yield, 30.6 g. (78%), m.p. 216–219°. A second crop, 3.1 g., was obtained by concentration of the filtrate. The product showed the same X-ray pattern and infrared and ultraviolet absorption spectra as did an authentic sample.[1b,g]

Synthesis of a Cyclopropyl Carbinol in the Amitriptyline Series

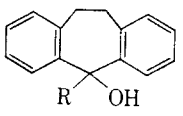
R. D. HOFFSOMMER, D. TAUB, AND N. L. WENDLER

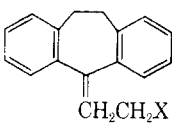
Merck Sharp & Dohme Research Laboratories, Merck & Co., Inc., Rahway, New Jersey

Received January 9, 1964

The cyclopropyl carbinol, 5-cyclopropyl-5-hydroxy-5H-dibenzo[*a,d*]-10,11-dihydrocycloheptene (II),[1a] an intermediate in a synthesis of amitriptyline, can be prepared advantageously from the vinyl carbinol, 5-hydroxy-5-vinyl-5H-dibenzo[*a,d*]-10,11-dihydrocycloheptene (I), with CH_2I_2 and zinc–copper couple.[2,3] The formation of accompanying amounts (7–8%) of 5-(γ-iodopropylidene)-5H-dibenzo[*a,d*]-10,11-dihydrocycloheptene (IV, X = $-CH_2I$) was also ascertained by conversion to 5-(γ-hydroxypropylidene)-5H-dibenzo[*a,d*]-10,11-dihydrocycloheptene (IV, X = $-CH_2OH$) with potassium acetate and concluding saponification. Treatment of the iodo compound with alkali directly produced the diene, 5-allylidene-5H-dibenzo[*a,d*]-10,11-dihydrocycloheptene.[1b]

The vinyl carbinol (I) rearranges with great ease in the presence of dilute perchloric acid to give the primary system (III, X = OH). Similarly, hydrogen bromide or chloride in acetic acid affords III, X = Br and Cl, respectively (compare ref. 1a).





I, R = $-CH{=}CH_2$ III, X = OH, Br, Cl
II, R = IV, X = $-CH_2I$, $-CH_2OH$

Experimental

5-Hydroxy-5-vinyl-5H-dibenzo[*a,d*]-10,11-dihydrocycloheptene (I).—A 100-ml. flask fitted with stirrer, Dry Ice–acetone condenser, nitrogen inlet, and addition funnel was charged with 1.17 g. (48 mmoles) of magnesium turnings. The magnesium metal was covered with 10 ml. of dry tetrahydrofuran (THF) and 2–3 ml. of a solution of 5.25 g. (49 mmoles) of vinyl bromide in 10 ml. of THF was added. The reaction mixture was warmed slightly until reaction started; the vinyl bromide solution was added dropwise, with stirring, at such a rate as to maintain a temperature of 50–60°. The addition was complete in 15 min. and stirring was continued under gentle reflux until all of the magnesium was consumed (2 hr.). A solution of 5.0 g. (24 mmoles) of 5H-dibenzo[*a,d*]-10,11-dihydrocycloheptene-5-one in 25 ml. of THF was added, with stirring, to the warm reaction mixture at a rate sufficient to maintain a temperature of 40–50°. The addition was complete in 25 min., accompanied by considerable darkening of the reaction mixture. Stirring and heating (50°) were continued for 1 hr. At the end of this time a thin layer chromatographic probe (Al_2O_3 1:1 benzene–cyclohexane) indicated that the reaction was complete. The reaction mixture was chilled in an ice bath and treated, dropwise, with 25 ml. of saturated ammonium chloride. The aqueous layer was extracted with two 15-ml. portions of ether and the combined ether–THF solutions were washed with 15 ml. of saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and taken to dryness *in vacuo* to yield 5.90 g. of the vinyl carbinol I as a yellow oil which exhibited the following properties: $\lambda_{max}^{CHCl_3}$ 2.7, 2.87, 6.18, 6.75, 6.9, 7.13, 7.62, 7.9, 8.63, 9.0, 9.48, 9.83, and 10.35 μ; λ_{max}^{MeOH} 2730 Å. (sh.) (ε 470), 2700 (sh.) (557), 2660 (sh.) (645), and 2630 (690). This material was utilized in the next reaction without purification.

5-Hydroxy-5-cyclopropyl-5H-dibenzo[*a,d*]-10,11-dihydrocycloheptene (II).—A 50-ml. flask fitted with a stirrer, condenser, and addition funnel was purged with dry nitrogen and charged with 1.53 g. of the copper–zinc couple,[4] 15 ml. of dry ethyl ether, and 2 crystals of iodine. Methylene iodide (4.90 g., 18.3 mmoles) was added and the reaction mixture was maintained at a gentle reflux for 30 min. The mixture was then cooled slightly and 2.00 g. (8.46 mmoles) of 5-hydroxy-5-vinyl-5H-dibenzo[*a,d*]-10,11-dihydrocycloheptene (I) in 5 ml. of dry ethyl ether was added slowly, with stirring, over a period of 25 min. The reaction mixture was subsequently stirred and refluxed for 2.25 hr. Samples for thin layer chromatography (Al_2O_3 1:1 benzene–cyclohexane) were withdrawn after 30 min. and after 1 hr. and indicated the reaction to be complete after 30 min. with no further change after 1 hr. The reaction mixture was cooled to room temperature and treated with 15 ml. of saturated ammonium chloride solution. The aqueous layer was extracted with 2 portions of ether and the combined ether solution was washed with two 15-ml. portions of saturated potassium carbonate solution, 15 ml. of saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated *in vacuo* to 2.26 g. of a yellow oil. The crude oil was redissolved in ether, treated with charcoal, filtered through Celite, and the ether replaced with hexane while concentrating to small volume. Seeding the solution with a crystal of authentic 5-hydroxy-5-cyclopropyl-5H-dibenzo[*a,d*]-10,11-dihydrocycloheptene (II),[1a] m.p. 69–71°, yielded 660 mg. of crystalline product with m.p. 68–69.5°. A mixture of the product crystals and authentic II did not depress the m.p., 68–71°. An additional 450 mg. of cyclopropyl carbinol II was obtained by alumina chromatography of the mother liquor to afford a total yield of 52% over the 2 steps.

An oily fraction from the chromatography (220 mg.) possessed essentially the same mobility and infrared spectrum as authentic γ-iodopropylidene derivative IV (X = $-CH_2I$).[1a] This oil was refluxed for 26 hr. with 200 mg. of potassium acetate in 6 ml. of acetone. The crude reaction product after work-up was saponified for 1 hr. with 50 mg. of potassium hydroxide in 4.5 ml. of aqueous methanol (1:9) and the product chromatographed on neutral alumina. Thereby was obtained crystalline IV (X = $-CH_2OH$),[1a] m.p. 86–88° not depressed on mixture with authentic material. The infrared spectra of this product was identical with that of authentic IV (X = $-CH_2OH$).

5-(β-Hydroxyethylidene)-5H-dibenzo[*a,d*]-10,11-dihydrocycloheptene III (X = OH).—A solution of 200 mg. (0.84 mmole) of 5-hydroxy-5-vinyl-5H-dibenzo[*a,d*]-10,11-dihydrocycloheptene (I) in 10 ml. of dioxane was treated at room temperature with 4 ml. of 2 *M* aqueous perchloric acid. The reaction mixture was stirred for 1 hr., then quenched by the addition of solid anhydrous potassium carbonate, filtered over anhydrous magnesium sulfate, and concentrated to dryness *in vacuo*. The residual yellow oil crystallized spontaneously on standing to yield, after recrystallization from ether–hexane, 120 mg. of the ethylidene alcohol III (X = −OH), m.p. 86–88°; λ_{max}^{MeOH} 2400 Å. (ε 13,942) and $\lambda_{max}^{CHCl_3}$ 2.66, 2.85, 6.73, 6.94, 8.93, and 9.9–10.0 μ.

Anal. Calcd. for $C_{17}H_{16}O$: C, 86.40; H, 6.82. Found: C, 86.19; H, 7.00.

5-(β-Bromoethylidene)-5H-dibenzo[*a,d*]-10,11-dihydrocycloheptene III (X = Br).—A solution of 1.20 g. (5.07 mmoles) of crude 5-hydroxy-5-vinyl-5H-dibenzo[*a,d*]-10,11-dihydrocycloheptene (I) in 15 ml. of glacial acetic acid was chilled to 10° and 10 ml. of a 15% solution of anhydrous hydrogen bromide in glacial acetic acid added. The reaction mixture was stirred at 10–15° for 30 min., then taken to dryness *in vacuo*, flushed with xylene, and pumped down again to yield 1.44 g. of a dark oil which crystallized partially. Chromatography of the crude product afforded colorless crystalline bromide III (X = Br), m.p. 108–110°; λ_{max}^{MeOH} 2425 Å. (ε 13,285); and $\lambda_{max}^{CHCl_3}$ 6.15, 6.73, 6.94, 7.35, 8.37, and 9.1 μ.

Anal. Calcd. for $C_{17}H_{15}Br$: C, 68.23; H, 5.05; Br, 26.71. Found: C, 68.33; H, 4.86; Br, 26.11.

In a similar experiment employing hydrogen chloride in acetic

(1) (a) R. D. Hoffsommer, D. Taub, and N. L. Wendler, *J. Org. Chem.*, **27**, 4134 (1962); (b) *ibid.*, **28**, 1751 (1963).

(2) H. E. Simmons and R. D. Smith, *J. Am. Chem. Soc.*, **81**, 4256 (1959).

(3) W. G. Dauben and G. H. Berezin, *ibid.*, **85**, 468 (1963). See also E. J. Corey and R. L. Dawson, *ibid.*, **85**, 1782 (1963).

(4) R. S. Shank and H. Shechter, *J. Org. Chem.*, **24**, 1825 (1959).

acid, the corresponding chloride III (X = Cl) was obtained, m.p. 93–96°.

Anal. Calcd. for $C_{17}H_{15}Cl$: C, 80.16; H, 5.89; Cl, 13.95. Found: C, 80.48; H, 5.91; Cl, 13.66.

Synthesis of 1,4-Naphthohydroquinone-2-carboxanilide and 1,4-Naphthoquinone-2-carboxanilide[1]

KENNETH SWIATEK AND STEPHEN B. BINKLEY

Department of Biological Chemistry, University of Illinois College of Medicine, Chicago, Illinois

Received November 3, 1963

Truit[2] reported that various derivatives of 2-acylamino-3-alkyl-1,4-naphthoquinone possess amebicidal activity. Buu-Hoi[3] reported that 1-naphthylamine, 1,5-naphthylenediamine, and similar derivatives of 2-chloro-1,4-naphthoquinone were capable of inhibiting the growth of *Mycobacterium tuberculosis*. N,N-Diethyl-4-chloro-1-hydroxy-2-naphthamide, ethyl 4-chloro-1-hydroxy-2-naphthalate and N-phenethyl-4-chloro-1-hydroxy-2-naphthamide were shown by Franzen and Binkley[5] to exhibit low antiprotozoal activity. It seemed quite likely that various substituted amide derivatives of 1,4-dihydroxy-2-naphthoic acid and the corresponding 1,4-naphthoquinone-2-carboxamide should be interesting biologically.

Experimental[5,6]

1,4-Dihydroxy-2-naphthoic Acid.[7]—When this compound was made according to the procedure of Homeyer and Wallingford,[7] a red oil was often obtained in the preparation of the intermediate compound, diethyl 1,4-dihydroxy-2,3-naphthalate. This difficulty was overcome when NaH was substituted for $NaOC_2H_5$ in the condensation of ethyl phthalate and ethyl succinate, and by running the reaction in anhydrous ether. The melting point of diethyl 1,4-dihydroxy-2,3-naphthalate[7] was raised from 62–64° to 74–74.5° when the product was recrystallized twice from petroleum ether (b.p. 30–60°).

1,4-Naphthohydroquinone-2-carboxanilide.—To a suspension of 16 g. (0.123 mole) of aniline hydrochloride in 800 ml. of acetonitrile was added 17.5 ml. of triethylamine followed by 25 g. (0.123 mole) of 1,4-dihydroxy-2-naphthoic acid and 54 g. (0.125 mole) of 1-cyclohexyl-3-(2-morpholinyl-(4)-ethyl) carbodiimide metho-*p*-toluenesulfonate. After stirring for 48 hr. at room temperature, the 1-cyclohexyl-3-(2-morpholinyl-(4)-ethyl)urea metho-*p*-toluenesulfonate was removed by filtration, and washed with 100 ml. of acetonitrile. The organic layers were combined and the solvent removed under reduced pressure. The crude product was dissolved in ether and the solution washed with *N* hydrochloric acid, *N* sodium bicarbonate, and finally water until the aqueous layer remained clear. Drying over $MgSO_4$ and removal of the ether yielded 12 g. of a mixture of yellow and red crystals. The crude material was dissolved in hot 95% ethanol, and subsequent cooling to room temperature gave red crystals (135 mg.), m.p. 215° dec. The structure of this compound remains unknown.

Anal. Calcd. for $C_{34}H_{24}N_2O_6$ (quinhydrone): C, 73.17; H, 4.39; N, 5.07. Found: C, 74.83; H, 4.47; N, 7.20.

Concentration of the mother liquor gave 10 g. of crude 1,4-naphthohydroquinone-2-carboxanilide. Five recrystallizations from benzene gave 3.70 g. (11%) of light tan crystals, m.p. 212° dec.

Anal. Calcd. for $C_{17}H_{13}NO_3$: C, 73.28; H, 4.71; N, 5.06. Found: C, 73.12; H, 4.87; N, 5.24.

Infrared absorption in KBr, 2.9 (OH), 3.1 (N–H), 6.2, and 6.3 μ (C=O); ultraviolet absorption in EtOH, λ_{max} 270 and 360 mμ; λ_{min} 245 and 328 mμ.

1,4-Naphthoquinone-2-carboxanilide.—To 260 mg. of 1,4-naphthohydroquinone-2-carboxanilide in anhydrous ether was added 2 g. of silver oxide and 2 g. of $MgSO_4$. The reaction mixture was stirred in the dark for 4 hr. The solution was filtered to remove the excess silver oxide and the $MgSO_4$. The ether solution was concentrated to yield 240 mg. of bright red-orange crystals. Recrystallization from anhydrous ether yielded 212 mg. (82%) of product, m.p. 140–141°.

Anal. Calcd. for $C_{17}H_{11}NO_3$: C, 73.50; H, 4.00; N, 5.05. Found: C, 73.26; H, 4.04; N, 5.36.

Infrared absorption in KBr, 3.1 (N–H), 6.1, 6.3 (C=O), and 5.9 μ (quinone C=O); ultraviolet absorption in EtOH, λ_{max} 252 and 334 mμ; λ_{min} 310 mμ.

Reaction of 1,4-Dihydroxy-2-naphthoic Acid with Benzyl Bromide.—To 10 g. (0.05 mole) of 1,4-dihydroxy-2-naphthoic acid in 50 ml. of ethanol and 25 ml. of water was added 40 ml. of 7 *N* KOH and 33 ml. of benzyl bromide over a 20 min. period. After cooling to room temperature, 300 ml. of water was added and the aqueous solution acidified with glacial acetic acid. Extraction of the solution with $CHCl_3$ and distillation of the $CHCl_3$ layer at 45° (0.58 mm.) resulted in a yellow sirup. The sirup was layered with anhydrous ether in a stoppered flask. White crystals separated after 2 weeks, 7 g., m.p. 142–143° (from ether). The analytical results are not in agreement with those expected for benzyl 1-hydroxy-4-O-benzyl-2-naphthalate.

Anal. Calcd. for $C_{25}H_{20}O_4$: C, 78.12; H, 5.20. Found: C, 85.00; H, 5.70. Calcd. for $C_{24}H_{20}O_2$: C, 84.70; H, 5.88.

When 1,4-naphthalenediol was treated with benzyl bromide and 7 *N* KOH and the reaction mixture worked up in the usual manner, dibenzyl 1,4-naphthohydroquinone was isolated. Recrystallization from ether gave white crystals, m.p. 142–143°. A mixture melting point with the product isolated previously caused no depression. The compound isolated was dibenzyl-1,4-naphthohydroquinone.

Acetylation of 1,4-Dihydroxy-2-naphthoic Acid with Acetic Anhydride or Isopropenyl Acetate.—Refluxing 1 g. of 1,4-dihydroxy-2-naphthoic acid with 10 ml. of acetic anhydride and 0.5 g. of sodium acetate for 1.5 hr. yielded 1,4-diacetoxynaphthalene,[8] recrystallized from ethanol, m.p. 124–125° (lit.[7,8] 125–127°). Refluxing 1 g. of 1,4-dihydroxy-2-naphthoic acid with 10 ml. of isopropenyl acetate and 1 drop of sulfuric acid for 2 hr. gave upon work-up, 220 mg. of 1,4-diacetoxynaphthalene, m.p. 125–126°.

(1) Supported by Grant CY3231, U. S. Public Health Service.

(2) P. Truit, F. M. Wood, and R. Hall, *J. Org. Chem.*, **25**, 1460 (1960).

(3) N. P. Buu-Hoi, *Bull. Soc. Chim.*, **11**, 578 (1944).

(4) J. S. Franzen and S. B. Binkley, *J. Org. Chem.*, **24**, 992 (1959).

(5) Analyses by Micro-Tech Laboratories, Skokie, Ill.

(6) All melting points are corrected. The infrared spectra were run on a Perkin-Elmer Infracord spectrophotometer and the ultraviolet spectra were taken on a Beckman DU spectrophotometer.

(7) A. H. Homeyer and V. H. Wallingford, *J. Am. Chem. Soc.*, **64**, 798 (1942).

(8) F. Russig, *J. Prakt. Chem.*, **62**, 30 (1900).

Book Reviews

Steroid Reactions: An Outline for Organic Chemists. By CARL DJERASSI. Holden-Day, Inc., San Francisco, Calif., 1963. vi + 657 pp. $9.75.

The last two decades have seen an enormous increase in the volume of literature on steroid chemistry. In a survey of reactions characteristic of this field both the steroid chemist and the general organic chemist face the dilemma of a complete literature search without sacrificing a significant slice of one's working time which, otherwise, could be spent in the laboratory. Prof. Djerassi, who is so well known for his contributions to steroids, has now come out with a book which every chemist in the field will receive with relief.

The book under review can be considered more appropriately as a catalog or atlas rather than a text book as it illustrates the examples without much description. It is divided into 14 sections, each devoted to a given reaction. Each section is composed of a comprehensive collection of examples of some particular reaction, which has been widely employed for steroids, and has been modified to suit specific requirements in individual cases.