Dibenzo[b,e][1,4]diazepines

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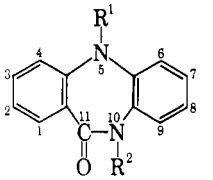
The synthesis of dibenzo[b,e][1,4]diazepines substituted in the 5- and 10-positions with dialkylaminoalkyl groups and their activity as pseudocholinesterase inhibitors are reported.

In 1924 Clemo, Perkin, and Robinson[1] reported the synthesis of 11H-dibenzo[b,e][1,4]diazepin-11-one (I) by the pyrolysis of N-(*o*-aminophenyl)anthranilic acid.



I $R^1 = R^2 = H$

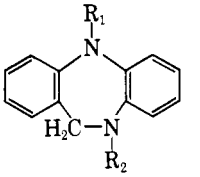
II $R^1 = H$, $R^2 = C_nH_{2n}N(R_3)(R_4)$, CH_3

III $R^1 = C_nH_{2n}N(R_3)(R_4)$, $R^2 = H$

IV $R^1 = C_nH_{2n}N(R_3)(R_4)$, $R^2 = C_nH_{2n}N(R_3)(R_4)$, CH_3

Several years later McCombie and co-workers[2] independently reported an unsuccessful attempt to prepare the same compound by the identical procedure. Since that time no report has appeared in the literature on the synthesis of this ring structure or any of its derivatives.

We became interested in preparing derivatives of the above structure in which the 5 and/or 10 positions are substituted with dialkylaminoalkyl groups II, III, IV. These could then be reduced with lithium aluminum hydride to the 10,11-dihydrodiazepines represented by the structures V, VI, and VII in which one or both of the nitrogen atoms is alkylated with a dialkylaminoalkyl group.

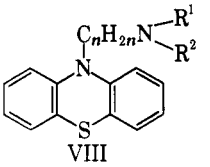


V $R^1 = H$, $R_2 = C_nH_{2n}N(R_3)(R_4)$

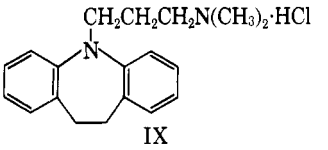
VI $R^1 = C_nH_{2n}N(R_3)(R_4)$, $R^2 = H$

VII $R^1 = C_nH_{2n}N(R_3)(R_4)$, $R^2 = C_nH_{2n}N(R_3)(R_4)$

Four of these types of compounds III, IV, VI, VII bear a structural resemblance to phenothiazine type compounds VIII, which possess tranquilizing activity, and to imipramine (IX),[3] which is useful as a psychic energizer in depressive states.



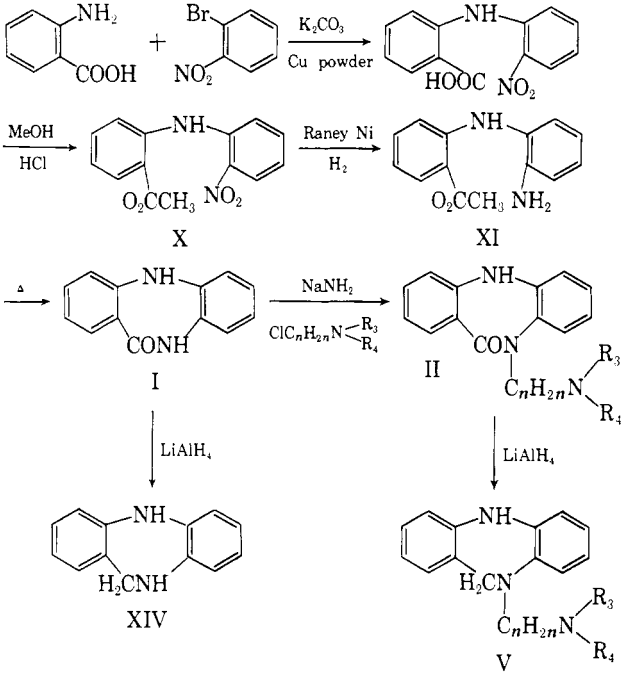
VIII



IX

The synthesis of compounds of type I, II, and V was effected by the scheme outlined in Chart I.

CHART I



The alkylation of anthranilic acid with 2-bromonitrobenzene is a modification of the procedure of Goldberg.[4] The original synthesis of I by Clemo, *et al.*,[1] involved reduction of the N-(*o*-nitrophenyl)anthranilic acid with ferrous sulfate, followed by ring closure of the resulting N-(*o*-aminophenyl)anthranilic acid with heating. In an improved synthesis we first converted the N-(*o*-nitrophenyl)anthranilic acid to the methyl ester X. Catalytic reduction in the presence of Raney nickel gives the corresponding amino compound XI which is converted to the diazepinone I in good yield on heating at 180–200°. Alkylation of 5,10-dihydro-11H-dibenzo[b,e][1,4]diazepin-11-one (I) with sodamide and dialkylaminoalkyl chloride in dioxane substitutes only at the 10-position, as shown by n.m.r. studies, to yield

(1) G. R. Clemo, W. H. Perkin, Jr., and R. Robinson, *J. Chem. Soc.*, **125**, 1770 (1924).

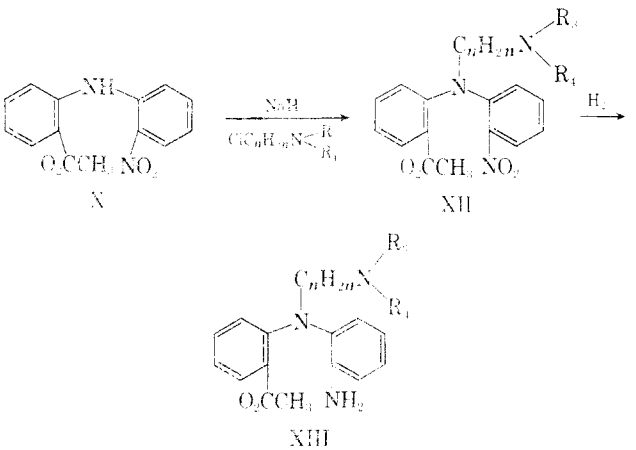
(2) H. McCombie, H. A. Scarborough, and W. A. Waters, *ibid.*, 353 (1928).

(3) W. Schindler and H. Hafliger, *Helv. Chim. Acta*, **37**, 472 (1954).

(4) J. Goldberg, *Ber.*, **39**, 1691 (1906).

II. Alkylating agents used were dimethyl- and diethylaminopropyl chloride, and diethylaminoethyl chloride. Alkylation with methyl iodide under similar conditions produces the 10-methyl derivative. Reduction of the parent ring compound and of the 10-diethylaminoethyl- and 10-dimethylaminopropyl derivatives with lithium aluminum hydride gives the corresponding reduced ring structures XIV, V.

The synthesis of the dibenzodiazepines alkylated at the 5-position was first attempted by alkylation of the parent dibenzodiazepine. Hauser, *et al.*,[5] have shown that β-diketones can be alkylated at the less reactive position by first forming the dipotassio salts and then treating them with the alkyl halide. An attempt to apply this chemistry to the synthesis of 5-substituted derivatives was unsuccessful. Reaction of I with 2 moles of potassium amide in liquid ammonia followed by treatment with 3-dimethylaminopropyl chloride gave a 50% return of starting material plus unidentified oils. The high return of starting material is probably due to the insolubility of the dipotassio salt in liquid ammonia. Further investigation of this reaction was discontinued when it was found that the 2-nitroanthranilic acid ester X can be alkylated in excellent yields with dialkylaminoalkyl chlorides to produce the N-alkylated product XII.



Catalytic reduction of these compounds produces the amino analogs XIII which can then be cyclized to the desired 5-alkylated 5,10-dihydro-11H-dibenzo[*b,e*][1,4]-diazepine-11-ones III by pyrolysis or, more smoothly, by heating in methanol in an autoclave at 100°. Compounds prepared in this series were those containing the dimethyl- and diethylaminopropyl, and the diethylaminoethyl side chains. Reduction with lithium aluminum hydride produces the corresponding 5-alkylated 10,11-dihydro-5H-dibenzo[*b,e*][1,4]diazepines VI. The N-oxide derivatives of the 5-alkylated 5,10-dihydro-11H-dibenzo[*b,e*][1,4]diazepin-11-ones XV, XVI (Table I) were prepared by reaction with hydrogen peroxide. The oxide is most likely on the side chain nitrogen since the unsubstituted diazepinone I does not form a salt.

Two compounds were prepared in which the 11H-dibenzo[*b,e*][1,4]diazepin-11-one is alkylated at both the 5- and 10-positions. Alkylation of 5-(2-diethylaminoethyl)-5,10-dihydro-11H-dibenzo[*b,e*][1,4]-diazepin-11-one (III, R^1 = 2-diethylaminoethyl) with methyl iodide and with 3-dimethylaminopropyl chloride produces the 10-methyl (IVa) and 10-(3-dimethylaminopropyl) (IVb) derivatives, respectively.

Most of the compounds were tested for inhibition of pseudocholinesterase. A few of them showed very good inhibition (Table I).

Subsequent to this work, reports have appeared in the patent literature on the synthesis of some compounds in the foregoing classes.[6] Additional references[7] have appeared since this paper was submitted for publication.

Experimental[8]

N-(*o*-Nitrophenyl)anthranilic Acid.—In a 2-l., three-necked, round-bottomed flask, provided with a mechanical stirrer, a reflux condenser, and a thermometer (up to 200°) were placed 600 g. (3.0 moles) of *o*-bromonitrobenzene, 300 g. (2.2 moles) of anthranilic acid, and 300 ml. of *n*-amyl alcohol. The mixture was heated in an oil bath and the stirrer was started after most of the chemicals had dissolved (80–90°). Then 3.0 g. of copper powder and 300 g. (2.2 moles) of potassium carbonate were added at once. A red reaction mixture was formed in about 15 min. The reaction temperature rose from 80° to 120°. At the same time there was formed a solid which hindered further stirring. The reflux condenser was replaced by a downwards slanting condenser allowing the formed water and solvent to be distilled from the reaction mixture. Meanwhile the temperature of the oil bath was increased steadily and was finally kept at 200–210° for 3 hr. The oil bath was replaced by a steam bath and the excess *o*-bromonitrobenzene was removed by steam distillation. After the distillation of *o*-bromonitrobenzene was complete, the solution was filtered and water was added, making the total volume of the red solution 5 l. The solution was cooled to room temperature overnight and filtered. Dilute hydrochloride acid (1:1) was carefully added to the filtrate until it was just acid to congo red. The ochre-colored precipitate was removed by filtration and washed with 1500 ml. of water. The product was dried *in vacuo* at 70°, yield 521 g. (62% based on anthranilic acid), m.p. 206–214°. No further purification was needed for the next step.

Methyl N-(*o*-Nitrophenyl)anthranilate (X).—In a 12-l., three-necked, round-bottomed flask, provided with a mechanical stirrer, a reflux condenser, and a gas inlet tube, were placed 348.0 g. (1.35 moles) of N-(*o*-nitrophenyl)anthranilic acid and 10 l. of commercial absolute methanol. The solid dissolved on heating on the steam bath. Hydrogen chloride was allowed to bubble through the refluxing solution for 7 hr. After 2–4 hr. a solid precipitated. After cooling overnight to room temperature the solid was isolated by filtration through a sintered glass funnel. The solid in the funnel was pressed to remove most of the solvent and then washed twice with 250-ml. portions of methanol. The orange compound was dried *in vacuo* over sodium hydroxide, yield 317 g. (86%), m.p. 155–157°. After one recrystallization from methanol the material melted at 156–157°.

Methyl N-(*o*-Aminophenyl)anthranilate (XI).—The nitro ester (X) (299.2 g., 1.1 moles) was dissolved in 8 l. of commercial absolute methanol and transferred to an autoclave equipped with a mechanical stirrer. A Raney nickel slurry (*ca.* 100 ml.) was added with methanol, was added, and the compound was reduced at room temperature at 50 p.s.i. (3.5 kg./cm.²). In 2 hr. 98% of the theoretical amount of hydrogen was consumed. The solution was filtered, the catalyst transferred to a 4-l. beaker, and was washed thoroughly twice with 500 ml. of warm methanol. The methanol solution was concentrated to 6000 ml. and 3000 ml. of hot water was added. The flask was placed in an ice bath and stirred for 3–4 hr. After filtration and drying *in vacuo* at room temperature a grey product (226 g., 85% yield) was obtained, melting at 101–102°. This material was pure enough for the next step. Recrystallization from dilute ethanol gave a colorless product, m.p. 102–103°.

(5) C. R. Hauser and T. M. Harris, *J. Am. Chem. Soc.*, **80**, 6360 (1958).

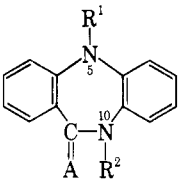
(6) (a) A. Wander, S. A., French Patents M 941, M 992, M 1060, M 1015, M 1102 (1963); (b) J. Druey and E. C. Davies, S. African Spec. No. 2994/61.

(7) (a) L. Hunziker, H. Lauener, and J. Schmutz, *Arzneimittel-Forsch.*, **13**, 324 (1963); (b) R. Pongs, *Schweiz. Med. Wochschr.*, **93**, 118 (1963).

(8) Analytical data for all compounds are listed in Tables I and II.

TABLE I

DIBENZO[b,e][1,4]DIAZEPINES[a]



Compound	A	R¹	R²	M.p., °C. (uncor.)	Formula	Calcd. / Found C	Calcd. / Found H	Calcd. / Found N	Inhibition of pseudocholinesterase % inhibition at 10^{-3} M	$[I]_{50}$
I	O	H	H	254–255	$C_{13}H_{10}N_2O$	74.27 74.25	4.79 4.91	13.33 13.71	67	1×10^{-4}
IIa	O	H	$(CH_2)_2N(C_2H_5)_2$	132–133[b]	$C_{19}H_{22}N_3O$	73.75 73.78	7.49 7.62	13.58 13.61	94	4×10^{-7}
IIb	O	H	$(CH_2)_3N(CH_3)_2$	119–121[a]	$C_{18}H_{21}N_3O$	73.19 73.18	7.17 7.25	14.23 14.17	89	5×10^{-6}
IIc	O	H	$(CH_2)_3N(C_2H_5)_2$	77–78[a]	$C_{20}H_{25}N_3O$	74.27 74.47	7.79 7.74	12.99 13.13	82	2×10^{-6}
IId	O	H	CH_3	207–208[b]	$C_{14}H_{12}N_2O$	74.99 74.75	5.38 5.51	12.49 12.60	15	
XIV	H_2	H	H	196.5–201 dec.[b]	$C_{13}H_{12}N_2$	79.35 79.56	6.50 6.16	14.28 14.37	84	9×10^{-5}
Va	H_2	H	$(CH_2)_2N(C_2H_5)_2 \cdot 2HCl$	199.5–200.5 dec.	$C_{19}H_{27}Cl_2N_3$	61.95 62.18	7.37 7.20	11.41 11.83	93	2×10^{-6}
Vb	H_2	H	$(CH_2)_3N(CH_3)_2 \cdot 2HCl$	176–177 dec.	$C_{18}H_{25}Cl_2N_3$	61.01 60.23	7.11 7.11	11.86 11.45	87	1×10^{-4}
IIIb	O	$(CH_2)_2N(C_2H_5)_2$	H	132–133.5[c]	$C_{19}H_{23}N_3O$	73.75 73.60	7.49 7.07	13.58 13.64	90	4×10^{-5}
IIIa	O	$(CH_2)_3N(CH_3)_2$	H	149–150[c]	$C_{18}H_{21}N_3O$	73.19 72.62	7.17 6.94	14.23 14.80	52	
IIIc	O	$(CH_2)_3N(C_2H_5)_2$	H	117–119[c]	$C_{20}H_{25}N_3O$	74.27 74.02	7.79 7.63	12.99 13.49	67	4×10^{-4}
VIb	H_2	$(CH_2)_2N(C_2H_5)_2 \cdot 2HCl$	H	221.5–223[d]	$C_{19}H_{27}Cl_2N_3$	61.95 61.83	7.39 7.45	11.41 11.11	76	5×10^{-5}
VIa	H_2	$(CH_2)_3N(CH_3)_2$	H	100.5–102[d]	$C_{18}H_{23}N_3$	76.83 76.78	8.24 7.90	14.93 15.03	77	3×10^{-4}
VIc	H_2	$(CH_2)_3N(C_2H_5)_2$	H	81–83[d]	$C_{20}H_{27}N_3$	77.62 77.47	8.80 8.39	13.58 13.38	87	7×10^{-5}
XVI	O	$(CH_2)_2NO(C_2H_5)_2$	H	165 dec.[e]	$C_{19}H_{23}N_3O_2$	70.13 69.66	7.12 7.16	12.91 12.77	44	
XV	O	$(CH_2)_3NO(CH_3)_2$	H	184.5–185.5[d]	$C_{18}H_{21}N_3O_2$	69.43 69.28	6.80 6.95	13.50 13.20	0	
IVa	O	$(CH_2)_2N(C_2H_5)_2 \cdot CH_3I$	CH_3	219.5–221[b]	$C_{21}H_{28}N_3IO$	54.20 54.30	6.06 6.07	9.02 8.88	63	4×10^{-4}
IVb	O	$(CH_2)_2N(C_2H_5)_2$	$(CH_2)_3N(CH_3)_2$	109–111.5					86	1×10^{-4}

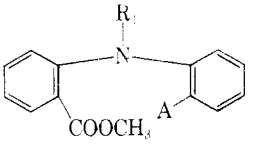
[a] Crystallized from methyl cyclohexane. [b] From 2-propanol. [c] From methanol. [d] From acetone. [e] All compounds prepared had satisfactory infrared spectra. [f] Pseudocholinesterase activity was measured by the manometric technique using human serum as a source of enzyme, a buffer consisting of 0.15 *M* NaCl, 0.04 *M* $MgCl_2$, and 0.025 *M* $NaHCO_3$, and acetylcholine at a concentration of 10^{-2} *M* as substrate.

5,10-Dihydro-11H-dibenzo[*b*,*e*][1,4]diazepin-11-one (I).—Methyl N-(*o*-aminophenyl)anthranilate (XI) (169.4 g.; 0.70 mole) was placed in a 500 ml., three-necked, round-bottomed flask provided with a mechanical stirrer, a short distillation condenser, and thermometer. The flask was heated in an oil bath. When the inside temperature was 180–200°, bubbles began to rise. After the oil bath had reached a temperature of 240–250° it was kept at this range for 1 hr. During this period, 26 ml. of liquid distilled and the dark reaction mixture became a semisolid mass. After cooling to room temperature, 100 ml. of ethanol (95%) was added and the lumps were crumbled with a spatula. The contents were transferred to a 1 l. erlenmeyer flask, ethanol (300 ml.) was added, and the mixture was heated on the steam bath for 15 min. with occasional swirling. After cooling to room temperature the solid was isolated by filtration. The material was triturated several times with ether (in total 1 l.) until no dark particles were present. The green-yellow product, dried *in vacuo* at 100°, weighed 126 g. (86%), m.p. 253–254°. Recrystallization of a small sample from pyridine gave a bright yellow compound melting at 254–255°.

10-(2-Diethylaminoethyl)-5,10-dihydro-11H-dibenzo[*b*,*e*][1,4]diazepine-11-one (IIa, $n = 2$, $R^3 = R^4 = C_2H_5$).—In a 1 l., three-necked, round-bottomed flask provided with a mechanical stirrer, reflux condenser, and thermometer were placed 31.5 g. (0.15 mole) of 5,10-dihydro-11H-dibenzo[*b*,*e*][1,4]diazepin-11-one (I) and 450 ml. of dioxane (distilled from $LiAlH_4$). The mixture was heated in an oil bath and after the compound had dissolved, 6.0 g. (0.154 mole) of sodium amide was added in small portions in the course of 1 hr. After the addition, the flask was heated to reflux temperature for 3.5 hr. During this period ammonia escaped and a white precipitate was formed. Then 20.4 g. (0.15 mole) of freshly distilled 2-diethylaminoethyl chloride was added dropwise at *ca.* 70° over a period of 30 min. The flask was heated to reflux temperature for 4 hr. The hot reaction mixture was filtered and the sodium chloride on the filter washed with a small amount of dioxane. The dioxane was removed *in vacuo* and the residue was dissolved in ether. Dilute hydrochloric acid was added carefully to the ether solution until the aqueous layer was slightly acid. The aqueous layer was separated, cooled, and transferred to another separatory funnel which was partly filled with ether. A potassium hydroxide solution was added until the aqueous layer remained basic. The ether solution was dried over anhydrous magnesium sulfate, filtered, and distilled. The residual oil was dissolved in ethyl acetate, treated with charcoal, and filtered. After distilling the solvent under reduced pressure an oil was obtained which soon crystallized (41.2 g., 88% yield). Two recrystallizations from isopropyl alcohol gave 31.0 g. (67% yield) of a white product, m.p. 132–133°.

TABLE II

DERIVATIVES OF METHYL N-PHENYLANTHRANILATE[a]



Compound	A	R_1	M.p., °C (uncor.)	Formula	Calcd. / Found C	H	N	Cl
X	NO_2	H	156–157	$C_{14}H_{12}N_2O_4$	61.76	4.44	10.29	
					61.90	4.79	10.46	
XIIb	NO_2	$(CH_2)_2N(C_2H_5)_2 \cdot HCl$	172.5–174	$C_{20}H_{26}ClN_3O_4$	58.89	6.43	10.30	
					58.61	6.43	10.52	
XIIa	NO_2	$(CH_2)_3N(CH_3)_2 \cdot HCl$	190–192	$C_{19}H_{24}ClN_3O_4$	57.90	6.14	10.65	9.00
					58.40	6.40	10.64	9.13
XIIc	NO_2	$(CH_2)_3N(C_2H_5)_2 \cdot HCl$	124–125.5	$C_{21}H_{28}ClN_3O_4$	59.78	6.69	9.96	
					59.50	6.71	10.14	
XI	NH_2	H	102–103	$C_{14}H_{14}N_2O_2$	69.40	5.81	11.56	
					69.10	5.60	11.50	
XIIIb	NH_2	$(CH_2)_2N(C_2H_5)_2 \cdot 2HCl$	192–193 dec.	$C_{20}H_{29}Cl_2N_3O_2$	57.97	7.05	10.12	17.11
					57.60	6.99	10.30	17.15
XIIIa	NH_2	$(CH_2)_3N(CH_3)_2 \cdot 2HCl$	205–206 dec.	$C_{19}H_{27}Cl_2N_3O_2$	57.10	6.79	10.50	17.72
					56.96	6.92	10.21	17.89
XIIIc	NH_2	$(CH_2)_3N(C_2H_5)_2 \cdot 2HCl$	199–200 dec.	$C_{21}H_{31}Cl_2N_3O_2$	58.80	7.30	9.82	
					58.61	7.42	9.69	

[a] All compounds prepared had satisfactory infrared spectra.

In a similar manner there were prepared the 10-(3-dimethylaminopropyl), the 10-(3-diethylaminopropyl) (IIc), and the 10-methyl (IId) compounds.

As indicated by n.m.r. studies, the amide hydrogen has been substituted. The parent compound showed, in addition to aromatic–hydrogen absorptions, an anilide–hydrogen absorption at 589 c.p.s. and an amine–hydrogen absorption at 470 c.p.s. The methylated compound IId showed the following absorptions: singlet at 206 c.p.s. (N-methyl hydrogens), doublet of doublets at 466, J_{ortho} = 8 c.p.s., J_{meta} = 1.5 c.p.s. (aromatic hydrogen adjacent to carbonyl split by *ortho* and *meta* neighbors), complex multiplet centered at about 431 c.p.s. (remaining aromatic hydrogens), broad singlet at 479 (the amine hydrogen). The disappearance of the anilide hydrogen absorption and the retaining of the amine hydrogen absorption after methylation was evidence that the methylation was at the anilide nitrogen.

The n.m.r. spectra were observed on a Varian DP-60 spectrometer operating at 60 Mc. on solutions (*ca.* 0.3 ml., *ca.* 0.15 *M*) of the samples in d_6-dimethyl sulfoxide. The spectra were calibrated against internal tetramethylsilane by the interpolation of audio-frequency side bands calibrated by a frequency counter. The precision of the $\Delta\nu$ is $>\pm 1$ c.p.s. The spectra were calibrated in c.p.s. downfield from tetramethylsilane to obviate the need for factoring unknown multiplets.

10,11-Dihydro-5H-dibenzo[*b*,*e*][1,4]diazepine (XIV).—In a 500-ml., three-necked, round-bottomed flask provided with a mechanical stirrer, a reflux condenser, and a gas inlet tube were placed 10.5 g. (0.05 mole) of 5,10-dihydro-11H-dibenzo[*b*,*e*][1,4]-diazepin-11-one (I) and 250 ml. of dry ether. The air in the flask was replaced by nitrogen. To the suspension was added, in the course of 60 min., 5.0 g. (0.13 mole) of lithium aluminum hydride. The mixture was refluxed for 30 hr. Then 50 ml. of *ca.* 2% sodium hydroxide was added dropwise with vigorous stirring. The solid was removed by filtration and transferred to a 1-l. erlenmeyer flask. Ether (200 ml.) was added and the mixture was heated with stirring for a few min. on the steam bath. The ether was removed and the undissolved solid again extracted twice with 200 ml. of ether. The combined ether solutions were shaken in a separatory funnel several times with a small amount of water until the aqueous layer remained colorless. The ether solution was dried and concentrated to *ca.* 100 ml. After cooling and filtering, 7.8 g. (80% yield) of a slightly yellow product was isolated. Recrystallization from isopropyl alcohol gave 6.0 g. (60% yield) of product. The white compound melted to a brown melt at 196.5–201°.

In similar fashion were prepared the 10-(2-diethylaminoethyl) and the 10-(3-dimethylaminopropyl) analogs. Since these compounds could not be crystallized, they were converted to their dihydrochlorides. This was done by dissolving the bases in absolute ethanol containing the exact amount of hydrogen chloride (*ca.* 0.5 *N*) for forming the dihydrochlorides. The clear solutions were placed in the refrigerator for several hours and during this time the dihydrochlorides precipitated. After filtering and drying *in vacuo* the compounds Va and Vb were analyzed. Compound Vb was hygroscopic and difficult to handle.

Methyl N-(3-Dimethylaminopropyl)-N-(*o*-nitrophenyl)anthranilate Hydrochloride (XIIc, n = 3, R^3 = R^4 = CH_3).—To a solution of 10.89 g. (40 mmoles) of methyl N-(*o*-nitrophenyl)anthranilate (X) in 120 ml. of toluene, dried by distillation and cooled to room temperature, was added 1.75 g. of 55% sodium hydride dispersion (40 mmoles of NaH). The mixture was stirred and slowly heated to reflux. Vigorous reaction set in. The mixture was refluxed for 3.5–4 hr., cooled, and 5.1 g. (42 mmoles) of freshly distilled 3-dimethyl-aminopropyl chloride in 25 ml. of dry toluene was added all at once. The solution was refluxed with stirring for 6 hr. and then stirred overnight at room temperature. To the cooled solution was added 25 ml. of water and cold 2 *N* hydrochloric acid until the mixture was acidic. The two layers were separated and the aqueous layer extracted twice more with toluene. If starting material crystallized out, it was filtered. The aqueous layer was made basic with potassium hydroxide solution and extracted thoroughly with ether. The ether layer was washed twice with water and once with saturated sodium chloride solution. The ether solution was dried over anhydrous magnesium sulfate, filtered, and the hydrochloride precipitated by the introduction of dry hydrogen chloride. This precipitate was recrystallized from 100 ml. of isopropyl alcohol to yield 4.5 g. of yellow to orange crystals, m.p. 187–190°. After one recrystallization from isopropyl alcohol, the melting point was 190–192°.

In similar fashion were prepared the monohydrochlorides of the N-(3-diethylaminoethyl) XIIb and the N-(2-diethylaminopropyl) XIIc analogs.

Methyl N-(3-Dimethylaminopropyl)-N-(*o*-aminophenyl)anthranilate Dihydrochloride (XIIIa, n = 3, R^3 = R^4 = CH_3).—A solution of 2.5 g. of methyl N-(3-dimethylaminopropyl)-N-(*o*-nitrophenyl)anthranilate hydrochloride (XIIa) in water was made basic with dilute potassium hydroxide solution and extracted with ether three times. The combined ether solutions were washed with water, dried with anhydrous sodium sulfate, and concentrated to yield 2.2 g. of the free base of starting material.

The base was dissolved in 50 ml. of absolute methanol and reduced at 50 lb. (22.5 kg.) pressure for 2 hr. in the presence of 2–3 ml. of Raney nickel emulsion. The pressure drop occurred

during the first 10–15 min. The mixture was filtered, concentrated to dryness, taken up in ether, and the ether solution dried with anhydrous magnesium sulfate. Introduction of dry hydrogen chloride precipitated the dihydrochloride (2.26 g.) which melted at 205–206° dec. after one recrystallization from 40 ml. of a 1:1 methanol–isopropyl alcohol mixture.

In similar fashion were prepared the dihydrochlorides of the diethylaminoethyl XIIIb and of the diethylaminopropyl XIIIc analogs.

5-(3-Dimethylaminopropyl)-5,10-dihydro-11H-dibenzo[*b*,*e*][1,4]diazepin-11-one (IIIa, n = 3, R^3 = R^4 = CH_3).—A solution of 3.07 g. of methyl N-(3-dimethylaminopropyl)-N-(*o*-aminophenyl)anthranilate dihydrochloride (XIIIa) was converted to the free base by treatment with aqueous KOH, followed by extraction with ether. The sirup, obtained upon removal of ether, was mixed with a small amount of powdered soft glass and heated from 120 to 155° over a period of 90 min. The mixture was partially dissolved in ether, filtered, and the ether solution concentrated to a small volume. Upon the addition of Skellysolve B, crystallization occurred; 360 mg., m.p. 144–145°. Trituration with ether raised the melting point to 147.5–149°.

A greatly increased yield (83%) was obtained by heating the base at 100° in methanol solution in an autoclave for 12 hr. to effect the ring closure. Concentration of the methanol solution followed by crystallization gave material melting at 149–150°.

Similarly the diethylaminoethyl IIIb and the diethylaminopropyl IIIc analogs were prepared.

5-(3-Dimethylaminopropyl)-5,10-dihydro-11H-dibenzo[*b*,*e*][1,4]diazepin-11-one N-Oxide (XV).—To a solution, cooled in ice, of 2.07 g. of 5-(3-dimethylaminopropyl)-5,10-dihydro-11H-dibenzo[*b*,*e*][1,4]diazepine-11-one (IIIa) in 13 ml. of 95% ethanol was added 1.5 ml. of 30% hydrogen peroxide. The solution was kept at room temperature for 2.5 days and any excess hydrogen peroxide decomposed at this time by stirring the solution with 135 mg. of 5% palladium-on-charcoal (washed with water) for 1 hr. at room temperature and 15 min. on the steam bath. The mixture was filtered and water (*ca.* 20 ml.) was added. The alcohol was removed under reduced pressure and the aqueous layer was concentrated to a sirup which was crystallized from acetone, 0.77 g., m.p. 174.5–178°. Recrystallization was effected by dissolving the crystals in methanol, removing the methanol to yield a sirup which was then crystallized from acetone, m.p. 184.5–185.5°.

The N-oxide XVI of 5-(diethylaminoethyl)-5,10-dihydro-11H-dibenzo[*b*,*e*][1,4]diazepin-11-one was similarly prepared; m.p. 165° dec.

5-(3-Dimethylaminopropyl)-10,11-dihydro-5H-dibenzo[*b*,*e*][1,4]diazepine (VIa, n = 3, R^3 = R^4 = CH_3).—A solution of 1.48 g. of 5-(3-dimethylaminopropyl)-11H-dibenzo[*b*,*e*][1,4]-diazepin-11-one (IIIa) and 290 mg. of lithium aluminum hydride in 150 ml. of anhydrous ether and 25 ml. of tetrahydrofuran (freshly distilled from $LiAlH_4$) was refluxed for 30 hr. To the cooled solution was added 4 ml. of 10% sodium hydroxide and the ether was decanted. The salts were washed twice with fresh ether and the combined ether solutions concentrated to give a sirup which crystallized. Crystallization from ether gave 800 mg. (3 crops), m.p. 95–96.5°. Recrystallization from acetone gave 600 mg., m.p. 100.5–102°.

In similar fashion the 2-diethylaminoethyl VIb and the 3-diethylaminopropyl VIc analogs were prepared. Compound VIb did not crystallize and was converted to its dihydrochloride in the usual way.

5-(2-Diethylaminoethyl)-5,10-dihydro-11H-dibenzo[*b*,*e*][1,4]diazepin-11-one 10-Methyl Methiodide (IVa).—To 3.09 g. (10 mmoles) of 5-(2-diethylaminoethyl)-11H-dibenzo[*b*,*e*][1,4]diazepin-11-one (IIIb) in 45 ml. of dry toluene was added 490 mg. of 52% sodium hydride dispersion in mineral oil (10.5 mmoles of NaH). The mixture was refluxed for 4 hr., cooled, and 4.75 g. (34 mmoles) of methyl iodide in 15 ml. of dry toluene was added. The mixture was refluxed for 14 hr., cooled, and 65 ml. of water was added. The mixture was shaken and the layers separated. The aqueous layer was re-extracted with toluene and freeze-dried to yield 4.5 g. of product. Crystallization from 70 ml. of hot isopropyl alcohol gave 3.05 g., m.p. 221.5–224°. Recrystallization from isopropyl alcohol gave an analytical sample, m.p. 219.5–221°.

5-(2-Diethylaminoethyl)-10-(3-dimethylaminopropyl)-5,10-dihydro-11H-dibenzo[*b*,*e*][1,4]diazepin-11-one Dihydrochloride [IVb, R^1 = $-CH_2CH_2N(C_2H_5)_2$, R^2 = $-CH_2CH_2CH_2N(CH_3)_2$].—To 9.27 g. (30 mmoles) of 5-(2-diethylaminoethyl)-5,10-dihydro-11H-dibenzo[*b*,*e*][1,4]diazepin-11-one (IIIb) in 80 ml. of toluene, dried by distillation, was added 1.48 g. of 52% sodium hydride dispersion in mineral oil (32 mmoles of NaH). The mixture was refluxed for 4 hr., cooled, and 4.02 g. (33 mmoles) of dimethylaminopropyl chloride in 12 ml. of dry toluene was added, followed by 10 ml. of distilled dimethylformamide. The mixture was refluxed for 6 hr., cooled to room temperature, diluted with 150 ml. water, and extracted with ether. The ether layer was washed with water, dried with anhydrous sodium sulfate, filtered, and concentrated to yield 11.5 g. of sirup. The sirup was taken up in anhydrous ether, dried thoroughly with magnesium sulfate, filtered in a dry room, and dry hydrogen chloride was introduced to yield a white fluffy powder, m.p. 109–111.5°. The material was very hygroscopic and a satisfactory analysis could not be obtained. The infrared spectrum, however, supports the proposed structure.

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Dihydroazepinone Chemistry. IV. 1-Aminoalkyl-1,3-dihydro-3,5,7-trimethyl-2H-azepin-2-ones[1a]

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The synthesis and pseudocholinesterase inhibitory activity of several 1-aminoalkyldihydroazepinones and certain related methiodides are described.

It has recently been discovered that the action of ethereal chloramine on hot solutions of sodium 2,6-dialkylphenoxides in excess 2,6-dialkylphenols results in facile ring enlargement of the phenoxide moieties to give 1,3-dihydro-2H-azepine-2-ones (I, R = lower alkyl; R^1 = H or lower alkyl) in good yield.[2] The ready availability of the dihydroazepinones in one step from commercially available phenols prompted examination of some potential applications of this unusual ring system to medicinal chemistry. During a program aimed at the exploitation of the chemistry of these novel and

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