Anhydrorosmarinecine acetate (picrate): m.p. 192–194° (reported,[2] m.p. 190–192°).

Anal. Calcd. for $C_{16}H_{18}N_4O_{10}$: C, 45.07; H, 4.26. Found: C, 44.92; H, 4.25.

Separation of the Acids: Senecic and Seneciphyllic Acids.—A silicic acid column (5 × 50 cm.) was prepared with a slurry of the adsorbent in chloroform. A solution of 1.0 g. of the mixed acids (from hydrolysis of the unresolved alkaloid) in a little acetone was placed on the column, and elution was carried out with an acetone (20%)–chloroform (80%) mixture, with the collection of 50-ml. fractions. **Senecic acid** appeared in fractions 45–51, m.p. 141–143°. Purified by recrystallization from ethyl acetate–petroleum ether (b.p. 60–80°) it had m.p. 144–147° (reported, m.p. 145–146°,[5] 151°,[2]), and $[\alpha]^{25}D$ +19.6° (*c*, 0.0138, ethanol).

Anal. Calcd. for $C_{10}H_{16}O_6$: C, 55.54; H, 7.46. Found: C, 55.37; H, 7.31.

Seneciphyllic acid, which appeared in fractions 52–60, m.p. 105–110°, was purified by recrystallization from ethyl acetate–petroleum ether (b.p. 60–80°), when it had m.p. 115–117° (reported,[6] m.p. 118–119°), and $[\alpha]^{25}D$ −9.0 (*c*, 0.0333, ethanol).

Anal. Calc. for $C_{10}H_{14}O_6$: C, 56.07; H, 6.59. Found: C, 56.32; H, 6.88.

Acknowledgment.—This work was part of a study supported by a National Science Foundation research grant, G-8821, and a U.S. Public Health Service research grant, RG-6457.

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(6) S. Masamune, *Chem. Ind.* (London), 21 (1959).

The Homoallylic Rearrangement in the Synthesis of Amitriptyline and Related Systems

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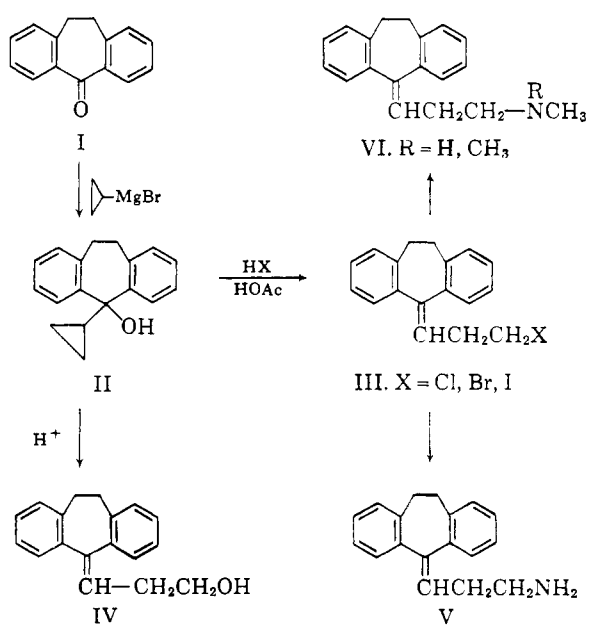
A novel synthesis of 5-(γ-dimethylaminopropylidene)-5H-dibenzo[*a,d*]-10,11-dihydrocycloheptene and related systems based on the homoallylic rearrangement is presented.

The effective psychotherapeutic drug amitriptyline (ELAVIL®) has been synthesized heretofore by the reaction between the Grignard reagent derived from γ-dimethylaminopropylchloride and 5H-dibenzo[*a,d*]-10,11-dihydro-5-cyclohepten-5-one.[1,4] The growing importance of an alternative approach to amitriptyline, which would likewise provide versatility in the synthesis of γ-functionally related systems, constituted the basis for the present work.

The condensation of 5H-dibenzo[*a,d*]-10,11-dihydrocyclohepten-5-one (I) with the Grignard reagent derived from cyclopropyl bromide[2] afforded the crystalline cyclopropylcarbinol (II), m.p. 73–74°, in high yield. The latter, on treatment with hydrogen chloride or hydrogen bromide in acetic acid solution, rearranged quantitatively to the corresponding γ-halopropenylcycloheptenes (III).[3,4] The corresponding iodo derivative (III. X = I) was produced from the bromide (III. X = Br) with sodium iodide in refluxing actone. The halo derivatives (III) were all highly crystalline individuals exhibiting characteristic absorption in the ultraviolet at 240 mμ (ε 14,000–17,000).

Rearrangement of the derived cyclopropylcarbinol (II) with dilute perchloric acid in dioxane at



25° proceeded smoothly with formation of the primary carbinol (IV) presumably by way of the

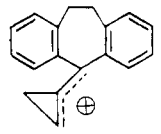
(1) (a) Belgian Patent, 584,061, Merck & Co., Inc.; *cf.* E. Jucker, *Chimia* (*Aarau*), **15**, 267 (1961); (b) British Patent, 858,187, 858,188, Hoffmann-LaRoche, A.G.; Belgian Patent, 609,095, Kefalas A/S; (c) M. Protiva, V. Hněvsová-Seidlová, Z. J. Vejdelek, F. Jerkovsky, Z. Votava, and J. Metysöva, *J. Med. Pharm. Chem.*, **4**, 411 (1961); (d) See also F. J. Villani, C. A. Ellis, C. Teichman, and C. Bigos, *ibid.*, **5**, 373 (1962); and South African Patent, R61/1889, Kefalas A/S.

(2) The authors are indebted to Professor H. Hart of Michigan State University for pertinent information concerning organometallic derivatives of cyclopropane.

(3) For examples of the rearrangement of cyclopropylcarbinols compare: O. Wallach, *Ann*, **360**, 82 (1908); T. A. Favorskaya and S. A. Fridman, *J. Gen. Chem. USSR*, **15**, 421 (1945); P. Bruylants and A. Dewael, *Bull. acad. roy. med. Belg.* (5), **14**, 140 (1928); M. Julia, S. Julia, and R. Guegan, *Compt. rend.*, **248**, 820 (1959). M. Julia, S. Julia, and S. Y. Tchen, *Bull. soc. chim. France*, 1849 (1961); M. S. Julia and B. S. Bourdillor, *Compt. rend.*, 951 (1961); M. Hanack, *Angew. Chem.*, **74**, 116 (1962).

(4) Since the completion of this work III (X = Br), prepared by another method, was reported by S. O. Winthrop, M. A. Davis, G. S. Meyers, J. G. Gavin, R. Thomas, and R. Barber, *J. Org. Chem.*, **27**, 230 (1962).

homoallylic ion VII. Rate measurements on the



VII

rearrangement II → IV in 0.1–0.5 *M* perchloric acid, as determined by the intensity increase with time of the 240-mμ band, clearly demonstrated the rearrangement to be unimolecular with $k = 4 \times 10^{-4}$ sec.$^{-1}$ (Fig. 1). Parallel rate studies on the related cyclopropylcarbinol, *i*-androstan-6β-ol-17-one (VIII),[5] determined polarimetrically, also established first-order kinetics for the rearrangement VIII → X with $k_{av} = 7.3 \times 10^{-4}$ sec.$^{-1}$ in 0.1 *M* perchloric acid (Fig. 2). Both homoallylic rearrangements, *viz.* II → IV and VIII → X, exhibited typical rate constant dependence on acidity and afforded straight line plots of log $[K/C_{H^+}]$ *vs.* C_{H^+} (Fig. 3).[6] The primary carbinol IV was smoothly converted to the chloride III (X = Cl) by thionyl chloride.

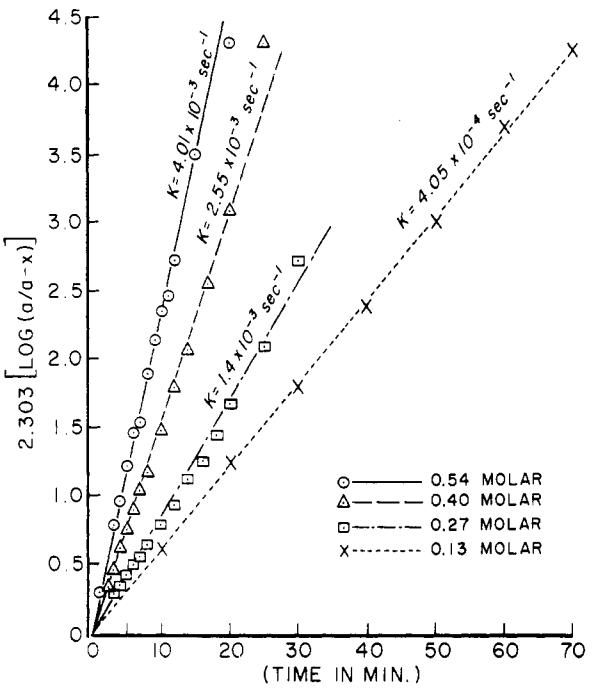
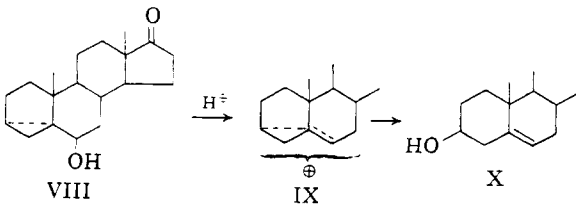


Fig. 1.—Plot of *K*'s at each acid concentration for transformation II → IV.



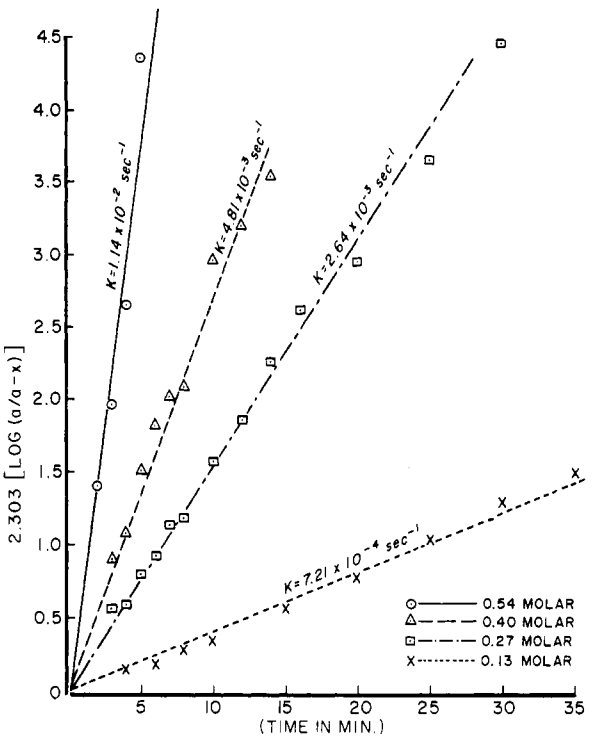


Fig. 2.—Plot of *K*'s at each acid concentration for transformation VIII → X.

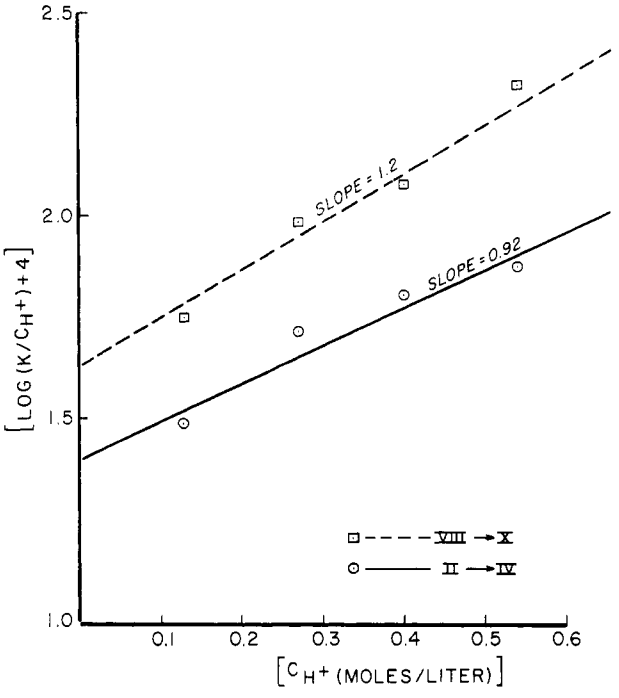


Fig. 3.—Comparison of rate constants for each transformation.

Treatment of either of the respective chloro or bromo derivatives, III, (X = Cl, Br) with dimethyl-

(5) A. Butenandt and L. A. Surányi, *Ber.* **75**, 591 (1942). A sample of this substance was kindly made available by Mr. T. Utne of these laboratories. For a survey of the *i*-steroid rearrangement see L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Co., New York, N. Y., 1959, p. 314.

(6) *Cf.* M. M. Kreevoy, *J. Am. Chem. Soc.*, **78**, 4236 (1956).

amine in benzene solution at 80° readily provided amitriptyline (VI. R = CH_3) isolated as it hydrochloride, m.p. 190–192°. On similar treatment of III (X = Br) with monomethylamine, the corresponding desmethylamitriptyline (VI. R = H) was produced and characterized as its hydrochloride, m.p. 210–213°. Amination of III (X = Br) in alcohol solution in turn afforded the primary amine (V), the hydrochloride of which had m.p. 258–263°. The primary amine V could also be prepared from the halo derivatives III by reaction with potassium phthalimide and concluding hydrazinolysis.

Experimental

Thin-layer chromatography (t.l.c.) was carried out on glass plates coated with alumina containing 5% calcium sulfate. Benzene and benzene–cyclohexane mixtures were the most generally used elution solvents. [Procedure of E. Stahl, *Chemiker Ztg.*, **82**, 323 (1958)].

5-Cyclopropyl-5-hydroxy-5H-dibenzo[*a,d*]**-10,11-dihydrocycloheptene** (**II**).—To a 250 ml., three-neck flask (flamed out and cooled under dry nitrogen) equipped with a stirrer, addition funnel, and ether-type condenser were charged 2.43 g. (0.1 g.-atom) of clean magnesium turnings and 25 ml. of dry tetrahydrofuran. Cyclopropyl bromide (13.3 g., 0.11 mole) in 25 ml. of dry tetrahydrofuran was added, dropwise with stirring, at a rate sufficient to maintain a gentle reflux. Gentle warming and stirring for about 45 min. were needed to start the reaction, after which no external heat was required. Stirring and refluxing were continued until all the metal was consumed (2 hr.). The reaction mixture was then cooled below the point of reflux, but not so low as to cause the Grignard reagent to precipitate, and 10.41 g. (0.05 mole) of 5H-dibenzo[*a,d*]-10,11-dihydrocyclohepten-5-one in 30 ml. of dry tetrahydrofuran was added with stirring in 15 min. The reaction mixture was stirred and refluxed for 1 hr., with 0.5-ml. aliquots being withdrawn and worked up periodically for thin-layer chromatography (t.l.c.) to follow the reaction. T.l.c. indicated that the reaction was complete in 1 hr., and indeed all of the probes spontaneously crystallized upon standing. The reaction mixture was chilled in an ice bath and treated with 75 ml. of saturated ammonium chloride solution. The layers were separated and just enough water added to dissolve the solid salts in the aqueous layer. The latter was extracted with two 40-ml. portions of ether. The combined organic layers were washed with 35 ml. of saturated salt solution, dried over magnesium sulfate, and taken to dryness *in vacuo* to yield 12.5 g. of crystalline II. An analytical specimen was prepared by crystallization from ether to yield material, m.p. 72.8–73.8°; λ_{max}^{MeOH} 263 mμ (630).

Anal. Calcd. for $C_{18}H_{18}O$: C, 86.36; H, 7.24. Found: C, 86.43; H, 7.40.

The above total product carbinol was use-tested by conversion in over 90% yield to crystalline chloride (III. X = Cl); see below.

5-(γ-Bromopropylidene)-5H-dibenzo[*a,d*]**-10,11-dihydrocycloheptene** (**III. X = Br**).—A solution of 5-cyclopropyl-5-hydroxydibenzo[*a,d*]-10,11-dihydrocycloheptene (1.3 g., 5.19 mmoles) in 20 ml. of glacial acetic acid was chilled to 10°. A solution of 15% hydrobromic acid in acetic acid (10 ml.) was added with stirring and the reaction mixture stirred at 10–15° for 0.5 hr.[7] The product precipitated in part during the reaction and was filtered, washed with water, and dried in air, 730 mg., m.p. 71–72°. Addition of water to the filtrate yielded the remainder of product as an oil which solidified on standing. The crystals were filtered, washed with water, and dried in air, 880 mg., single spot by t.l.c.; total yield 1.61 g. (98%). The analytical sample was crystallized from ether–petroleum ether, m.p. 69–71°; λ_{max}^{MeOH} 240 mμ (17,100); $\lambda_{max}^{CHCl_3}$ 3.27, 3.35, 3.43, 6.1, 6.21, and 6.34 μ.

Anal. Calcd. for $C_{18}H_{17}Br$: C, 69.01; H, 5.47; Br, 25.51. Found: C, 68.95; H, 5.15; Br, 25.57.

5-(γ-Chloropropylidene)-5H-dibenzo[*a,d*]**-10,11-dihydrocycloheptene** (**III. X = Cl**).—(a) A solution of 5-cyclopropyl-5-hydroxy-5H-dibenzo[*a,d*]-10,11-dihydrocycloheptene (II) (100 mg., 0.4 mmole) in 5 ml. of glacial acetic acid was cooled to 10° and 1 ml. of 15% hydrochloric acid in acetic acid was added with stirring and the reaction mixture stirred at 10–15° for 3 hr. Aliquots were withdrawn at intervals for t.l.c., which indicated quantitative conversion to III (X = Cl) within 15 min. The reaction mixture was concentrated to dryness *in vacuo* at room temperature and flushed three times with benzene. The crystalline residue was crystallized from ether–petroleum ether, m.p. 83–84°; λ_{max}^{MeOH} 240 mμ (13,900).

Anal. Calcd. for $C_{18}H_{17}Cl$: C, 80.43; H, 6.37; Cl, 13.19. Found: C, 79.98; H, 6.50; Cl, 13.10.

(b) Treatment of a solution of 50 mg. of 5-(γ-hydroxypropylidene)-5H-dibenzo[*a,d*]-10,11-dihydrocycloheptene (IV) in 3 ml. of dry benzene containing 1 drop of pyridine with 65 mg. of thionyl chloride in 2 ml. of dry benzene at reflux for 3 hr. on a steam bath yielded crystalline III, m.p. 78–79°, identical by t.l.c. and mixed m.p. (78–81°), with material obtained from treatment of 5-hydroxy-5-cyclopropyl-5H-dibenzo[*a,d*]-10,11-dihydrocycloheptene (II) with hydrochloric acid in acetic acid.

5-(γ-Iodopropylidene)-5H-dibenzo[*a,d*]**-10,11-dihydrocycloheptene** (**III. X = I**).—A solution of 200 mg. (0.636 mmole) of 5-(γ-bromopropylidene)-5H-dibenzo[*a,d*]-10,11-dihydrocycloheptene (III, X = Br) and 360 mg. (2.4 mmoles) of sodium iodide in 10 ml. of acetone was refluxed for 18 hr. The reaction mixture was then cooled to room temperature and filtered to remove the precipitated sodium bromide, which amounted to 60 mg. (91.5%). The filtrate was concentrated to dryness and the residue triturated with water to yield an oil. This oil was extracted with ether, the ether solution washed with saturated salt solution, dried over magnesium sulfate, treated with charcoal, filtered through Celite, and the residue crystallized from ether–petroleum ether; 210 mg. (93% yield), m.p. 54–60°. The analytical sample was recrystallized from petroleum ether, m.p. 56.2–59°; λ_{max}^{MeOH} 243 mμ (14,700).

Anal. Calcd. for $C_{18}H_{17}I$: C, 60.01; H, 4.75; I, 35.23. Found: C, 59.87; H, 4.70; I, 35.55.

5-(γ-Hydroxypropylidene)-5H-dibenzo[*a,d*]**-10,11-dihydrocycloheptene** (**IV**).—A solution of 500 mg. of 5-cyclopropyl-5-hydroxy-5H-dibenzo[*a,d*]-10,11-dihydrocycloheptene (II) in 15 ml. of dioxane was treated with 9 ml. of 2 *M* perchloric acid, at room temperature, for a total of 6 hr. Samples for t.l.c. were withdrawn after 1, 3, and 6 hr., and showed the reaction to be complete and clean after 1 hr., with no further change after 6 hr. Ether (50 ml.) and excess potassium bicarbonate were added, the mixture was filtered through magnesium sulfate, and the filtrate concentrated to dryness to give an essentially quantitative yield of crystalline IV. Recrystallization of a sample from ether gave analytically pure IV, m.p. 89–90°; λ_{max}^{MeOH} 238 mμ (13,800); $\lambda_{max}^{CHCl_3}$ 2.73, 2.9, 3.25, 3.31, 6.2, 6.34, and 9.6 μ.

Anal. Calcd. for $C_{18}H_{18}O$: C, 86.36; H, 7.24. Found: C, 86.44; H, 7.16.

5-(γ-Dimethylaminopropylidene)-5H-dibenzo[*a,d*]**-10,11-dihydrocycloheptene** (**VI. R = CH_3**) **Hydrochloride.**—A solution of 100 mg. (0.372 mmole) of 5-(γ-chloropropylidene)-5H-dibenzo[*a,d*]-10,11-dihydrocycloheptene (III. X = Cl) in 1 ml. of benzene in a Pyrex Carius tube was saturated with dimethylamine at 10°. The tube was sealed, allowed to stand at 95° for 18 hr., then cooled and opened. The benzene solution was washed successively with 5% potassium bicarbonate, water, and saturated salt solution, dried over magnesium sulfate, and taken to dryness *in vacuo*.

(7) The reaction was followed for a 6-hr. period and was found to be complete in 15 min., with no further change in 6 hr.

The residual oil was dissolved in ether and treated with ether saturated with hydrogen chloride. The resulting mixture was concentrated to dryness in a stream of nitrogen and the residue upon trituration with ether yielded 60 mg. of crystalline VI (R = CH_3) hydrochloride, m.p. 190–192°. A mixed melting point with authentic amitriptyline hydrochloride showed no depression, m.p. 190.5–193°. This material had an infrared spectrum in chloroform identical with that of amitriptyline hydrochloride; λ_{max}^{MeOH} 240 mμ (13,800).

Anal. Calcd. for $C_{20}H_{24}NCl$: C, 76.53; H, 7.71; N, 4.46. Found: C, 76.24; H, 7.63; N, 4.58.

5-(γ-Methylaminopropylidene)-5H-dibenzo[*a,d*]-10,11-dihydrocycloheptene (VI. R = H) Hydrochloride.—In the same manner as described for the preparation of VI (R = CH_3) a 100-mg. sample (0.372 mmole) of 5-(γ-chloropropylidene)-5H-dibenzo[*a,d*]-10,11-dihydrocycloheptene (III. X = Cl) was converted to VI (R = H). The latter was converted to its hydrochloride in ether solution, (50 mg.), m.p. 200–210°, which after recrystallization from ether–ethanol, melted at 213–215°. A mixed melting point with authentic material showed no depression; $\lambda_{max.}^{MeOH}$ 240 mμ (13,900).

Anal. Calcd. for $C_{19}H_{22}NCl$: C, 76.10; H, 7.39; N, 4.67. Found: C, 75.61; H, 7.05; N, 4.38.

5-(γ-Aminopropylidene)-5H-dibenzo[*a,d*]-10,11-dihydrocycloheptene (V) Hydrochloride.—(a) A solution of 1.0 g. (3.19 mmoles) of 5-(γ-bromopropylidene) 5H-dibenzo[*a,d*]-10,11-dihydrocycloheptene (III. X = Br) in 25 ml. of absolute ethanol in a Carius tube was saturated with anhydrous ammonia at 0°. The tube was sealed, allowed to stand at 100° for 18 hr., then cooled and opened. The clear, light tan ethanol solution was taken to dryness *in vacuo*, the residue treated with charcoal in ethanol, filtered, and again taken to dryness *in vacuo*. Trituration of the residue with benzene yielded 900 mg. of crystalline material. A 500-mg. sample of this material was dissolved in 50 ml. of hot water and the resulting cloudy solution filtered, the filtrate cooled and treated with 5% potassium bicarbonate solution to a pH of 9. The aqueous mixture was extracted with three 20-ml. portions of ethyl acetate and the combined extracts were dried over magnesium sulfate and taken to dryness *in vacuo*. The residual oil was dissolved in 18 ml. of ether and treated with 8 ml. of ether saturated with hydrogen chloride to precipitate V as its hydrochloride (230 mg.), m.p. 245–255°. Recrystallization from ethanol yielded material, m.p. 258–263°; λ_{max}^{MeOH} 239 mμ (13,700).

Anal. Calcd. for $C_{18}H_{20}NCl$: C, 75.65; H, 7.05; Cl, 12.40. Found: C, 75.35; H, 7.33; Cl, 12.19.

(b) A solution of 1.30 g. (7 mmoles) of potassium phthalimide in 15 ml. of dimethylformamide and 2 ml. of water was added to 1.78 g. (6.6 mmoles) of 5-(γ-chloropropylidene)-5H-dibenzo[*a,d*]-10,11-dihydrocycloheptene (III. X = Cl) in 10 ml. of dimethylformamide, and the resulting clear solution heated on a steam bath for 16 hr. The reaction mixture was then cooled to room temperature and diluted with 25 ml. of chloroform and 150 ml. of water. The aqueous layer was extracted with two 15-ml. portions of chloroform, and the combined chloroform extracts washed successively with 15 ml. of water, 15 ml. of 0.2 *N* sodium hydroxide, 15 ml. of water, and 20 ml. of saturated salt solution. The chloroform solution was dried over magnesium sulfate and taken to dryness *in vacuo*. The solid white residue after trituration with 50% ether–petroleum ether and filtration yielded 1.18 g. (3.1 mmoles) of 5-(γ-phthalimidopropylidene)-5H-dibenzo-[*a,d*]-10,11-dihydrocycloheptene which had m.p. 140–146° and $\lambda_{max}^{CHCl_3}$ 5.7 and 5.9 μ. This material without further purification was refluxed for 2 hr. with 185 mg. (3.1 mmoles) of hydrazine hydrate in 10 ml. of 95% ethanol. The mixture was cooled to room temperature and acidified with concentrated hydrochloric acid until acid to Congo Red paper, filtered, and the precipitate washed with 95% ethanol. The precipitate was dissolved in 35 ml. of hot water, filtered through Celite, and taken to dryness *in vacuo*. The residue was recrystallized by dissolving in ethanol, concentration to 10–15 ml. followed by dilution with 20 ml. of ether to yield 400 mg. of 5-(γ-aminopropylidene)-5H-dibenzo[*a,d*]-10,11-dihydrocycloheptene (V) hydrochloride, m.p. 256–262°. An additional 240 mg. was obtained from the aqueous ethanolic mother liquors.

Rate Study Procedures.—(a) The acid hydrolysis of the 5-hydroxy-5-cyclopropyl-5H-dibenzo[*a,d*]-10,11-dihydrocycloheptene (II) was followed by measuring the increase of absorption with time at 240 mμ on a Bausch & Lomb 505 recording spectrometer. A 2-ml. sample of a stock solution of 15 mg. of the carbinol in 500 ml. of spectro grade dioxane (12.0×10^{-5} moles/l.) were mixed with 2 ml. of the appropriate molarity stock solution of aqueous perchloric acid (*e.g.*, 0.2 *M* stock solution for a 0.1 *M* final reaction mixture) directly in the cell. Measurements made at 25°.

(b) The rearrangement of the *i*-steroid (VIII) was followed by measuring the decrease in rotation at 365 mμ on a Zeiss photoelectric precision polarimeter. A 2-ml. sample of a stock solution of 10 mg. of the steroid in 10 ml. of spectro grade dioxane (3.46×10^{-3} moles/l.) were mixed with 2 ml. of the appropriate molarity stock solution of aqueous perchloric acid and placed in a 1-dm. cell. Measurements made at 24°.

The *K*'s were calculated from the equation $Kt = \ln (a/a - x)$, where t = time (sec.), a = initial concentration of reactant (moles/l.), and x = concentration of product (moles/l.) at time t.

A New Interpretation of the Lithium Aluminum Hydride Reduction of Arylaminomethylenemalonate Esters

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Received August 20, 1962

The lithium aluminum hydride reduction of diethyl 2-naphthylaminomethylenemalonate (*4*) is shown unequivocally to yield 2-(2-naphthylaminomethyl)-2-propen-1-ol (*5*). This result proves that the previous interpretation[2] of the reduction is in error. A mechanism for this conversion is presented.

During the course of some synthetic studies, we reduced diethyl 2-pyridylaminomethylenemalonate (*1*) with lithium aluminum hydride. A single product, isolated in 78% yield, was assigned the 2-(2-pyridylaminomethyl)-2-propen-1-ol structure (*2*) on the basis of analysis of the fumarate salt, and infrared and nuclear magnetic resonance (n.m.r.) spectra. Catalytic hydrogenation of compound *2* gave a dihydro amino alcohol for which the

(1) Present address: Nalco Chemical Co., Chicago 38, Ill.

(2) R. L. Shivalkar and S. V. Sunthankar, *J. Am. Chem. Soc.*, **82**, 718 (1960).