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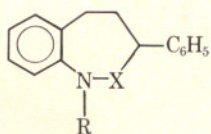
Agents Acting on the Central Nervous System. X. 1-Substituted 3-Phenyl-2,3,4,5-tetrahydro-1H-1-benzazepines

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In view of the clinically useful CNS activity of dibenzazepines, 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-tetralone² on treatment with HN₃ 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 LiAlH₄ 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 CH₃COOH gave the corresponding carbamoyl derivative (IId), while condensation with ClCH₂COCl gave the chloroacetyl compound (IIe) which on condensing with 4-(β -hydroxyethyl)piperazine followed by LiAlH₄ reduction gave IIg.



I, X = CO
II, X = CH₂

- a, R = H
- b, R = (CH₂)₂N(C₂H₅)₂
- c, R = (CH₂)₃N(C₂H₅)₂
- d, R = CONH₂
- e, R = COCH₂Cl
- f, R = COCH₂N(CH₂)₂N(CH₂)₂OH
- g, R = (CH₂)₂N(CH₂)₂N(CH₂)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

(LD₅₀ (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 (LD₅₀ (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 Section³

3-Phenyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (Ia).—Concentrated H₂SO₄ (3 ml) was added dropwise to a stirred mixture of 2-phenyl-1-tetralone (2.22 g, 0.01 mole), AcOH (12 ml), and NaN₃ (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 C₁₆H₁₅NO: 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 C₁₆H₁₇NO₂·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 NaNO₂ (1.38 g, 0.02 mole). CuSO₄ (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 (Na₂SO₄) 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 LiAlH₄ (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 LiAlH₄ was decomposed by addition of ethyl acetate followed by water. The reaction mixture was extracted with ethyl acetate, the extract was dried (Na₂SO₄), the solvent was removed, and the residue was crystallized from benzene–petroleum ether; mp 124°, yield 1.88 g (75%).

Anal. Calcd for C₁₆H₁₇N: 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 C₁₆H₁₇N·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 H₂SO₄, the acidic layer was made alkaline, the liberated base was taken up in ether, the ether solution was dried (Na₂SO₄), and the solvent was removed. The residue was chromatographed

(1) R. Kuhn, *Schweiz. Med. Wochschr.*, **87**, 1135 (1957).
(2) M. S. Newman, *J. Am. Chem. Soc.*, **60**, 2949 (1938).

(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 $C_{22}H_{30}N_2O$: 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 $C_{24}H_{31}N_5O_2$: 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 $C_{24}H_{31}N_5O_2 \cdot 2HCl$: 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 IIg as a pale yellow viscous oil; yield 3.31 g (90%).

Anal. Calcd for $C_{24}H_{33}N_5O$: 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 $C_{24}H_{33}N_5O \cdot C_6H_5N_3O_7$: N, 13.81. Found: N, 13.62.

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