Synthesis and Local Anesthetic Activity of Benzo[*b*]furan Derivatives

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Received January 17, 1977, from the **Department of Chemistry, College of Pharmacy, and the* ‡*Department of Experimental Medicine and Pharmacology, Faculty of Medicine, Tehran University, Tehran, Iran.* Accepted for publication March 29, 1977.

Abstract □ Several 2-dialkylaminoethyl 3-methyl-2-benzo[*b*]furancarboxylates, 2-dialkylaminoethyl 3-methyl-2-benzo[*b*]furancarbamates, and 3-methyl-2-benzo[*b*]furancarboxamide derivatives were prepared and tested for local anesthetic activity. Piperidinoethyl 3-methyl-2-benzo[*b*]furancarbamate, 2-diethylaminoethyl 3-methyl-2-benzo[*b*]furancarboxylate, and *N*-(2-diethylaminoethyl)-3-methyl-2-benzo[*b*]furancarboxamide were the most potent.

Keyphrases □ Benzo[*b*]furan derivatives—synthesized, local anesthetic activity evaluated □ Anesthetic activity, local—various benzo[*b*]furan derivatives evaluated □ Structure–activity relationships—various benzo[*b*]furan derivatives evaluated for local anesthetic activity

Diethylaminoethyl 3-methyl-2-benzo[*b*]furancarboxylate (3-methylcoumarilate) has been reported to have spasmolytic activity (1). Some carbamic acids having the benzo[*b*]furan moiety showed antifungal activity (2). It also has been demonstrated that benzoic acid derivatives having the dialkylaminoethyl moiety and dialkylaminoacetanilides have potent local anesthetic activity with low toxicity (3, 4).

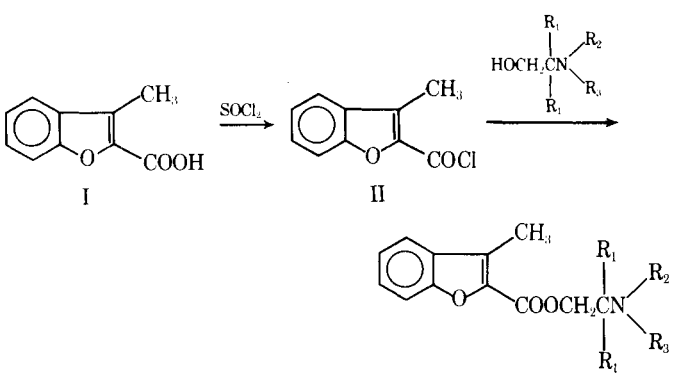
In a continuing effort to find a potent local anesthetic compound with low toxicity, a series of dialkylaminoethyl 3-methyl-2-benzo[*b*]furancarboxylates, 2-dialkylaminoethyl 3-methyl-2-benzo[*b*]furancarbamates, and 3-methyl-2-benzo[*b*]furancarboxamide derivatives was prepared and efficacy was determined.

RESULTS AND DISCUSSION

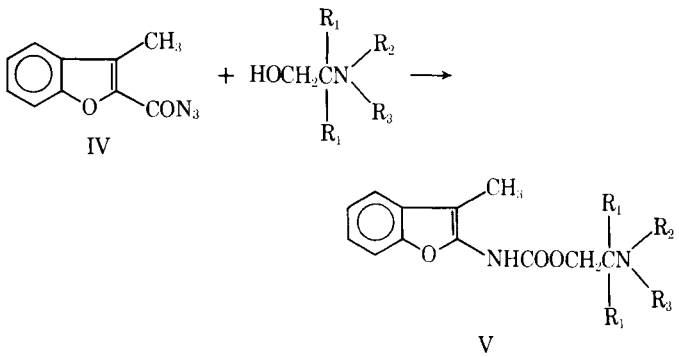
Chemistry—Dialkylaminoethyl 3-methyl-2-benzo[*b*]furancarboxylates were synthesized using readily available 3-methyl-2-benzo[*b*]furancarboxylic acid (I) (5). Reaction of I with thionyl chloride and subsequent reaction of the acyl halide with dialkylaminoethanol gave the desired compound (Scheme I).

3-Methyl-2-benzo[*b*]furancarbamic acid esters (V) were obtained through the reaction of 3-methyl-2-benzo[*b*]furancarboxazide (IV) (2) with 2-dialkylaminoethanol (Scheme II).

Finally, 3-methyl-2-benzo[*b*]furancarboxamide derivatives (VII or VIII) were obtained through the reaction of either IV or 3-methyl-2-benzo[*b*]furancarboxyl chloride (II) with 2-dialkylaminoethylamine or *N*-methylpiperazine (VI) (Scheme III).



Scheme I



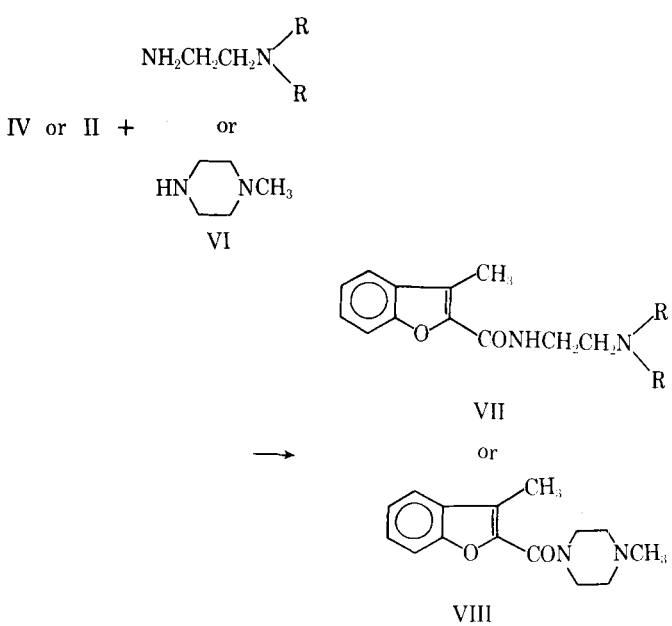
Scheme II

The physical data for the prepared compounds are summarized in Tables I–III.

Pharmacological Assay—The compounds listed in Tables I–III were screened for surface anesthetic activity. The conjunctival sac of rabbits was kept filled with the aqueous solution of the hydrochloride salt of the compounds for 60 sec. The cornea was tested once every minute, and the duration of anesthesia was followed for 18 min. Cocaine was used for comparison.

The results are presented in Table IV.

Compounds III*b*, V*e*, and VII*b* were the most potent. The LD_{50} values of III*b* and V*e* in mice, estimated by the moving average method (6), were 240.8 (204–289.3) and 59.1 (55–63.5) mg/kg, respectively, when injected intraperitoneally. Animals tolerated all substances locally. Apart from a transient irritation, no conjunctival intolerance or corneal opalescence was observed 24 and 48 hr and 1 week after drug application.



Scheme III

Table I—Physical Constants of 2-Dialkylaminoethyl 3-Methyl-2-benzo[*b*]furancarboxylates

Compound	R_1	R_2	R_3	Yield, %	Melting Point[a]	Formula[b]	Analysis, % Calc.	Found
III*a*	H	CH_3	CH_3	90	189–190°	$C_{14}H_{18}ClNO_3$	C 59.26	59.42
							H 6.35	6.12
							N 4.94	4.81
III*b*	H	C_2H_5	C_2H_5	94	180–181°	$C_{16}H_{22}ClNO_3$	C 61.64	61.51
							H 7.06	7.12
							N 4.49	4.32
III*c*	H	C_4H_9	C_4H_9	80	140–141°	$C_{20}H_{30}ClNO_3$	C 65.31	65.45
							H 8.16	8.23
							N 3.81	3.91
III*d*	H	CH_3	$CH_2C_6H_5$	78	170–171°	$C_{20}H_{22}ClNO_3$	C 66.76	66.55
							H 6.12	6.01
							N 3.89	3.95
III*e*	H	—$(CH_2)_4$—		91	194–195°	$C_{16}H_{20}ClNO_3$	C 62.04	62.22
							H 6.46	6.57
							N 4.52	4.63
III*f*	H	—$(CH_2)_5$—		95	120–121°	$C_{17}H_{22}ClNO_3$	C 63.06	63.14
							H 6.80	6.92
							N 4.33	4.16
III*g*	H	—$(CH_2CH_2)_2O$		85	200–201°	$C_{16}H_{20}ClNO_3$	C 58.99	58.81
							H 6.14	6.02
							N 4.30	4.15
III*h*	CH_3	CH_3	CH_3	65	209–210°	$C_{16}H_{22}ClNO_3$	C 61.64	61.51
							H 7.06	7.01
							N 4.49	4.38

[a] Unless otherwise indicated, the recrystallization solvent was ethanol–ethyl acetate. [b] IR, NMR, and mass spectra of all compounds were as expected.

Table II—Physical Constants of 2-Dialkylaminoethyl 3-Methyl-2-benzo[*b*]furancarbamates

Compound	R_1	R_2	R_3	Yield, %	Melting Point	Formula[a]	Analysis, % Calc.	Found
V*a*	H	CH_3	CH_3	65	134–135°[b]	$C_{14}H_{18}N_2O_3$	C 64.12	64.25
							H 6.87	6.93
							N 10.69	10.73
V*b*	H	C_2H_5	C_2H_5	70	173–174°[c]	$C_{16}H_{22}N_2O_3$	C 66.21	66.05
							H 7.59	7.41
							N 9.66	9.50
V*c*	H	C_4H_9	C_4H_9	75	—[d]	$C_{20}H_{30}N_2O_3$	C 69.36	69.16
							H 8.67	8.48
							N 8.09	8.26
V*d*	H	CH_3	$CH_2C_6H_5$	68	—[d]	$C_{20}H_{22}N_2O_3$	C 71.00	71.18
							H 6.51	6.32
							N 8.28	8.46
V*e*	H	—$(CH_2)_5$—		70	200–201°	$C_{17}H_{22}N_2O_3$	C 67.55	67.66
							H 7.28	7.15
							N 9.27	9.14
V*f*	H	—$(CH_2CH_2)_2O$		70	194–195°	$C_{16}H_{20}N_2O_4$	C 63.16	63.01
							H 6.58	6.64
							N 9.21	9.40
V*g*	CH_3	CH_3	CH_3	67	—[d]	$C_{16}H_{22}N_2O_3$	C 66.21	66.35
							H 7.59	7.72
							N 9.66	9.82

[a] IR, NMR, and mass spectra of all compounds were as expected. [b] This compound was crystallized as a picrate from ethanol. [c] This compound was crystallized as a hydrochloride from absolute ethanol. [d] This compound resisted crystallization as a free base or as a salt.

Table III—Physical Constants of *N*-(2-Dialkylaminoethyl)-3-methyl-2-benzo[*b*]furancarboxamide

Compound	R	Yield, %	Melting Point[a]	Formula[b]	Analysis, % Calc.	Found
VII*a*	CH_3	84	69–70°	$C_{14}H_{18}N_2O_2$	C 68.29	68.43
					H 7.32	7.45
					N 11.38	11.26
VII*b*	C_2H_5	90	45–46°	$C_{16}H_{22}N_2O_2$	C 70.07	70.24
					H 8.03	8.12
					N 10.22	10.18
VII*c*	—$(CH_2)_4$—	88	72–73°	$C_{16}H_{20}N_2O_2$	C 70.59	70.75
					H 7.35	7.12
					N 10.29	10.18
VII*d*	—$(CH_2)_2O(CH_2)_2$—	90	55–56°	$C_{16}H_{20}N_2O_3$	C 66.67	66.49
					H 6.94	6.81
					N 9.72	9.55
VIII	—	98	258–260°[c]	$C_{15}H_{18}N_2O_2$	C 69.77	69.65
					H 6.97	6.99
					N 10.85	10.74

[a] Unless otherwise indicated, the crystallization solvent was petroleum ether and the compound was prepared by Method A (see *Experimental*). [b] IR, NMR, and mass spectra of all compounds were as expected. [c] This compound was crystallized as a hydrochloride from absolute ethanol; it was synthesized by Method B (see *Experimental*).

Table IV—Local Anesthetic Activity of Benzo[*b*]furan Derivatives[a]

Compound[b]	Concentration, %	Potency	Duration, min
IIIa	1	0.85 (0.75–0.95)	13–18
IIIb	1	1.0	Over 18
	0.5	0.96 (0.91–1.0	16–18
	0.25	0.41 (0.30–0.53)	6–8
IIIc	1	0.75 (0.65–0.85)	10–15
IIId	1	0.85 (0.76–0.93)	13–17
IIIe	1	0.62 (0.51–0.74)	9–15
IIIf	1	1.0	Over 18
	0.5	0.68 (0.57–0.79)	11–13
IIIg	1	0.82 (0.73–0.91)	12–18
IIIh	1	0	0
Vb	1	0.72 (0.61–0.83)	13–15
Ve	1	1.0	Over 18
	0.25	0.75 (0.64–0.85)	11–15
Vf	1	0.97 (0.93–1.0)	17–18
VIIa	1	0	0
VIIb	1	0.96 (0.91–1.0)	16–18
	0.50	0.84 (0.75–0.93)	14–16
	0.25	0.57 (0.45–0.68)	10–14
VIIc	1	0.84 (0.76–0.92)	13–16
VIId	1	0	0
VIII	1	0	0
Cocaine	0.25	1.0	Over 18
	0.125	0.89 (0.82–0.96)	11–18

[a] Surface anesthesia was tested according to the method of M. R. A. Chance and H. J. Lobstein, *J. Pharmacol. Exp. Ther.*, **82**, 203 (1944). Anesthetic potency was calculated for the first 18 min [A. H. Campbell, J. A. Strasse, G. H. Lord, and J. E. Willson, *J. Pharm. Sci.*, **57**, 2045 (1968)]. A potency of 1.00 indicates an onset of anesthesia in 1 min and a duration of at least 18 min. [b] Compounds of Tables I–III not included in this table could not be dissolved in water and were not tested.

EXPERIMENTAL[1]

Compound II—A mixture of I (17.68 g, 0.01 mole) (5) in 100 ml of thionyl chloride was refluxed for 4 hr. The excess of thionyl chloride was evaporated under reduced pressure, and the residue was distilled to give II (16 g, 82%), bp 114–116°/6 mm Hg, mp 64–65° (hexane).

Anal.—Calc. for $C_{10}H_7ClO_2$: C, 61.70, H, 3.60. Found: C, 61.85; H, 3.79.

2-Dimethylaminoethyl 3-Methyl-2-benzo[*b*]furancarboxylate (IIIa)—A solution of 2-dimethylaminoethanol (0.89 g, 0.01 mole) and II (1.945 g, 0.01 mole) in 20 ml of benzene was refluxed for 4 hr. The solvent was evaporated, and the residue was crystallized from ethanol–ethyl acetate to give IIIa (2.55 g, 90%), mp 189–190°; IR (potassium bromide): 1715 cm^{-1} (ester); NMR (deuterochloroform, as free base): δ 7.66–7.17 (m, 4H, aromatic), 4.43 (t, 2H, OCH_2), 2.66 (t, 2H, CH_2N), 2.53 (s, 3H, CH_3), and 2.33 (s, 6H, NCH_3) ppm; *m/e* 247.

Compounds IIIb–IIIh were prepared similarly (Table I).

2-Dimethylaminoethyl 3-Methyl-2-benzo[*b*]furancarbamate (Va)—A solution of IV (2.01 g, 0.01 mole) (2) and 2-dimethylaminoethanol (0.89 g, 0.01 mole) in 20 ml of benzene was refluxed for 4 hr. The solvent was evaporated, and the residue was crystallized as a picrate, mp 134–135°; IR (potassium bromide, as free base): 1720 and 1249 cm^{-1} (ester); NMR (deuterochloroform, as free base): δ 7.50–7.00 (m, 5H, aromatic and NH), 4.23 (t, 2H, OCH_2), 2.56 (t, 2H, CH_2N), 2.23 (s, 6H, NCH_3), and 2.07 (s, 3H, CH_3) ppm; *m/e* 262.

Compounds Vb–Vg were prepared similarly (Table II).

***N*-(2-Diethylaminoethyl)-3-methyl- 2- benzo[*b*]furancarboxamide (VIIb)**—*Method A*—A solution of IV (2.01 g, 0.01 mole) and 2-diethylaminoethylamine (1.16 g, 0.01 mole) in 30 ml of benzene was refluxed for 2 hr, and the solvent was evaporated. The residue was crystallized from petroleum ether to give VIIb (2.5 g, 91%), mp 45–46°; IR (potassium bromide): 3300 (NH) and 1650 (amide) cm^{-1}; NMR (deuterochloroform): δ 7.73–7.00 (m, 5H, aromatic and NH), 3.5 (unresolved t, $CONCH_2$), 2.69 (t, 2H, CH_2N), 2.66 (s, 3H, CH_3), 2.54 (q, 4H, NCH_2), and 1.60 (t, 6H, CH_3) ppm; *m/e* 274.

Method B—A solution of II (1.945 g, 0.01 mole) and 2-diethylaminoethylamine (1.16 g, 0.01 mole) in 30 ml of benzene was refluxed for 2 hr. The solvent was evaporated, and the residue was crystallized from ethyl acetate to give VIIb as the hydrochloride (2.8 g, 90%), mp 129–130°, and as a free base, mp 45–46° (petroleum ether).

Compounds VIIa, VIIc, VIId, and VIII were prepared similarly (Table III).

[1] Melting points were taken on a Kofler hot-stage microscope and are uncorrected. IR spectra were recorded using a Perkin-Elmer 267 spectrophotometer. Mass spectra were recorded on a Varian Mat III instrument. NMR spectra were determined with a Varian T-60A instrument.

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Determination of Ionization Constants in Mixed Aqueous Solvents of Varying Composition by a Single Titration

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Received February 14, 1977, from *Physico-Chemistry Department, Janssen Pharmaceutica, 2340 Beerse, Belgium.* Accepted for publication April 8, 1977.

Abstract □ A potentiometric titration method is proposed in which only one titration is necessary to obtain pK'a values for different solvent compositions. The method allows the results to be extrapolated to the value for pure water. Examples are given, and the advantages and disadvantages of the method are discussed.

Keyphrases □ Ionization constants—potentiometric determination in mixed aqueous solvents of various composition □ Potentiometry—determination of ionization constants in mixed aqueous solvents of various composition

The use of mixed aqueous solvents for the potentiometric determination of ionization constants has disadvantages and should be avoided if possible. However, the solubility requirements for aqueous titrations are often too demanding, and many compounds are not suited for spectrophotometric analysis. Although Albert and Serjeant