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.

Acknowledgment.—We are grateful to Riker Laboratories, Northridge, California, for making available the screening results and gifts of chemicals and to Mr. J. Saran and his associates for microanalysis.

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

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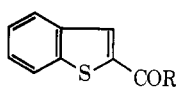
Many of the clinically efficacious local anesthetics are dialkylaminoalkylamides and dialkylaminoalkyl esters of a variety of carboxylic acids.[2] In this laboratory there has been considerable interest in the synthesis and pharmacological evaluation of compounds possessing the benzo[*b*]thiophene nucleus,[1,3] 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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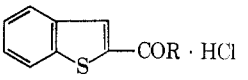
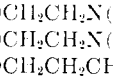
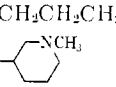
TABLE I
AMIDE AND ESTER HYDROCHLORIDES OF BENZO[*b*]THIOPHENE-2-CARBONYLIC ACID



Compd	R	Purified yield, %[b]	Mp, °C	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Nitrogen, % Calcd	Nitrogen, % Found
I	$OCH_2CH_2N(CH_3)_2$	45 (A)	187–188	$C_{13}H_{16}ClNO_2S$	54.60	54.43	5.66	5.91	4.91	5.19
II	$OCH_2CH_2N(C_2H_5)_2$	18 (B)	153–154	$C_{15}H_{20}ClNO_2S$	57.45	57.51	6.42	6.60	4.46	4.40
III	$OCH_2CH_2CH_2N(CH_3)_2$	65 (C)	200–201	$C_{14}H_{18}ClNO_2S$	56.10	55.76	6.05	6.30	4.67	4.70
IV	$OCH_2CH_2CH_2N(C_2H_5)_2$[a]	79 (D)	144–145	$C_{16}H_{22}ClNO_2S$	58.61	58.89	6.77	7.00	4.27	4.25
V		27 (B)	248–249	$C_{15}H_{18}ClNO_2S$	57.77	57.77	5.81	6.01	4.49	4.47
VI	$NHCH_2CH_2N(C_2H_5)_2$	43 (E)	151–152	$C_{15}H_{21}ClN_2OS$	57.58	57.65	6.77	6.77	8.95	8.72
VII		57 (F)	269–271	$C_{17}H_{17}ClN_2OS$	56.64	56.40	5.77	5.98	10.81	10.62

[a] Lit.[5] mp 144–145°. [b] Recrystallizing solvents: A, 2-propanol; B, propanol; C, absolute ethanol; D, chloroform-benzene; E, *n*-amyl alcohol; F, chloroform-ether.

TABLE II
PHARMACOLOGICAL SCREENING RESULTS

Compd	Local anesthetic potency duration, min[a]	HCl writhing[b] protected/tested
I	0	0/5
II	0	0/5
III	0[c]	0/5
IV	0[c]	1/5
V	5	0/5
VI	55	2/5
VII	0[c]	1/5
Lidocaine HCl	50	*d*

[a] 0.25 ml of 2% solution/conjunctival sac. [b] 50 mg/kg ip. [c] Produced moderate irritation. [d] ED_{50} for acetylsalicylic acid is 50 mg/kg: A. D. Rudzik and J. H. Mennear, *J. Pharm. Pharmacol.*, **17**, 326 (1965).

Compound VI, the most active, did not produce any apparent irritation, and had an LD_{50} of 170 mg/kg.[12]

The compounds were also evaluated for their potential analgetic activity by the HCl writhing[13] and the infrared hot bulb[14] tests. The HCl writhing test indicated none of the compounds to be of sufficient analgetic activity to antagonize the HCl response in greater than 50% of the test animals at a dose of 50 mg/kg. Since VI was the most active of the series, it was subjected to the infrared hot bulb test at a dose of 100 mg/kg and produced a 2.6 times increase over control; however, clonic convulsions were observed in four of the test animals. Morphine sulfate (5 mg/kg) produced a 6.8 times increase over controls, indicating it to be approximately 50 times more active than VI in this test. Pharmacological screening results are given in Table II.

Experimental Section[15]

Benzo[*b*]thiophene-2-carbonyl Chloride (III).—I (20 g, 0.113 mole) and 35 ml of $SOCl_2$ were heated gently for 2.5 hr. The $SOCl_2$ was azeotroped off with benzene and the resulting white solid was recrystallized from benzene-cyclohexane to give 18 g (81%) of white needles, mp 84–86°.[10]

Amides and Esters of I.—III (7.0 g, 0.036 mole) was added to 1 equiv of each of six amines or alcohols dissolved in 50 ml of dry benzene. Following the addition at room temperature, each flask became warm and white solids soon separated from flasks I–V. An oil separated from flask VI. Flasks I–V were then heated to a gentle reflux for 2 hr while flask VI was allowed to reflux overnight. The flasks were cooled and the solids collected. Physical constants of the compounds prepared are found in Table I.

1-(2-Benzo[*b*]thenoyl)-4-methylpiperazine Hydrochloride (VII).—III (3.0 g, 1.52 mmoles) was treated with a solution containing 140 ml of H_2O, 3 ml of N-methylpiperazine, and 11 ml of 10% NaOH. The mixture was stirred for 15 min, and the solid was collected, dried, converted to the hydrochloride salt, and recrystallized from $CHCl_3$–Et_2O to yield 2.24 g of white plates.

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(12) Intraperitoneally in mice.

(13) E. T. Eckhardt, F. Cheplovitz, M. Lipo, and W. M. Govier, *Proc. Soc. Exptl. Biol. Med.*, **98**, 186 (1954).

(14) F. N. Marshall, W. R. Jones, and L. C. Weaver, *ibid.*, **116**, 912 (1964).

(15) Melting points were taken on a Mel-Temp capillary melting point apparatus and are corrected. The microanalyses were performed by Midwest Microlabs, Inc., Indianapolis, Ind.

Synthesis and Preliminary Pharmacological Evaluation of a Series of N,N′-Arylidenebis(acid amides)[1]

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Synthesis and biological activity studies of N,N′-benzylidenebisnicotinamide in our laboratories revealed that this compound possessed actions reflecting CNS depression. Its marked sedative action and relative freedom from gross symptoms of toxicity gave impetus

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