Table II. Hydrolysis of Ethoxycarbonyl Derivatives

Starting material	I Compd	R_1	R_2	R_3	R_4	Yield, %	Mp, °C	Solv used for recrystn	Formula[a]	ED_{20}, mg/kg	Relative activity calcd by ED_{20} (Reserpine = 1.00)
12 (800 mg)	14	H	OH	OCH_3	H	63 (450 mg)	162–164	$CHCl_3$–hexane	$C_{33}H_{38}N_2O_8 \cdot H_2O$	2.1	0.67
13 (1.5 g)	15	H	OCH_3	OH	H	78 (1.0 g)	259–260	MeOH	$C_{33}H_{38}N_2O_8 \cdot H_2O$	0.8	1.75

[a] See Table I, footnote *a*.

Pharmacology. In general, rescinnamine-like compounds differ from reserpine in hypotensive effect because of its dose dependence and they seem to have a lower adverse effect than that of reserpine. Therefore, the antihypertensive activity of rescinnamine-like compounds was examined by comparison with rescinnamine and reserpine by the canulation method in the unanesthetized, spontaneously hypertensive rat.[9] After iv injection of compounds to groups of 3 rats, the ratio of hypotensive effect for 5 hr was calcd by ED_{20}. The ED_{20} value was calcd by the dose–response regression line. The effect of rescinnamine-like compounds in decreasing the systemic blood pressure depended upon the dose used, and **9** and **15** were the most effective among the 7 compounds shown in Table I.

Experimental Section†

Methyl Reserpate (3). After addn of 0.27 ml of H_2O and 150 ml of THF to a soln of 0.34 g of Na in 300 ml of MeOH, 5 g of reserpine–HCl was added to the resulting soln which was stirred for 24 hr at room temp. The reaction mixt was evapd to give a residue, a soln of which in $CHCl_3$ was washed (satd $NaHCO_3$ and H_2O) and dried (Na_2SO_4). Evapn of the solvent gave a yellowish powder, which was recrystd from MeOH to give 2.87 g (93%) of **3** as colorless needles, mp 233–239°; lit.[2] mp 235–240°.

Esterification of Methyl Reserpate (3). A mixt of 2 g of 3,4-dimethoxycinnamic acid (**4**),[4] 2 ml of $SOCl_2$, and 20 ml of PhH was refluxed for 3 hr. The excess of $SOCl_2$ and PhH was distd off to give the acid chloride as a solid, which was dissolved in PhH. The resulting soln was added to a mixt of 1 g of methyl reserpate and 30 ml of pyridine. The mixt was allowed to stand with occasional shaking at room temp for 24 hr, acidified with dil HCl, and extd ($CHCl_3$). After washing with satd $NaHCO_3$ and H_2O, the $CHCl_3$ layer was distd off to give a brown gum, which was triturated with Et_2O and then recrystd from MeOH–$CHCl_3$ to afford 0.81 g (55%) of **9** as colorless needles, mp 180–181°.

Preparation of the Phenolic Bases. To a mixt of 20 mg of Na, 25 ml of MeOH, and 1 drop of H_2O, a soln of 800 mg of the 3′-ethoxycarbonyl-4′-methoxycinnamate (**12**) in 25 ml of THF was added. After stirring at room temp for 2 hr, followed by addn of 1 drop of AcOH, the reaction mixt was evapd to give a residue, a soln of which in $CHCl_3$ was washed (satd $NaHCO_3$ and H_2O) and dried (Na_2SO_4). Evapn of the solvent gave a brown gum, which was recrystd from $CHCl_3$–hexane to give 450 mg (63%) of **14** as a yellowish powder, mp 162–164°.

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†Melting points were taken with a Yanagimoto Micro apparatus (MP-S_2) and are not corrected. Ir spectra were taken with a type EPI-3 Hitachi recording spectrometer. Mass spectra were measured with a Hitachi RMU-7 spectrometer. Nmr spectra were measured with a Hitachi R-20 instrument in $CDCl_3$ soln (Me_4Si).

Analgetics Based on the Pyrrolidine Ring. 7

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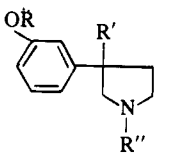
In a previous paper of this series[1] it was shown that whereas profadol (I, R = H; R′ = Pr; R″ = Me) exhibited a high level of analgetic activity, replacement of the *N*-methyl group with *N*-*n*-propyl afforded an analog that was inactive in the rat tail pressure test. There was a similar fall off in



I

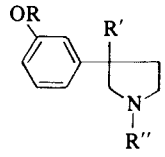
analgetic activity in the *O*-methyl analogs on increasing the chain length of R″ from methyl, through ethyl, to *n*-propyl (*i.e.*, I, R = Me; R′ = Pr; R″ = Me, Et, or Pr).

Thus it was surprising to find that on further increasing the chain length of the *N*-alkyl group, analgetic properties were again in evidence and that the *N*-*n*-pentyl analog (I, R = H; R′ = Pr; R″ = $(CH_2)_4Me$) of profadol showed analgetic properties superior to those of codeine in rats. This paper describes the chemistry and pharmacology of compounds that have been prepared to explore this further aspect of the pyrrolidine analgetics.

Chemistry. The *m*-(1-alkyl-3-alkyl-3-pyrrolidinyl)phenols tested as potential analgetics were prepared by standard procedures, the methods used being indicated in the Experimental Section.

An interesting aspect of the physical chemistry of the pyrrolidines was seen in the course of preparing the optical enantiomers of *m*-(3-isobutyl-3-pyrrolidinyl)phenol. When measured in ethanol, the values of $[\alpha]D$ for these optical enantiomers were very close to zero, and it was necessary to

Table I. Substituted Pyrrolidines



Compound No.	R	R′	R″	Mp or bp (mm), °C	Method	Yield, %	Formula	Analyses	
1	Me	$(CH_2)_2Me$	$(CH_2)_3Me$	143–145 (1.0)	A	68	$C_{18}H_{29}NO$		
2	Me	$(CH_2)_2Me$	$(CH_2)_4Me$	146–150 (0.7)	A	64	$C_{19}H_{31}NO$	C, H, N	
3	Me	$(CH_2)_2Me$	$(CH_2)_5Me$	170–174 (1.4)	A	73	$C_{20}H_{33}NO$		
4	H	$(CH_2)_2Me$	$COCH_2CHMe_2$	133–135.5	*a*	95	$C_{18}H_{27}NO_2$	C, H, N	
5	Me	CH_2CHMe_2	$(CH_2)_3Me$	142–144 (0.5)	A	70	$C_{19}H_{31}NO$		
6	Me	CH_2CHMe_2	$(CH_2)_4Me$	152–155 (0.4)	A	79	$C_{20}H_{33}NO$	C, H, N	
7	Me	CH_2CHMe_2	$(CH_2)_5Me$	164–166 (0.6)	A	75	$C_{21}H_{35}NO$	C, H, N	
8	Me	CH_2CHMe_2	$(CH_2)_2CHMe_2$	145–147 (1.0)	A	75	$C_{20}H_{33}NO$	C, H, N	
9	Me	CH_2CMe_3	$(CH_2)_4Me$	155 (0.4)	A	78	$C_{21}H_{35}NO$		
10	H	$(CH_2)_2Me$	$(CH_2)_3Me$	180–182 (0.4)	B	77	$C_{17}H_{27}NO$		Citrate salt. *Anal.* ($C_{23}H_{35}NO_8$) C, H, N
11	H	$(CH_2)_2Me$	$(CH_2)_4Me$	158–160 (1.0)	B	77	$C_{18}H_{29}NO$	C, H, N	
12	H	$(CH_2)_2Me$	$(CH_2)_5Me$	190 (1.0)	B	70	$C_{19}H_{31}NO$		Citrate salt. *Anal.* ($C_{25}H_{39}NO_8$) C, H, N
13	H	$(CH_2)_2Me$	$(CH_2)_2CHMe_2$	164 (0.4)	*b*	68	$C_{18}H_{29}NO$	C, H, N	Citrate salt. *Anal.* ($C_{24}H_{37}NO_8$) C, H, N
14	H	CH_2CHMe_2	$(CH_2)_3Me$	163–164 (0.4)	B	81	$C_{18}H_{29}NO$	H, N; C[c]	Citrate salt. *Anal.* ($C_{24}H_{29}NO_8$) H, N; C[d]
15	H	CH_2CHMe_2	$(CH_2)_4Me$	172 (0.5)	B	71	$C_{19}H_{31}NO$	C, H, N	Citrate salt. *Anal.* ($C_{25}H_{39}NO_8$) C, H, N
16	H	CH_2CHMe_2	$(CH_2)_5Me$	184 (0.7)	B	80	$C_{20}H_{33}NO$		Citrate salt. *Anal.* ($C_{26}H_{41}NO_8$) C, H, N
17	H	CH_2CHMe_2	$(CH_2)_2CHMe_2$	174–176 (1.0)	B	63	$C_{19}H_{31}NO$	C, H, N	Citrate salt. *Anal.* ($C_{25}H_{39}NO_8 \cdot 0.5H_2O$) C, H, N
18	H	CH_2CMe_3	$(CH_2)_4Me$	182–184 (0.5)	B	72	$C_{20}H_{33}NO$		Citrate salt. *Anal.* ($C_{26}H_{41}NO_8 \cdot 0.5H_2O$) C, H, N
19	Me	CH_2CHMe_2	CH_2Ph	178–180 (0.7)	A	73	$C_{22}H_{29}NO$		
20	H	CH_2CHMe_2	CH_2Ph	84–86	*e*	89	$C_{21}H_{27}NO$	C, H, N	
21	H	CH_2CHMe_2	CH_2Ph	109–110	C		$C_{21}H_{27}NO$	C, H, N	$[\alpha]^{23}D$ +47.2° (*c* 1.020 g/100 ml, EtOH)
22	H	CH_2CHMe_2	CH_2Ph	106–108	C		$C_{21}H_{27}NO$	C, H, N	$[\alpha]^{25}D$ −43.5° (*c* 0.993 g/100 ml, EtOH)
23	H	CH_2CHMe_2	H	183–184	D[f]	87	$C_{14}H_{22}ClNO$	C, H, N	$[\alpha]^{23}D$ +18.7° (*c* 1.003 g/100 ml, EtOH)
24	H	CH_2CHMe_2	H	132–133	D	*g*	$C_{14}H_{21}NO$	C, H, N	$[\alpha]^{24}D$ −1.0° (*c* 0.953 g/100 ml, EtOH). $[\alpha]^{25}D$ +12.2° (*c* 0.990 g/100 ml, 0.1 *N* HCl)
25	H	CH_2CHMe_2	H	182–183	D[h]	75	$C_{14}H_{22}ClNO$	C, H, N	$[\alpha]^{24}D$ −16.5° (*c* 0.990 g/100 ml, EtOH)
26	H	CH_2CHMe_2	H	131–132	D	*i*	$C_{14}H_{21}NO$	C, H, N	$[\alpha]^{24}D$ +0.7° (*c* 0.957 g/100 ml, EtOH) $[\alpha]^{25}D$ −10.2° (*c* 0.987 g/100 ml, 0.1 *N* HCl)
27	H	CH_2CHMe_2	$(CH_2)_4Me$	184–186 (0.1)	E	50	$C_{19}H_{31}NO$	C, H, N	$[\alpha]^{24}D$ +26.0° (*c* 0.970 g/100 ml, EtOH)
28	H	CH_2CHMe_2	$(CH_2)_4Me$	191 dec	E	*j*	$C_{58}H_{80}N_2O_{10}$	C, H, N	$[\alpha]^{24}D$ +4.7° (*c* 0.467 g/100 ml, DMA[k])
29	H	CH_2CHMe_2	$(CH_2)_4Me$	192 (0.2)	E	71	$C_{19}H_{31}NO$	H, N; C[l]	$[\alpha]^{24}D$ −26.6° (*c* 0.980 g/100 ml, EtOH)
30	H	CH_2CHMe_2	$(CH_2)_4Me$	147 dec	E	*m*	$C_{33}H_{49}NO_9$	C, H, N	$[\alpha]^{23}D$ −45.9° (*c* 0.493 g/100 ml, DMA[k])

[a]Prepared by the action of BBr_3 on crude 3-(*m*-methoxyphenyl)-1-isopentanoyl-3-propylpyrrolidine. [b]Prepared by the action of LAH on compound **4**. [c]C: calcd 78.5; found 77.9. [d]C: calcd 61.65; found 61.1. [e]Prepared by refluxing compound **19** with HBr. [f]Hydrochloride salt as needles from *i*-PrOH–Et_2O. [g]Rods from C_6H_6–petroleum ether. [h]Microcrystalline hydrochloride from *i*-PrOH–Et_2O. [i]Cubes from C_6H_6–hexane. [j]Salt with (−)-di-*p*-toluate ester of D-tartaric acid (2 moles of base; 1 mole of acid) as needles from EtOH. [k]DMA represents dimethylacetamide. [l]C: calcd 78.8; found 78.1. [m]Salt with (−)-di-*p*-toluate ester of D-tartaric acid (1:1) as needles from EtOH.

carry out the determinations in 0.1 *N* hydrochloric acid to obtain significant figures. This phenomenon highlights the care that must be exercised in using the optical rotation as a means of following the progress of the resolution of a base involving the fractional crystallization of its salt with an optically active acid.

Experimental Section†

The physical properties of the *m*-(1-alkyl-3-alkyl-3-pyrrolidinyl)-phenols tested as potential analgetics, and of novel intermediates, are listed in Table I. The synthetic procedures used are indicated below.

3-Isobutyl-3-(*m*-methoxyphenyl)-1-*n*-pentylpyrrolidine. Method A. 3-Isobutyl-3-(*m*-methoxyphenyl)pyrrolidine[2] (10 g), K_2CO_3 (13 g), DMF (30 ml), and *n*-pentyl bromide (7 g) were stirred at room temperature for up to 3 days. The mixture was filtered and the residue washed with EtOH. The washings and filtrate were evaporated to half bulk, poured into H_2O, and extracted with C_6H_6. The crude product isolated from the C_6H_6 was purified by distillation *in vacuo*.

***m*-(3-Isobutyl-1-*n*-pentyl-3-pyrrolidinyl)phenol. Method B.** 3-Isobutyl-3-(*m*-methoxyphenyl)-1-*n*-pentylpyrrolidine was converted to the hydrochloride and demethylated with BBr_3.[3] Citrate salts of this and analogous 3-pyrrolidinylphenols were prepared by addition of a solution of the base in Et_2O to an Et_2O solution of citric acid. The salts did not melt sharply but softened above 55°.

Optical Enantiomers of *m*-(1-Benzyl-3-isobutyl-3-pyrrolidinyl)-phenol. Method C. The optical enantiomers of *m*-(1-benzyl-3-isobutyl-3-pyrrolidinyl)phenol were prepared by crystallization of its salt with *d*-tartaric acid from EtOH. The salt of the *d* enantiomer crystallized out while that of the *l* enantiomer was obtained on evaporation of the mother liquors. The two enantiomers were obtained from their respective salts by neutralization with 6 *N* NH_3.

Optical Enantiomers of *m*-(3-Isobutyl-3-pyrrolidinyl)phenol. Method D. Hydrogenation of *m*-(1-benzyl-3-isobutyl-3-pyrrolidinyl)-phenols in ethanolic HCl in the presence of 10% Pd/C at atmospheric pressure and 55°, afforded the appropriate *m*-(3-isobutyl-3-pyrrolidinyl)phenol hydrochlorides. The free bases were liberated with 6 *N* NH_3.

Optical Enantiomers of *m*-(3-Isobutyl-1-pentyl-3-pyrrolidinyl)-phenols. Method E. (+)-*m*-(3-Isobutyl-3-pyrrolidinyl)phenol (18 g) and K_2CO_3 (15 g) in DMF (120 ml) were stirred at 70° and pentanoyl chloride (11 ml) was added dropwise. The mixture was stirred at 80° for 4 hr. The reaction mixture was worked up by conventional procedures and the crude *N*-acyl pyrrolidine isolated from $CHCl_3$. Reduction of the latter in THF with LAH afforded the (+) enantiomer of *m*-(3-isobutyl-1-pentyl-3-pyrrolidinyl)phenol. Both enantiomers formed crystalline salts from ethanol with (−)-di-*p*-toluate ester of D-tartaric acid.

Pharmacology. Acute lethal toxicities and analgetic (antimechanoceptive) potencies were estimated in young male rats by the intraperitoneal route as described earlier.[4] 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. Thoughtful use of such procedures has been highly predictive of the kind of central pain-relieving 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.[5]

All compounds studied were administered as the citrate salt except **11**, which was dissolved with an equivalent of HCl. The vehicle was 1 ml of 0.9% (w/v) NaCl/100 g of rat. Through administrative accident, the isomers of **15** (**28** and **30**) were dissipated in unrelated work and will not be resynthesized in the near future.

Results are set out in Table II.

The research described in this report involved animals maintained in animal care facilities fully accredited by the American Association for Accreditation of Laboratory Animal Care.

Discussion

It is apparent from Table II that the new optimum long-chain N-alkylation falls at *N*-*n*-pentyl in the presence of at least two different 3-alkylations, *viz.*, 3-*n*-Pr (as in profadol) and 3-CH_2CHMe_2 (*i.e.*, I, R = H; R′ = *n*-Pr or CH_2CHMe_2; R″ = $(CH_2)_4Me$). This is the third type of optimum N substituent now located in the profadol series. The first, among short chains, falls at N-Me as in profadol itself.[6,7] The second, superior in degree, falls at N-$(CH_2)_2C_6H_4$-*p*-R.[7] The new optimum, at N-$(CH_2)_4Me$, is generally inferior in degree (Table II).

In a preceding paper[2] it was found that substitution of certain branched chains at the 3 position (3-$CHMe_2$, 3-CHEtMe, 3-CH_2CHMe_2, or 3-CH_2CMe_3) for the 3-*n*-Pr in profadol improved the activity and/or the activity:toxicity ratio when N-Me was retained as in profadol, but that on going to N-$(CH_2)_2C_6H_4$-*p*-R this was not clearly so. Analogously, it is now found that two such branched alkylations at the 3 position are not favorable on going from N-Me to the new N-$(CH_2)_4Me$ (Table II), thus providing another example of interaction between N and 3 substituents in their biological effects. Such interactions between N-substitution and O-methylation (I, R = Me) and between the latter and further substitution on the pyrrolidine ring were described earlier.[6,7]

Compounds **11** and **15**, the best of the new group, were tested for suppression of morphine abstinence signs in monkeys by Dr. J. Villarreal. The first slightly suppressed abstinence signs at an sc dose of 8 mg/kg and produced convulsions at 16 mg/kg. The second yielded no clear evidence of suppression at 8 or 16 mg/kg, but failed to precipitate abstinence in monkeys not withdrawn from their morphine. Neither, therefore, is likely to have less liability in inducing physical dependence than profadol itself.

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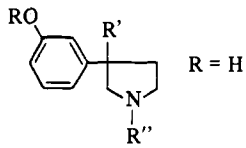
Table II. Pyrrolidines Tested as Analgetics



No.	R′	R″	Estd ip potency[a]	Estd av ip lethal dose (mg of base/kg)[b]	(Potency × lethal dose)[c]/(0.8 × 133)
d	$(CH_2)_2Me$	H	None[e]	119	
d		Me	2.5	83	1.9
d		$(CH_2)_2Me$	None[e]	60	
10		$(CH_2)_3Me$	(0.8)[f]	52	(0.4)
11		$(CH_2)_4Me$	1.5	129	1.9
12		$(CH_2)_5Me$	1.1	147[g]	<1.5[g]
13		$(CH_2)_2CHMe_2$	0.7	91	0.6
h	CH_2CHMe_2	Me	2.7	137	3.5
14		$(CH_2)_3Me$	(0.3)[f]	121	(0.3)
15		$(CH_2)_4Me$	2.5	66	1.5
16		$(CH_2)_5Me$	1.1	149[g]	<1.5[g]
17		$(CH_2)_2CHMe_2$	0.6	122	0.7
h	CH_2CMe_3	Me	3.8	129	4.6
18		$(CH_2)_4Me$	1.3	146[g]	<1.8[g]

[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.[3] [d] Ref 1. [e] At 0.25 the estd lethal dose. [f] Figures in parentheses are obtained by extrapolation; an effect equivalent to the reference, 11.3 mg of codeine base/kg was not actually obtained at 0.25 the estd lethal dose. [g] Incomplete solution, especially at lethal dose levels; hence lethal dose and index (last column) probably biased upward and potency sometimes downward. [h] Ref 2.

†Melting points are corrected and were determined in a capillary tube (using a Townson & Mercer Ltd. apparatus). Boiling points are uncorrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. Where symbols are omitted, the intermediate concerned was not obtained analytically pure.

H. Oliver for the microanalyses, Miss E. M. Tanner for the optical rotations, and Mrs. P. Varner, Mr. M. D. Stephens, and Miss J. Wax for participation in the biological work.

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New Compounds

Synthesis of New Glycido Derivatives. 2-Dimethylaminoethyl Triphenylglycidate and 2-Dimethylaminoethyl 2,3,3-Triphenylglycidyl Ether

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Some time ago[1] one of us described the synthesis of triphenylglycidonitrile and derivatives (**1a–d**). Since many basic alkyl esters of diarylhydroxyacetic acid and many basic alkyl diaryl ethers are endowed with interesting biological activity, it seemed of interest to us to prepare **2** and **3** and to test them for antispasmodic, anticonvulsant, antitussive, analgetic, and antiinflammatory activities.

$(C_6H_5)_2CN_2 + C_6H_5COCN \longrightarrow (C_6H_5)_2C\!\!<\!\!\overset{O}{}\!\!>\!\!CRC_6H_5$

1a, R = CN
b, R = $CONH_2$
c, R = COOH
d, R = $COOCH_3$
e, R = CH_2OH

2, R = $CH_2OCH_2CH_2N(CH_3)_2$
3, R = $COOCH_2CH_2N(CH_3)_2$

The title compounds revealed a good antiinflammatory activity not accompanied, however, by an equally good analgetic action. None of the other actions investigated showed anything of interest.

Experimental Section†

Triphenylglycidonitrile (1a), triphenylglycidamide (1b), triphenylglycidic acid (1c), and methyl triphenylglycidate (1d) were prepared as previously described.[1]

2,3,3-Triphenylglycidol (1e). MeOH (10.6 g, 0.33 mole) was added dropwise at −5° into a stirred suspension of LAH (4.4 g, 0.11 mole) in anhyd THF (250 ml). After 15-min stirring, methyl triphenylglycidate (**1d**) (9.1 g, 0.027 mole) was added portionwise. The mixt was stirred at room temp for 3 hr and then moist Et_2O and H_2O were added cautiously. The sepd solid was washed (Et_2O) and the aqueous layer was extd with Et_2O. The combined organic solns were washed (H_2O), dried, and evapd to dryness. The residue was recrystd from ligroin (bp 90–100°) to give **1e** (7.3 g, 87.6% yield) as colorless crystals, mp 104°. *Anal.* ($C_{21}H_{18}O_2$) C, H.

2-Dimethylaminoethyl 2,3,3-Triphenylglycidyl Ether·HCl (2). Finely powdered $NaNH_2$ (1.35 g, 0.34 mole) was added to a soln of **1e** (9.5 g, 0.031 mole) in PhH (95 ml) and the mixt was refluxed for 1 hr with stirring. After cooling to room temp, an 8.77% soln of dimethylaminoethyl bromide (0.04 mole) in PhH was added dropwise. After an addl 1-hr stirring, the mixt was dild with excess Et_2O and then extd with 10% HCl soln. The oil which sepd from the acid soln was extd with $CHCl_3$. The $CHCl_3$ soln was evapd to dryness and the residue was taken up with Et_2O and filtered to give **2** (5.3 g, 41% yield) as a colorless solid, mp 159° dec. *Anal.* ($C_{25}H_{28}ClNO_2$) C, H, Cl, N.

2-Dimethylaminoethyl Triphenylglycidate·HCl (3). Compound **1c** (10 g, 0.031 mole) and dimethylaminoethyl chloride (5.6 g, 0.052 mole) were dissolved in Me_2CHOH (95 ml) and the soln was refluxed for 3 hr. After cooling to room temp, excess H_2O was added to the mixt. The resulting aqueous soln was basified with 10% NaOH soln and the basic material was extd with Et_2O. The Et_2O ext was washed (H_2O) and evapd to dryness to give a waxy product which was converted to a cryst solid by addition of 10% HCl soln. The solid was filtered and recrystd from EtOH–Et_2O to give **3** (6.3 g, 47% yield) as a colorless solid, mp 203° dec. *Anal.* ($C_{25}H_{26}ClNO_3$) C, H, Cl, N.

†Melting points are uncorrected and were taken on a Büchi capillary melting point apparatus. All compounds were analyzed for C, H, N and the analytical results were within ±0.4% of the theoretical value.

References

(1) G. F. Bettinetti and A. Donetti, *Gazz. Chim. Ital.*, 96, 965 (1966).

Alkyl Derivatives of Tetrahydroisoquinoline, 1-Phenylpiperazine, and 4-Diphenylmethylpiperidine

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Many useful medicinal compounds[1,2] are based upon the isoquinoline, piperazine,[3,4] and piperidine[5-7] ring systems. As part of a general screening program we have prepared[8] some cyclopropylmethyl and cyclobutylmethyl derivatives of these systems[9] by reduction of the corresponding amides. These compounds show an increasing separation of the aromatic portion of the molecule from the *N*-cycloalkyl group.

Some preliminary screening results on mice, which also include 4-diphenylmethylpiperidine (**3g**, R = H), are presented in Table II. The diphenylmethylpiperidines and phenylpiperazines were found to have a CNS depressant action