Cleavage of this ketone (220 g.) by means of sodium amide (50 g.) was also effected in considerably higher yield 135 g. (79%) of *α,α-dimethyl-δ-phenylvaleramide* being obtained after only 6 hours' refluxing. The product crystallized from cyclohexane in colorless needles, m.p. 92°.

Anal. Calcd. for $C_{13}H_{19}NO$: C, 76.1; H, 9.3. Found: C, 76.0; H, 9.3.

On the other hand, the Hofmann degradation of this amide (80 g.) gave a considerably lower yield (34%, 27 g.) of *α,α-dimethyl-δ-phenylbutyl isocyanate*, as a colorless oil, b.p. 154°/18 mm., n_D^{22} 1.5236.

Anal. Calcd. for $C_{13}H_{17}NO$: C, 76.8; H, 8.4. Found: C, 76.5; H, 8.5.

Hydrolysis of 27 g. of this isocyanate gave only 3 g. of *α,α-dimethyl-δ-phenylbutylamine* (VIII), as a colorless liquid, b.p. 148°/21 mm., n_D^{25} 1.5348. The corresponding *hydrochloride* was obtained in ether medium as colorless, sublimable needles, m.p. 189° (decomp.).

Anal. Calcd. for $C_{12}H_{20}ClN$: Cl, 16.6. Found: Cl, 16.3.

PARIS V^e, FRANCE

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLLEGE OF PHARMACY, UNIVERSITY OF ILLINOIS]

Catalytic Hydrogenation of Ethyl 5,6-Benzocoumarin-3-carboxylate[1]

JAMES E. GEARIEN AND KENNETH J. LISKA

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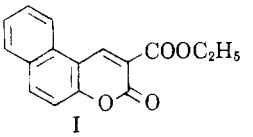
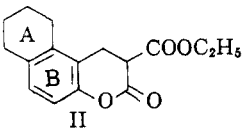
The stepwise hydrogenation of ethyl 5,6-benzocoumarin-3-carboxylate (I), using W-1 Raney nickel as the catalyst, yielded ethyl 2,3,7,8,9,10-hexahydro-3-keto-1*H*-naphtho[2,1-*b*]pyran-2-carboxylate (II), 2-(2-hydroxy-5,6,7,8-tetrahydro-1-naphthylmethyl)propane-1,3-diol (III), and 1-isobutyl-2-decalol (IV), the last identified tentatively. At low pressure, with platinum oxide as the catalyst, and in the presence of hydrochloric acid, I yielded diethyl (2-hydroxy-1-naphthylmethyl)-malonate (V). Characterization of I and of its hydrogenated derivatives was accomplished by conversion to the amides.

In the course of an investigation leading to the preparation of several compounds with possible medicinal activity, it became necessary to study the stepwise hydrogenation of ethyl 5,6-benzocoumarin-3-carboxylate (I).



I

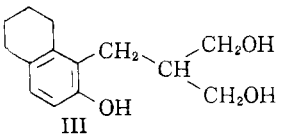
Saturation of the 3,4 double bond in I was reported by Smith and Horner[2] who obtained ethyl 3,4-dihydro-5,6-benzocoumarin-3-carboxylate by the low pressure hydrogenation of I at room temperature and in the presence of small amounts of Raney nickel catalyst. It was found that the time of this reaction could be greatly decreased if a higher ratio of catalyst to unsaturated compound was employed. When hydrogenations using large amounts of Raney nickel were allowed to proceed for over 24 hours a previously unreported compound was isolated in high yield. This new compound was prepared more conveniently by hydrogenating I at room temperature and at pressures up to 1900 pounds per square inch. Ultraviolet and infrared analyses showed this compound to be ethyl 2,3,-7,8,9,10 - hexahydro - 3 - keto - 1*H* - naphtho - [2,-1-*b*]pyran-2-carboxylate (II). The ultraviolet spectrum of II in cyclohexanol exhibited maxima at 274 and 283 millimicrons, indicating the oxygenated tetralin structure.[3] The infrared spectrum, in liquid petrolatum, showed carbonyl absorption both at 1729 and 1760 cm.$^{-1}$, attributable to a saturated ester group and a vinyl type lactone, respectively. This carbonyl absorption was identical with that of the simple dihydrobenzocoumarin. A 1,2,3,4-tetrasubstituted benzene structure[4] in II was confirmed by an infrared absorption band at 816 cm.$^{-1}$ A vinyl type lactone function in II and a 1,2,3,4-tetrasubstituted benzene ring can exist only if ring B is aromatic.



II

The formation of II in the W-1 Raney nickel catalyzed hydrogenation of I confirms Stork's postulation[5] that almost any type of substitution on one benzene ring of naphthalene will stabilize that ring toward reduction.

At 90°, and under a hydrogen pressure of 1520 pounds per square inch, hydrogenation of I yielded a mixture of products. Only one compound, 2-(2 - hydroxy - 5,6,7,8 - tetrahydro - 1 - naphthylmethyl)propane-1,3-diol (III) was isolated from the



III

mixture. The ultraviolet absorption curve of III in 95% ethanol, exhibited a single, somewhat broad

(1) Abstracted from a thesis submitted by Kenneth J. Liska to the faculty of the University of Illinois in partial fulfillment of the requirements for the degree of Doctor of Philosophy, July, 1956.

(2) L. Smith and L. Horner, Jr., *J. Am. Chem. Soc.*, **60**, 678 (1938).

(3) R. Friedel and M. Orchin, *Ultraviolet Spectra of Aromatic Compounds*, John Wiley, New York, N. Y., 1951, Spectrum No. 52.

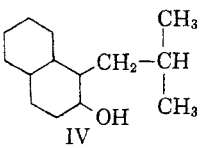
(4) P. Launer and D. McCauley, *Anal. Chem.*, **23**, 1975 (1951).

(5) G. Stork, *J. Am. Chem. Soc.*, **69**, 576 (1947).

maximum at 284 millimicrons (log ϵ 3.29), corresponding to the spectrum of 5,6,7,8-tetrahydro-2-naphthol.[3] The compound was readily soluble in dilute base and was reprecipitated unchanged by the addition of excess acid. An infrared spectrum of III indicated the 1,2,3,4-tetra-substituted benzene structure (C=C stretching vibration 1594 cm.$^{-1}$; C—H deformation 807 cm.$^{-1}$), as well as a polyhydroxylated system (OH stretching vibrations 3375, 3230, and 2670 cm.$^{-1}$; phenolic C—O stretch 1272 cm.$^{-1}$; primary alcohol C—O stretch 1051 cm.$^{-1}$). After III had been removed from the products of the 90° hydrogenation, an oil remained. Ultraviolet spectral analysis of the oil indicated a large proportion of benzenoid structure, and it was concluded that if any decalin derivatives were present, their amount was very small. Saponification of the oil, with subsequent testing for carboxyl groups, indicated only traces of esters present.

The isolation of III and of the unidentified nonsaponifiable oil from the 90° hydrogenation indicated that, with W-1 Raney nickel, hydrogenation of ethyl 5,6-benzocoumarin-3-carboxylate to a decalin derivative was not possible without reduction of the ester groups. This was true even when the ratio of catalyst to hydrogen acceptor was greater than two to one.

At 140°, and under hydrogen pressures up to 2900 pounds per square inch, hydrogenation of I to decalin derivatives was readily achieved. Distillation of the crude reaction oil indicated a mixture of two, and possibly three, components. At 140°, hydrogenolysis was very extensive, and only a trace of esters was present. When the esters were removed by saponification, and the oily, nonsaponifiable residue carefully distilled, a nearly pure fraction was obtained which, from its infrared spectrum, was tentatively identified as 1-isobutyl-2-decalol (IV) (secondary alcohol OH stretching



IV

vibration 3445 cm.$^{-1}$, C—O stretch 1093 cm.$^{-1}$; isopropyl group: CH_3 deformation 1450, 1375, and 1343 cm.$^{-1}$).

When the benzocoumarin ester (I) was hydrogenated at either low or high hydrogen pressures and at room temperature, using platinum oxide as the catalyst, only the 3,4-dihydro compound was obtained. When a small amount of hydrochloric acid was added as an activator in the low pressure, platinum oxide-catalyzed hydrogenation of I, the product was diethyl (2-hydroxy-1-naphthylmethyl)-malonate (V).

All of the hydrogenation products containing ester groups were characterized by conversion to their amides. When 5,6-benzocoumarin-3-carboxylate was allowed to stand with alcoholic ammonia at room temperature, the lactone function remained intact, and the product was 5,6-benzocoumarin-3-bond carboxamide. Hydrogenation of the 3,4 double bond in I decidedly affected the course of ammonolysis. Ethyl 3,4-dihydro-5,6-benzocoumarin-3-carboxylate and ethyl 2,3,7,8,9,10-hexahydro-3-keto-1*H*-naphtho[2,1-*b*]pyran-2-carboxylate (II) when treated with ammonia both yielded the corresponding diamides. Diethyl (2-hydroxy-1-naphthylmethyl)malonate was similarly converted to (2-hydroxy-1-naphthylmethyl)malonamide.

EXPERIMENTAL[6]

Ethyl 3,4-dihydro-5,6-benzocoumarin-3-carboxylate (I).[2] A suspension of 4.03 g. (0.015 mole) of finely powdered ethyl 5,6-benzocoumarin-3-carboxylate[7] in 250 ml. of absolute ethanol was hydrogenated at room temperature and at a hydrogen pressure of 44 p.s.i., using 6.6 g. of freshly prepared W-1 Raney nickel[8] as the catalyst. The time of the reaction was 1.5 hr. To the reaction vessel was added 75 ml. of absolute ethanol, and the suspension was warmed on the steam bath until all of the product had dissolved. While still warm, the contents of the reaction vessel were filtered, and the colorless filtrate evaporated to a volume of 150 ml. Upon chilling, the solution yielded 2.98 g. of the pure product, m.p. 113–114°. An additional 0.36 g. of less pure product, m.p. 111.5–112.5°, was obtained by evaporating the mother liquor to a volume of 40 ml. and chilling. The total yield was 3.34 g. (82.4%). Smith and Horner[2] reported that the compound melted at 113–114°.

Ethyl 2,3,7,8,9,10-hexahydro-3-keto-1H-naphtho[2,1-b]-pyran-2-carboxylate (II). A suspension of ethyl 5–6-benzocoumarin-3-carboxylate (13.41 g., 0.05 mole) in 450 ml. of absolute ethanol was hydrogenated at a hydrogen pressure of 1890 p.s.i. and at room temperature, using 17.6 g. of W-1 Raney nickel as the catalyst. The time of the reaction was 24 hr. The contents of the reaction vessel were warmed to dissolve the product which had precipitated from solution. After removal of the catalyst by filtration, the filtrate was condensed to a volume of 150 ml. and chilled. There was deposited 8.79 g. of white needles, m.p. 78–80°; a second crop of product was obtained by further condensation, which, after recrystallization from absolute ethanol, melted at 77–78°. The total yield was 9.60 g. (70.0%).

Anal. Calcd. for $C_{16}H_{14}O_4$: C, 70.05; H, 6.61. Found: C, 69.87; H, 6.82.

The analytically pure product melted at 79.5–80.5°; ultraviolet spectrum in cyclohexane (log ϵ): 274 mμ (3.12), 283 mμ (3.12).

Diethyl (2-hydroxyl-1-naphthylmethyl)malonate. Two grams (7.45 millimoles) of ethyl 5,6-benzocoumarin-3-carboxylate was dissolved in 240 ml. of absolute ethanol, and 9.6 ml. of absolute ethanol saturated with anhydrous hydrogen chloride gas was added. Fifty milligrams of Adams Catalyst[9] was added and the mixture was hydrogenated at 45 p.s.i. of hydrogen at room temperature for 9 hr. After removal of the catalyst, the liquid was condensed to a volume of 30 ml. Chilling produced 0.76 g. (32.2%) of product, m.p.

(6) Melting points and boiling points are uncorrected. Unless otherwise noted, carbon-hydrogen analyses were performed by Weiler and Strauss, Microanalytical Laboratory, Oxford, England.

(7) E. Knoevenagel and F. Schroeter, *Ber.*, **37**, 4486 (1904).

(8) L. Covert and H. Adkins, *J. Am. Chem. Soc.*, **54**, 4116 (1932).

(9) R. Adams, V. Voorhees, and R. Shriner, *Org. Syntheses*, **Coll. Vol. I**, 463 (1941).

109.5–110°; mixed melting point with ethyl 3,4-dihydro-5,6-benzocoumarin-3-carboxylate 89–100°. The compound crystallized from ligroin (90–120°) in the form of beautiful white needles. It was immediately soluble in cold 1% sodium hydroxide solution; ultraviolet spectrum in 95% ethanol (log ϵ); 270 mμ (3.61), 280 mμ (3.73), 292 mμ (3.65), 325 mμ (3.39), and 337 mμ (3.45).

Anal. Calcd. for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37. Found: C, 68.77; H, 6.13.

2-(2-Hydroxy-5,6,7,8-tetrahydro-1-naphthylmethyl)propane-1,3-diol (III). Ethyl 5,6-benzocoumarin-3-carboxylate (10.73 g., 0.04 mole), in 450 ml. of absolute ethanol, with 24.7 g. of freshly prepared W-1 Raney nickel, was hydrogenated at 90° and 1520 p.s.i. of hydrogen. The reaction time was 24 hr. After removal of the catalyst and solvent, the crude reaction product was obtained as a viscous oil. The oil was first triturated with ligroin (30–60°), and then with ether to yield white crystals which were filtered, washed with ligroin, and then with a little dry ether. The yield was 1.03 g. (11%), m.p. 149–151°. After three recrystallizations from water-ethanol, the white crystals melted at 153–154°; ultraviolet spectrum in 95% ethanol (log ϵ): 284 mμ (3.29).

Anal.[10] Calcd. for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 70.93; H, 8.73.

The compound was immediately soluble in 8% sodium hydroxide solution, from which it reprecipitated unchanged by the addition of excess acid. An ethanolic solution gave a green color with ferric chloride solution. Attempts to prepare a crystalline acetate or 3,5-dinitrobenzoate derivative failed.

1-Isobutyl-2-decalol (IV). A suspension of ethyl 5,6-benzocoumarin-3-carboxylate (13.41 g., 0.05 mole) in 450 ml. of absolute ethanol was hydrogenated at a hydrogen pressure of 1850 p.s.i. and at 140°, using 20.9 g. of W-1 Raney nickel as the catalyst. The total reaction time was 29 hr. The oil (8.93 g.) which remained after removal of the catalyst and solvent was refluxed with 30 ml. of 10% sodium hydroxide for 3 hr. The remaining oil was separated and fractionated to give 2.27 g. of a mobile, colorless oil, b.p. 66–98° (0.06 mm.). This liquid was redistilled and the fraction having a boiling point of 66–68° (0.055 mm.) was collected, n_D^{25} 1.4980.

Anal.[10] Calcd. for $C_{14}H_{26}O$: C, 79.93; H, 12.46. Found: C, 79.91; H, 11.71.

Repeated attempts to prepare a crystalline 3,5-dinitrobenzoate or phenylurethane failed.

5,6-Benzocoumarin-3-carboxamide. Fifteen milliliters of a 6% solution of ammonia in absolute ethanol and 1.0 g. (.373 mole) of ethyl 5,6-benzocoumarin-3-carboxylate were placed in a 50-ml. flask, and the flask was stoppered. Immediate solution occurred when the flask was swirled. After standing at room temperature for 64 hrs. the flask was chilled in an ice bath and the resulting precipitate collected by filtration, washed with ethanol, and recrystallized from glacial acetic acid. Light yellow needles were obtained, m.p. 297–298°; the yield was 0.83 g. (93%).

Anal. Calcd. for $C_{14}H_9NO_3$: N, 5.86. Found: N, 5.81.

Ethanol and glacial acetic acid solutions of the carboxamide exhibited a very intense blue fluorescence. Hydrolysis of the carboxamide, followed by acidification, yielded an acidic compound which melted at 236–237° (dec.). Sachs and Brigl[11] reported a melting point of 234–235° for 5,6-benzocoumarin-3-carboxylic acid.

(2-Hydroxy-1-naphthylmethyl)malonamide. Ethyl 3,4-dihydro-5,6-benzocoumarin-3-carboxylate (2.75 g., 0.0102 mole) dissolved instantly in 30 ml. of 6% alcoholic ammonia solution. The stoppered reaction vessel was allowed to stand at room temperature for 60 hr. The crystals which resulted were collected by filtration and washed with 10 ml. of ethanol. There was obtained 2.47 g. (94.0%) of product, m.p. 213–214° (with copious evolution of ammonia). λ_{max} (95% ethanol): 270 mμ (log ϵ 3.60), 280 (3.73), 292 (3.65), 326 (3.36), 335 (3.40).

Anal. Calcd. for $C_{14}H_{14}N_2O_3$: C, 65.10; H, 5.46; N, 10.84. Found: C, 65.27; H, 5.64; N, 10.97.

The compound was soluble in 2*N* sodium hydroxide solution, from which it was recovered unchanged by the addition of excess acid. A warmed suspension of the compound in ethanol did not give a color with ferric chloride solution.

(2-Hydroxy-5,6,7,8-tetrahydro-1-naphthylmethyl)malonamide. Ethyl 2,3,7,8,9,10-hexahydro-3-keto-1*H*-naphtho[2,1-*b*]pyran-2-carboxylate (1.0 g., 3.64 millimoles) was dissolved in 5.4 ml. of 6% alcoholic ammonia solution. The stoppered reaction vessel containing the solution was allowed to stand for 2 hr. and the white precipitate which had formed was collected by filtration. After one recrystallization from a large volume of absolute ethanol-acetone (1:1), there was obtained 0.66 g. (69.1%) of white crystals, m.p. 198.5–199.5° (with evolution of gas); ultraviolet spectrum in 95% ethanol (log ϵ) 285 mμ (3.40).

Anal. Calcd. for $C_{14}H_{18}N_2O_3$: N, 10.68. Found: N, 10.56.

Acknowledgment. One of the authors is indebted to the American Foundation for Pharmaceutical Education for financial assistance during the period of this work. The infrared analyses were performed by Mr. James Brader of the University of Illinois, Urbana, Ill.

CHICAGO, ILL.

(10) Analysis performed by Micro-Tech Laboratories, Skokie, Ill.

(11) F. Sachs and P. Brigl, *Ber.*, **44**, 2091 (1911).

[CONTRIBUTION FROM THE FOREST PRODUCTS LABORATORY UNIVERSITY OF CALIFORNIA, RICHMOND, CALIF.]

On the Structure of the Photodimer of Thymoquinone

EUGENE ZAVARIN

Received June 24, 1957

It has been demonstrated that the photodimerization of thymoquinone takes place along the less hindered 3,4-double bond with the formation of the corresponding cyclobutane derivative. The proposed analogous formula for the 2-methylnaphthoquinone photodimer has been spectroscopically substantiated.

The chemistry of the dimer of thymoquinone formed by irradiating the quinone in thin crystalline layers with daylight has been the subject of several papers. The material consists of pale yellow crystals that melt at 200–201° and on further heating, dissociate to give thymoquinone. On reduction by a variety of reagents, hydrothymoquinone is formed. With hydroxylamine di- or tetraoxime is