out $p$-$NO_2$ or -$NH_2$ on phenethyl, clear activity is reduced by this substitution when the phenolic function is free (**8** and **9** *vs.* **6**) and in some cases lost when it is methylated (**14** and **15** *vs.* **11**). In the pyrrolidines, however, activity is reduced by N-phenethylation only in conjunction with O-methylation, remaining of clear quality; and when the phenolic function is left unmuzzled in otherwise optimal pyrrolidines, activity considerably increases on going from N-methyl to N-phenethyl (with or without $p$-$NH_2$) without proportionate increase in toxicity (ref 1 and unpublished work by the authors). Thus, a favorable interaction between the unmuzzled $m$-phenolic function and N-phenethylation allowed by the pyrrolidine nucleus is not present with the azetidine nucleus.

Furthermore, divergence between the azetidines and pyrrolidines occurs with respect to the optimal unbranched length of 3-alkylation. Whereas this was clearly propyl in the pyrrolidines as concerns both activity and activity : toxicity ratio,[1] it has shifted toward butyl in the azetidines, at least as concerns activity (**19** *vs.* **6** and **21**, **20** *vs.* **11** and **23**).

Substitution of a carbonyl function in place of methyl on the nitrogen led to inactivity or lack of clear activity (**12** and **16**).

In general, the levels of activity and activity : toxicity ratio achieved in the azetidines are surprisingly comparable with those achieved in the pyrrolidines.

**Acknowledgments.**—The authors are indebted to Dr. R. E. Bowman for advice and encouragement, to Mr. F. H. Oliver for microanalyses, to Miss E. M. Tanner for the physical chemistry measurements, and to Mr. J. D. Tomkinson for some technical assistance. M. Welford, L. Lembke, J. Wax, and R. Mills cooperated in the pharmacological work.

# Analgetics Based on α-Phenyl-3-pyrrolidineacetic Acid

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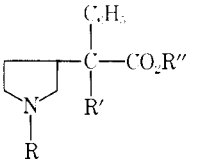
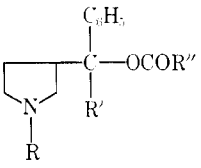
Several 1-alkyl-α-phenyl-3-pyrrolidineacetic acid esters were prepared and tested for their analgetic activity. The potencies of the compounds were similar to their reversed esters and were generally in the range of *d*-propoxyphene.

Continuing our investigation of drugs based on the pyrrolidine nucleus,[1] we have prepared a series of esters of substituted α-phenyl-3-pyrrolidineacetic acids (I) (Table I) for study as analgetics.



I

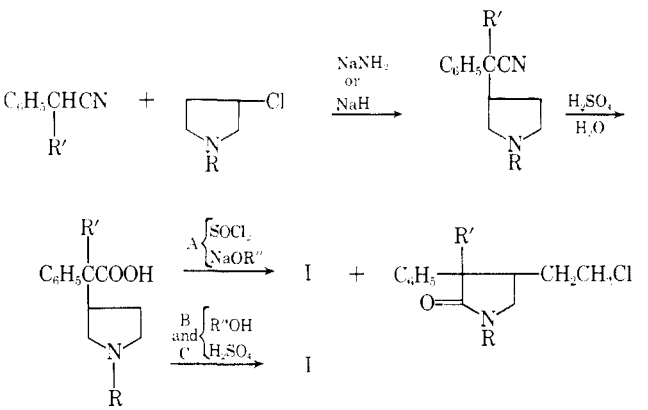
These compounds are structural analogs of meperidine and are the reversed esters of a series of analgetics (II) being reported simultaneously.[2] They were prepared by the alkylation of the appropriate phenylacetonitrile with a 1-substituted 3-chloropyrrolidine, hydrolysis of the product nitrile to the amino acid, and esterification as shown in Chart I.



II

An attempt to prepare the ethyl ester from 1-ethyl-α,α-diphenyl-3-pyrrolidineacetyl chloride hydrochloride by treating an ethanol solution with pyridine gave only rearrangement to 1-ethyl-4-(2-chloroethyl)-3,3-diphenyl-2-pyrrolidinone.[1] The acid chloride was successfully converted to its ethyl ester, however, by adding it to a solution of sodium ethoxide in ethanol.

CHART I



The analgetic activity of these compounds was determined by a modification of the Nilsen method[2,3] (electrical stimulation of a mouse tail) and is compared in the table with the activity of the corresponding reversed esters of structure type II.

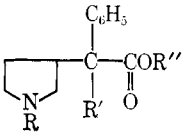
When R′ ≠ $C_6H_5$, diastereoisomers exist for each structure. These were separated in two examples and the analgetic activity was determined for each of the racemates. No significant difference in analgetic potency was observed between the diastereoisomeric racemates in compounds of type I or II.

(1) (a) C. D. Lunsford, A. D. Cale, Jr., J. W. Ward, B. V. Franko, and H. Jenkins, *J. Med. Chem.*, **7**, 302 (1964); (b) A. D. Cale, Jr., H. Jenkins, B. V. Franko, J. W. Ward, and C. D. Lunsford, *ibid.*, **10**, 214 (1967).

(2) G. C. Helsley, J. A. Richman, C. D. Lunsford, H. Jenkins, R. P. Mays, W. H. Funderburk, and D. N. Johnson, *ibid.*, **11**, 472 (1968).

(3) P. Nilsen, *Acta Pharmacol. Toxicol.*, **18**, 10 (1961).

TABLE I



| No. | R | R′ | R″ | Method | Salt | % yield | Yield[a] of pyrrolidinone | Mp or bp (mm), °C | Comparative analgetic potencies[e] No. analgetic/no. tested I | II |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | $i$-$C_4H_9$ | $C_6H_5$ | $C_2H_5$ | A | Fumarate | 37 | 32 | 152–153[b] | 0/5 | ... |
| 2 | $i$-$C_3H_7$ | $C_6H_5$ | $C_2H_5$ | A | ... | 51 | 23 | 172–174 (0.03) | 5/10 | ... |
| 3 | $CH_3$ | $C_6H_5$ | $C_2H_5$ | A | ... | 25 | 13 | 166–168 (0.03) | 0/5 | ... |
| 4 | $c$-$C_6H_{11}$ | $C_6H_5$ | $C_2H_5$ | A | ... | 37 | 17 | 210–215 (0.15) | 1/5 | ... |
| 5 | $C_2H_5$ | $C_6H_5$ | $C_2H_5$ | A | ... | 50 | 10 | 168–170 (0.04) | 2/5 | 2/5[f] |
| 6 | $i$-$C_3H_7$ | H | $CH_3$ | B | HCl | 13[c] | .. | 172.5–174[d] | 2/5 | 5/10[f] |
| 7 | $i$-$C_3H_7$ | H | $CH_3$ | B | HCl | 8[c] | .. | 159–161[d] | 2/5 | ... |
| 8 | $C_2H_5$ | $C_2H_5$ | $C_2H_5$ | C | ... | 13 | .. | 89–92 (0.001) | 1/5 | 2/5[g] |
| | | | | | | | | | | 2/5[g] |

[a] The 2-pyrrolidinones were obtained as described in method A and were shown to be identical by mmp with the compounds of ref 1. [b] Recrystallized from 4-methyl-2-pentanone. [c] The distilled crude base (mixed isomers) was obtained in 79% yield. [d] See method B for isomer purification. [e] All analgetic tests were run at 20 mg/kg ip calculated as the free base and tested 15 min postdrug. [f] R″ = $C_2H_5$. [g] The diastereoisomers of this structure were separated and tested individually.

The limited experimental data on the present compounds show their analgetic potencies to be essentially the same as those of their reversed esters and generally in the range of *d*-propoxyphene.

## Experimental Section

Melting points were taken in open capillaries in an oil bath using a thermometer calibrated against reference standards. Microanalyses were done by Micro-Tech Laboratories, Skokie, Ill., Schwarzkopf Microanalytical Laboratory, Woodside, N. Y., Galbraith Microanalytical Laboratories, Knoxville, Tenn., and Mrs. Ruby Higgins of the A. H. Robins Control Laboratory. All compounds reported gave microanalytical values for C, H, and N within ±0.30% of the calculated values.

**1-Alkyl-α-phenyl-3-pyrrolidineacetonitriles.**—The preparation of the starting nitriles, except those in the following two procedures, has been reported previously.[1b]

**α,1-Diethyl-α-phenyl-3-pyrrolidineacetonitrile (9)** was prepared from 2-phenylbutyronitrile by the same method as the 1-alkyl-α,α-diphenyl-3-pyrrolidineacetonitriles[1a] except $NaNH_2$ was replaced with NaH to eliminate the by-product, 2-phenylbutyramide; yield 48%, bp 139–140° (0.1 mm). This product is presumed to be a mixture of diastereoisomers.

**1-Isopropyl-α-phenyl-3-pyrrolidineacetonitrile (10)** was prepared by the same method as the 1-alkyl-α,α-diphenyl-3-pyrrolidineacetonitriles;[1a] yield 64%, bp 130–135° (0.1 mm). Gas chromatography on an Apiezon L column indicated that this product was approximately a 1:1 mixture of the diastereoisomers.

**Method A. Ethyl 1-Isopropyl-α,α-diphenyl-3-pyrrolidineacetate.**—To 75 g (0.243 mole) of 1-isopropyl-α,α-diphenyl-3-pyrrolidineacetonitrile[1a] was added 500 g of 70% $H_2SO_4$. The solution was heated at 130–140° for 48 hr, poured on ice, made basic with 50% NaOH, and extracted with $CHCl_3$. The $CHCl_3$ and a middle layer were separated from the $H_2O$ layer. (When the N-substituent was isobutyl or cyclohexyl there was no middle layer.) The mixture was acidified with HCl gas, the small $H_2O$ layer which formed was separated, and the $CHCl_3$ was dried ($Na_2SO_4$) and concentrated *in vacuo*. The residue was dissolved in 400 ml of $SOCl_2$ and allowed to stand 48 hr at 25°. The excess $SOCl_2$ was removed using a rotary evaporator at 2 mm and as little heat as possible. The residue was dissolved in EtOH (200 ml) with cooling in an ice bath. The EtOH solution was added dropwise at 10–15° to an EtOH solution of NaOEt (46 g of Na in 1500 ml of EtOH) and stirred 0.5 hr at 25°. The mixture was partitioned between $H_2O$ and ligroin (bp 60–110°) and the water layer was extracted with $CHCl_3$. The ligroin was extracted with 3 *N* HCl (when the N-substituent was cyclohexyl the hydrochloride separated as an oil which was taken off with the $H_2O$ layer) and the ligroin and $CHCl_3$ were combined (solution A). The acid solution was made basic with NaOH and extracted with ether and the ether was dried ($Na_2SO_4$), concentrated, and distilled.

**4-(2-Chloroethyl)-1-isopropyl-3,3-diphenyl-2-pyrrolidinone.**—Solution A from above was concentrated and the residue was crystallized twice from $i$-$Pr_2O$. A mixture melting point with authentic compound[1a] was undepressed.

**Method B. Methyl 1-Isopropyl-α-phenyl-3-pyrrolidineacetate.**—A solution of 93 g (0.405 mole) of (1-isopropyl-3-pyrrolidinyl)phenylacetonitrile in 500 g of 70% $H_2SO_4$ was heated at 130° for 48 hr. The solution was cooled to 95° and 400 ml of MeOH was added slowly beneath the surface of the liquid with continuous distillation. The pot residue was poured on ice, made basic with NaOH, and extracted with $CHCl_3$. The $CHCl_3$ was dried ($Na_2SO_4$), concentrated, and distilled; yield 84 g (79%), bp 160–162° (0.03 mm).

**Separation of Isomers. β Isomer** (The higher melting isomer was arbitrarily designated β).—The above ester (10 g) in 50 ml of boiling isobutyl methyl ketone was treated with 2 g of dry HCl in 50 ml of isobutyl methyl ketone. The solution was allowed to cool and the resulting mixture was filtered. The filtrate (solution A) was saved and the crystals (5 g, mp 137–152°) were recrystallized three times from isobutyl methyl ketone; yield 1.5 g, mp 172.5–174°.

**α Isomer.**—Solution A was concentrated and the residue was crystallized four times from EtOAc; yield 0.9 g, mp 159–161°, mmp (with the isomer prepared above) 145–152°.

**Method C. Ethyl α,1-Diethyl-α-phenyl-3-pyrrolidineacetate.**—A solution of 20 g (0.083 mole) of α-(1-ethyl-3-pyrrolidinyl)-α-phenylbutyronitrile in 150 g of 70% $H_2SO_4$ was heated at 130° for 90 hr. Absolute EtOH (2 l.) was introduced subsurface at a pot temperature of 105–130° with the simultaneous distillation of EtOH and $H_2O$ over a period of 4 hr. The solution was poured on ice, basified with 50% NaOH, and extracted with $i$-$Pr_2O$. The $i$-$Pr_2O$ was dried ($Na_2SO_4$), concentrated, and distilled. This product is presumed to be a mixture of diastereoisomers.

**Base-Promoted Rearrangement of 1-Ethyl-α,α-diphenyl-3-pyrrolidineacetyl Chloride.**—1-Ethyl-α,α-diphenyl-3-pyrrolidineacetic acid (1 g) was dissolved in 30 ml of $SOCl_2$ and allowed to stand at 25° for 16 hr. The excess $SOCl_2$ was removed *in vacuo* with a minimum of steam heating. The ir spectrum showed a strong peak at 5.62 (acid chloride) and a medium peak at 5.92 μ (rearranged product). The residue was dissolved in 50 ml of EtOH, 5 ml of pyridine was added, and the solution was allowed to stand for 6 hr. The solution was concentrated. Ir spectra of the residue showed an absence of peaks at 5.62 and 5.78 (ester) while giving a strong band at 5.92 μ.

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