Experimental Section

Melting points were determined on a Mettler FP 1 apparatus and the microanalyses on an F and M 185 C, H, and N analyzer. Where anal. are indicated only by the symbols of the elements anal. values obtained were within ±0.4% of the calcd values. Compds gave satisfactory uv, ir, and nmr spectral data obtained, resp, on Perkin-Elmer Model 137, Unicam SP 100, and Varian Associates A60A spectrometers. Optical rotations were measured in MeOH at 25°. Circular dichroism curves were measured in MeOH at 25° with a Roussel Jouan Dichrograph 185 and are expressed in mol ellipticity units $[\theta]$.

Methyl 5-[2-(Benzyl-*tert*-butylamino)-1-hydroxyethyl]-2-benzyloxybenzoate (2).—This compound was prepared by condensing methyl 2-benzyloxy-5-bromoacetylbenzoate[1] with *tert*-butylbenzylamine in EtCOMe and reducing the crude product with $NaBH_4$ in EtOH by the general procedures already described.[1] The product, mp 96° [from C_6H_6–petr ether (bp 60–80°)], was obtd in 43% yield from the bromo ketone. *Anal.* ($C_{28}H_{33}NO_4$) C, H, N.

Resolution of Methyl 5-[2-(benzyl-*tert*-butylamino)-1-hydroxyethyl]-2-benzyloxybenzoate.—The racemic ester (30 g, 0.064 mole) and (−)-di-*p*-toluoyltartaric acid (25.6 g, 0.064 mole)[10] in EtOAc (350 ml) at 70° were allowed to cool to room temp to give (*R*)-(+)-methyl 5-[2-benzyl-*tert*-butylamino)-1-hydroxyethyl]-2-benzyloxybenzoate (−)-di-*p*-toluoyltartrate (1:1): 27 g; mp 139.9°; $[\alpha]_D$ −48° (*c* 1.0). Two recrystns from EtOAc gave material of constant mp and rotation: 16 g; mp 148.2°; $[\alpha]_D$ −47° (*c* 1.5). *Anal.* ($C_{48}H_{51}NO_{12}$) C, H, N.

This salt (11 g) in EtOAc was extd several times with $NaHCO_3$ soln, dried (Na_2SO_4), and filtered through a small quantity of basic alumina. The eluate was evapd under reduced pressure and the residue crystd from petr ether (bp 60–80°) to give (*R*)-(+)-(**2**) as colorless needles: 4.5 g; mp 87°, $[\alpha]_D$ + 18.3° (*c* 0.35). *Anal.* ($C_{28}H_{33}NO_4$) C, H, N.

(*R*)-(+)-α¹-(Benzyl-*tert*-butylaminomethyl)-4-benzyloxy-*m*-xylene-α,α'-diol (3).—A soln of (*R*)-(+)-(**2**) (2.5 g, 0.005 mole) in dry THF (25 ml) was added with stirring to LAH (0.5 g, 0.0125 mole) in dry THF (50 ml). The mixt was heated to reflux and then cooled, and the excess hydride was decompd by cautious addn of H_2O. The THF soln was filtered through Hyflo, and the solvent was removed under reduced pressure. The residue was dissolved in Et_2O, dried ($MgSO_4$), and evapd to give the diol as a colorless oil: 2.1 g; $[\alpha]_D$ +7.9° (*c* 0.45). *Anal.* ($C_{26}H_{33}NO_3$) C, H, N.

(*R*)-(−)-α¹-(*tert*-Butylaminomethyl)-4-hydroxy-*m*-xylene-α,α'-diol Acetate (Salt) Monomethanolate (4).—A soln of (*R*)-(+)-(**3**) (2 g) in EtOH was hydrogenated at room temp and atm pressure in the presence of 10% Pd/C (0.7 g). Uptake of H_2 ceased after 6 min. The catalyst and solvent were removed, and the residue was converted into an acetate salt with 10% HOAc in EtOAc. Recrystn from MeOH–Et_2O gave (*R*)-(−)-salbutamol acetate (salt) monomethanolate: mp 144.3°; $[\alpha]_D$ −36.9° (*c* 0.27); CD (*c* 0.37) $[\theta]_{260}$ 0, $[\theta]_{280}$ −569 (max), $[\theta]_{295}$ 0. *Anal.* ($C_{16}H_{29}NO_6$) C, H, N.

(*S*)-(+)-α¹-(*tert*-Butylaminomethyl)-4-hydroxy-*m*-xylene-α,α'-diol acetate (salt) monomethanolate (4) was obtd by a procedure similar to that described above for the (R)-(−) isomer but using (+)-di-*p*-toluoyltartaric acid.[11] Thus (*S*)-(−)-(**2**), (+)-di-*p*-toluoyltartrate, had mp 150.7°, $[\alpha]_D$ +47° (*c* 1.2). *Anal.* ($C_{48}H_{51}NO_{12}$) C, H, N. This was converted into (*S*)-(−)-(**2**), free base: mp 87°; $[\alpha]_D$ −18.4° (*c* 0.38). *Anal.* ($C_{28}H_{33}NO_4$) C, H, N. Reduction with LAH gave the diol (*S*)-(−)-(**3**) as an oil, $[\alpha]_D$ −8.18° (*c* 0.48). *Anal.* ($C_{27}H_{33}NO_3$) C, H, N. Hydrogenation of (*S*)-(−)-(**3**) then gave (*S*)-(+)-salbutamol which was purified as its acetate (salt) monomethanolate: mp 145.7°; $[\alpha]_D$ +36.9° (*c* 0.23); CD (*c* 0.23) $[\theta]_{260}$ 0, $[\theta]_{278}$ +683 (max), $[\theta]_{295}$ 0. *Anal.* ($C_{16}H_{19}NO_6$) C, H, N.

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(10) From (+)-tartaric acid see (a) D. A. A. Kidd, *J. Chem. Soc.*, 4675 (1961); (b) A. Stoll and A. Hofmann, *Helv. Chim. Acta*, **26**, 922 (1943).

(11) From (−)-tartaric acid: see J. H. Hunt, *J. Chem. Soc.*, 1926 (1957).

Synthesis and Local Anesthetic Activity of *N*-Diethylaminoacetyl Derivatives of Naphthylalkylamines

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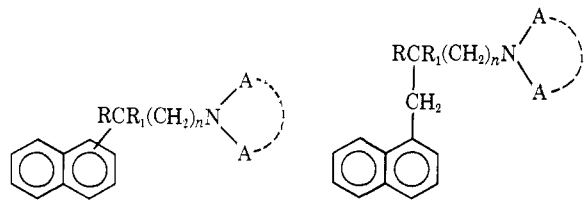
Our finding[1] that some α-naphthylalkylamines possess marked local anesthetic activity has led us to synthesize an extensive series of *N*-diethylaminoacetyl derivatives of naphthylalkylamines of the general structures I–III, in which R was H, or alkyl, or aminoalkyl; R_1 was $NHCOCH_2NEt_2$ or $CH_2NHCOCH_2NEt_2$; NAA was a tertiary amino group; n = 2–4.



I, substituted at position 1
II, substituted at position 2

III

The new substances (Table I) were obtained by allowing the corresponding amines to react in $CHCl_3$ with $(BrCH_2CO)_2O$ and subsequently treating the bromoacetyl derivatives with excess Et_2NH. To prevent the tertiary amino groups from quaternization, the bromoacetylation was accomplished in the presence of 1 or 2 equiv of AcOH.

Many of the compds displayed a marked local anesthetic activity. In particular, **22**, **27**, **28**, **31**, and **46** were as active as lidocaine, but irritant.

Experimental Section[2]

The intermediate amines were prepd as previously described.[3] **The *N*-diethylaminoacetyl derivatives of naphthylalkylamines** are listed in Table I, and their prepn is well illustrated by the following example.

***N*-[4-Diethylaminoacetamidomethyl-4-(α-naphthyl)-5-methylheptyl]piperidine (38).**—A soln of $(BrCH_2CO)_2O$ (14.35 g, 0.055 mole) in $CHCl_3$ (30 ml) was dropped at 5° into a stirred soln of *N*-[4-aminomethyl-4-(α-naphthyl)-5-methylheptyl]piperidine (15 g, 0.042 mole) and AcOH (2.56 g, 0.042 mole) in $CHCl_3$ (50 ml). The mixt was stirred for 1 hr at room temp, poured into excess Et_2NH (44.5 g), and stirred for an addnl 1 hr. The soln was then evapd to dryness, and the residue was taken up in Et_2O, washed (H_2O), and dried ($MgSO_4$). The solvent was evapd and

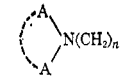
(1) S. Casadio, G. Pala, T. Bruzzese, C. Turba, and E. Marazzi-Uberti, *J. Med. Chem.*, **13**, 418 (1970).

(2) Melting points are corrected and were taken on a Büchi capillary melting point apparatus.

(3) G. Pala, A. Donetti, C. Turba, and S. Casadio, *J. Med. Chem.*, **13**, 668 (1970).

TABLE I

PHYSICAL PROPERTIES AND LOCAL ANESTHETIC ACTIVITY OF *N*-DIETHYLAMINOACETYL DERIVATIVES OF NAPHTHYLALKYLAMINES

Compd	R	R_1		Structure	Yield, %[a]	Mp, °C	Formula[b]	Local anesthetic act. (mouse), %[c]
1	H	$NHCOCH_2N(C_2H_5)_2$	$(CH_3)_2N(CH_2)_2$	I	57.7	85	$C_{21}H_{31}N_3O$[b]	60
2	*i*-C_3H_7	$NHCOCH_2N(C_2H_5)_2$	$(CH_3)_2N(CH_2)_2$	I	19	180	$C_{24}H_{37}N_3O$	50
3	H	$CH_2NHCOCH_2N(C_2H_5)_2$	$(CH_3)_2N(CH_2)_2$	I	36	90	$C_{22}H_{33}N_3O$	40
4	CH_3	$CH_2NHCOCH_2N(C_2H_5)_2$	$(CH_3)_2N(CH_2)_2$	I	53	100	$C_{23}H_{35}N_3O$	60
5	C_2H_5	$CH_2NHCOCH_2N(C_2H_5)_2$	$(CH_3)_2N(CH_2)_2$	I	37.3	110	$C_{24}H_{37}N_3O$	80
6	*n*-C_3H_7	$CH_2NHCOCH_2N(C_2H_5)_2$	$(CH_3)_2N(CH_2)_2$	I	48.2	130	$C_{25}H_{39}N_3O$	30
7	*i*-C_3H_7	$CH_2NHCOCH_2N(C_2H_5)_2$	$(CH_3)_2N(CH_2)_2$	I	46	145	$C_{25}H_{39}N_3O$	70
8	*n*-C_4H_9	$CH_2NHCOCH_2N(C_2H_5)_2$	$(CH_3)_2N(CH_2)_2$	I	48	110	$C_{26}H_{41}N_3O$	10
9	*i*-C_4H_9	$CH_2NHCOCH_2N(C_2H_5)_2$	$(CH_3)_2N(CH_2)_2$	I	45	120	$C_{26}H_{41}N_3O$	60
10	*sec*-C_4H_9	$CH_2NHCOCH_2N(C_2H_5)_2$	$(CH_3)_2N(CH_2)_2$	I	55.2	140	$C_{26}H_{41}N_3O$	60
11	$(CH_3)_2N(CH_2)_2$	$CH_2NHCOCH_2N(C_2H_5)_2$	$(CH_3)_2N(CH_2)_2$	I	12.6	120	$C_{26}H_{42}N_4O$[m]	30
12	*i*-C_3H_7	$CH_2NHCOCH_2N(C_2H_5)_2$	$CH_3(C_2H_5)N(CH_2)_2$	I	34.6	145	$C_{26}H_{41}N_3O$	80
13	*sec*-C_4H_9	$CH_2NHCOCH_2N(C_2H_5)_2$	$CH_3(C_2H_5)N(CH_2)_2$	I	46	145	$C_{27}H_{43}N_3O$	60
14	*i*-C_3H_7	$CH_2NHCOCH_2N(C_2H_5)_2$	$(C_2H_5)_2N(CH_2)_2$	I	40.6	105	$C_{27}H_{43}N_3O$	30
15	*sec*-C_4H_9	$CH_2NHCOCH_2N(C_2H_5)_2$	$(C_2H_5)_2N(CH_2)_2$	I	64.5	135	$C_{28}H_{45}N_3O$	30
16	$(C_2H_5)_2N(CH_2)_2$	$CH_2NHCOCH_2N(C_2H_5)_2$	$(C_2H_5)_2N(CH_2)_2$	I	39.8	235	$C_{30}H_{50}N_4O$[m]	60
17	*n*-C_3H_7	$CH_2NHCOCH_2N(C_2H_5)_2$	*d*	I	31.4	125	$C_{27}H_{41}N_3O$	20
18	*i*-C_3H_7	$CH_2NHCOCH_2N(C_2H_5)_2$	*d*	I	64	150	$C_{27}H_{41}N_3O$	80
19	*n*-C_4H_9	$CH_2NHCOCH_2N(C_2H_5)_2$	*d*	I	66	130	$C_{28}H_{43}N_3O$	50
20	*i*-C_4H_9	$CH_2NHCOCH_2N(C_2H_5)_2$	*d*	I	58.8	145	$C_{28}H_{43}N_3O$	30
21	*sec*-C_4H_9	$CH_2NHCOCH_2N(C_2H_5)_2$	*d*	I	59.4	135	$C_{28}H_{43}N_3O$	10
22	H	$CH_2NHCOCH_2N(C_2H_5)_2$	*e*	I	66.1	110	$C_{25}H_{37}N_3O$	90
23	CH_3	$CH_2NHCOCH_2N(C_2H_5)_2$	*e*	I	53.5	140	$C_{26}H_{39}N_3O$	80
24	C_2H_5	$CH_2NHCOCH_2N(C_2H_5)_2$	*e*	I	36	150	$C_{27}H_{41}N_3O$	80
25	*i*-C_3H_7	$CH_2NHCOCH_2N(C_2H_5)_2$	*e*	I	75	160	$C_{28}H_{43}N_3O$	40
26	*i*-C_4H_9	$CH_2NHCOCH_2N(C_2H_5)_2$	*e*	I	60.2	160–162	$C_{29}H_{45}N_3O$	40
27	*sec*-C_4H_9	$CH_2NHCOCH_2N(C_2H_5)_2$	*e*	I	67.6	140	$C_{29}H_{45}N_3O$	90
28	*e*	$CH_2NHCOCH_2N(C_2H_5)_2$	*e*	I	63.5	245	$C_{32}H_{50}N_4O$[m]	90
29	H	$CH_2NHCOCH_2N(C_2H_5)_2$	*f*	I	55.3	105	$C_{24}H_{35}N_3O_2$	80
30	CH_3	$CH_2NHCOCH_2N(C_2H_5)_2$	*f*	I	45	160	$C_{25}H_{37}N_3O_2$	30
31	C_2H_5	$CH_2NHCOCH_2N(C_2H_5)_2$	*f*	I	76	160–163	$C_{26}H_{39}N_3O_2$	90
32	*i*-C_3H_7	$CH_2NHCOCH_2N(C_2H_5)_2$	*f*	I	79	170	$C_{27}H_{41}N_3O_2$	50
33	*i*-C_4H_9	$CH_2NHCOCH_2N(C_2H_5)_2$	*f*	I	72.2	155	$C_{28}H_{43}N_3O_2$	0
34	*sec*-C_4H_9	$CH_2NHCOCH_2N(C_2H_5)_2$	$(CH_3)_2N(CH_2)_3$	I	30	130	$C_{27}H_{43}N_3O$	60
35	$(CH_3)_2N(CH_2)_3$	$CH_2NHCOCH_2N(C_2H_5)_2$	$(CH_3)_2N(CH_2)_3$	I	32	85	$C_{28}H_{46}N_4O$[m]	10
36	*sec*-C_4H_9	$CH_2NHCOCH_2N(C_2H_5)_2$	*g*	I	70	95–100	$C_{29}H_{45}N_3O$	20
37	*i*-C_3H_7	$CH_2NHCOCH_2N(C_2H_5)_2$	*h*	I	61.2	140	$C_{29}H_{45}N_3O$	80
38	*sec*-C_4H_9	$CH_2NHCOCH_2N(C_2H_5)_2$	*h*	I	77	110	$C_{30}H_{47}N_3O$	70
39	*sec*-C_4H_9	$CH_2NHCOCH_2N(C_2H_5)_2$	*i*	I	66	140	$C_{29}H_{45}N_3O_2$	10
40	*sec*-C_4H_9	$CH_2NHCOCH_2N(C_2H_5)_2$	$(CH_3)_2N(CH_2)_4$	I	31.7	130	$C_{28}N_{45}N_3O$	70
41	*i*-C_3H_7	$CH_2NHCOCH_2N(C_2H_5)_2$	*j*	I	58.7	110	$C_{29}H_{45}N_3O$	60
42	*sec*-C_4H_9	$CH_2NHCOCH_2N(C_2H_5)_2$	*j*	I	50.8	125	$C_{30}H_{47}N_3O$	10
43	*i*-C_3H_7	$CH_2NHCOCH_2N(C_2H_5)_2$	*k*	I	31.5	105	$C_{30}H_{47}N_3O$	30
44	*sec*-C_4H_9	$CH_2NHCOCH_2N(C_2H_5)_2$	*l*	I	76.4	155–160	$C_{30}H_{47}N_3O_2$	10
45	*i*-C_3H_7	$CH_2NHCOCH_2N(C_2H_5)_2$	$(CH_3)_2N(CH_2)_2$	II	47.5	100	$C_{25}H_{39}N_3O$	30
46	*i*-C_3H_7	$CH_2NHCOCH_2N(C_2H_5)_2$	*e*	III	71	130	$C_{29}H_{45}N_3O$	100
47	*sec*-C_4H_9	$CH_2NHCOCH_2N(C_2H_5)_2$	*e*	III	74.2	125	$C_{30}H_{47}N_3O$	30
Lidocaine·HCl								100

[a] Crystallized product. [b] All compounds were dihydrochloride salts except where noted; they were analyzed for C, H, N and the anal. values were within ±0.4% of the theor values. [c] The compounds were tested subcutaneously at a concentration of 10 mg/ml [C. Bianchi, *Brit. J. Pharmacol.*, 11, 104 (1956)]. [d] 2-(1-Pyrrolidinyl)ethyl. [e] 2-Piperidinoethyl. [f] 2-Morpholinoethyl. [g] 3-(1-Pyrrolidinyl)propyl. [h] 3-Piperidinopropyl. [i] 3-Morpholinopropyl. [j] 4-(1-Pyrrolidinyl)butyl. [k] 4-Piperidinobutyl. [l] 4-Morpholinobutyl. [m] Trihydrochloride salts.

the new residue was distd to give 15.8 g of **38** as a viscous and colorless oil, bp 220–224° (0.1 mm), which was converted with dry HCl in Et_2O into a cryst hydrochloride, mp 110°.

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