then evaporated under reduced pressure on the steam bath with a rotatory evaporator. The residue was shaken with a mixture of 250 ml. of ether and 100 ml. of water. The aqueous phase was separated and extracted with 200 ml. of ether. The ether solutions were washed in series with 100 ml. of water, 100 ml. of 5% sodium bicarbonate solution, and three 100-ml. portions of water; they were then combined and dried over anhydrous magnesium sulfate. The ether was evaporated leaving 679 mg. (98.6%) of 3β-methoxy-19-hydroxyandrost-5-en-17-one (VI), m.p. 143–146°. Recrystallization of this material from methanol–water solution yielded 574 mg., m.p. 147–149°. For analysis 272.9 mg. of this latter sample was recrystallized from methanol–water solution to yield 241 mg., m.p. 147.5–149°, $[\alpha]^{23}D$ +10.2°.

Anal. Calcd. for $C_{20}H_{30}O_3$: C, 75.44; H, 9.50. Found: C, 75.64; H, 9.50.

E. Acetylation of 3β,19-Dihydroxyandrost-5-en-17-one (II).—A solution prepared from 151 mg. (0.00050 mole) of II, 2 ml. (0.02 mole) of acetic anhydride, and 6 ml. of pyridine was allowed to stand at room temperature for 23 hr. The resulting solution was shaken with a mixture of 150 ml. of ether and 100 ml. of water. The aqueous phase was separated and extracted with 100 ml. of ether. The ether solutions were washed in series with 100 ml. of water, 100 ml. of 1 *N* hydrochloric acid, two 50-ml. portions of water, 100 ml. of 5% sodium bicarbonate solution, and three 50-ml. portions of water; they were then combined and dried over anhydrous magnesium sulfate. The ether was evaporated leaving 191 mg. (99%) of 3β,19-diacetoxyandrost-5-en-17-one (IV) as an oil which crystallized on cooling in a Dry Ice–acetone bath, m.p. 104–107°. For analysis this material was recrystallized from ether–petroleum ether solution to yield 164 mg., m.p. 109–110°.

Anal. Calcd. for $C_{22}H_{32}O_5$: C, 71.09; H, 8.30. Found: C, 71.22; H, 8.50.

F. Acetylation of 3β-Methoxy-19-hydroxyandrost-5-en-17-one (VI).—A solution prepared from 302 mg. (0.00095 mole) of VI, 4 ml. (0.04 mole) of acetic anhydride, and 12 ml. of pyridine was allowed to stand at room temperature for 23 hr. The product was isolated as described previously for the acetylation of 3β,19-dihydroxyandrost-5-en-17-one (II), to yield 332 mg. (97%) of 3β-methoxy-19-acetoxyandrost-5-en-17-one (VII), m.p. 66–67.8°. For analysis this material was recrystallized from ether–petroleum ether solution to yield 272 mg., m.p. 67–68°, $[\alpha]^{21}D$ −37.3°.

Anal. Calcd. for $C_{22}H_{32}O_4$: C, 73.29; H, 8.95. Found: C, 73.27; H, 9.09.

Acknowledgment.—The author wishes to thank Dr. Wayne Cole and Dr. Paul Kurath of these laboratories for helpful discussions regarding this work. N.m.r. spectra were determined by Mr. R. Kriese under the supervision of Dr. R. W. Mattoon. Infrared spectra were recorded by Mr. W. Washburn and associates. Analyses were carried out under the supervision of Messrs. E. F. Shelberg and O. Kolsto.

Synthesis of Amitriptyline and Related Substances. Hydroboration of 5-Allylidene-5*H*-dibenzo[*a*,*d*]-10,11-dihydrocycloheptene

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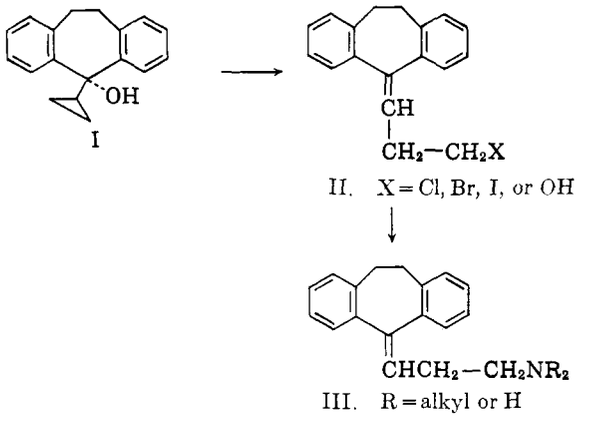
A new route to 5-(γ-dimethylaminopropylidene)-5*H*-dibenzo[*a*,*d*]-10,11-dihydrocycloheptene and related systems by way of hydroboration of a butadiene intermediate has been realized.

Synthesis of the psychotherapeutic drug, amitriptyline (XI), has been accomplished heretofore in the main by way of simple Grignard coupling of γ-dimethylaminopropylchloride with 5*H*-dibenzo[*a*,*d*]-10,11-dihydrocyclohepten-5-one followed by dehydration.[1]

Recently we showed[2] that the carbinol (I), derived from 5*H*-dibenzo[*a*,*d*]-10,11-dihydrocyclohepten-5-one (IV) and cyclopropylmagnesium bromide, rearranges quantitatively to 5-(γ-halopropylidene) (II. X = Cl or Br) and 5-(γ-hydroxypropylidene)-5*H*-dibenzo-10,11-dihydrocycloheptene (II. X = OH) in the presence of anhydrous halogen acids or aqueous mineral acids, respectively. The γ-halo[3] as well as the γ-hydroxy systems, moreover, possess the distinct advantage of providing not only a direct route to amitriptyline, but also to nearly any γ-substituted derivative through choice of the appropriate nucleophile.

A new route to the key γ-halopropylidene and γ-hydroxypropylidene derivatives, II, has now been realized and constitutes the subject of the present report.

The allylcarbinol V formed from 5*H*-dibenzo[*a*,*d*]-10,11-dihydrocyclohepten-5-one (IV) and allylmagnesium bromide is a somewhat unstable compound and readily loses water; for example, by refluxing a cyclohexane solution of this carbinol with a trace of *p*-toluenesulfonic acid, there is afforded the unstable diene 5-allylidene-5*H*-dibenzo-10,11-dihydrocycloheptene (VI) absorbing at 268 mμ (17,200). The same diene is obtained from amitriptyline by Hofmann degradation by way of the quarternary methiodide (VII).

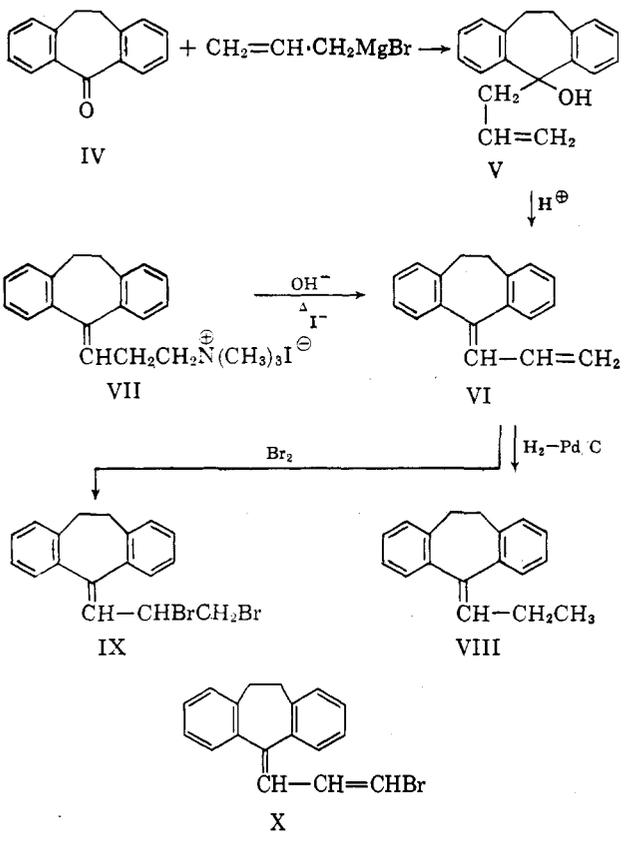


The diene VI exhibits a pronounced tendency toward polymerization. Samples stored in closed containers slowly deteriorate with the production, to a limited extent, of formaldehyde as ascertained by

(1) (a) Belgian Patent 584,061, Merck & Co., Inc; *Cf.* E. Jucker, "Chemie der Psychotropen Pharmaka," *Chimia*, **15**, 267 (1961); (b) British Patents, 858,187; 858,188, Hoffmann-LaRoche A.G.; (c) Belgian Patent 609,095, Kefelas A/S; (d) M. Protiva, V. Hnevsova-Seidlova, Z. J. Vejdelek, F. Jerkovsky, Z. Votava, and J. Metysova, *J. Med. Pharm. Chem.*, **4**, 411 (1961); (e) see also F. J. Villani, C. A. Ellis, C. Teichman and C. Bigos, *ibid.*, **5**, 373 (1962); and South African Patent R611/1889, Kefalas A/S.

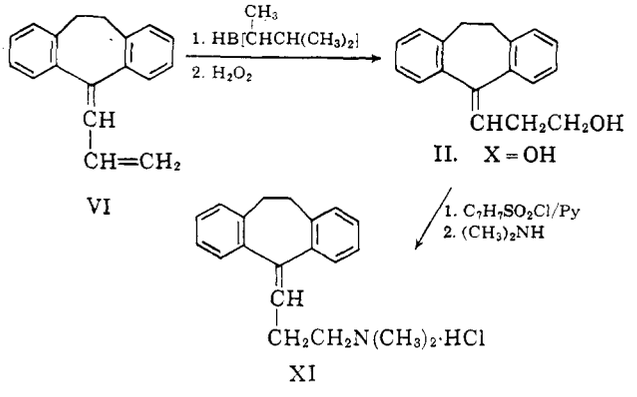
(2) R. D. Hoffsommer, D. Taub, and N. L. Wendler, *J. Org. Chem.*, **27**, 4134 (1962).

(3) Compare also S. O. Winthrop, M. A. Davis, G. S. Meyers, J. G. Gavin, R. Thomas, and R. Barber, *ibid.*, **27**, 230 (1962).



chromotropic acid titration. The diene can be readily separated from polymeric impurities by virtue of its exclusive solubility in petroleum ether, thereby providing material of adequate quality for further chemical transformations. The diene VI readily absorbed one mole of hydrogen to give the crystalline propylidene derivative VIII, m.p. 49–51.6° with λ_{max} 238 mμ (12,700). Similarly, the diene VI added one mole of bromine to provide the crystalline dibromide IX, m.p. 92–94° with λ_{max} 243 mμ (15,400). The same dibromide was obtained from the allylcarbinol V when the latter was allowed to stand with bromine in chloroform solution for several days. Attempts to prepare a γ-dieneamine derivative by reaction of the dibromide IX with dimethylamine were unsuccessful. The major product from this reaction appeared to be the bromodiene X, λ_{max} 280 mμ (21,500).

Conversion of the diene VI to 5-(γ-hydroxypropylidene)-5*H*-dibenzo[*a*,*d*]-10,11-dihydrocycloheptene (II. X = OH) was accomplished in good yield by hydroboration with di-*sec*-isoamylborane and concluding oxidation according to the method of Zweifel, Nagase, and Brown.[4] The primary carbinol II (X = OH) in the form of its *p*-toluenesulfonic ester was smoothly converted to amitriptyline XI with dimethylamine in benzene solution at 85°. This same carbinol was likewise converted essentially quantitatively with thionyl chloride to the corresponding chloro derivative II (X = Cl).



Experimental

5-Allyl-5-hydroxy-5*H*-dibenzo[*a*,*d*]-10,11-dihydrocycloheptene (V).—To a solution of allylmagnesium bromide prepared from 2.88 g. of magnesium and 14.5 g. of allyl bromide in 120 cc. of ether was added dropwise 8.3 g. of 5*H*-dibenzo[*a*,*d*]-10,11-dihydrocyclohepten-5-one dissolved in 50 cc. of ether. The reaction mixture was stored overnight and subsequently decomposed with ammonium chloride solution. The ether layer was separated, dried, and concentrated to a viscous oil. Although this product was chromatographed on neutral alumina and obtained as single spot material by t.l.c. on alumina (1:1 hexane–benzene) [wt., 9.5 g. (75%); $\lambda_{max}^{CH_3OH}$ 263.5, ε 600; $\lambda_{max}^{CHCl_3}$ 2.8 μ (OH), 6.08, 6.26, and 6.71 μ (φ)], it could not be obtained analytically pure.

A 200-mg. sample of the allylcarbinol in 5 cc. of chloroform was treated with one equivalent of bromine. The bromine was consumed immediately, the solution was concentrated to an oil which crystallized after several days to give 240 mg. of the dibromide IX, m.p. 94–96°, identical with a sample prepared by bromination of the diene VI.

Formation of the Diene VI. (A).—A solution of 1.3 g. of allylcarbinol V in 100 cc. of hexane was treated with 130 mg. of *p*-toluenesulfonic acid and refluxed 0.5 hr. on the steam bath. At the end of this period, the reaction mixture was cooled, washed with potassium bicarbonate solution, dried over magnesium sulfate, and concentrated to a thick oil. The latter was submitted to short-path distillation and afforded 0.5 g. of diene, b.p. 160° at 0.3 mm., $\lambda_{max}^{CH_3OH}$ 267.5 mμ, ε 17,200. N.m.r. spectrum: 2.88 (m) (aromatic), 3.50 (m) and 4.75 (m) (vinylic H), 6.97 τ (broad) (10,11-CH). This compound proved to be too unstable to permit ready analysis, low carbon values being obtained.

(B) From 5-(γ-Dimethylaminopropylidene)-5*H*-dibenzo[*a*,*d*]-10,11-dihydrocycloheptene Methiodide (VII).—A solution (10.0 g.) of 5-(γ-dimethylaminopropylidene)-5*H*-dibenzo[*a*,*d*]-10,11-dihydrocycloheptene hydrochloride in 250 ml. of water was treated with 7 ml. of concentrated ammonium hydroxide and the resulting mixture extracted with one 100-ml. portion and three 50-ml. portions of ether. The combined ether extracts were dried over sodium sulfate and taken to dryness *in vacuo*. The residual yellow oil, as the free base, was dissolved in 75 ml. of methyl ethyl ketone, treated with 5.68 g. of methyl iodide in 25 ml. of methyl ethyl ketone, and allowed to stand overnight at room temperature. The reaction mixture was then chilled and filtered to yield 12.73 g. (85% yield) of the methiodide, VII. Recrystallization of a 1-g. sample from 25 ml. of hot acetone containing 4 ml. of ethanol yielded crystals with m.p. 187–188.5°, and $\lambda_{max}^{CHCl_3}$ 4.15, 6.2, and 6.7 μ.

Anal. Calcd. for $C_{21}H_{26}NI$: C, 60.14; H, 6.25; I, 30.26. Found: C, 60.10; H, 6.14; I, 30.58.

A suspension of 1.0 g. of the methiodide of 5-(γ-dimethylaminopropylidene)-5*H*-dibenzo[*a*,*d*]-10,11-dihydrocycloheptene (VII) in 30 ml. of 10% aqueous potassium hydroxide solution was heated on a steam bath for 0.5 hr. At the end of this time, the reaction mixture was cooled to room temperature and extracted with two 25-ml. portions of ether. The combined ether extracts were washed successively with three 10-ml. portions of water, 10 ml. of saturated salt solution, and dried over magnesium sulfate. The solvent was removed *in vacuo* to yield 580 mg. of a yellow oil with $\lambda_{max}^{dioxane}$ 267 mμ, ε 15,000; $\lambda_{max}^{CHCl_3}$ 6.19, 6.75, 6.95, 10.0, and 10.98 μ. The infrared spectrum of this material was the same as that of diene obtained in part A.

5-Propylidene-5*H*-dibenzo[*a*,*d*]-10,11-dihydrocycloheptene (VIII).—A solution of 200 mg. of the diene VI in 25 ml. of benzene was hydrogenated at atmospheric pressure over 100 mg. of 5% palladium on charcoal. Removal of the solvent and catalyst yielded 170 mg. of crystalline propylidene compound VIII with m.p. 49–51.6°; $\lambda_{max}^{dioxane}$ 238 mμ, ε 13,300; $\lambda_{max}^{CHCl_3}$ 3.4, 6.05, 6.75, 6.9, 6.96 (sh), 7.38 and 8.85 μ.

(4) G. Zweifel, K. Nagase, and H. C. Brown, *J. Am. Chem. Soc.*, **84**, 190 (1962).

Anal. Calcd. for $C_{18}H_{18}$: C, 92.25; H, 7.74. Found: C, 91.81; H, 7.47.

5-(β,γ-Dibromopropylidene)-5*H*-dibenzo[*a*,*d*]-10,11-dihydrocycloheptene (IX).—A solution of 1.39 g. of bromine in 25 ml. of chloroform was added dropwise to a solution of 2.0 g. of the diene VI in 75 ml. of chloroform at room temperature and at such a rate that the reaction mixture remained colorless. After a total of 1.28 g. of bromine had been added (the reaction mixture failed to absorb bromine further), the addition was stopped and stirring continued for 40 min. The reaction mixture was taken to dryness *in vacuo*, the residual oil dissolved in hexane, filtered through Celite, concentrated to a small volume, seeded, and chilled to yield 3.0 g. of crystalline dibromide with m.p. 92–94°; λ_{max}^{MeOH} 242.5 mμ, ε 15,300; $\lambda_{max}^{CHCl_3}$ 6.2, 6.78, 6.92, 7.36, and 8.83 μ.

Anal. Calcd. for $C_{18}H_{16}Br_2$: C, 55.12; H, 4.11; Br, 40.76. Found: C, 55.33; H, 4.29; Br, 40.80.

Reaction of the Dibromide IX with Dimethylamine.—A solution of 1.0 g. of the dibromide IX in 10 ml. of benzene saturated with dimethylamine was heated in a sealed tube at 85° overnight. The reaction mixture was taken to dryness, the residue triturated with ether, and 480 mg. (74.5%) of dimethylamine hydrobromide, m.p. 132–133.6°, was filtered off. The filtrate yielded 770 mg. of oily residue which was chromatographed over 25 g. of neutral alumina. The hexane fractions eluted 400 mg. of noncrystalline material, essentially single spot by t.l.c., which had λ_{max}^{MeOH} 280 mμ, and an n.m.r. spectrum compatible with the vinyl bromide X. This substance could not be obtained analytically pure.

5-(γ-Hydroxypropylidene)-5*H*-dibenzo[*a*,*d*]-10,11-dihydrocycloheptene (II. X = OH).—A solution of 2.0 g. of the diene VI in 25 ml. of dry tetrahydrofuran was treated, at 0° and under dry nitrogen, with 3.8 ml. of a 2.28 *M* solution of di-*sec*-isoamylborane[4] in 4 ml. of tetrahydrofuran and allowed to stand at 0–5° for 1 hr. Water, 2 ml., was added (at 0°) to decompose any excess di-*sec*-isoamylborane, the mixture was allowed to come to room temperature and was oxidized by the addition of 4 ml. of 2.5 *N* sodium hydroxide and 2.7 ml. of 30% hydrogen peroxide. The aqueous layer was saturated with solid, anhydrous potassium carbonate, the layers separated, and the aqueous layer extracted with 10 ml. of tetrahydrofuran. The combined organic extracts were dried over magnesium sulfate, and the solvent removed *in vacuo*. The residue, on trituration with petroleum ether (b.p. 30–60°), yielded 1.45 g. (67%) of first crop crystalline alcohol identical (mixture melting point, ultraviolet, and infrared) with a sample produced by the procedure reported previously.[2]

5-(γ-Chloropropylidene)-5*H*-dibenzo[*a*,*d*]-10,11-dihydrocycloheptene (II. X = Cl).—A solution of 50 mg. of the primary carbinol II (X = OH) in 3 ml. of benzene containing 1 drop of pyridine was treated dropwise with 65.6 mg. of thionyl chloride in 2 ml. of benzene at room temperature and refluxed on a steam bath for 3 hr. The reaction mixture was then evaporated to dryness *in vacuo*. The residue was triturated with benzene, the benzene solution filtered, and taken to dryness *in vacuo* to give a quantitative yield of the crystalline chloride II (X = Cl identical with a sample obtained by a previously reported method.[2]

Conversion of the Primary Carbinol II (X = OH) to 5-(γ-Dimethylaminopropylidene)-5*H*-dibenzo[*a*,*d*]-10,11-dihydrocycloheptene Hydrochloride (XI).—A solution of 400 mg. of the pirmary carbinol II (X = OH) in 5 ml. of dry pyridine, chilled to 0°, was treated with 400 mg. of *p*-toluenesulfonyl chloride. The reaction mixture was allowed to stand overnight at 0–4°. At the end of this period, the reaction mixture was poured over 15–20 ml. of crushed ice and extracted with three 10-ml. portions of chloroform. The combined extracts were washed with 5-ml. portions of cold 2.5 *N* hydrochloric acid until the last wash was acidic, then washed with 10 ml. of excess potassium bicarbonate solution, followed by 10 ml. of saturated salt solution. The solution was finally dried over magnesium sulfate and taken to dryness *in vacuo* to yield 620 mg. (96.5%) of crude, noncrystalline tosylate. This material had $\lambda_{max}^{CHCl_3}$ 6.3, 7.40, 8.45, 8.55, 9.15, and 12.29 μ.

Anal. Calcd. for $C_{25}H_{24}O_3S$: S, 7.92. Found: S, 7.21.

This tosylate was treated with dimethylamine in benzene in a sealed tube at 85° as described previously[2] to yield 360 mg. (77.5%) of first crop crystalline product, m.p. 191–193°, which was identical with an authentic sample of amitriptyline XI.

1,5-Naphthyridine and Some of Its Alkyl Derivatives

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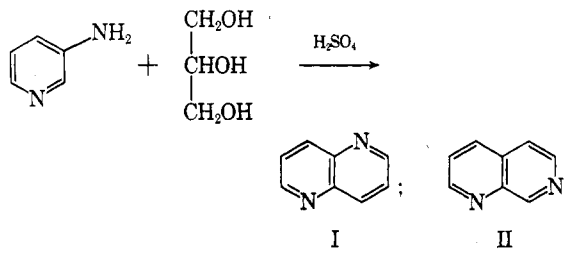
The preparation of 1,5-naphthyridine from 3-aminopyridine and glycerol in the Skraup reaction led to the isolation of 1,2,3,4-tetrahydro-1,5-naphthyridine and 3-methyl- and 3-ethyl-1,5-naphthyridine as by-products. The structures of these products were established by independent syntheses and explanations for their mode of formation are suggested. The isomeric 1,7-naphthyridine, prepared independently, was totally absent as a product of the 3-aminopyridine reaction. Oxidation of 3-ethyl-1,5-naphthyridine gave the expected 1,5-naphthyridine-3-carboxylic acid; however, 3-methyl-1,5-naphthyridine under the same conditions surprisingly gave 3-acetamidopicolinic acid. A possible mechanism for this oxidation is proposed. The infrared spectra of the various 1,5- and 1,7-naphthyridines have been correlated.

1,5-Naphthyridine (I) has appeared in the literature several times,[1-4] resulting from the Skraup reaction with 3-aminopyridine. In no instance was the isomeric 1,7-naphthyridine (II) detected, although its formation cannot be excluded rigorously, since purification was by crystallization exclusively. It seemed reasonable to expect that some of the 1,7-isomer would be formed, particularly since the analogous reaction with *m*-substituted anilines invariably gave both possible isomers.[5] For this reason, and also because we required a large quantity of pure 1,5-naphthyridine, we have examined the Skraup reaction with 3-aminopyridine in detail.



Preliminary experiments established that (1) the maximum crude yield was obtained in the presence of boric acid, and (2) this crude product, on chromatography, gave a fraction with the characteristic 1,5-naphthyridine ultraviolet spectrum and a fraction with the characteristic 3-aminopyridine spectrum. A convenient large-scale purification method then was

(1) B. Bobranski and E. Sucharda, *Ber.*, **60**, 1081 (1927).
(2) C. R. Hauser and G. A. Reynolds, *J. Org. Chem.*, **15**, 1224 (1950).
(3) E. P. Hart, *J. Chem. Soc.*, 1879 (1954).
(4) A. Albert, *ibid.*, 1790 (1960).
(5) M. H. Palmer, *ibid.*, 3645 (1962), and references therein.