcoholic solutions, because palladium oxide of the Adams type probably contains a small amount of alkaline substances,[6] which may affect the formation of 5β ketone to increase.[4,7]



M = Catalyst metal

Figure 1.

TABLE I

RATIO OF 5β TO 5α KETONE FORMED IN THE HYDROGENATION OF 3-OXO-4-ENE STEROIDS WITH PALLADIUM CATALYSTS

	Compd				
Solvent	I	II	III	Acetate of II	Acetate of III
EtOH + 20% NaOH, 0.1 ml	11.5	6.3[a]	2.09	...	...
t-BuOH	1.35[a]	...	...	...	...
i-PrOH	1.38[a]	0.74[a]	1.68[a]	0.80[a]	1.10[a]
EtOH	1.34[a]	0.52[a]	1.25[a]	1.43[a]	2.04[a]
EtOH + 3 *N* HCl, 0.1 ml	1.44	0.46	1.18	1.95[a]	3.93[a]
AcOH	2.85	0.52	2.02	1.48[a]	4.44[a]
CF_3COOH	3.12	...	...	...	...
AcOH + 3 *N* HCl, 0.1 ml	4.56	0.95	3.17	2.70[a]	12.1[a]

[a] Palladium hydroxide was used as the catalyst. In other cases palladium oxide catalyst was used.

From the results of Table I it is obvious that the formation of 5β-ketone increases under acidic conditions irrespective to the ketones investigated. These results are in line with those reported by Augustine,[3] but not with those reported by McQuillin and his coworkers that the presence of acid decreased the yield of 5β-ketone in the hydrogenation of I and II.[4] For the predominant formation of *cis* ketones in acidic medium, Augustine[3] has proposed a mechanism which involves a 1,4 addition of hydrogen *via* the protonated ketone as an intermediate. When his explanation is applied to the steroid ketones having the C-19 methyl

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(3) R. L. Augustine, *J. Org. Chem.*, **23**, 1853 (1958); R. L. Augustine and A. D. Broom, *ibid.*, **25**, 802 (1960); R. L. Augustine, *ibid.*, **28**, 152 (1963).

(4) F. J. McQuillin, W. O. Ord, and P. L. Simpson, *J. Chem. Soc.*, 5996 (1963).

(5) A direct formation of the ethoxy compounds from the starting unsaturated ketones may also be possible, since such compounds were found in the products at the intermediate stages of the hydrogenation. Details of this reaction will be published elsewhere.

(6) The palladium hydroxide used in this study probably contains a smaller amount of alkali than the palladium oxide of Adams type, since the resulting catalyst catalyzes the formation of ethoxy compounds from ketones in ethanol more efficiently than the catalyst from the oxide, the reaction being depressed by the presence of alkali. *Cf.* C. W. Keenan, B. W. Giesemann, and H. A. Smith, *J. Am. Chem. Soc.*, **76**, 229 (1954).

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