Acknowledgment.—The author wishes to thank Mr. F. Szabo for his careful technical assistance.

New Psychotropic Agents.[1] II. Derivatives of 5,6-Dihydrodibenz[b,e]azepine (5,6-Dihydromorphanthridine)

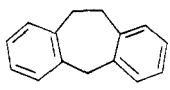
STANLEY O. WINTHROP,[2] M. A. DAVIS,[2] F. HERR,[3] J. STEWART,[3] AND ROGER GAUDRY

Ayerst Research Laboratories, Montreal, Canada

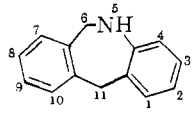
Received June 25, 1962

Sodium borohydride treatment of 6,11-diketo-5,6-dihydrodibenz[b,e]azepine produced 11-hydroxy-6-keto-5,6-dihydrodibenz[b,e]azepine. Alkylation with 3-dimethylaminopropylmagnesium chloride also gave an 11-hydroxy derivative, 11-(3-dimethylaminopropyl)-11-hydroxy-6-keto-5,6-dihydrodibenz[b,e]azepine. This latter compound was used as an intermediate for the synthesis of other 11-substituted dibenz[b,e]azepines. The pharmacological activities of some of these compounds are discussed briefly.

In the course of an investigation of the pharmacological properties of compounds containing tricyclic ring systems analogous to the phenothiazine ring, it was found that certain derivatives of dibenzo [a,d][1,4] cycloheptadiene (I) exhibited a number of interesting effects on the central nervous system.[1]



I



II

One of these compounds, namely, 5-(3-dimethylaminopropylidene)-dibenzo[a,d][1,4]cycloheptadiene, has since found clinical usage as an antidepressant agent.[4] It was of interest to investigate similar derivatives of ring systems structurally related to I. The present paper describes a part of this study, the synthesis of 5,6-dihydrodi-

(1) For the first paper in this series, see S. O. Winthrop, M. A. Davis, G. S. Myers, J. G. Gavin, R. Thomas, and R. Barber, *J. Org. Chem.*, **27**, 230 (1962).

(2) Department of Chemistry.

(3) Department of Pharmacology.

(4) (a) F. J. Ayd, Jr., *Psychosomatics*, **I**, 320 (1960). (b) W. Dorfman, *Psychosomatics*, **I**. 153 (1960). (c) H. Freed, *Am. J. Psychiat.*, **117**, 455 (1960).

benz[b,e]azepine (II) derivatives. In these compounds the carbon atom at the 10-position of the dibenzo[a,d][1,4]cycloheptadiene ring is replaced by a nitrogen atom.

Dibenz[b,e]azepines have been mentioned in the literature as early as 1913 when the synthesis of compounds referred to as 6,11(5H)-morphanthridinediones were reported.[5] Since that time a number of workers have prepared mono- and disubstituted 6,11-diketo-5,6-dihydrodibenz[b,e]azepines. Amino, chloro, bromo and alkyl substituents in positions 2, 3, 4, 8 and 9 have been reported.[6] The parent ring compound, 5,6-dihydrodibenz[b,e]azepine along with its 5-methyl derivative and related quaternary compounds have been synthesized by Wittig.[7] A number of 5-(dialkylaminoalkyl) and 5-acyl derivatives of 5,6-dihydrodibenz[b,e]azepines were studied by Protiva[8] as possible antihistamines. A recent patent describes a series of 5 - (dialkylaminoalkyl) - 5,6 - dihydro - 5,6 - diketodibenz[b,e]-azepines which are claimed to have antispasmodic properties without significant anticholinergic or antihistaminic side effects.[9] No substituents in the 11-position, however, have been reported to date with the exception of the 11-ketone.

It was of interest to prepare an 11-hydroxy-5,6-dihydrodibenz-[b,e]azepine for pharmacological evaluation in connection with another study being carried out in these laboratories. The catalytic hydrogenation of 6,11-diketo-5,6-dihydrodibenz[b,e]azepine (III) has been reported by Wittig[7] to give 6-keto-5,6-dihydrodibenz[b,e]-azepine indicating an easy reductive cleavage of the carbon–oxygen bond with the loss of the 11-hydroxyl group. Lithium aluminum hydride reduction of III similarly caused reductive cleavage to give II. The synthesis of an 11-hydroxy compound was, however, accomplished when the reaction was carried out using sodium borohydride giving 11-hydroxy-6-keto-5,6-dihydrodibenz[b,e]azepine (IV).

The successful alkylation of 6,11-diketo-5,6-dihydrodibenz[b,e]-azepine with 3-dimethylaminopropylmagnesium chloride to yield 11 - (3 - dimethylaminopropyl) - 11 - hydroxy - 6 - keto - 5,6- dihydrodibenz[b,e]azepine (V) provided a route to the synthesis of the 11-substituted compounds desired for the present study. Any alkylation of the amide carbonyl was kept to a minimum by carrying out

(5) Akt. Ges. Für. Aniline Fabrikation, German Patent 258,343 (1912).

(6) A. Wolfram and E. Hausdörfer, (a) German Patent 551,256 (1928). (b) P. Kränzlein, *Ber.*, **70**, 1952 (1937). (c) W. Bradley, and H. E. Nursten, *J. Chem. Soc.*, 2170 (1951). (d) N. S. Dokunikhin and T. N. Kurdyumova, *Sbornik Statei Obschei Khim.*, **2**, 1411 (1953). (e) G. Caronna and S. Palazzo, *Gazz. Chim. Ital.*, **83**, 533 (1953).

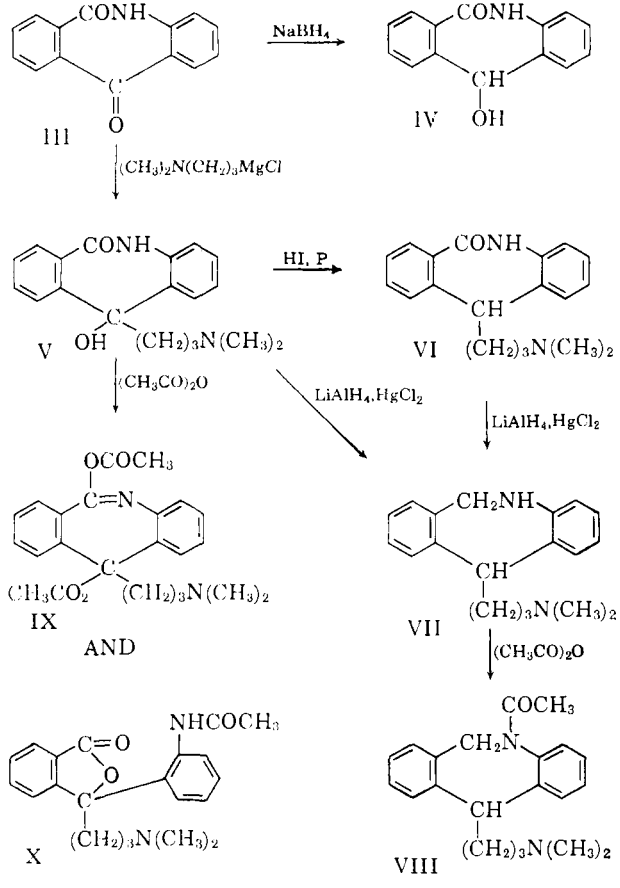
(7) G. Wittig, G. Closs, and F. Minderman, *Ann.*, **594**, 88 (1955).

(8) M. Borovicka and M. Protiva, *Chem. Listy*, **51**, 1344 (1957).

(9) L. H. Werner, U. S. Patent 2,973,354, Feb. 28, 1961.

the reaction using an inverse addition procedure. Treatment of V with hydriodic acid and red phosphorus then gave 11-(3-dimethylaminopropyl)-6-keto-5,6-dihydrodibenz[b,e]azepine (VI), an 11-deoxy compound. An attempt to reduce the amide carbonyl of V with lithium aluminum hydride in ether was unsuccessful, only starting material being recovered. Reduction of the amide carbonyl was done with lithium aluminum hydride and mercuric chloride in boiling tetrahydrofuran solution but was accompanied by the removal of the 11-hydroxyl group to yield 11-(3-dimethylaminopropyl)-5,6-dihydrodibenz[b,e]azepine (VII), a 6,11-deoxy compound. This compound was also prepared from VI in a similar manner. Acetic anhydride treatment of VII gave an N-acetyl derivative (VIII).

Attempts to synthesize an 11-(3-dimethylaminopropylidene)



compound by dehydration of the tertiary carbinol V were unsuccessful. Acidic dehydrating agents invariably led to an intramolecular N → O acyl migration with the formation of a phthalide ring, easily recognized by its infrared spectrum. The use of potassium hydroxide in ethylene glycol at elevated temperatures was equally unsuccessful. In one case, however, when V was heated under reflux for 16 hours with boiling acetic anhydride, an appreciable quantity of 11-(3-dimethylaminopropyl)-6,11-diacetoxydibenz[b,e]azepine (IX) was produced along with the expected phthalide compound (X).

Pharmacological Activity.—The compounds were studied in the series of pharmacological tests used in this laboratory to screen for antidepressant and other central activity. The tests included were: the determination of acute toxicity (LD_{50}), potentiation of a subhypnotic dose of ethanol, protection against maximal electroshock seizures (MES), mydriatic action, depression of orientational hypermotility, ataxic effect and influence on a conditioned response (runway test). A detailed description of these methods has been reported previously.[10] The compounds were tested further against the contractions induced by acetylcholine and histamine in isolated guinea pig ileum. The results are presented in Table I. For comparative purposes the results obtained for amitriptyline are also included. The doses for the *in vivo* tests and the concentrations for the *in vitro* tests are expressed in terms of the free base in all cases.

As none of the structural changes made in the compounds resulted in a parallel increase or decrease in activity in the different pharmacological tests, it is not possible to establish any simple structure–activity relationships. It can be seen, however, that compounds VI and VII had the most potent central (see potentiation of narcosis and effect on conditioned runway response) and peripheral effects. None of the compounds was able to protect against electroshock convulsions and compound IX appeared to have little or no activity in all of the tests used.

Experimental

5,6-Dihydrodibenz[b,e]azepine (II).—To lithium aluminum hydride (3.4 g., 0.09 mole) and ether (130 ml.) was added 6,11-diketo-5,6-dihydrodibenz[b,e]azepine[6e] (5.0 g., 0.03 mole) in small portions. The reaction mixture was heated under reflux for 4 hr., after which the complex was decomposed by the cautious addition of water in the usual manner. The ether was removed *in vacuo* and the residue recrystallized from methanol to give 2.3 g. (43% yield) of product, m.p. 130–132° (lit.[7] m.p. 130–131°).

(10) F. Herr, J. Stewart, and M. P. Charest, *Arch. int. Pharmacodyn.*, **134**, 388 (1961).

TABLE I

RESULTS OF THE PHARMACOLOGICAL INVESTIGATIONS

Compound No.	LD_{50} (approx.) mg./kg. mice i.p.	Potentiation of narcosis ED_{50} mg./kg. mice i.p.	MES ED_{50} mg./kg. mice i.p.	Mydriasis,[a] caused by 0.25 LD_{50} mice i.p.	% Difference in motility 0.25 LD_{50} rats i.p.	Ataxia approx. ED_{50} mg./kg. rats i.p.	Runwa./ approx. ED_{50} mg./kg. rats i.p.	Antiacetylcholine[b] EC_{50} μg./ml.	Antihistamine[b] EC_{50} μg./ml
V	250–300	25 ± 5.8	>70	+4.8	−52	175	40	0.2–0.5	0.1–0.5
VI	175–200	5.3 ± 0.5	>45	+40	0	>100 (death)	7	0.011 ± 0.006	0.026 ± 0.004
VII	120–130	5.5 ± 0.95	>35	+34	−30	50	20	0.15 ± 0.03	0.0056 ± 0.0007
VIII	100–120	>40	>30	+1.8	−25	40	27	0.17 ± 0.018	1.1 ± 0.18
IX	360–400	115 ± 3.6	>90	0	0	>270	>90	>20	>20
Amitriptyline	83 ± 2.5	7.9 ± 0.8	10 ± 0.8	+19	−37	53	8	0.038 ± 0.003	0.004 ± 0.001

[a] The numbers represent unit increases over control pupil diameter. +40 is approximately the maximal dilation. [b] EC_{50} is the concentration which inhibited the normal response to 0.1 μg./ml. of either acetylcholine or histamine by 50%. Note: > means that the compound was inactive up to the dose indicated in the table.

Anal. Calcd. for $C_{14}H_{13}N$: C, 86.12; H, 6.71; N, 7.17. Found: C, 85.74; H, 7.16; N, 7.22.

11-Hydroxy-6-keto-5,6-dihydrodibenz[b,e]azepine (IV).—Sodium borohydride (6.84 g., 0.18 mole) dissolved in water (25 ml.) containing 10% sodium hydroxide (1.5 ml.) was added dropwise to a suspension of 6,11-diketo-5,6-dihydrodibenz-[b,e]azepine (10.0 g., 0.045 mole) in methanol (200 ml.). After the exothermic reaction had subsided, the mixture was stirred for 2½ hr. at room temperature and then heated on a water bath at 60° for an additional 1.5 hr. After cooling, the product was separated by filtration, washed with very dilute acetic acid and then recrystallized from dioxane to yield 5.0 g., m.p. 248–250° dec. Microanalysis showed the presence of an impurity which was assumed to be some borate ester. Accordingly, the material was heated in refluxing water for 1 hr., collected, dried and recrystallized once from methyl isobutyl ketone–dimethylformamide to give 2.7 g., 27% yield, of product, m.p. 245–248° dec.; $\nu_{max.}$ (Nujol) 3350 (associated OH), 1663 cm.$^{-1}$ (amide carbonyl). A small amount of impurity remained even after repeated recrystallizations.

Anal. Calcd. for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.08; H, 5.04; N, 6.19.

11-Hydroxy-11-(3-dimethylaminopropyl)-6-keto-5,6-dihydrodibenz[b,e]azepine (V).—A solution of dimethylaminopropylmagnesium chloride, prepared from magnesium (10.7 g., 0.468 mole) and dimethylaminopropyl chloride (56.5 g., 0.468 mole) in 160 ml. of tetrahydrofuran, was added dropwise to 6,11-diketo-5,6-dihydrodibenzo[b,e]azepine (34 g., 0.15 mole) in 3 l. of toluene at reflux temperature. The addition was completed in 1 hr. and heating was continued for an additional 18 hr. The reaction mixture was cooled and shaken with 2.5 l. of aqueous ammonium chloride. The aqueous layer was then further extracted with ether and the combined organic layers washed with water. The organic extracts were dried and concentrated to yield 30 g. of crude product, m.p. 150–163°. One recrystallization from acetone gave 20 g., m.p. 188–189° (42% yield) which was analytically pure; $\nu_{max.}$ (Nujol) 3350 (associated OH), 1650 cm.$^{-1}$ (amide carbonyl).

Anal. Calcd. for $C_{19}H_{22}N_2O_2$: C, 73.52; H, 7.14; N, 9.02. Found: C, 73.58; H, 7.14; N, 9.29.

11-(3-Dimethylaminopropyl)-6-keto-5,6-dihydrodibenz[b,e]azepine (VI).—11-Hydroxy-11-(3-dimethylaminopropyl)-6-keto-5,6-dihydrodibenz[b,e]azepine (10 g., 0.0325 mole) was dissolved in 120 ml. of glacial acetic acid containing 53 ml. of 56% hydriodic acid and 10 g. of red phosphorus. The reaction mixture was stirred and heated at reflux for 20 hr. The insoluble material was removed by filtration and the filtrate evaporated *in vacuo*, leaving the crude hydriodide as an oily residue. This was dissolved in 400 ml. of ethylene dichloride and washed with 150 ml. of 5% sodium hydroxide and then with water. The organic layer was dried over sodium sulfate and concentrated to yield 8 g. of base, as an oily residue, which crystallized on trituration with acetone to give a solid with m.p. 125–130°. Two recrystallizations from acetone–ether gave a sample with m.p. 131–133° which was still not analytically pure.

Anal. Calcd. for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52. Found: C, 76.85; H, 7.45; N, 9.60.

The compound was further purified by conversion to its hydrochloride salt. The base was dissolved in ether and hydrogen chloride gas was bubbled in, causing the hydrochloride to precipitate as a gum. This was crystallized from 2-pro-

panol to yield 4.2 g. (40% yield) of solid with m.p. 214–216°. Two recrystallizations from acetonitrile raised the melting point to 220–222°. The absence of the hydroxyl group was confirmed by its infrared spectrum; $\nu_{max.}$ (Nujol) 1645 cm.$^{-1}$ (amide carbonyl).

Anal. Calcd. for $C_{19}H_{23}ClN_2O$: N, 8.47; Cl, 10.71. Found: N, 8.79; Cl, 10.49.

The product was also characterized as its hydriodide salt. A sample of the original oil residue from the hydriodic acid reduction was crystallized from acetone–methanol to give a solid hydriodide salt with m.p. 232–234°. A second recrystallization from acetone–methanol did not change the melting point.

Anal. Calcd. for $C_{19}H_{23}IN_2O$: N, 6.64; I, 30.08. Found: N, 6.55; I, 30.22.

11-(3-Dimethylaminopropyl)-5,6-dihydrodibenz[b,e]azepine (VII). Method A.—11-Hydroxy-11-(3-dimethylaminopropyl)-6-keto-5,6-dihydrodibenz[b,e]azepine (9.4 g., 0.03 mole), lithium aluminum hydride (4.45 g., 0.12 mole), and mercuric chloride (0.92 g., 0.003 mole) were added to 200 ml. of tetrahydrofuran. The reaction mixture was stirred and heated at reflux for 16 hr. The excess hydride was destroyed by the addition of water in a dropwise manner and the inorganic solids were removed by filtration. The filtrate was dried over sodium sulfate and then evaporated *in vacuo* to yield 8 g. of product as an oily residue. The residue was taken up in ether and a small amount of insoluble material was removed. The ether solution was then extracted with dilute hydrochloric acid. The aqueous layer was made basic and extracted with ether. This ether extract, after drying over sodium sulfate, was treated with an ether solution of maleic acid, causing the product to precipitate as the maleate salt, 5 g. (40% yield) with m.p. 138–140°. Two recrystallizations from 2-propanol raised the melting point to 146–148°. The absence of the hydroxyl and carbonyl groups was confirmed by infrared spectra.

Anal. Calcd. for $C_{23}H_{28}N_2O_4$: C, 69.67; H, 7.12; N, 7.06. Found: C, 69.16; H, 7.41; N, 7.05.

Method B.—The title compound was also prepared by an alternate unambiguous route. 11-(3-Dimethylaminopropyl)-6-keto-5,6-dihydrodibenz[b,e]azepine (2.5 g., 0.008 mole), lithium aluminum hydride (1.12 g., 0.008 mole) and mercuric chloride (0.0008 mole) were added to 75 ml. of tetrahydrofuran. The reaction mixture was heated for 16 hr. and worked up in the same manner as in the preceding paragraph to give 1.7 g. of a maleate salt (52% yield), m.p. 146–148°, which was identical in every way to the product of Method A.

11-(3-Dimethylaminopropyl)-6,11-diacetoxydibenz[b,e]azepine (IX).—11-Hydroxy-11-(3-dimethylaminopropyl)-6-keto-5,6-dihydrodibenz[b,e]azepine (23 g., 0.074 mole) was dissolved in 450 ml. of acetic anhydride and heated at reflux for 20 hr. The acetic anhydride was removed *in vacuo* and the residue triturated with 500 ml. of 1 *N* sodium hydroxide and extracted with ether. The ether extract was dried and treated with hydrogen chloride to yield 9.8 g. of a crude hydrochloride as a gum. It was crystallized from a 2-propanol–ether solution to yield 7.5 g. (23% yield), m.p. 228–230°. One recrystallization raised the melting point to 230–232°. Infrared and microanalysis indicated a 6,11-diacetate compound; $\nu_{max.}$ (Nujol) 1765, 1715 and 1693 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{27}ClN_2O_4$: N, 6.50; Cl, 8.23. Found: N, 6.51; Cl, 8.53.

3-(3-Dimethylaminopropyl)-3-(*o*-acetamidophenyl)phthalide (X).—The aqueous phase from the ether extraction in the previous paragraph was adjusted to pH 7

and re-extracted with ether. The ether extract was dried and treated with hydrogen chloride to yield 17 g. (60% yield) of a crude hydrochloride. It was crystallized from 2-propanol–methanol solution to yield 14 g., m.p. 210–212°. A second recrystallization did not change the melting point. Infrared, chemical properties and microanalysis all indicated the structure of the title compound, $\nu_{max.}$ (Nujol) 1767 (lactone), 1682 cm.$^{-1}$ (amide).

Anal. Calcd. for $C_{21}H_{25}ClN_2O_3$: N, 7.21; Cl, 9.14. Found: N, 7.16; Cl, 9.38.

11-(3-Dimethylaminopropyl)-5-acetyl-5,6-dihydrodibenz[b,e]azepine (VIII).—11-(3-Dimethylaminopropyl)-5,6-dihydrodibenz[b,e]azepine maleate (7.6 g., 0.019 mole) was dissolved in water and the base liberated by the addition of aqueous sodium hydroxide. The aqueous mixture was extracted with ether, the ether layer dried and then evaporated *in vacuo* to yield a light brown, viscous oil. Acetic anhydride (50 ml.) was added and the reaction mixture heated at reflux for 2 hr. The excess acetic anhydride was removed *in vacuo* and the residue triturated with aqueous sodium hydroxide and then taken up in ether. After drying the ether extract over sodium sulfate, hydrogen chloride gas was bubbled in causing the hydrochloride to precipitate as an amorphous solid, 3 g., m.p. 150–190°. One recrystallization from 2-propanol gave 1.5 g. (22% yield), m.p. 235–238°. A second recrystallization did not change the melting point; $\nu_{max.}$ (Nujol) 1635 cm.$^{-1}$ (amide carbonyl).

Anal. Calcd. for $C_{21}H_{27}ClN_2O$: N, 7.81; Cl, 9.88. Found: N, 7.47; Cl, 9.70.

Acknowledgments.—The authors wish to thank Mr. W. J. Turnbull for the analyses; Dr. Gilles Papineau-Couture, Mrs. J. Jachner and Mr. M. Boulerice for the infrared and ultraviolet spectra. The capable technical assistance of Messrs. J. G. Gavin, R. A. Thoma and Miss Marie-Paule Charest is acknowledged.