was warmed to 60° for 30 min, filtered, and vacuum evaporated to an oil. The oil was slurried in 150 ml of saturated salt solution, extracted with ethyl acetate, dried with Drierite, and vacuum evaporated to an oil (10.7 g) which was slow to crystallize. The solid material was recrystallized from ether: uv λ_{max} 241 mμ (ethanol).

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Agents Acting on the Central Nervous System. X. 1-Substituted 3-Phenyl-2,3,4,5-tetrahydro-1H-1-benzazepines

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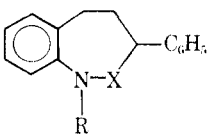
In view of the clinically useful CNS activity of dibenzazepines,[1] the synthesis of 1-substituted 3-phenyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-ones (I) and 1-substituted 3-phenyl-2,3,4,5-tetrahydro-1H-1-benzazepines (II) has been carried out. 2-Phenyl-1-tetralone[2] on treatment with HN_3 gave 3-phenyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (Ia). The structure of Ia was confirmed by hydrolysis to 2-phenyl-4-(2-aminophenyl)butyric acid, followed by deamination, when α,γ-diphenylbutyric acid was obtained. 3-Phenyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (Ia) on reduction with $LiAlH_4$ gave 3-phenyl-2,3,4,5-tetrahydro-1H-1-benzazepine (IIa). Ia and IIa on treatment with NaH and the appropriately substituted halides gave Ib, Ic, IIb and IIc, respectively. IIa on treatment with NaCNO and CH_3COOH gave the corresponding carbamoyl derivative (IId), while condensation with $ClCH_2COCl$ gave the chloroacetyl compound (IIe) which on condensing with 4-(β-hydroxyethyl)piperazine followed by $LiAlH_4$ reduction gave IIg.



I, X = CO
II, X = CH_2

a, R = H
b, R = $(CH_2)_2N(C_2H_5)_2$
c, R = $(CH_2)_3N(C_2H_5)_2$
d, R = $CONH_2$
e, R = $COCH_2Cl$
f, R = $COCH_2N$⟨⟩$N(CH_2)_2OH$
g, R = $(CH_2)_2N$⟨⟩$N(CH_2)_2OH$

Biological Activity.—The methods used for screening have been described earlier. Except for 1-(γ-diethylaminopropyl)-3-phenyl-2,3,4,5-tetrahydro-1H-1-benzazepine and 1-β-[4-(β-hydroxyethyl)piperazinyl]ethyl-3-phenyl-2,3,4,5-tetrahydro-1H-1-benzazepine, none of the compounds showed any significant effect on the central nervous or cardiovascular systems nor did any of the compounds show any diuretic or hypoglycemic activity. 1-(γ-Diethylaminopropyl)-3-phenyl-2,3,4,5-tetrahydro-1H-1-benzazepine (IIc) at 16 mg/kg ip (LD_{50} (mice) 82 mg/kg ip) counteracted amphetamine toxicity, while 1-β-[4-(β-hydroxyethyl)piperazinyl]-ethyl-3-phenyl-2,3,4,5-tetrahydro-1H-1-benzazepine at 17 mg/kg ip (LD_{50} (mice) 86 mg/kg ip) gave protection against maximal electroshock seizures and antagonized the action of 5-hydroxytryptamine on isolated guinea pig ileum up to a concentration of 10^{-6} g/ml.

Experimental Section[3]

3-Phenyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (Ia).—Concentrated H_2SO_4 (3 ml) was added dropwise to a stirred mixture of 2-phenyl-1-tetralone (2.22 g, 0.01 mole), AcOH (12 ml), and NaN_3 (1.30 g, 0.02 mole) at 50–60°, and stirring was continued for 2 hr after the completion of the addition. The reaction mixture was then poured onto crushed ice (200 g), the product which separated was filtered, washed with ice-cold aqueous ethanol (50%), and crystallized from benzene–petroleum ether (bp 40–60°); mp 192–194°, yield 1.42 g (60%).

Anal. Calcd for $C_{16}H_{15}NO$: C, 81.01; H, 6.32; N, 5.90. Found: C, 81.08; H, 6.42; N, 5.48.

γ-(o-Aminophenyl)-α-phenylbutyric Acid Hydrochloride.—A mixture of Ia (2.37 g, 0.01 mole) and 6 *N* HCl (100 ml) was refluxed for 4 hr, cooled, and filtered. The filtrate on concentration gave a colorless crystalline product which was recrystallized from ethanol–ether; mp 200°, yield 2.56 g (95%).

Anal. Calcd for $C_{16}H_{17}NO_2 \cdot HCl$: C, 65.86; H, 6.17; N, 4.80. Found: C, 65.49; H, 6.49; N, 5.20.

α,γ-Diphenylbutyric Acid.—A solution of γ-(o-aminophenyl)-α-phenylbutyric acid hydrochloride (2.91 g, 0.01 mole) in 6 *N* HCl (15 ml) was treated below 20° with $NaNO_2$ (1.38 g, 0.02 mole). $CuSO_4$ (0.04 g) and ethanol (25 ml) were added to the diazonium salt solution and the mixture was heated at 60–70° for 30 min, then cooled, and extracted with ethyl acetate. The extract was dried (Na_2SO_4) and the solvent was removed. The residue was crystallized from benzene–petroleum ether; mp and mmp (with authentic sample of α,γ-diphenylbutyric acid) 70° (lit.[2] mp 72°).

3-Phenyl-2,3,4,5-tetrahydro-1H-1-benzazepine (IIa).—A solution of Ia (2.37 g, 0.01 mole) in dry tetrahydrofuran (THF) (75 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (0.95 g, 0.025 mole) in dry THF (25 ml). The mixture was stirred and refluxed for 12 hr and cooled and the excess $LiAlH_4$ was decomposed by addition of ethyl acetate followed by water. The reaction mixture was extracted with ethyl acetate, the extract was dried (Na_2SO_4), the solvent was removed, and the residue was crystallized from benzene–petroleum ether; mp 124°, yield 1.88 g (75%).

Anal. Calcd for $C_{16}H_{17}N$: C, 86.09; H, 7.62; N, 6.27. Found: C, 86.37; H, 8.04; N, 6.59.

Hydrochloride, from ethanol–ether, colorless needles, mp 217–218°.

Anal. Calcd for $C_{16}H_{17}N \cdot HCl$: C, 73.98; H, 6.93; N, 5.39. Found: C, 74.14; H, 7.01; N, 5.35.

1-(β-Diethylaminoethyl)-3-phenyl-2,3,4,5-tetrahydro-1H-1-benzazepine (IIb).—A mixture of IIa (2.23 g, 0.01 mole) and NaH (1 g, 50%) in dry dioxane (15 ml) was refluxed for 1 hr and cooled. To this a solution of β-diethylaminoethyl chloride (1.35 g, 0.01 mole) in dry toluene (5 ml) was added and the mixture was refluxed for 1 hr, cooled, and filtered. The filtrate was evaporated to dryness under reduced pressure, the residue was extracted with ether, the ether solution in turn was extracted with 1 *N* H_2SO_4, the acidic layer was made alkaline, the liberated base was taken up in ether, the ether solution was dried (Na_2SO_4), and the solvent was removed. The residue was chromatographed

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(3) Melting points were recorded in a bath.

on basic alumina (grade I) using benzene as the eluent when the desired product was obtained as a pale yellow viscous oil; yield 3.0 g (95%).

Anal. Calcd for $C_{22}H_{30}N_2$: C, 81.98; H, 9.31; N, 8.69. Found: C, 82.02; H, 9.44; N, 8.43.

Oxalate, colorless crystals from ethanol; mp 138–140°.

Anal. Calcd for $C_{22}H_{30}N_2 \cdot (COOH)_2$: C, 69.90; H, 7.76; N, 6.79. Found: C, 69.62; H, 8.08; N, 6.34.

1-(β-Diethylaminoethyl)-3-phenyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (Ib).—Ia (1.18 g, 0.005 mole) on treatment with NaH (0.48 g, 50%) and β-diethylaminoethyl chloride (0.67 g, 0.005 mole), under the conditions described above for IIb, gave Ib as a pale yellow liquid, yield 1.0 g (60%).

Anal. Calcd for $C_{22}H_{28}N_2O$: C, 78.57; H, 8.33; N, 8.33. Found: C, 78 50; H, 8.98; N, 8.74.

1-(γ-Diethylaminopropyl)-3-phenyl-2,3,4,5-tetrahydro-1H-1-benzazepine (IIc) was obtained in a similar manner from IIa (3.34 g, 0.015 mole), NaH (1.5 g, 50%), and γ-diethylaminopropyl chloride (2.99 g, 0.02 mole) as a pale yellow oil; yield 3.27 g (65%).

Anal. Calcd for $C_{23}H_{32}N_2$: C, 82.14; H, 9.52; N, 8.33. Found: C, 81.84; H, 9.83; N, 7.92.

Oxalate, colorless leaflets from ethanol; mp 130–132°.

Anal. Calcd for $C_{23}H_{32}N_2 \cdot (COOH)_2$: N, 6.57. Found: N, 6.75.

1-Carbamoyl-3-phenyl-2,3,4,5-tetrahydro-1H-1-benzazepine (IId).—A mixture of IIa (1.11 g, 0.005 mole) and NaCNO (0.65 g, 0.01 mole) in AcOH (15 ml) was stirred for 3 hr at 50–60°, cooled, and poured into water. The product which separated was collected on a filter and crystallized from benzene–petroleum ether (bp 60–80°) as colorless shining plates, mp 202°, yield 1.19 g (90%).

Anal. Calcd for $C_{17}H_{18}N_2O$: C, 76.69; H, 6.76; N, 10.52. Found: C, 77.01; H, 6.87; N, 10.29.

1-(Chloroacetyl)-3-phenyl-2,3,4,5-tetrahydro-1H-1-benzazepine (IIe).—A mixture of IIa (2.23 g, 0.01 mole), chloroacetyl chloride (1.13 g, 0.01 mole), and K_2CO_3 (2 g) in dry xylene (50 ml) was refluxed for 3 hr. The reaction mixture was filtered and the filtrate was evaporated under reduced pressure. The residue on crystallization from benzene–petroleum ether gave IIe as colorless crystals, mp 155–157°, yield 2.69 g (95%).

Anal. Calcd for $C_{18}H_{18}ClNO$: C, 72.12; H, 6.01; N, 4.57. Found: C, 72.31; H, 6.23; N, 4.86.

1-[4-(β-Hydroxyethyl)piperazinyl]acetyl-3-phenyl-2,3,4,5-tetrahydro-1H-1-benzazepine (IIf).—A mixture of IIe (2.99 g, 0.01 mole), 4-(β-hydroxyethyl)piperazine (2.6 g, 0.02 mole), and dry benzene (50 ml) was refluxed for 20 hr, cooled, and filtered. The filtrate was extracted with 3 *N* HCl and the acidic extract was made alkaline with Na_2CO_3 solution. The product which separated was taken up in ether, the ether extract was washed with water and dried (Na_2SO_4), and the solvent was removed. IIf was obtained as a thick viscous liquid and was purified by chromatography on basic alumina (grade I) using benzene as the eluent; yield 3.33 g (85%).

Anal. Calcd for $C_{24}H_{31}N_3O_2$: C, 73.28; H, 7.88; N, 10.69. Found: C, 73.42; H, 8.21; N, 10.40.

Hydrochloride, colorless needles from ethanol–ether; mp 155–157°.

Anal. Calcd for $C_{24}H_{31}N_3O_2 \cdot 2HCl$: C, 61.80; H, 7.08; N, 9.01. Found: C, 61.62; H, 7.41; N, 9.23%.

1-β-[4-(β-Hydroxyethyl)piperazinyl]ethyl-3-phenyl-2,3,4,5-tetrahydro-1H-1-benzazepine (IIg).—IIf (3.93 g, 0.00 mole) in dry THF (50 ml) was reduced with $LiAlH_4$ (1.90 g, 0.05 mole) in dry THF (25 ml), as described above, to give II g as a pale yellow viscous oil; yield 3.31 g (90%).

Anal. Calcd for $C_{24}H_{33}N_3O$: C, 75.99; H, 8.70; N, 11.08. Found: C, 76.18; H, 9.00; N, 10.81.

Hydrochloride, colorless crystals from ethanol–ether; mp 150–155° (hygroscopic); **picrate**, pale yellow needles from ethanol; mp 235–238°.

Anal. Calcd for $C_{24}H_{33}N_3O \cdot C_6H_3N_3O_7$: N, 13.81. Found: N, 13.62.

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Amides and Esters of Benzo[*b*]thiophene-2-carboxylic Acid[1]

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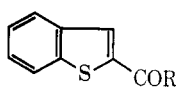
Many of the clinically efficacious local anesthetics are dialkylaminoalkylamides and dialkylaminoalkyl esters of a variety of carboxylic acids.[2] In this laboratory there has been considerable interest in the synthesis and pharmacological evaluation of compounds possessing the benzo[*b*]thiophene nucleus,[1,3] which has resulted in the preparation of some amides and esters of benzo[*b*]thiophene-2-carboxylic acid[4] (I) of structure II.



II

A related series of dialkylaminoalkyl esters of I have been claimed to be useful as hypotensive, antiviral, and antifungal agents,[5] as have some benzo[*b*]thiophene-2-carboxamides.[6] The isosterically related dialkylaminoalkyl esters of indole-2-carboxylic acid have been shown to possess local anesthetic activity,[7] while some indole-2-carboxamides demonstrated hypotensive activity.[8] The isoelectronically related dialkylaminoalkyl esters of 2-naphthoic acid were reported to exhibit local anesthetic activity.[9] Physical constants of the compounds prepared are recorded in Table I.

The amides and esters of I were prepared by converting I to benzo[*b*]thiophene-2-carbonyl chloride (III)[10] and subsequently treating each of six amines or alcohols dissolved in benzene with 1 equiv of III. The products were isolated as amine hydrochlorides. 1-(2-Benzo[*b*]thenoyl)-4-methylpiperazine (VII) was prepared *via* a Schotten–Baumann reaction.[11]

Pharmacology.—Topical local anesthesia was assayed by the rabbit corneal test. The conjunctival sac was instilled with 0.25 ml of 2% test solution and lidocaine hydrochloride (2%) was used as the standard.

(1) Contribution No. 1434. Part X in the series of Benzo[*b*]thiophene Derivatives. For part IX see E. Campaigne, T. Bosin, and E. S. Neiss, *J. Med. Chem.*, **10**, 270 (1967). Taken from the thesis to be submitted by T. Bosin to Indiana University for the Ph.D. degree.

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