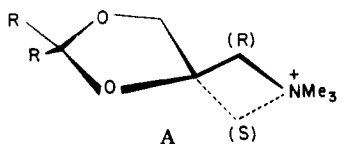
value of 6.33 for (*R*)-4-dimethylaminomethyl-1,3-dioxolane methiodide, approximately that reported by Belleau and Lavoie.[9]

In marked contrast, in the *S* series progressive alkyl substitution causes an initial decrease in pD_2 value with DMD and this is approximately equal in both the *R* and *S* series. Additional alkyl substitution produces no further change in pD_2 but rather causes a progressive decrease in i.a. (Figure 1).

Two points deserve emphasis from these findings. First, whether one considers this series of dioxolanes as the racemates[1] or as the enantiomers, the parent compound CD has uniquely high agonist activity. Obviously, this must reflect a contribution made by the 2-methyl group of CD beyond that predicted by the π value; quite possibly this indicates a highly productive interaction of this ligand with the receptor relative to other members of this series.[1,9] The second point of emphasis concerns the divergent effects of 2,2-dialkyl substitution upon the pD_2 and i.a. parameters and the ultimate inversion in stereoselectivity. Despite the fact that these parameters are probably complex functions of the total transduction sequence initiated by the agonist-receptor interaction,[10] some tentative conclusions concerning the significance of the data in Table I do seem possible.

Previous work aimed at defining the active conformation of these agents when bound at the muscarinic receptor suggests a conformation (see structure A) in which the $-N^+Me_3$



group is maximally extended from the dioxolane ring.[11,12] Examination of models of the enantiomeric pairs of the 2,2-dialkyl-substituted dioxolanes listed in Table I shows that they can present in identical fashion the same functional groups to a receptive surface save for the methylene group of the trimethylaminomethyl side chain (structure A). It would thus be anticipated that there would be a constant difference in activity (pD_2, i.a., or both) between each enantiomeric pair produced by this single difference of interaction. This is clearly not so and other explanations must be sought.

The explanation that we wish to advance is based on our previously expressed hypothesis[12,13] that there may exist partially overlapping subsites with different molecular requirements (approximately "polar" and "nonpolar," Figure 2) for ligands active at the muscarinic receptor and on the fact that β-Me substitution into ACh serves not to increase muscarinic activity but only to maintain it in the *S* enantiomer and to decrease it in the *R* enantiomer.[12,14] Accordingly, with increasing nonpolar (2-alkyl) substitution in the 1,3-dioxolane series, there is an increasing tendency for binding in the nonpolar area which is more pronounced for the 4-*S* enantiomers because of the detrimental β-Me effect. The activity difference between (*R*)- and (*S*)-CD probably represents a true stereoselectivity of interaction at the polar subsite but further substitution may cause the two enantiomers to bind in different subsites. At the polar subsite the effects of addition 2-alkyl substitution into CD are seen as decreases in affinity of the *R* enantiomers while at the nonpolar subsite the same substitutions have no effect on affinity but decrease i.a. and this results in the observed inversion of stereoselectivity at DPD. It is of interest that it is at hexyl N^+Me_3 in the alkyltrimethylammonium series that i.a. decreases from 1.0 to 0.9 and that the effective

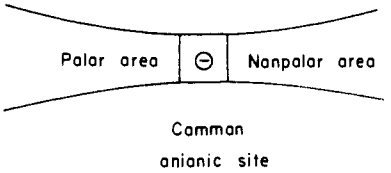


Figure 2. Schematic representation of the muscarinic receptor site showing a common anionic area with adjacent polar and nonpolar subsites for interaction with polar and nonpolar side chains, respectively, of agonist molecules.

chain length in DED ($C_2H_5CO_1CCN^+$) is also C_6.[8,12] This may represent the transition point in binding orientation.

The proposal advanced above is to be recognized as tentative; nevertheless, it accords with previous proposals of multiple ligand binding orientations in this and other macromolecular systems[12] including such enzymes as carboxypeptidase,[15] subtilisin,[16] and, of particular relevance, acetylcholinesterase.[17,18] Furthermore, the work reported here suggests a cautionary note in the interpretation of stereoselectivity data.

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Analgetic-Antiinflammatory Activity of Prenyl Derivatives of Basic Naphthylalkylnitriles and Naphthylalkylamides Chemically Related to Naphthypramide

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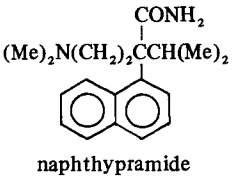
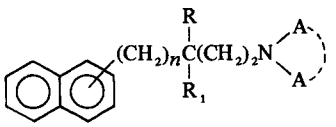
In prior communications,[1,2] it has been reported from this laboratory that α-isopropyl-α-(2-dimethylaminoethyl)-1-naphthylacetamide (naphthypramide) possesses a noteworthy

antiinflammatory activity which, unfortunately, is not accompanied by an equally good analgetic action. In the attempt at increasing this activity, many compounds chemically related to naphthypramide have been synthesized and tested for antiinflammatory and analgetic action,[2-5] but the results were unsatisfactory.



naphthypramide

The importance of the presence of the prenyl (3-methyl-2-butenyl) group in the structure of analgetic drugs, which has been recognized lately (pentazocine,[6] prenazone[7]), has now prompted us to synthesize and test for analgetic and antiinflammatory activity a number of prenyl derivatives of basic naphthylalkylnitriles and naphthylalkylamides of the general structures I and II (Table I).



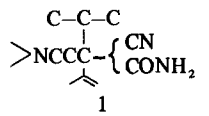
I, substituted at position 1
II, substituted at position 2
R = H, alkyl, prenyl, or 3-diprenylaminoethyl
R_1 = CN or $CONH_2$
NAA = *tert*-amino group
n = 0 or 1

Pharmacology. Pharmacological investigation included studies of acute toxicity,[8] behavioral effects,[9] analgesia in mice[10-12] and in rats,[13] and antiinflammatory,[13] diuretic,[14] and uricosuric[15] actions. Phenylbutazone and dihydrochlorothiazide were used as reference standards.

The most interesting results are given in Table II. First, the nitriles appear to be less toxic than the corresponding amides, both in mice and in rats. Compounds **4**, **5**, **7**, **11**, and **15** showed orally in mice, but not in rats, CNS depression which appeared as a decrease of the spontaneous motility and as motor incoordination and decrease of body muscle tonus. As for analgetic action, many of the compounds significantly increased the pain threshold of the inflamed paw in rats but did not alter the pain threshold for the normal paw. Compounds **4**, **7**, **14**, **18**, **24**, and **25** significantly inhibited the carrageenan-induced edema. Lowering of the screening dose led to a noticeable reduction of either analgetic or antiinflammatory activity. At the oral dose of 10 mg/kg, only **25** and **29** displayed a noteworthy diuretic action, even though inferior to that of dihydrochlorothiazide. In none of the other assays did the compounds exert any significant activity.

The most interesting feature revealed during this investigation is, as expected, the marked analgetic activity shown by many of the substances. Under the point of view of antiinflammatory activity coupled with analgetic action, the most interesting compounds **7** and **18** appear to be distinctly inferior to naphthypramide. In fact, compound **7** suffered a noticeable reduction of both these activities on lowering the screening dose, while compound **18** [α-prenyl-α-(2-dimethylaminoethyl)-1-naphthylacetamide, the prenyl analog of naphthypramide] was found active at doses which are near the LD_{50}.

From these considerations and taking into account the skeleton **1**, that we previously reported to represent the best structure for high-potency antiinflammatory and analgetic compounds,[4] the final conclusion may be drawn that in this



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structure replacement of the branched alkyl group (C-C-C moiety) with a prenyl one leads to substances of minor interest.

Experimental Section†

Except for the following **α-(2-diprenylaminoethyl)-1-naphthylacetonitrile** (7) and **α-prenyl-1-naphthylpropionitrile**, all the intermediate nitriles were prepared as previously described.[3,4,16]

1-Diprenylamino-2-hydroxyethane. Prenyl bromide (205.9 g, 1.38 mol) was added dropwise to a stirred suspension of 1-amino-2-hydroxyethane (126.3 g, 2.07 mol) in Et_2O (2 l.). After 40 hr of stirring at room temperature, H_2O was added and the organic layer was washed (H_2O), dried ($MgSO_4$), evaporated, and distilled at 99–100° (0.6 mm) to give a colorless oil (100.6 g, 73.8%). *Anal.* ($C_{12}H_{23}NO$) C, H, N.

1-Diprenylamino-2-chloroethane. $SOCl_2$ (21.88 g, 0.184 mol) was added at 0–5° to a stirred solution of 1-diprenylamino-2-hydroxyethane (30.22 g, 0.15 mol) and pyridine (3.76 g, 0.0475 mol) in petroleum ether (bp 40–70°, 300 ml). The suspension was stirred for 18 hr at room temperature and poured into excess H_2O, and then the separated aqueous solution was washed with petroleum ether and made basic with $NaHCO_3$. The oil that separated was extracted (Et_2O), and the extract was washed once with H_2O, dried ($MgSO_4$), evaporated, and distilled at 87–90° (0.4 mm) to give a colorless oil (25.7 g, 77.8%). *Anal.* ($C_{12}H_{22}ClN$) C, H, Cl, N.

α-(2-Diprenylaminoethyl)-1-naphthylacetonitrile (7). Finely powdered $NaNH_2$ (3.62 g, 0.093 mol) was added portionwise to a stirred solution of 1-naphthylacetonitrile (15.5 g, 0.093 mol) in dry PhH (70 ml). The mixture was refluxed for 3 hr, and then 1-diprenylamino-2-chloroethane (20 g, 0.093 mol) was added during 30 min. The suspension was refluxed for 10 hr, cooled, and decomposed by cautious addition of H_2O. The organic solution was worked up in the usual manner to give, on distillation, 18 g of 7 as a colorless oil, bp 182–184° (0.1 mm).

Ethyl 2-Cyano-5-methyl-4-hexenoate. Ethyl cyanoacetate (87.3 g, 0.772 mol) was added with stirring to a solution of Na (18.15 g, 0.79 g-atom) in anhydrous EtOH (300 ml). After 30 min of stirring at room temperature, prenyl bromide (126.5 g, 0.85 mol) was dropped in during 10 min, the mixture was refluxed for 3 hr, and the EtOH solution was evaporated to dryness. The residue was taken up in Et_2O, washed (H_2O), dried ($MgSO_4$), evaporated, and distilled at 66–68° (0.2 mm) to give a colorless oil (43.36 g, 31%). *Anal.* ($C_{10}H_{15}NO_2$) C, H, N.

α-Carbethoxy-α-prenyl-1-naphthylpropionitrile. Ethyl 2-cyano-5-methyl-4-hexenoate (126.3 g, 0.697 mol) was added with stirring to a solution of Na (17.64 g, 0.76 g-atom) in anhydrous EtOH (500 ml). The mixture was stirred for 30 min at room temperature and then a solution of 1-chloromethylnaphthalene (137.5 g, 0.77 mol) in anhydrous EtOH (70 ml) was added dropwise. After 18 hr of stirring at reflux temperature, the EtOH was evaporated and the oily residue was taken up in Et_2O. The organic solution was washed (H_2O), dried ($MgSO_4$), and evaporated, and the residue was distilled at 175–180° (0.2 mm) to give a colorless oil (183 g, 81.7%). *Anal.* ($C_{21}H_{23}NO_2$) C, H, N.

α-Prenyl-1-naphthylpropionitrile. α-Carbethoxy-α-prenyl-1-naphthylpropionitrile (182.8 g, 0.57 mol) was refluxed for 30 hr with 95% EtOH (50 ml) and 35% KOH solution (410 g); then the mixture was diluted (H_2O), washed (Et_2O), and acidified with 1:1 HCl. The precipitate was extracted with Et_2O, and the organic layer was washed (H_2O) and dried ($MgSO_4$). Removal of the solvent left 156.3 g (93.8%) of crude α-carboxy-α-prenyl-1-naphthylpropionitrile, which was directly heated at 200° in the presence of Cu dust until CO_2 evolution was complete (10 hr). Distillation at 175–177° (0.5 mm) gave a viscous colorless oil (41.2 g, 31%). *Anal.* ($C_{18}H_{19}N$) C, H, N.

Prenyl derivatives of basic naphthylalkylnitriles and naphthylalkylamides are listed in Table I, and their preparation is illustrated by the following methods.

Method A. α-Prenyl-α-(2-dimethylaminoethyl)-1-naphthylace-

†Boiling points are uncorrected. Melting points were taken on a Büchi capillary melting point apparatus and are corrected. Where analyses are indicated only by symbols of the elements, the analytical results were within ±0.4% of the theoretical values.

Table I. Prenyl Derivatives of Basic Naphthylalkylnitriles and Naphthylalkylamides

Compd	R	R_1	N(A)(A)	Structure	n	Method	Reaction time, hr	Yield, %[a]	Mp or bp, °C (mm)	Crystn solvent	Formula[b]
1	$(CH_3)_2C{=}CHCH_2$	CN	$N(CH_3)_2$	I	0	A	22	70	186–189	EtOAc	$C_{21}H_{26}N_2 \cdot HCl$
2	$(CH_3)_2C{=}CHCH_2$	CN	$NCH_3(C_2H_5)$	I	0	A	15	51	154–155	EtOAc	$C_{22}H_{28}N_2 \cdot HCl$
3	$(CH_3)_2C{=}CHCH_2$	CN	$N(C_2H_5)_2$	I	0	A	8	58	128–130	EtOAc	$C_{23}H_{30}N_2 \cdot HCl$
4	$(CH_3)_2C{=}CHCH_2$	CN	1-Pyrrolidinyl	I	0	A	14	45	163–165	EtOAc	$C_{23}H_{28}N_2 \cdot HCl$
5	$(CH_3)_2C{=}CHCH_2$	CN	Piperidino	I	0	A	13	71	158–160	EtOAc	$C_{24}H_{30}N_2 \cdot HCl$
6	$(CH_3)_2C{=}CHCH_2$	CN	Morpholino	I	0	A	13	47	152–153	EtOAc	$C_{23}H_{28}N_2O \cdot HCl$
7	H	CN	*c*	I	0	*d*	10	56	182–184 (0.1)		$C_{24}H_{30}N_2$
8	CH_3	CN	*c*	I	0	B	12	41	185–187	H_2O	$C_{25}H_{32}N_2 \cdot HCl$
9	C_2H_5	CN	*c*	I	0	B	2	30	174–176	EtOAc	$C_{26}H_{34}N_2 \cdot HCl$
10	*i*-C_3H_7	CN	*c*	I	0	B	12	47	186–188	H_2O	$C_{27}H_{36}N_2 \cdot HCl$[e]
11	*sec*-C_4H_9	CN	*c*	I	0	B	12	31	196–198	H_2O	$C_{28}H_{38}N_2 \cdot HCl$
12	$(CH_3)_2C{=}CHCH_2$	CN	*c*	I	0	A	15	78	166–167	EtOAc	$C_{29}H_{38}N_2 \cdot HCl$
13	*f*	CN	*c*	I	0	B[g]	2	51	227–229 (0.02)		$C_{36}H_{51}N_3$
14	*i*-C_3H_7	CN	*c*	I	1	A[h]	38	27	163–164	EtOAc	$C_{28}H_{38}N_2 \cdot HCl$
15	$(CH_3)_2C{=}CHCH_2$	CN	$N(CH_3)_2$	I	1	A[h]	30	18	173–176	PhH	$C_{22}H_{28}N_2 \cdot HCl$
16	$(CH_3)_2C{=}CHCH_2$	CN	$N(CH_3)_2$	II	0	A	17	72	246–247	EtOH	$C_{21}H_{26}N_2 \cdot HCl$
17	*i*-C_3H_7	CN	*c*	II	0	B	2	45	185–187	EtOAc	$C_{27}H_{36}N_2 \cdot HCl$
18	$(CH_3)_2C{=}CHCH_2$	$CONH_2$	$N(CH_3)_2$	I	0	C	122	61	117–118	Ligroin	$C_{21}H_{28}N_2O$
19	$(CH_3)_2C{=}CHCH_2$	$CONH_2$	$NCH_3(C_2H_5)$	I	0	C	170	47	79–81	Petroleum ether	$C_{22}H_{30}N_2O$
20	$(CH_3)_2C{=}CHCH_2$	$CONH_2$	$N(C_2H_5)_2$	I	0	C	163	79	85–87	Petroleum ether	$C_{23}H_{32}N_2O$
21	$(CH_3)_2C{=}CHCH_2$	$CONH_2$	1-Pyrrolidinyl	I	0	C	78	57	134–136	EtOH–H_2O	$C_{23}H_{30}N_2O$
22	$(CH_3)_2C{=}CHCH_2$	$CONH_2$	Piperidino	I	0	C	161	70	104–106	Petroleum ether	$C_{24}H_{32}N_2O$
23	$(CH_3)_2C{=}CHCH_2$	$CONH_2$	Morpholino	I	0	C	78	52	117–118	EtOH–H_2O	$C_{23}H_{30}N_2O_2$
24	H	$CONH_2$	*c*	I	0	C	3	55	98–100	EtOH–H_2O	$C_{24}H_{32}N_2O$[i]
25	CH_3	$CONH_2$	*c*	I	0	C	134	72	100–102[j]	Et_2O	$C_{25}H_{34}N_2O \cdot HCl$
26	C_2H_5	$CONH_2$	*c*	I	0	C	206	51	198–200[j]	EtOAc	$C_{26}H_{36}N_2O \cdot HCl$
27	$(CH_3)_2C{=}CHCH_2$	$CONH_2$	*c*	I	0	C	85	71	77–80	Petroleum ether	$C_{29}H_{40}N_2O$
28	*f*	$CONH_2$	*c*	I	0	C	362	31	*k*		$C_{36}H_{53}N_3O$
29	$(CH_3)_2C{=}CHCH_2$	$CONH_2$	$N(CH_3)_2$	II	0	C	170	66	111–113	Cyclohexane	$C_{21}H_{28}N_2O$

[a] Crystallized or distilled product. [b] Analyzed for C, H, N, and Cl. [c] Diprenylamino. [d] For the preparation, see the Experimental Section. [e] N: calcd, 6.89; found, 6.42. [f] 2-Diprenylaminoethyl. [g] Isolated as base. [h] Alkylation with 1-dimethylamino-2-chloroethane was carried out using KNH_2 in place of $NaNH_2$. [i] C: calcd, 79.08; found, 80.08. [j] Isolated as the HCl salt using dry HCl in Et_2O solution. [k] Thick oil.

Table II. Pharmacological Results

No.	LD_{50} (mouse), mg/kg po	Approx LD_{50} (rat), mg/kg po	Analgetic activity[a] (rat)		Antiinflammatory activity[b] (rat)	
			% increase of the pain threshold of the inflamed paw, av ± std dev	mg/kg po	% inhibition of edema, av ± std dev	mg/kg po
1	325	>400	235.0 ± 40.6	100	16.6 ± 7.7	100
2	213	>800	119.7 ± 67.3	100	10.6 ± 4.8	100
3	213	>400	254.5 ± 45.5	100	19.3 ± 8.5	100
4	572	>400	107.5 ± 34.5	100	20.6 ± 9.3	100
5	418	>400	223.3 ± 43.6	100	17.0 ± 8.4	100
6	>800	>400	196.1 ± 40.0	100	4.5 ± 9.4	100
7	>800	>400	173.6 ± 46.8	100	24.6 ± 6.6	100
8	711	>800	164.4 ± 40.2	100	5.7 ± 6.8	100
9	572	>800	228.1 ± 55.8	100	17.6 ± 4.3	100
10	426	>800	134.2 ± 46.2	100	4.5 ± 8.1	100
11	>800	>800	190.7 ± 45.4	100	10.6 ± 8.9	100
12	>800	>800	219.1 ± 38.5	100	13.4 ± 9.4	100
13	283	>800	196.0 ± 37.6	100	13.1 ± 6.8	100
14	566	>800	118.9 ± 45.5	100	25.5 ± 5.3	100
15	572	>800	255.5 ± 39.8	100	0 ± 7.0	100
16	188	>800	243.9 ± 29.3	100	4.9 ± 3.3	100
17	>800	>800	45.3 ± 30.2	100	14.4 ± 6.7	100
18	78	143	203.5 ± 44.3	50	24.2 ± 4.0	50
19	123	71	117.5 ± 27.2	25	8.3 ± 6.5	25
20	81	71	119.6 ± 24.7	25	0 ± 4.0	25
21	106	71	102.1 ± 24.8	25	9.8 ± 3.8	25
22	62	57	3.7 ± 23.3	25	9.3 ± 5.1	25
23	123	177	231.5 ± 41.6	100	7.3 ± 6.0	100
24	188	353	114.1 ± 65.3	100	21.6 ± 4.6	100
25	213	353	87.2 ± 47.6	100	20.6 ± 3.8	100
26	162	283	133.3 ± 28.2	100	8.9 ± 9.5	100
27	123	283	65.1 ± 48.7	100	9.3 ± 9.0	100
28	376	>800	215.1 ± 33.1	100	9.7 ± 4.5	100
29	123	286	209.2 ± 33.4	100	18.3 ± 3.3	100
Naphthypramide	1086	1030	134.8 ± 32.4	100	23.8 ± 2.1	100
Phenylbutazone			227.5 ± 31.2	100	33.5 ± 2.1	100

[a] Carrageenan-induced pain. Five animals per compound. [b] Carrageenan-induced edema. Five animals per compound.

tonitrile Hydrochloride (1). $NaNH_2$ was prepared by adding Na (10.17 g, 0.44 g-atom) to anhydrous NH_3 (450 ml) in the presence of $Fe(NO_3)_3 \cdot 9H_2O$ (0.3 g). A solution of α-(2-dimethylaminoethyl)-1-naphthylacetonitrile (88 g, 0.37 mol) in anhydrous Et_2O (130 ml) was added, followed after 1 hr by prenyl bromide (66 g, 0.44 mol). The mixture was stirred for 22 hr; then the NH_3 was allowed to evaporate, PhH was added to the residue, and H_2O was dropped in cautiously. The organic layer was washed (H_2O) and extracted with 10% HCl solution. From the acid solution an oil separated that was evaporated to dryness together with the PhH layer. The residue was crystallized from EtOAc to give 88.5 g of 1 as colorless crystals, mp 186–189°.

Method B. α-Isopropyl-α-(2-diprenylaminoethyl)-1-naphthylacetonitrile Hydrochloride (10). Finely powdered $NaNH_2$ (6.67 g, 0.17 mol) was added in small portions to a stirred solution of α-isopropyl-1-naphthylacetonitrile (30 g, 0.14 mol) in dry PhH (160 ml). The mixture was refluxed for 5 hr, and then 1-diprenylamino-2-chloroethane (46 g, 0.21 mol) was added dropwise during 1 hr. The suspension was refluxed for 16 hr, cooled to room temperature, and decomposed by cautious addition of H_2O. The organic solution was washed (H_2O) and extracted with 10% HCl solution, and the oil that separated from the acid solution was isolated and crystallized from H_2O to give 28.6 g of 10 as colorless crystals, mp 186–188°.

Method C. α-Prenyl-α-(2-dimethylaminoethyl)-1-naphthylacetamide (18). A solution of 1 (88 g, 0.257 mol) and KOH (72.08 g, 1.285 mol) in 95% EtOH (750 ml) was refluxed for 9 hr. The EtOH was removed, H_2O was added to the residue, and the mixture was extracted with PhH. The organic layer was washed (H_2O) and worked up in the usual manner to give, on crystallization from ligroin, 50.7 g of 18 as colorless crystals, mp 117–118°.

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