by column chromatography on Al_2O_3. Elution with C_6H_6–EtOAc afforded ester **4** (1.30 g, 66%). The MeI was prepared in Et_2O and recrystallized from EtOAc–MeOH, mp 233°. *Anal.* ($C_{23}H_{36}NO_2I$) C, H, N.

4(e)-Cyano-*trans*-2-decalone Ethylene Ketal (28).—A solution of 4(a)-cyano-*trans*-2-decalone ethylene ketal (**23**) (4.12 g, 0.018 mole) was refluxed for 70 hr in 20 ml of PhMe with 0.5 g of a 50% dispersion of NaH in mineral oil (previously washed with PhMe). The mixture was cooled, poured onto ice, and extracted with C_6H_6. The organic extracts were combined, washed with H_2O, and dried ($MgSO_4$). Evaporation of solvent afforded **28** as a tan oil (3.70 g, 89%). A sample of **28** was purified for elemental analysis by preparative tlc on Al_2O_3 (C_6H_{14}–Et_2O, 1:1). *Anal.* ($C_{13}H_{19}NO_2$) C, H, N.

4(e)-Dimethylaminomethyl-*trans*-2-decalone Ethylene Ketal (29).—A solution of 4(e)-cyano-*trans*-2-decalone ethylene ketal (**28**) (4.20 g, 0.019 mole) was reduced with excess LAH according to the directions for **16** to afford 2.90 g (0.013 mole, 68%) of the intermediate primary amine as a yellow oil.

Using the same method as shown for **17**, 0.496 g (0.002 mole) of the primary amine was converted into **29** (0.49 g, 86%). The MeI of **29** was prepared in C_6H_6 and recrystallized from EtOAc–MeOH, mp 210°. *Anal.* ($C_{16}H_{30}NO_2I$) C, H, N.

4(e)-Dimethylaminomethyl-*trans*-2-decalone (30).—As described in the synthesis of **26**, **29** (5.82 g, 0.023 mole) was converted into 3.58 g (0.017 mole, 75%) of **30**.

4(e)-Dimethylaminomethyl-2-hydroxy-2-phenyl-*trans*-decalin (31 and 32).—Compound **30** (2.33 g, 0.011 mole) was treated, as described for the synthesis of **27**, to give a liquid residue which was chromatographed on neutral Al_2O_3 (activity grade II). Elution with C_6H_6–EtOAc afforded **31** (1.26 g, 36%) followed by **32** (0.632 g, 18%).

The equatorial phenyl isomer **31** was a viscous material which could not be crystallized. The MeI of **31** was prepared in Et_2O and recrystallized from EtOAc–MeOH, mp 233°. *Anal.* ($C_{20}H_{32}NOI$) C, H, N.

The axial phenyl isomer **32** was recrystallized from EtOH–H_2O, mp 123–124°. *Anal.* ($C_{19}H_{29}NO$) C, H, N. Compound **32** (0.05 g) was dissolved in 5 ml of 10% HCl and stirred for 3 hr at 30°. The solution was cooled in an ice bath made basic with 10% NaOH, and extracted with Et_2O. The extracts were combined, dried ($MgSO_4$), and evaporated to afford 0.047 g of a mixture which was shown by tlc and column chromatography to consist of two components, a nonpolar compound of high R_f and the equatorial phenyl isomer **31**.

4(e)-Dimethylaminomethyl-2(e)-phenyl-2(a)-propionoxy-*trans*-decalin (5).—Using the method for the synthesis of **4**, compound **31** (1.15 g, 0.004 mole) gave a brown oil which was chromatographed on a column of Al_2O_3. Elution with C_6H_6 afforded 0.39 g (25%) of **5**. *Anal.* ($C_{22}H_{33}NO_2$) C, H, N.

4(e)-Dimethylaminomethyl-2(a)-phenyl-2(e)-propionoxy-*trans*-decalin (6).—A solution of 0.212 g (0.007 mole) of **32** treated as described for **4** gave a brown syrup which was purified by column chromatography on neutral Al_2O_3 (activity grade II). Elution with C_6H_6 and C_6H_6–EtOAc provided the equatorial ester **6** (0.177 g, 70%). *Anal.* ($C_{22}H_{33}NO$) C, H, N.

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Analgetics Based on the Pyrrolidine Ring. V

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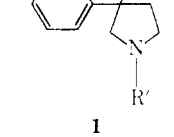
The synthesis of some new *m*-(3-propyl-3-pyrrolidinyl)phenols and the preliminary evaluation of their analgetic activities are described. A new optimum of activity has been found with *p*-R-phenethyl substitution on the pyrrolidine N. O-Methylation was much more deleterious than with the original *N*-Me optimum.

Previous papers[2,3] in this series have described an extensive number of pyrrolidines of diversified types. They can be represented by the general formula **1**. Further work on *m*-(1-methyl-3-propyl-3-pyrrolidinyl)-



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phenol (**1**, R = H; R′ = Me), now designated profadol, has shown that this compound is a potent analgetic with a particularly interesting spectrum of pharmacological activity.[4]

In the last paper in this series, some Me ethers of pyrrolidines with large N substituents were described. In particular, the (*p*-aminophenethyl)pyrrolidine [**1**, R = Me; R′ = $(CH_2)_2C_6H_4$-*p*-NH_2] showed definite analgetic activity. This paper describes experiments designed to investigate further the analgetic activity of pyrrolidine compounds in which the Me group has been replaced by a large substituent. Some additional work to examine the effect of substituents in the phenolic OH is also described.

Chemistry.—The synthesis of N-substituted pyrrolidines of type **1** by direct alkylation, or by N-acylation followed by reduction of the amide, is described in the Experimental Section. In the latter cases, where O-demethylation with BBr_3 was involved in the syn-

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thesis, it was found preferable to effect it on the amide prior to reduction rather than as the final stage. Straightforward procedures were not, however, always applicable and other routes were devised. In particular, difficulty was experienced in the O-demethylation of certain 1-alkyl-3-(*m*-methoxyphenyl)-pyrrolidines. *O*-Benzyl and *O*-tetrahydropyranyl derivatives of *m*-(1-acetyl-3-propyl-3-pyrrolidinyl)phenol were deacetylated (method L) to give useful intermediates available for N-substitution. The reaction of styrene oxide with 3-propyl-3-[*m*-(tetrahydropyran-2-yl)oxy]phenylpyrrolidine followed by removal of the tetrahydropyranyl protecting group (method G) proved to be a satisfactory route to the 1-(β-hydroxyphenethyl)pyrrolidine (**53**), since debenzylation of the appropriate *O*-benzylphenol did not always yield a satisfactory product in this particular instance.

Among other procedures, the ketal of 4-chlorobutyrophenone[5] has been used for N-alkylation of 3-(*m*-methoxyphenyl)-3-propylpyrrolidine; subsequent hydrolysis with alcoholic H_2SO_4 afforded 4-[3-(*m*-methoxyphenyl)-3-propyl-1-pyrrolidinyl]butyrophenone (method T). The enamine reaction (method A) and the Mannich reaction (method R) have also been utilized. Hydrogenation of 3-(*m*-methoxyphenyl)-1-(3-phenyl-2-propynyl)-3-propylpyrrolidine in the presence of Pd–$CaCO_3$ (poisoned by quinoline)[6] (method S) afforded 1-*cis*-cinnamyl-3-(*m*-methoxyphenyl)-3-propylpyrrolidine.

On debenzylation of 3-(*m*-acetoxyphenyl)-1-benzyl-3-propylpyrrolidine by hydrogenation (method H), it was of interest that O → N migration of the acetyl group occurred, affording an intermediate 3-pyrrolidinylphenol with the N protected.

In the course of routine examination of the physicochemical properties of the compounds prepared in this work, it was of interest to find that the ir amide absorption of 1-[(3,4-dihydroxyphenyl)acetyl]-3-(*m*-hydroxyphenyl)-3-propylpyrrolidine [**1**, R = H; R′ = $COCH_2C_6H_3$-3,4-$(OH)_2$] was at 1590 cm^{-1} in Nujol, unusually low. Even in $CHCl_3$ solution, it was still low at 1595 cm^{-1} but when examined in THF, it shifted to 1640 cm^{-1}, a more normal wave length.

Experimental Section[7]

Pyrrolidines used as starting materials were prepared by methods previously described.[2,3] The physical properties of new pyrrolidines prepared in this work appear in Table I and relevant experimental details are given below.

1-(1-Cyclohexen-1-yl)-3-(*m*-methoxyphenyl)-3-propylpyrrolidine. Method A.—*p*-Toluenesulfonic acid (0.2 g) and PhMe (30 ml) were added to cyclohexanone (4.9 g; 0.05 mole) and 3-(*m*-methoxyphenyl)-3-propylpyrrolidine (10.95 g; 0.05 mole) in PhMe (30 ml) and the mixture refluxed for 5 hr in a Dean–Stark apparatus. It was evaporated to dryness and distillation of the residue afforded the product as a colorless liquid.

3-(*m*-Methoxyphenyl)-1-phenyl-3-propylpyrrolidine. Method B.—The above cyclohexenylpyrrolidine (4.5 g) was heated with 10% Pd–C (0.55 g) under a slow stream of N_2 at 300° for 16 hr. The mixture was cooled, EtOH added, and the catalyst filtered off. Concentration of the filtrate and distillation of the residue afforded the 1-phenylpyrrolidine as a colorless viscous oil.

Phenol Esters. Method C.—The appropriate pyrrolidinylphenol was refluxed in pyridine with the acid anhydride for 2 hr. The mixture was evaporated to dryness and the product purified by distillation.

1-Alkylpyrrolidines. Method D.—The appropriate halide (0.1 mole) in dry DMF was added to the appropriate pyrrolidine (0.1 mole) and K_2CO_3 (0.2 mole) in dry DMF (20 ml). The mixture was maintained at 35–50° overnight, and poured into H_2O. The product was isolated with C_6H_6 and purified by distillation. In certain cases, the bases were converted into their hydrochlorides. In addition to the compounds listed in Table I the previously described[2] 1-benzyl-3-(*m*-methoxyphenyl)-3-propylpyrrolidine was also obtained by this method in 86% yield.

Pyrrolidinylphenols. Method E.—(Methoxyphenyl)pyrrolidines were converted into the corresponding phenols with HBr as previously described.[3]

Method F.—Methyl ethers were also converted into phenols by treatment with BBr_3 as described in earlier work.[8] Where the pyrrolidine was available only as the base and not as the hydrochloride, the base was dissolved in CH_2Cl_2 and the solution saturated with HCl at 0° before treating with BBr_3.

Method G.—As an example of the conversion of a tetrahydropyranyl ether into the corresponding phenol, 1-benzyl-3-propyl-3-{*m*-[(tetrahydropyran-2-yl)oxy]phenyl}pyrrolidine (4 g) in EtOH (15 ml) was stirred with 2 *N* H_2SO_4 (30 ml) for 15 min. The EtOH was evaporated and the residue poured into 5 *N* NaOH (100 ml). The solution was saturated with CO_2 and the liberated base extracted with Et_2O. *m*-(1-Benzyl-3-propyl-3-pyrrolidinyl)phenol (2.3 g) obtained by this method was identical with that from method E.

***m*-(1-Acetyl-3-propyl-3-pyrrolidinyl)phenol. Method H.**—Three different synthetic approaches were used. (a) 3-(*m*-Acetoxyphenyl)-1-benzyl 3-propylpyrrolidine (33.7 g) in EtOH (350 ml) was hydrogenated in the presence of 10% Pd–C (9 g) at atmospheric pressure and room temperature. The catalyst was filtered off; evaporation of the filtrate afforded a pale green oil which crystallized on standing. Recrystallization from C_6H_6–petroleum ether (bp 40–60°) afforded the 1-acetylpyrrolidine as white cubes (85% yield).

(b) Ac_2O (50 ml) was added to 3-(*m*-hydroxyphenyl)-3-propylpyrrolidine (5.3 g)[3] in pyridine (50 ml). The mixture was left overnight at room temperature and refluxed for 2 hr. It was evaporated to dryness and reevaporated three times from xylene to give the crude diacetyl compound as a light red glass (6.6 g; 88%). The crude diacetylpyrrolidine was dissolved in EtOH (15 ml) and stirred vigorously with 2 *N* NaOH (125 ml) for 40 min. The mixture was extracted with Et_2O, the aq solution charcoaled and saturated with CO_2. The 1-acetylpyrrolidine (67% yield) was extracted with C_6H_6.

(c) 1-Acetyl-3-(*m*-methoxyphenyl)-3-propylpyrrolidine, prepared as described in method J, was treated with BBr_3.[8] *m*-(1-Acetyl-3-propyl-3-pyrrolidinyl)phenol was obtained in 87% yield.

***N*-Acyl-*O*-alkyl-3-pyrrolidinylphenol. Method I.**—The O-alkylation of *m*-(1-acetyl-3-propyl-3-pyrrolidinyl)phenol is illustrated by the following. The acetylpyrrolidine (9.9 g) in DMF (20 ml) was added to a stirred suspension of NaH (1.95 g; 50% dispersion in oil) in DMF (20 ml). The mixture was heated to 45°. To the white pasty mass EtBr (3.2 ml) was added dropwise with stirring. The mixture was stirred for 1 hr and the resultant light orange solution evaporated to 0.25 volume, poured into H_2O (500 ml), and extracted with C_6H_6 (3 × 50 ml). The dried C_6H_6 solution was evaporated and the residue distilled *in vacuo*.

1-Acetyl-3-(*m*-methoxyphenyl)-3-propylpyrrolidine. Method J.—Ac_2O (40 ml) was added to 3-(*m*-methoxyphenyl)-3-propylpyrrolidine (21.9 g) in glacial AcOH (40 ml) and the mixture refluxed for 1 hr. Excess solvent, etc., was removed by distillation *in vacuo* and the residue poured into 2 *N* NaOH (125 ml). The product was extracted into Et_2O and purified by distillation.

1-Acetyl-3-(*m*-propoxyphenyl)-3-propylpyrrolidine. Method K.—Hydrogenation of a [*m*-(allyloxy)phenyl]pyrrolidine (8.6 g) in 96% EtOH (50 ml) in the presence of 10% Pd–C at atmospheric pressure and 50°, afforded a convenient route to the corresponding O-Pr compound.

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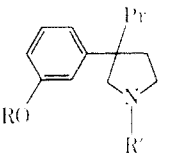
TABLE I

PYRROLIDINES



	R	R'	Bp, °C (mm)	Method	Yield, %	$n^{20}D$	Formula	Analyses
1	Me		166–170 (0.5)	A	62	1.5498	$C_{20}H_{29}NO$	C, H, N
2	Me	Ph	170–173 (0.3)	B	60	1.5888	$C_{20}H_{25}NO$	C, H, N
3	COMe	CH_2Ph	183–188 (0.7)	C	82	1.5472	$C_{22}H_{27}NO_2$	C, H, N
4		CH_2Ph	190–196 (0.25)	D	38	1.5570	$C_{23}H_{33}NO_2$	C, H, N
5	H	CH_2Ph	192–197 (0.8); 108–109[a]	E, G	60; 73		$C_{20}H_{25}NO$	C, H, N
6	Me	$[CH_2]_2Ph$	184–186 (0.7)	D	67	1.5531	$C_{22}H_{29}NO$	H, N; C[b]
7	Me	$[CH_2]_2Ph$	167–168[a]	D		[c]	$C_{22}H_{30}ClNO$	C, H, N
8	H	$[CH_2]_2Ph$	138–140[a]	E, M	38		$C_{21}H_{27}NO$	C, H, N
9	COMe	$[CH_2]_2Ph$	147–149[a]	C	68	[c]	$C_{23}H_{30}ClNO_2$	C, H, N
10	H	COMe	148–149[a]	H	[d]		$C_{15}H_{21}NO_2$	C, H, N
11	CH_2Ph	COMe	216–220 (0.3)	I	90	1.5695	$C_{22}H_{27}NO_2$	C, H, N
12	$CH_2CH{=}CH_2$	COMe	173–178 (0.3)	I	98	1.5426	$C_{18}H_{25}NO_2$	C, H, N
13	Et	COMe	160–163 (0.3)	I	83	1.5360	$C_{17}H_{25}NO_2$	C, H, N
14	Me	COMe	153–158 (0.4)	J	86	1.5388	$C_{16}H_{23}NO_2$	C, H, N
15	Pr	COMe	169–171 (0.3)	K	91	1.5328	$C_{18}H_{27}NO_2$	C, H, N
16	CH_2Ph	H	171–174 (0.3); 65–67[a]	L	80		$C_{20}H_{25}NO$	C, H, N
17	CH_2Ph	H	79–80[a]	L		[c]	$C_{20}H_{26}ClNO \cdot H_2O$	C, H, N
18	$CH_2CH{=}CH_2$	H	123–126 (0.4)	L	97	1.5406	$C_{16}H_{23}NO$	C, H, N
19	Pr	H	112–116 (0.1)	L	85	1.5283	$C_{16}H_{25}NO$	C, H, N
20	Et	H	110–112 (0.2)	L	82	1.5321	$C_{15}H_{23}NO$	H, N; C[e]
21	CH_2Ph	$[CH_2]_2Ph$	216–222 (0.3)	D	64	1.5755	$C_{28}H_{33}NO$	H, N; C[f]
22	Me	$[CH_2]_3Ph$	147–148[a]	D	72	[c]	$C_{23}H_{32}ClNO$	C, H, N
23	H	$[CH_2]_3Ph$	157–161[a]	F	72	[c]	$C_{22}H_{30}ClNO$	C, H, N
24	Me	$[CH_2]_2OPh$	202–205 (0.8)	D	69	1.5518	$C_{22}H_{29}NO_2$	C, H, N
25	H	$[CH_2]_2OPh$	217–220 (0.7); 102–103[a]	U	40		$C_{21}H_{27}NO_2$	C, H, N
26	H	$[CH_2]_2C_6H_4$-*p*-NO_2	108–110[a]	F	60	[g]	$C_{21}H_{27}BrN_2O_3$	C, H, N
27	H	$[CH_2]_2C_6H_4$-*p*-NH_2	145–150[a]	N	78	[c]	$C_{21}H_{28}N_2O \cdot 1.95HCl \cdot 2H_2O$	C, H, Cl, N
28	Me	$COCH_2C_6H_4$-*p*-OMe	238–242 (0.6)	O	53	1.5665	$C_{23}H_{29}NO_3$	C, H, N
29	CH_2Ph	$COCH_2C_6H_4$-*p*-OMe	280–290 (0.6)	O	67		$C_{29}H_{33}NO_3$	H, N; C[h]
30	Me	$[CH_2]_2C_6H_4$-*p*-OMe	194–198 (0.4)	P	93	1.5506	$C_{23}H_{31}NO_2$	C, H, N
31	Me	$[CH_2]_2C_6H_4$-*p*-OMe	136–137[a]	P		[c]	$C_{23}H_{32}ClNO_2$	C, H, N
32	CH_2Ph	$[CH_2]_2C_6H_4$-*p*-OMe	254–257 (0.5)	P	71	1.5780	$C_{29}H_{35}NO_2$	C, H, N
33	H	$[CH_2]_2C_6H_4$-*p*-OMe	106–108[a]	M	92	[c]	$C_{22}H_{30}ClNO_2 \cdot H_2O$	C, H, N
34	H	$[CH_2]_2C_6H_4$-*p*-OH	188–190[a]	F	91		$C_{21}H_{27}NO_2$	C, H, N
35	H	$[CH_2]_2C_6H_4$-*p*-OH	213–215[a]	F		[c]	$C_{21}H_{28}ClNO_2$	C, H, N
36	Me	$[CH_2]_2C_6H_3$-(3,4-diOMe)	214–215 (0.5)	P	70	1.5526	$C_{24}H_{33}NO_3$	C, H, N
37	Me	$[CH_2]_2C_6H_4$-*m*-OMe	200–202 (0.5)	P	85	1.5521	$C_{23}H_{31}NO_2$	C, H, N
38	Me	$[CH_2]_2C_6H_4$-*o*-OMe	196–198 (0.5)	P	76	1.5545	$C_{23}H_{31}NO_2$	C, H, N
39	H	$[CH_2]_2C_6H_3$-(3,4-diOH)[i]	78–80[a]	F	71		$C_{22}H_{33}NO_7$	C, N; H[k]
40	H	$[CH_2]_2C_6H_4$-*m*-OH	82–84[a]	F	43		$C_{21}H_{27}NO_2 \cdot 0.5C_6H_6$	C, H, N
41	H	$[CH_2]_2C_6H_4$-*o*-OH	47–49[a]	F	83		$C_{21}H_{27}NO_2$	C, H, N
42	COMe	$[CH_2]_2C_6H_4$-*p*-OCOMe	232–236 (0.3)	Q	78	1.5380	$C_{25}H_{31}NO_4$	C, H, N
43	COMe	$[CH_2]_2C_6H_3$-(3,4-di-OCOMe)	See text	Q	85		$C_{27}H_{33}NO_6$	C, H, N
44	H	$COCH_2C_6H_3$-(3,4-di-OH	205–207[a]	F[l]	66		$C_{21}H_{25}NO_4$	C, H, N
45	H	$COCH_2C_6H_4$-*m*-OH	124–125[a]	F[l]	62		$C_{21}H_{25}NO_3$	H, N; C[m]
46	CH_2Ph	$[CH_2]_2COPh$	75–76[a]	R	30		$C_{29}H_{33}NO_2$	C, H, N
47	Me	$CH_2C{\equiv}CPh$	184–189 (0.2)	R	75	1.5755	$C_{23}H_{27}NO$	C, H, N
48	Me	$CH_2CH{=}CHPh$[n]	178–181 (0.3)	S	74	1.5720	$C_{23}H_{29}NO$	C, H, N

TABLE I (*Continued*)

	R	R′	Bp, °C (mm)	Method	Yield, %	$n^{20}D$	Formula	Analyses
49	Me		230–232 (0.9)	D	90	1.5446	$C_{26}H_{35}NO_3$	C, H, N
50	Me	$[CH_2]_3COPh$	228–230 (0.9)	T	93	1.5543	$C_{24}H_{31}NO_2$	C, H, N
51	Me	$CH_2CHOHPh$	130–132[a]	U	26	*c*	$C_{22}H_{30}NO_2$	C, H, N
52	CH_2Ph	$CH_2CHOHPh$	238–243 (0.3)	U	60		$C_{28}H_{33}NO_2$	H, N; C[o]
53	H	$CH_2CHOHPh$	224–228 (0.4)	G	32		$C_{21}H_{27}NO_2$	H, N; C[p]
54	Et	Me	107–111 (0.3)	V	85	1.5262	$C_{16}H_{25}NO$	C, H, N
55	$CH_2CH=CH_2$	Me	108–110 (0.2)	V	83	1.5296	$C_{17}H_{25}NO$	C, H, N
56	Pr	Me	110–114 (0.1)	V	76	1.5236	$C_{17}H_{27}NO$	C, H, N
57	CH_2Ph	Me	162–165 (0.3)	V	84	1.5682	$C_{21}H_{27}NO$	C, H, N
58	CH_2Ph	Me	69–70[a]	V		*c*	$C_{21}H_{28}ClNO \cdot H_2O$	C, H, N
59	Me	CH_2CO_2Et	148–153 (0.5)	D	80	1.5163	$C_{18}H_{27}NO_3$	H, N; C[q]
60	Me	$CH_2CONHPh$	69–70[a]	W	45		$C_{22}H_{28}N_2O_2$	C, H, N

[a] Melting point. [b] C: calcd, 81.7; found, 81.1. [c] Hydrochloride. [d] See text. [e] C: calcd, 77.2; found, 78.0. [f] C: calcd, 84.1; found, 83.3. [g] Hydrobromide. [h] C: calcd, 78.5; found, 78.0. [i] In isolating this compound by dissolving in 6 *N* ammonia, careful pH control (using ammonium acetate as buffer) appeared to be necessary. [j] Succinate salt. [k] H: calcd, 7.3; found, 7.8. [l] From the crude amide prepared by method O. [m] C: calcd, 74.3; found 73.8. [n] *cis* Isomer. [o] C: calcd, 80.9; found, 80.3. [p] C: calcd, 77.5; found, 78.2. [q] C: calcd 70.8; found 70.1.

***O*-Alkylpyrrolidinylphenols. Method L.**—1-Acetyl-3-(*m*-ethoxyphenyl)-3-propylpyrrolidine (9.1 g) in EtOH (60 ml) was refluxed with a solution of KOH (45 g) in EtOH (160 ml) and H_2O (60 ml) for 18 hr. The solution was evaporated to half-bulk and diluted with H_2O (250 ml) and the product extracted with Et_2O.

Debenzylation. Method M.—The [*m*-(benzyloxy)phenyl]pyrrolidine (0.05 mol) was debenzylated by hydrogenation in EtOH in the presence of 10% Pd–C (0.5 g) at atmospheric pressure. Removal of the catalyst, followed by evaporation of the filtrate, gave the pyrrolidinylphenol.

***m*-[1-(*p*-Aminophenethyl)-3-propyl-3-pyrrolidinyl]phenol·HCl. Method N.**—*m*-[1-(*p*-Nitrophenethyl)-3-propyl-3-pyrrolidinyl]-phenol·HBr (12.4 g) in EtOH was hydrogenated at atmospheric pressure in the presence of 10% Pd–C (0.75 g). The catalyst was filtered off and the filtrate evaporated. The residue was basified with $NaHCO_3$ and dissolved in MeOH and 3 *N* methanolic HCl (25 ml) added. Evaporation afforded a cream residue which was dissolved in *i*-PrOH, the solution charcoaled, and Et_2O containing a trace of HCl added to the filtrate. The cream crystalline hydrochloride had mp 145–150°. Potentiometric titration (50% EtOH) was as expected but indicated that the product was slightly short of HCl.

3-(*m*-Methoxyphenyl)-1-[*p*-methoxyphenyl)acetyl]-3-propylpyrrolidine. Method O.—3-(*m*-Methoxyphenyl)-3-propylpyrrolidine (2.2 g) was suspended in 2 *N* NaOH (10 ml) and H_2O (5 ml) and cooled to 5°. (*p*-Methoxyphenyl)acetyl chloride[9] (1.7 g) in C_6H_6 (5 ml) was added with stirring. The mixture was stirred at 5–10° for 0.5 hr, allowed to warm up to room temperature, and stirred for a further 2 hr. The mixture was extracted with Et_2O, the Et_2O solution washed with 2 *N* NaOH, H_2O, and 2 *N* HCl, and evaporated. Distillation gave the product (2.0 g) as a colorless oil.

The corresponding 3-[*m*-(benzyloxy)phenyl]pyrrolidine was prepared similarly.

1-(*p*-Methoxyphenethyl)-3-(*m*-methoxyphenyl)-3-propylpyrrolidine. Method P.—The appropriate amide (9.3 g; see above) in Et_2O (50 ml) was refluxed with a suspension of LAH (3.2 g) in Et_2O (75 ml) for 4 hr. Normal work-up procedures gave the 1-(*p*-methoxyphenethyl)pyrrolidine which afforded a hydrochloride as white cubes.

1-(*p*-Acetoxyphenethyl)-3-(*m*-acetoxyphenyl)-3-propylpyrrolidine. Method Q.—1-(*p*-Hydroxyphenethyl)-3-(*m*-hydroxyphenyl)-3-propylpyrrolidine·HCl (8.0 g), AcONa (8.0 g), and Ac_2O (80 ml) were heated on the steam bath with stirring for 1 hr. The mixture was cooled, poured into ice–water (500 ml), and stirred for 15 min. The aq solution was extracted with Et_2O (100 ml) and adjusted to pH 7 with 6 *N* NH_3. The diacetate was isolated with Et_2O and purified by distillation.

3-(*m*-Acetoxyphenyl)-1-(3,4-diacetoxyphenethyl)-3-propylpyrrolidine, prepared by a similar method, decomposed on distillation. In a repeat preparation it was found that the yellow glass, obtained on evaporation of the final Et_2O extracts, analyzed for the required triacetate.

Method R.—This method utilises the Mannich reaction, the pyrrolidine serving as the amine, and is based on work reported by El'stov, *et al.*[10] 3-[*m*-(Benzyloxy)phenyl]-3-propylpyrrolidine (8.85 g), EtOH (50 ml), 4 *N* ethanolic HCl (10 ml), paraformaldehyde (1.8 g), and acetophenone (3.6 ml) were refluxed for 20 hr in the presence of a trace of HCl. The solution was evaporated, the residue poured into H_2O and extracted with Et_2O. The aq layer, containing the oily hydrochloride, was basified (5 *N* NaOH) and the product isolated with Et_2O.

In another experiment, acetophenone was replaced by phenylacetylene and the ethanolic HCl omitted. The mixture was refluxed for 3 hr and poured into 2 *N* HCl. Subsequent work-up was as above.

1-*cis*-Cinnamyl-3-(*m*-methoxyphenyl)-3-propylpyrrolidine. Method S.—3-(*m*-Methoxyphenyl)-1-(3-phenyl-2-propynyl)-3-propylpyrrolidine (6.7 g) was hydrogenated at room temperature and pressure in the presence of Pd–$CaCO_3$ (poisoned by quinoline) (0.25 g). Normal work-up procedures afforded the cinnamylpyrrolidine.

4-[3-(*m*-Methoxyphenyl)-3-propyl-1-pyrrolidinyl]butyrophenone. Method T.—The ketal **49** (0.025 mole) in EtOH (100 ml) was hydrolyzed by refluxing with 2 *N* H_2SO_4 (175 ml) for 2 hr, H_2O (200 ml) was added, the solution was basified with solid K_2CO_3, and the product was extracted with Et_2O.

α-Phenyl-1-pyrrolidineethanols. Method U.—3-(*m*-Methoxyphenyl)-3-propylpyrrolidine (4.0 g), styrene oxide (4.0 g), and C_6H_6 (40 ml) were refluxed for 16 hr. Solvent was removed and ethereal HCl added to the residue. The hydrochloride was recrystallized from *i*-PrOH–Et_2O.

(Alkoxyphenyl)-1-methylpyrrolidines. Method V.—(Alkoxyphenyl)pyrrolidines were N-methylated by heating with HCO_2H (98%) and aq CH_2O (40%) at 120° until evolution of CO_2 ceased. The mixture was refluxed for 2.5 hr, cooled, and poured into ice-cold K_2CO_3 solution and the product extracted into Et_2O.

3-(*m*-Methoxyphenyl)-3-propyl-1-pyrrolidineacetanilide. Method W.—Aniline (4.8 g) was added to a solution of EtMgBr [from Mg (1.4 g) and EtBr (7.5 g)] in Et_2O (200 ml). After refluxing for 15 min, ethyl 3-(*m*-methoxyphenyl)-3-propyl-1-pyrrolidineacetate (7.03 g) in Et_2O (40 ml) was added and the mixture refluxed for a further 30 min. After cooling and addition of saturated NH_4Cl, the anilide was isolated from the Et_2O as white plates crystallizing from petroleum ether (bp 60–80°).

3-{*m*-[(Tetrahydropyran-2-yl)oxy]phenyl}-3-propylpyrrolidine. Method X.—*m*-(1-Acetyl-3-propyl-3-pyrrolidinyl)phenol (10.2 g) was suspended in 2,3-dihydropyran (31.0 ml). A few drops of concd HCl were added and the mixture heated to 50° for 2.5 hr, followed by 16 hr at room temperature. Et_2O was added, the mixture washed with 2 *N* NaOH, and a yellow oil (32 g) isolated

(9) J. C. Cain, J. L. Simonsen, and C. Smith, *J. Chem. Soc.*, **103**, 1035 (1913).

(10) A. V. El'stov, A. G. Chigarev, and N. T. Starykh, *J. Gen. Chem. U.S.S.R.*, **34**, 3385 (1964).

from the Et_2O. Hydrolysis of the *N*-acetyl compound with ethanolic KOH (method L above) afforded a yellow oil (87% overall yield), bp 149–154° (0.3 mm), ($n^{20}D$ = 1.5342), which was N-alkylated directly.

***m*-[1-(2-Phenoxyethyl)-3-propyl-3-pyrrolidinyl]phenol. Method Y.**—*m*-(3-Propyl-3-pyrrolidinyl)phenol (6.15 g) in DMF (30 ml), $NaHCO_3$ (6.3 g), and 2-phenoxyethyl bromide (6.03 g) in DMF (20 ml) were stirred at 45° for 17 hr. The cooled mixture was poured into H_2O (150 ml), 2 *N* NaOH (100 ml) added, and the mixture extracted with Et_2O. The main bulk of the (phenoxyethyl)pyrrolidine was present in the Et_2O extracts from which it was isolated. The product was purified by distillation or by recrystallization from MeOH.

Pharmacology.—Acute lethal toxicities and antinociceptive (analgetic) potencies were estimated in young male rats by the intraperitoneal route as described earlier[11] in some detail. Essentially, the antinociceptive potencies are based reciprocally on doses estimated to cause equivalent elevations of the amount of mechanical pressure on the tail required to elicit squeaking. It is pertinent to note that thoughtful use of such procedures has been highly predictive of the kind of central pain-releaving action possessed by narcotics ("agonist" type) while they have not been useful in showing the kind possessed by certain "narcotic antagonists" except, perhaps, in small part.[5a]

When possible, soluble addition salts, or bases with equivalent HCl, were dissolved in 1 ml of 0.9% w/v NaCl/100 g of rat. Numerous exceptions forced by poor solubilities are noted in Tables II and III.

A little over half (31) of the compounds listed in Table I were studied in rats. In the five instances where both the base and its salt are listed, only the salts were studied. Several compounds (22) were consumed as intermediates in the synthesis of other pyrrolidines (**1**, **3**, **4**, **11–15**, **18–21**, **28**, **29**, **32**, **36–38**, **45**, **46**, **52**, **59**). The sample of **53** was too small for biological study. Compound **44** was tested for general neuromotor effects in mice; doses up to 250 mg/kg administered intraperitoneally in suspension were without clear effect.

Discussion

Substitutions on N.—As in profadol itself, N-methylation clearly had been the optimum among N substitutions previously reported.[2,3] However, most[3] of the earlier exploration of heavier N substitutions was done with the phenolic function methylated, and it was necessary to study possible biological interactions of such substitutions with the heretofore superior free phenolic function as it exists in profadol.

The essential result with the heavier N substitutions (Table II) is that on going from N-methylation to N-phenethylation, either with or without *p*-NH_2, an unmuzzled *m*-phenolic function on the 3-Ph becomes more critical in biological effects. Whereas with O-methylation inferior though clear antinociceptive activity occurred, with the phenolic function unmuzzled a new and higher optimum of potency or potency:toxicity ratio was obtained. With *p*-OH on the N-phenethyl, although solubility at biologically tolerable pH deteriorated, superior potency could still be demonstrated with the 3-*m*-phenol unmuzzled. With the generally less advantageous *p*-NO_2 or *p*-OMe on the *N*-phenethyl, differences in biological effects between the free and muzzled 3-*m*-phenolic function could not be shown clearly; while *m*-OH, *o*-OH, and 3,4-$(OH)_2$ led to progressively deteriorating albeit still fairly clear activity with the 3-*m*-phenol free.

With and/or without methylation of the 3-*m*-phenol, considerable variety of N substitutions aside from Me and phenethyl (with *p*-H, NH_2, OH, OMe, NO_2, or *m*-OH) have failed to yield clear antinociceptive activity of the traditional (agonist) type such as demonstrable by the method used (Table II): higher alkyl, with varying degrees and types of oxidation; acyl; Ph; CH_2Ph; C_2Ph with varying oxidation or insertions of O or N; C_3Ph or C_4Ph with varying oxidations.

***m*-[1-(*p*-Aminophenethyl)-3-propyl-3-pyrrolidinyl]-phenol.**—Compound **27** (**1**, R = H; R′ = $[(CH_2)]_2C_6H_4$-*p*-NH_2), most potent by the ip route and desirably soluble as the 2HCl salt, has been compared in some detail with profadol (**1**, R = H; R′ = Me). Time-action studies of the antinociceptive action in rats by the subcutaneous and oral routes, using experimental designs described elsewhere,[4a] confirmed the superior parenteral potency; it was 2.3(1.7 to 3.1)$_{95\%}$ times that of profadol (base:base) by the subcutaneous route. However, by the oral route this compound was only 0.83(0.48 to 1.3)$_{95\%}$ as potent as profadol, indicating a lower oral:parenteral efficiency ratio. Furthermore, no significant qualitative differences between this new compound and profadol could be demonstrated in shapes of time-action curves or in ratios of activity to occurrence of sublethal side effects by either route. Finally, while the new compound resembled profadol[4a,b] in failing to suppress signs of withdrawal of morphine from heavily dependent monkeys, it differed from profadol[4a,c] in not clearly precipitating signs of withdrawal in such monkeys while they were receiving their regular morphine injections.[12] Its physical dependence liability, therefore, may be greater than profadol's.

Acylation of the 3-*m*-Phenolic Function.—As reviewed in Table III, varying acylation (**1**, R = COMe, COEt, CO-*n*-Pr, or CO-*i*-Pr; R′ = Me) had resulted in constant, moderate reduction in potency of profadol without striking alterations of the potency:toxicity ratio. We have suggested that this constant potency with varying acylation results from *in vivo* hydrolysis of the esters to profadol.[3] This inference is supported by the finding that acylation of the $N(CH_2)_2Ph$ compound, diacylation of the $N(CH_2)_2C_6H_4$-*p*-OH compound, and triacylation of the $N(CH_2)_2C_6H_3$-3,4-$(OH)_2$ compound result in analogous slight to moderate changes in biological properties (Table II).

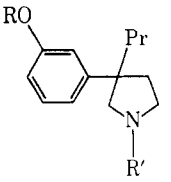
It is conceivable that delay in such hydrolysis might prolong the duration of action. Time-action studies by the oral route, using the same experimental designs indicated above, did, indeed, suggest some slight prolongation of action of the several esters of profadol by comparison with profadol itself, but the magnitude of prolongation was not considered useful. It should be pointed out that prolongation by a parenteral route could be greater because of avoiding high initial portal concentrations of drug.

Alkylation of the 3-*m*-Phenolic Function.—It was found earlier[2,3] that O-methylation of profadol reduces its potency by one-half and lowers its potency:toxicity index to the level of prodilidine's. It is now found (Table III) that certain higher O-alkylations (**1**; R = Et, *n*-Pr, CH_2CHCH_2, CH_2Ph; R′ = Me) still further reduce the level and quality of activity. It is recalled that O-methylation also shuts off an increasingly deleterious effect of increasing length of 2-*n*-alkylation

(11) J. F. Cavalla, J. Davoll, M. J. Dean, C. S. Franklin, D. M. Temple, J. Wax, and C. V. Winder, *J. Med. Pharm. Chem.*, **4**, 1 (1961).

(12) Personal communication from Dr. J. E. Villarreal of the University of Michigan.

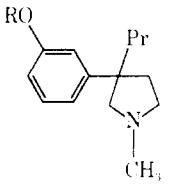
TABLE II: SUBSTITUTIONS ON N



No.	R′	Estd ip potency[a]	Estd av ip lethal dose (mg of base/kg)[b]	Potency × lethal dose / (0.8 × 133)[c]
R = H				
d	Me	2.5	83	1.9
d	H	(0.1)[e]	119	(0.1)
d	*n*-Pr	None[f]	60	
10	COMe	None[g,h]	>1600[g]	
5	CH_2Ph	None[f,g]	378[g]	
8	$(CH_2)_2Ph$	4.9	259[i]	<12.[i]
26	$(CH_2)_2C_6H_4$-*p*-NO_2	0.2[i]	375[i]	0.7
27	$(CH_2)_2C_6H_4$-*p*-NH_2	5.8	52	2.8
35	$(CH_2)_2C_6H_4$-*p*-OH	3.5[i]	117[i]	<3.8[i]
33	$(CH_2)_2C_6H_4$-*p*-OMe	0.6[i]	126[i]	<0.7[i]
40	$(CH_2)_2C_6H_4$-*m*-OH	0.6[i,k]	145[i,k]	<0.8[i]
41	$(CH_2)_2C_6H_4$-*o*-OH	0.3[i,k]	183[i,k]	(<0.4)[i]
39	$(CH_2)_2C_6H_3$-3,4-$(OH)_2$	0.05[i]	≥1190[i]	*ca.* 0.5[i]
25	$(CH_2)_2OPh$	(0.3)[e]	77	(0.2)
23	$(CH_2)_3Ph$	None[f,j]	492[j]	
R = COMe				
d	Me	1.7	97	1.5
d	*n*-Pr	None[f]	59	
9	$(CH_2)_2Ph$	3.7	59	2.0
42	$(CH_2)_2C_6H_4$-*p*-OCOMe	3.9	137[i]	<5.0[i]
43	$(CH_2)_2C_6H_3$-3,4-$(OCOMe)_2$	(0.05?)[e,l]	≥400[l]	(0.2?)[l]
R = Me				
d	Me	1.3	67	0.8
d	Et	(0.4)[e]	64	(0.2)
d	*n*-Pr	(0.3)[e]	84	(0.2)
d	$CH_2C{\equiv}CH$	(0.2)[e]	168	(0.3)
d	*n*-Hep	None[f,m]	387[m]	
d	$(CH_2)_2O(CH_2)_2OH$	(0.2)[e]	137	(0.2)
2	Ph	None[h,m]	>1600[m]	
d	CH_2Ph	(0.1)[e,i]	189[i]	(<0.2)[i]
7	$(CH_2)_2Ph$	0.8	293[i]	<2.4[i]
d	$(CH_2)_2C_6H_4$-*p*-NO_2	0.4[i]	167[i]	<0.6[i]
d	$(CH_2)_2C_6H_4$-*p*-NH_2	0.9	56	0.5
31	$(CH_2)_2C_6H_4$-*p*-OMe	0.6	99	0.6
51	$CH_2CHOHPh$	(0.2)[e]	82	(0.2)
d		(0.1)[e]	112	(0.1)
24	$(CH_2)_2OPh$	(0.2)[e]	146	(0.3)
60	$CH_2CONHPh$	None[g,h]	>1600[g]	
22	$(CH_2)_3Ph$	(0.3)[n]	372[i]	(<1.1)[i,n]
48	$CH_2CH{=}CHPh$ (*cis*)	None[f,m]	461[m]	
47	$CH_2C{\equiv}CPh$	None[f,i]	1130[i]	
d	$(CH_2)_2CHOHPh$	(0.5)[e]	59	(0.3)
d	$(CH_2)_2CH(OCOC_2H_5)Ph$	0.2[i]	317[i]	(<0.5)[i]
d	$(CH_2)_2COPh$	(0.6)[e,i]	59[i]	(<0.3)[i]
49		None[f,m]	218[m]	
50	$(CH_2)_3COPh$	None[f,m]	346[m]	
R = CH_2Ph				
58	Me	0.8	59[i]	(<0.4)[i]
17	H	None[f]	95[i]	

[a] Relative to codeine (base/base) 30 min after treatment. [b] From small numbers of young, male, Sprague–Dawley rats of differing lots. [c] 1,2-Dimethyl-3-phenyl-3-propionoxypyrrolidine (prodilidine) of the earlier ester series is set equal to 1.[11] [d] See ref 2 and 3. [e] Figures in parentheses were obtained by extrapolation. An effect equivalent to the reference, 11.3 mg of codeine base/kg, was not actually obtained at one-fourth the lethal dose. [f] At one-fourth the lethal dose. [g] Base suspended in saline–acacia. [h] At 400 mg/kg. [i] Incomplete solution, especially at lethal dose levels; hence lethal dose and index (last column) probably biased upward and potency sometimes downward. [j] Hydrochloride or hydrobromide suspended in vegetable oil. [k] With NaOH. [l] Sample was exhausted before the estimates were completed. [m] Base dissolved and/or suspended in vegetable oil. [n] Prostration at one-fourth and one-eighth the lethal dose; inferior to 11.3 mg of codeine base/kg at one-sixteenth the lethal dose; hence quality of activity questionable.

TABLE III
SUBSTITUTIONS IN THE PHENOLIC HYDROXYL



No.	R	Estd ip potency[a]	Estd av ip lethal dose (mg of base/kg)[b]	Potency × $\frac{\text{lethal dose}}{(0.8 \times 133)}$[c]
d	H	2.5	83	1.9
d	COMe	1.7	97	1.5
d	COEt	1.8	91	1.6
d	CO-*n*-Pr	1.7	137	2.2
d	CO-*i*-Pr	1.7	103	1.6
d	Me	1.3	67	0.8
54	Et	(1.1)[e]	36	(0.4)
56	*n*-Pr	(0.8)[e]	35[i]	(<0.3)[i]
55	$CH_2CH{=}CH_2$	(0.8)[e]	43	(0.3)
58	CH_2Ph	0.8	59[i]	(<0.4)[i]

[a-e,i] See corresponding footnotes of preceding table.

apparently associated with changing zwitterionic properties of the free phenol[3] and reverses (*supra*) a favorable effect of going from NMe to *N*-phenethyl or *para* substituted phenethyl (not occurring with azetidines[8]).

It is interesting to consider the analogy in the relationships between profadol and its Me ether and between morphine and codeine. The improvement in oral:parenteral efficiency of codeine over morphine is well known. Analogously, in graded dose, time–action studies, we have found that on going from the parenteral to the oral route the potency of the Me ether of profadol improves from about 0.5 that of profadol (Table III) to $0.90(0.71 \text{ to } 1.2)_{95\%}$. However, no significant change in the shape of the time–action curves could be shown, and, unfortunately, the acute toxicity of the ether by the oral route became $2.0(1.5 \text{ to } 3.9)_{95\%}$ times that of free profadol. Presumably, etherification improves the lipid–aqueous distribution coefficient to enhance intestinal absorption, and shuts off metabolic conjugation.

Recapitulation.—While studies of the general structure **1** continue, some major inferences to this point can be recapitulated. In terms of traditional (agonist type) antinociceptive action in rats, (a) the single O function in the *meta* position of the phenyl nucleus is essental. (b) Of 3-*n*-alkylations the 3-*n*-Pr is apparently optimal. (c) Further substitutions in the pyrrolidine nucleus have been deleterious, except that (d) tertiary N is essential. (e) Optima appear with NMe and with $N(CH_2)_2Ph$ (with or without certain *para* substitutions). (f) Varying acylation of the *m*-phenolic function results in a mild, fairly constant reduction of potency, possibly associated with a fairly facile *in vivo* deacylation needed for full activity. (g) *m*-O-Methylation reduces potency except when it muzzles an unfavorable zwitterionic interaction of 2-alkylation with the phenolic function; it often increases toxicity; it can increase oral:parenteral efficiency; and (by contrast with azetidines[8]) it muzzles a favorable effect of going from NMe to $N(CH_2)_2Ph$ (with or without *para* substitution). (h) Higher O-alkylation is still more unfavorable to degree and quality of activity. (i) By contrast with piperidines,[13] the pyrrolidines (**1**) exhibit varying degrees of apparent separation of narcotic-like physical dependence liability, as evaluated in monkeys, from narcotic-like (agonist) antinociceptive action.

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(13) S. M. McElvain and D. H. Clemens, *J. Amer. Chem. Soc.*, **80**, 3915 (1958).