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,  $\mathbb{R}^3 = \mathbb{R}^4 = \mathbb{CH}_3$ ).— 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 ng., 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-11Hdibenzo[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,  $\mathbb{R}^3 = \mathbb{R}^4 = \mathbb{CH}_3$ ).--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<sub>4</sub>) 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,  $\mathbf{R}^1 = -\mathbf{CH}_2\mathbf{CH}_2\mathbf{N}(\mathbf{C}_2\mathbf{H}_5)_2$ ,  $\mathbf{R}^2 = -\mathbf{CH}_2\mathbf{CH}_2\mathbf{CH}_2\mathbf{N}$ -(CH<sub>3</sub>)<sub>2</sub>].-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<sup>1a</sup>

## LEO A. PAQUETTE<sup>1b</sup> and Jack K. Reed

Research Laboratories of The Upjohn Company, Kalamazoo, Michigan

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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 2,6dialkylphenoxides 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;

(1) (a) Paper III: L. A. Paquette, J. Org. Chem., in press; (b) author to whom correspondence should be sent: Department of Chemistry, The Ohio State University, Columbus 10, Ohio.  $R^1 = H$  or lower alkyl) in good yield.<sup>2</sup> 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 <sup>(2)</sup> (a) L. A. Paquette, J. Am. Chem. Soc., **84**, 4987 (1962); (b) *ibid.*, **85**, 3288 (1963).



interesting, unsaturated, seven-membered heterocycles, we were led to prepare several aminoalkyl derivatives of I in an effort to obtain useful physiological activity.

In an earlier paper in this series,<sup>2b</sup> it was reported that treatment of the dihydroazepinone system I with sodium hydride in anhydrous dimethylformamide<sup>3</sup> produced an anion which, when alkylated with methyl iodide, afforded the corresponding N-methyl derivative. Utilization of this procedure with chloroalkyl amines has now been evaluated and found to produce 1-aminoalkyldihydroazepinones (see Table I) in good yield.

Several of these bases were converted with methyl iodide in absolute ethanol to their corresponding methiodides.

An alternate route to the title compounds was sought, with the purpose of obtaining an intermediate suitable for conversion in very few steps to a variety of 1-aminoalkyldihydroazepinones. Reaction of the sodium salt of I ( $R = R^1 = CH_3$ ) in dimethylformamide with 2chloroethylacetate gave the expected 1-(2-acetoxyethyl)-1,3-dihydro-3,5,7-trimethyl-2H-azepin-2-one (Ha).<sup>4</sup>



The related alcohol IIb, conveniently obtained by basic saponification of IIa, was converted to its noncrystalline tosylate IIc in the usual manner. Solvolysis of the crude tosylate in excess morpholine gave the same N-morpholinoethyl derivative (as its hydrochloride) that was produced by direct alkylation. The over-all yield of this sequence was only 20.3%, thus discouraging its further use as a method of choice for our intended purpose.

**Pharmacology.**—With the exception of compound IV, the 1-aminoalkyl-1,3-dihydro-3,5,7-trimethyl-2H-azepin-2-ones were found to be relatively potent inhibitors of pseudocholinesterase activity (Table II).<sup>5</sup> The inhibitory action of these compounds on this enzyme system is apparently of little specificity in this case, for no differentiation can be seen between compounds possessing gross stimulant effects and those showing depressant activity at nonlethal doses. Further, at nonlethal doses, mice did not exhibit signs of marked parasympathetic stimulation (salivation, lacrimation, urination, or defecation). It is worthy of note, however, that the majority of the substances described herein are quite toxic, showing approximate  $LD_{50}$ values of 56 mg./kg. i.p. or less.

## **Experimental**<sup>6</sup>

General Procedure for Alkylation.—To a stirred solution of 15.1 g. (0.10 mole) of 1,3-dihydro-3,5,7-trimethyl-2H-azepin-2one (I,  $\mathbf{R} = \mathbf{R}^1 = \mathbf{CH}_3$ )<sup>26</sup> in 100 ml. of dry dimethylformanide was added in several portions 4.65 g. (0.10 mole) of 51.5% sodium hydride-oil dispersion. The solution was heated at 60° for 45-60 min. when evolution of hydrogen had ceased and was then cooled to 5-10° with an ice bath. N-( $\beta$ -Chloroethyl)-morpholine [36.0 g. (0.12 mole) of a 50% by weight toluene solution] was added below 20°. When the addition was completed, the mixture was stirred at room temperature for 2.5-16 hr. The dimethylformamide was removed under reduced pressure, ether was added, and the precipitated sodium chloride was separated by filtration and washed well with additional ether. The combined ethereal filtrates were evaporated and the residual oil was dist.lled.

In the case of the 1-aminoalkyldihydroazepinones, the distilled liquid was then generally converted directly to its hydrochloride salt by treatment of an ethereal solution of the amine with ethereal hydrogen chloride.

The yields in Table I are based on the quantity of distilled base. The hydrochlorides were recrystallized from ethanolether to obtain pure samples.

General Procedure for Quaternary Salt Formation.—To a solution of 0.10 mole of the 1-aminoalkyldihydroazepinone in 65 ml. of absolute ethanol was added a 3-4 molar excess of methyl iodide. The resulting solution was refluxed for 3.5-4.5 hr. After cooling, the solvent was evaporated and the residue was recrystallized from ethanol-ether. Yields in Table II were based on the weight of product at this stage. Further recrystallizations of the methiodides from ethanol-ether gave the analytical samples.

1-(2-Acetoxyethyl)-1,3-dihydro-3,5,7-trimethyl-2Hazepin-2-one (IIa).-To a solution of 30.2 g. (0.20 mole) of I  $(R = R^1 = CH_3)$  in 150 ml. of anhydrous dimethylformamide was added in portions 9.4 g. (0.20 mole) of 51.5% sodium hydrideoil dispersion. The solution was stirred at 60° for 0.5 hr., cooled to  $-5^{\circ}$ , and treated dropwise with 30.6 g. (0.25 mole) of chloroethyl acetate below 0°. The reaction mixture was allowed to warm to room temperature and kept there overnight. Ether (200 ml.) was added, and the precipitated inorganic solids were separated by filtration and washed well with ether. The combined filtrates were evaporated under reduced pressure and the residue was carefully distilled to give 11.2 g. of recovered I [crystalline distillate, b.p. 105-112° (0.25 mm.), m.p. 132-133°] and 18.1 g. (60.6% based on recovered I) of the acetate IIa, b.p. 116–120° (0.25 mm.), n<sup>26</sup>D 1.5018. Redistillation of this material for analysis gave a colorless liquid, b.p. 133–134° (0.4 mm.),  $n^{26}{\rm D}$ 1.4998;  $\nu^{\text{neat}}$  1745 (ester carbonyl) and 1675 cm.<sup>-1</sup> (amide carbonyl);  $\lambda_{\text{max}}^{\text{EtoH}}$  251 mu (4900).

Anal. Calcd. for  $C_{13}H_{19}NO_3$ : C, 65.80, H, 8.07; N, 5.90. Found: C, 65.89; H, 8.03; N, 5.99.

1-(2-Hydroxyethyl)-1,3-dihydro-3,5,7-trimethyl-2H-azepin-2-one (IIb).—To a solution of 11.9 g. (0.05 mole) of the

<sup>(3)</sup> It is important to note that we have been unable to produce this anion with such reagents as sodium ethoxide in ethanol or sodium amide in liquid ammonia.

<sup>(4)</sup> A similar study was made on the use of 2-bromoethyl acetate as the source of the acetoxyethyl group. In all runs, a near quantitative yield of sodium bromide was obtained, accompanied by excellent recovery quantities of the dihydroazepinone. The reaction, which was rapid, probably proceeded by an E2 elimination of hydrogen bromide to afford vinyl acetate (which we did not attempt to isolate).

<sup>(5)</sup> Pseudocholinesterase activity was determined manometrically utilizing various inhibitor concentrations. The enzyme source was human serum and acetylcholine  $(10^{-1} M)$  was the substrate. [I]<sub>30</sub> values were estimated graphically. Compounds listed as inactive did not inhibit at least 50% at  $10^{-3} M$ .

<sup>(6)</sup> Melting points and boiling points are corrected. The authors are indebted to the Physical and Analytical Chemistry Department of The Upjohn Co. under the direction of Dr. Donald R. Myers for the microanalyses and spectral data.

I	
TABLE	

1-Aminoalkyl-1,3-dihydro-3,5,7-yrimethyl-2h-azepin-2-ones



, % Found	$10.20 \\ 9.99$	9.76	9.08	9.39	9.47	8.99	8.65	6.95	6.80	6.50
Nitrogen, Caled.	10.27 9.77	9.84	9.31	9.65	9.38	8.96	8.96	6.90	7.18	6.48
en, % Found	$9.34 \\ 9.44$	8.81	8.26	10.37	9.04	8.93	9.53	6.26	7.65	7.93
Hydrog Caled.	$\begin{array}{c} 9.24 \\ 9.49 \end{array}$	8.85	8.38	10.41	9.11	9.34	9.34	6.70	6.97	7.70
on, % Found	61.91 63.05	63.43	59.62	74.07	64.13	64.89	65.04	46.94	49.45	52.83
Carb Caled.	61.63 62.80	63.25	59.88	74.43	64.30	65.26	65.26	47.29	49.23	52.78
Pormula	C14H25CIN2() C15H27CIN2()	$C_{15}H_{25}CIN_2()$	$\mathrm{C_{15}H_{25}ClN_2O_2}$	$C_{15}H_{30}N_{2}O$	$C_{16}H_{zr}CIN_2O$	$\mathrm{C}_{\mathrm{I7}}\mathrm{H}_{29}\mathrm{CIN}_{2}\mathrm{O}$	CITH29CIN20	C16H271N2()2	$C_{16}H_{27}IN_2O$	C <sub>19</sub> H <sub>33</sub> IN <sub>2</sub> ()
M.p. of HCl salt, °C.	169-169.5 159-160	197-198	222-224	Not cryst.	247-249	171-173	172-173	218-219 dec.	180-182	861-761
Yield, %	$21.2 \\ 86.5$	73.4	78.2	92.2	91.7	63.3	85.9	75.0	72.3	11.0
B.p. of base, °C. (mn.)	121-127(0.3) 123(0.3)	$126 - 138\left(0.13 ight)$	$150 - 158 \left( 0.15  ight)$	136-147 (0.2)	$129 - 150\left(0.3 ight)$	146 - 151(0.15)	$136 - 164\left(0.20 ight)$			
ж	$-(\operatorname{CH}_2)_2 \operatorname{N}(\operatorname{CH}_3)_2$ $-(\operatorname{CH}_2)_2 \operatorname{N}(\operatorname{C}_2 \operatorname{H}_3)_2$	(CH <sub>2</sub> ) <sub>2</sub> N	$-(CH_2)_{kN}$	~(CH <sub>3</sub> ) <sub>M</sub> CH <sub>3</sub> CH <sub>3</sub>	-CH <sub>2</sub> CHN CH <sub>3</sub> CHN	(CH <sub>2</sub> h <sub>A</sub> N)	-CH <sub>2</sub> CH <sub>2</sub> N	$-CH_2CH_2 \stackrel{+}{} N 0 I^-$	$-CH_2CH_2 \pm N \int CH_3$ I	$-CH_2CH_2 \xrightarrow{+}_{H_3C} CH_3$ $I \xrightarrow{-}_{H_3C} CH_3$
Compound	II	III	IV	Λ	IA	ΝI	VIII	XI	X	IX

TABLE 11

Compound	Approximate LD <sub>60</sub> mg., kg. l.p., mouse <sup>a</sup>	Pseudocholm esterase 1748 - M	$\frac{\text{Other}}{\text{actions}^{h}}$
I	56	$5  imes 10^{-1}$	Depressant
II	56	$8 \times 10^{-5}$	
111	56	$1 \times 10^{-1}$	
IV	562		Depressant
$\mathbf{V}_{i}$	1000	$2 \times 10^{-1}$	$\mathbf{s}$ timulant
V1	75	$3 imes 10^{-5}$	$\mathbf{s}$ timulant
V11	56	$3 \times 10^{-2}$	
VHI	56	$3 imes 10^{-5}$	
1.N	56	$5 \times 10^{-1}$	
X	42	$2 \times 10^{+1}$	Stimulant
ХI	24	$3 \times 10^{-1}$	

"Toxicity was determined in groups of 4 albino mice per dose utilizing doses decreasing in 0.5 log intervals from 4000 mg./kg. (intraperitoneal route). The LD<sub>a0</sub> was estimated by the method of Spearman and Karber and the 95% confidence intervals are approximately  $\pm 0.3$  log units. Observations of the effects of these compounds on behavior were carried out simultaneously with the determination of toxicity. "All compounds caused convulsions in lethal doses: the observations in this column apply to effects seen at nonlethal doses.

acctate 11a in 75 ml. of ethanol was added a solution of 2.4 g. (0.06 mole) of sodium hydroxide in 15 ml. of water. The solution was stirred under reflux for 2 hr. and at room temperature overnight. The solvent was removed under reduced pressure and the residue was taken up in methylene chloride and a small amount of water. The water layer was separated and the organic layer was dried, filtered, and evaporated. The residue was distilled to give 8.8 g,  $(90.7^{+}v)$  of a colorless viscous oil, b.p.  $132^{-}134^{++}0.30^{-}$ 0.35 mm,  $v_{\rm e}$  A sample of liquid, b.p.  $134^{++}0.35$  mm,  $v_{\rm e}\approx 0.1.5265^{-}$ , was submitted for analysis:  $v^{\rm rec}/3420$  (OH stretching) and  $1665^{-}$  cm,  $v^{+}$  (unide earbory).

Anal. Caled. for  $C_{11}H_{17}NO_2(=C, -67.66)$ ; H, 8.78); N, 7.17. Found: C, 67.33; H, 8.89; N, 6.94.

Alternate Preparation of 1-(2-Morpholinoethyl)-1,3-dihydro-3,5,7-trimethyl-2H-azepin-2-one Hydrochloride via Hc. An ice-cold solution of 4.9 g, (0.025 mole) of Hb in 35 ml, of pyridine was treated with 5.35 g, (0.025 mole) of p-toluenesulfonyl chloride in several pertions. The resulting solution was stored at 5<sup>+</sup> for 2 days. Lee water (300 ml.) was added and, after standing at 5<sup>o</sup> for 2 hr, the aqueous solution was extracted with other. The combined ether layers were washed with cold X hydrochloric acid, dried, filtered, and evaporated. The residual oil, which did not crystallize, was used without further purification.

The crude tosylate from this was dissolved in 10 mL of morpholine and the solution was allowed to stand overnight at room temperature. Crystals had separated: ether was added, and the precipitated solid was separated by filtration. The filtrate was evaporated under reduced pressure and the residual oil was converted to its hydrochloride, 1.34 g,  $(20.3)_{\pm}$  over-all), m.p. 219– 223° dec. The infrared spectrum of this material was identical with that of the sample prepared by the alternate route. A mixture melting point showed no depression.

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# Synthesis of Unsymmetrical Diphenylalkenes<sup>1</sup>

JEAN-FRANÇOIS MIQUEL,<sup>2</sup> HANS WÅHLSTAM, KNUT OLSSON, AND BERTH SUNDBECK

Institute of Pharmacology, Uppsala University, Uppsala, and Research Laboratory, AB Ferrosan, Malmo, Sweden

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Bis-(p-methoxyphenyl)-alkenes have been prepared by action of the Grignard reagent from p-bromoanisole on the esters of carboxylic acids. In the same manner using cycloalkanecarboxylic acids some bis-(p-methoxyphenyl)-cycloalkylidene methanes have also been prepared. Their demethylation by potassium hydroxide triethyleneglycol was in several cases accompanied by the formation of the ethane derivatives. Ultraviolet absorption data are discussed.

The present tendency in steroid hormone research is to look for substances with a more specific action on different tissues or organs.<sup>3</sup> Surprisingly little has been done in this respect with synthetic estrogens belonging to the stilbestrol-hexestrol series. This is probably due to the fact that interest in these substances was particularly high at a time when it was necessary to discover inexpensive and potent estrogenic substances.

An investigation of the specific action of hexestrol and stilbestrol analogs on different biological receptors was therefore decided on in our Institutions. Several results have already been presented.<sup>4,5</sup> This report concerns the synthesis of diphenols, their ethers, and esters belonging to the class of *unsym*-diphenylethylene. Some substances from this series have already been found to possess the ability to interfere with the vaginal estrus reaction induced by estradiol benzoate.<sup>6</sup> Their relations to diethylstilbestrol and trianisylethylene, in terms of spatial structure, have also been discussed.<sup>7</sup>

All eighteen compounds were synthesized by the same method, by reaction of *p*-methoxyphenylmagnesium bromide with esters. The methyl or ethyl esters, which are all known compounds, were prepared from the corresponding acids by way of the acid chlorides. The following were not commercially available: 2,3-dimethylbutanoic acid, <sup>5</sup> 2-ethylpentanoic acid, <sup>9</sup> 2-methyl-4-pentenoic acid, <sup>10</sup> 2-methylhexanoic acid, <sup>9</sup> 2-butylhexanoic acid, <sup>11</sup> cycloheptanecarboxylic acid, <sup>12</sup> and cyclooctanecarboxylic acid, <sup>12</sup> Of these, the two cyclic

For the previous paper in this series see J. F. Miquel, Bull, Soc. Chim. France, 239 (1962).

<sup>(2)</sup> École Nationale Supérieure de Chimie, Université de Montpellier, France.

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