Analgetics Based on the Pyrrolidine Ring. II.

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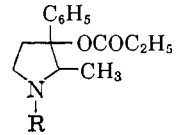
A series of analogs of 1,2-dimethyl-3-phenyl-3-propionoxypyrrolidine, an analgetic in the codeine range, has been prepared, and the activities are reported.

The discovery of analgetic activity in 1,2-dimethyl-3-phenyl-3-propionoxypyrrolidine (Ib)[1] has led to the synthesis of a number of analogs with the aim both of defining the limits of activity in the series and of enhancing the activity found in the parent compound. Most of the compounds described in this paper are those where the group on the nitrogen atom of the pyrrolidine ring of formula I is the one modified, although five are those where modification is made to the phenyl group in the 3-position.

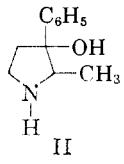
Chemistry.—In preparing our initial compounds[1] the group on the nitrogen atom was introduced at an early stage and the required pyrrolidinols were prepared by reaction of phenyllithium with the appropriately substituted pyrrolidone. As these nitrogen substituents grew larger, however, it was decided to use 2-methyl-3-phenyl-3-propionoxypyrrolidine[1] (Ia) as the starting material and condense the secondary amino group with aralkyl halides, epoxides, anhydrides and Mannich bases to give those compounds listed in Table III.



Ia, R = H
b, R = Me

The *p*-aminophenethyl analog (12) was prepared in two ways: one by direct coupling of *p*-aminophenethyl chloride with the secondary base and the other, better, method by catalytic reduction of the related *p*-nitro compound.

(1) 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).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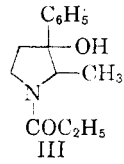
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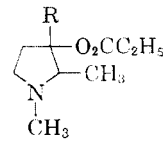
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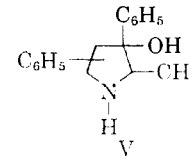

V

IVa, R = *o*-tolyl d, R = *m*-trifluoromethylphenyl,
b, R = *p*-tolyl e, R = *m*-methoxyphenyl
c, R = *o*-pyridyl

Condensation of the secondary amine (Ia) with epoxides presented difficulty only insofar as the stability of the secondary amine (Ia) itself was concerned, the compound slowly undergoing acyl migration at room temperature and more rapidly at elevated temperatures with the formation of the tertiary alcohol (III). This rearranged product gave a hydrochloride with ethereal hydrogen chloride.

The Mannich base (17) was also prepared in two ways: by the direct reaction of acetophenone with formaldehyde and the base, and the better method, used by Fry and May,[2] where the base reacts with (2-benzoylethyl)trimethylammonium iodide. The resulting ketone could be reduced with potassium borohydride to the alcohol (18) whereas with lithium aluminum hydride the diol was obtained. Either of these could be propionylated to the dipropionate (19).

The acid compound (20) was made from succinic anhydride and the base.

Those compounds where substitution lies in the 3-phenyl substituent were prepared following the general synthetic details given in our earlier paper.[1] In the case of compound (IVe) it was found impossible to prepare the required *m*-methoxyphenyllithium (*cf.*[3]) either by treating *m*-bromoanisole with lithium or with butyllithium. The corresponding Grignard reagent was prepared readily but like phenylmagnesium bromide[1] did not react smoothly with the ketone; however, by a tedious purification procedure, the desired alcohol was obtained in small yield and subsequently propionylated.

In the course of preparing large quantities of the intermediate (Ia) it was found that reaction of 1-benzyl-2-methyl-3-pyrrolidone[1] with phenyllithium gave a small yield of a compound where a second phenyl group appears to have entered the molecule. Ultraviolet spectra showed that this second phenyl group could not be in a diphenyl residue suggesting, by elimination, that it lies in the pyr-

(2) E. M. Fry and E. L. May, *J. Org. Chem.*, **24**, 116 (1959).
(3) G. Wittig and G. Fuhrmann, *Ber.*, **73B**, 1197 (1940).

rolidine ring. Catalytic removal of the benzyl group gave the alcohol (V) which was found to form a 1:1 molecular compound with the singly phenylated alcohol (II), having a melting point significantly higher than its components.

Experimental

Preparation of N-Substituted Pyrrolidines.—2-Methyl-3-phenyl-3-propionoxy pyrrolidine hydrochloride[1] (5.85 g., 1 mole) in dimethylformamide (35 ml.) was treated with sodium carbonate (3.5 g., 1.5 mole) followed, with stirring, by *n*-heptyl bromide (3.9 g., 1 mole). The resulting mixture was then stirred overnight at 100°, cooled, poured into water (300 ml.) and the precipitated oil extracted with ether. The ether extracts were dried (Na_2SO_4) then treated with an ethereal solution of hydrogen chloride to give 1-*n*-heptyl-2-methyl-3-phenyl-3-propionoxy-pyrrolidine hydrochloride as a white powder, m.p. 163–164°, yield 6.4 g. (82%). An analytical specimen crystallized from a 2-propanol–ether mixture had m.p. 166–167°.

Anal. Calcd. for $C_{21}H_{33}NO_2 \cdot HCl$: C, 68.6; H, 9.3; N, 3.8. Found: C, 68.4; H, 9.1; N, 3.6.

The several compounds prepared by the above method are listed in Table I. For the preparation of some intermediates, see refs. 4–8.

1-*n*-Butyl-2-methyl-3-phenyl-3-pyrrolidinol.—Reaction of 1-*n*-butyl-2-methyl-3-pyrrolidone (b.p. 78°(10 mm)., $n^{20}D$ 1.4500, prepared following the method given for the analogous 1-methyl compound) with phenyllithium[1] gave the required alcohol as a yellow oil, b.p. 110° (0.8 mm.), $n^{20}D$ 1.5218.

Anal. Calcd. for $C_{15}H_{23}NO$: C, 77.2; H, 9.9; N, 6.0. Found: C, 77.0; H, 9.7; N, 6.1.

Similarly from 1-*n*-amyl-2-methyl-3-pyrrolidone (b.p. 88° (10 mm.), $n^{20}D$ 1.4500) was prepared *1-n-amyl-2-methyl-3-phenyl-3-pyrrolidinol*, b.p. 163–166° (10 mm.), $n^{20}D$ 1.5167.

Anal. Calcd. for $C_{16}H_{25}NO$: C, 77.7; H, 10.2; N, 5.7. Found: C, 77.6; H, 10.3; N, 5.7.

1-*n*-Butyl-2-methyl-3-phenyl-3-propionoxypyrrolidine (2).—The preceding alcohol (54 g.) in pyridine (50 ml.) was treated with propionic anhydride (200 ml.) and held at 100° for 5 hr. The mixture was concentrated and distilled *in vacuo* to give the ester, b.p. 143° (0.8 mm.), m.p. 63° (from light petroleum); yield 61.8 g. (92%).

Anal. Calcd. for $C_{18}H_{27}NO_2$: C, 74.7; H, 9.4; N, 4.8. Found: C, 74.6; H, 9.6; N, 4.9.

The hydrochloride crystallized from ethanol–ether mixtures as plates, m.p. 207°.

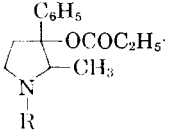
Anal. Calcd. for $C_{18}H_{27}NO_2 \cdot HCl$: C, 66.4; H, 8.7; N, 4.3. Found: C, 66.7; H, 9.0; N, 4.4.

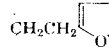
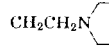
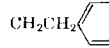
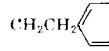
Similarly, *1-n-amyl-2-methyl-3-phenyl-3-propionoxypyrrolidine* was prepared b.p. 138° (0.7 mm.), $n^{20}D$ 1.5040.

(4) C. Crisan, *Ann. chim.*, [13] **1**, 436 (1956).
(5) R. Brown and F. N. Woodward, *J. Chem. Soc.*, 42 (1948).
(6) E. D. Amstutz and J. Plucker, *J. Am. Chem. Soc.*, **63**, 206 (1941).
(7) J. P. Mason and H. W. Block, *ibid.*, **62**, 1443 (1940).
(8) H. Sobotka, *Ber.*, **62**, 2191 (1929).

TABLE I

N-SUBSTITUTED-2-METHYL-3-PHENYL-3-PROPIONOXYPYRROLIDINES



R	Form	M.p., °C.	Solvent	Temp., °C.	Time of heating, hr.	Yield, %	Formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
i-C_4H_9	Base	56–58	*a*	100	4	90	$C_{18}H_{27}NO_2$	74.7	9.4	4.8	74.6	9.8	4.7
i-C_4H_9	HCl	156–158					$C_{18}H_{27}NO_2 \cdot HCl$	66.3	8.7	4.3	65.9	8.8	4.3
$(CH_2)_4OC_2H_5$[b]	HCl	150–152	*a*	100	16	70	$C_{20}H_{31}NO_3 \cdot HCl$	64.9	8.7	3.8	65.2	9.0	3.6
$(CH_2)_2O(CH_2)_2OH$[c]	HCl	139–140	*a*	100	16	55	$C_{18}H_{27}NO_4 \cdot HCl$	60.4	7.9	3.9	60.8	8.3	3.7
$CH_2CH_2C_6H_5$	HCl	172–173	*d*	Reflux	24	65	$C_{22}H_{27}NO_2 \cdot HCl$	70.7	7.6		70.7	7.8	
$CH_2CH{=}CHC_6H_5$	Base	86	*e*	100	16	40	$C_{23}H_{27}NO_2$	79.1	7.8	4.0	79.4	8.1	4.1
$CH_2CH{=}CHC_6H_5$	Tartrate	180–181					$C_{27}H_{33}NO_8$	64.9	6.7	2.8	64.5	6.7	2.9
 [f]	HCl	193 (dec.)	*a*	100	16	60	$C_{20}H_{25}NO_3 \cdot HCl$	66.0	7.2	3.9	65.8	7.2	3.7
 [g]	HCl	210	*b*	Reflux	5	85	$C_{20}H_{30}N_2O_3 \cdot 2HCl$	57.3	7.7	6.7	57.0	8.0	6.5
 [h]	HCl	177–179	*a*	60	16	80[i]	$C_{22}H_{26}N_2O_4 \cdot HCl$	63.1	6.5	8.5[i]	63.4	6.3	8.6[i]
 [h]	HCl	263–266[l]	*a*	100	16	25[m]	$C_{22}H_{28}N_2O_2 \cdot 2HCl$	62.1	7.1	6.6	61.9	6.7	6.5
CH_2CH_2OH	HCl	194–196	*a*	100	16	90	$C_{16}H_{23}NO_3 \cdot HCl$	61.2	7.7	4.5	61.2	7.5	4.4

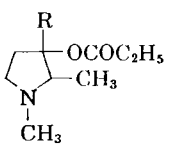
[a] Dimethylformamide. [b] 4-Chlorobutyl ethyl ether was prepared by the method given by Crisan.[4] [c] Diethyleneglycol chlorhydrin prepared by the method of Brown and Woodward.[5] [d] Ethanol. [e] Butanol. [f] 2-α-Furylethyl chloride prepared

TABLE I NOTES (*Continued*)

by the method of Amstutz and Plucker.[6] [g] (2-Chlorethyl)-4-morpholine hydrochloride was prepared following the method of Mason and Block.[7] In this experiment one extra mole of sodium carbonate was used. [h] *p*-Nitrophenethyl bromide was prepared using the method of Sobotka.[8] [i] This material could be prepared in 70% yield by propionylation of the corresponding alcohol. [j] Cl determination. [k] *p*-Aminophenethyl chloride hydrochloride was prepared using the method of Sobotka.[8] [l] Shrinks at 230° [m] This material can be obtained in 83% yield by catalytic hydrogenation, with palladized charcoal, of the analogous nitro compound in ethanol in the presence of one mole of hydrogen chloride.

TABLE II

1,2-DIMETHYL-3-PROPIONOXY-3-SUBSTITUTED PYRROLIDINES

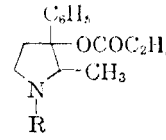


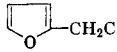
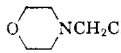
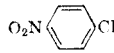
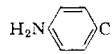
R	Form	B.p.° (mm.)	$n^{20}D$	Yield, %	Formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
o-$CH_3C_6H_4$	Base	139–140 (1.0)	1.5233	83	$C_{16}H_{23}NO_2$	73.5	8.9	5.4	73.6	9.1	5.3
	HCl	180–182[a]			$C_{16}H_{23}NO_2 \cdot HCl$	64.5	8.1	4.7	64.2	8.1	4.5
p-$CH_3C_6H_4$	Base	138–139 (1.0)		84	$C_{16}H_{23}NO_2$				73.5	8.9	5.3
	HCl	198–199[a]			$C_{16}H_{23}NO_2 \cdot HCl$				64.2	8.3	4.4
2-Pyridyl	Base	115–119 (0.6)	1.5174	70	$C_{14}H_{20}N_2O_2$	67.7	8.1	11.3	68.0	8.0	11.2
m-$CF_3C_6H_4$	HCl	184–185 (dec.)[a]		80	$C_{16}H_{20}F_3NO_2 \cdot HCl$	10.1[b]	16.2[c]	4.0	9.7[b]	16.4[c]	3.8
m-$CH_3OC_6H_4$	Base	54–56[a]		70	$C_{16}H_{23}NO_3$	69.3	8.4	5.1	69.5	8.4	4.9

[a] M.p. [b] Cl analysis. [c] F analysis.

TABLE III

SUBSTITUTION ON THE NITROGEN ATOM



Compound	R	Estimate of i.p. potency[a]	Est. of average i.p. lethal dose,[b] mg. base/Kg.	(Potency) × (Lethal Dose)[c] / 0.8 × 133
1	CH_3	0.8	133	1.0
2	n-C_4H_9	0.6	141	0.8
3	i-C_4H_9	0.3	211	0.6
4	n-C_5H_{11}	0.5	122	0.6
5	$C_2H_5O(CH_2)_4$	(0.2)[d]	120	(0.2)
6	$HO(CH_2)_2O(CH_2)_2$	0.5	261	1.1
7	$C_6H_5CH_2CH_2$	0.4	116	0.5
8	$C_6H_5CH{=}CHCH_2$	0.4	192	0.7
9		(0.3)	93	(0.3)
10		(0.2)	146	(0.2)
11		0.9	342[e]	3.0[e]
12		1.3	57	0.7
13	$HOCH_2CH_2$	0.4	264	1.0
14	$HOCH_2CH(OH)CH_2$	0.1	423	0.4
15	$C_6H_5CH(OH)CH_2$	0.3[f]	140[f]	0.4[f]
16	$C_6H_5OCH_2CH(OH)CH_2$	0.4	163	0.6
17	$C_6H_5COCH_2CH_2$	(0.4)[f]	72[f]	(0.3)[f]
18	$C_6H_5CH(OH)(CH_2)_2$	(0.8)	37	(0.3)
19	$C_6H_5CH(OCOC_2H_5)(CH_2)_2$	(0.6)	64	(0.3)
20	$HOCOCH_2CH_2CO$	None[g]	>1000	—

[a] Relative to codeine (base/base), 30 min. after treatment. [b] From small numbers of young, male, Sprague-Dawley rats of differing lots. [c] Compound No. 1 thus arbitrarily assigned unity. [d] Figures in parentheses obtained by extrapolation. Effect equivalent to 11.3 mg. codeine (base)/kg. not actually attained at one-quarter lethal dose. [e] Incomplete solution at toxic dose levels. Figure probably biased upward. [f] Partially suspended. [g] At 200 mg./kg.

Anal. Calcd. for $C_{19}H_{29}NO_2$: C, 75.2; H, 9.6; N, 4.6. Found: C, 75.3; H, 9.6; N, 4.9.

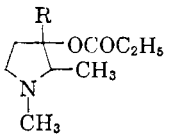
The *hydrochloride* had m.p. 187–189°.

Anal. Calcd. for $C_{19}H_{29}NO_2 \cdot HCl$: C, 67.1; H, 8.9; N, 4.1. Found: C, 67.4; H, 9.0; N, 4.0.

1-(2,3-Dihydroxypropyl)-2-methyl-3-phenyl-3-propionoxypyrrolidine (14).—2-Methyl-3-phenyl-3-propionoxypyrrolidine hydrochloride (10 g.) was treated with N aqueous sodium carbonate (100 ml.) and the liberated base extracted three

TABLE IV

SUBSTITUTION IN POSITION 3



Compound	R	Estimate of i.p. potency[a]	Est. of average i.p. lethal dose.[b] mg. base/kg.	(Potency) × (Lethal Dose)[c] / 0.8 × 133
1	C_6H_5	0.8	133	1.0
21	o-$CH_3C_6H_4$	(0.3)[d]	81	(0.2)
22	p-$CH_3C_6H_4$	None[e]	128	—
23	2-Pyridyl	0.2	422	0.7
24	m-$CF_3C_6H_4$	None[e]	109	—
25	m-$CH_3OC_6H_4$	None[e]	137	—

[a] At one-quarter the "average lethal dose." [b–e] Same as in Table III.

times with 75 ml. of benzene. The benzene extracts were concentrated *in vacuo* at room temperature to one-third volume, then treated with glycidol (4.2 g.; 1.5 mole) and refluxed gently for 4 hr., cooled, diluted with ether then treated with ethereal hydrogen chloride to give a sticky solid. This was crystallized from a 2-propanol–ether mixture to give needles, 9.0 g. (70%), m.p. 160–165°, unchanged on recrystallization.

Anal. Calcd. for $C_{17}H_{25}NO_4 \cdot HCl$: C, 59.4; H, 7.6; N, 4.1. Found: C, 59.1; H, 7.9; N, 4.1.

Using the above method but substituting styrene oxide (6.0 g.) for the glycidol *1-(2-hydroxyphenylethyl)-2-methyl-3-phenyl-3-propionoxypyrrolidine hydrochloride* (15), m.p. 179–181°, was obtained in 75% yield.

Anal. Calcd. for $C_{22}H_{27}NO_3 \cdot HCl$: C, 67.8; H, 7.2; N, 3.6. Found: C, 68.0; H, 7.4; N, 3.6.

Substituting glycidyl phenyl ether (8.4 g.), *1-(2-hydroxy-3-phenoxypropyl)-2-methyl-3-phenyl-3-propionoxypyrrolidine hydrochloride* (16), m.p. 148–150° was obtained in 76% yield.

Anal. Calcd. for $C_{23}H_{29}NO_4 \cdot HCl$: C, 65.9; H, 7.2; N, 3.3. Found: C, 66.2; H, 7.2; N, 3.4.

1-(2-Benzoylethyl)-2-methyl-3-phenyl-3-propionoxypyrrolidine (17).—2-Methyl-3-phenyl-3-propionoxypyrrolidine hydrochloride (10 g.) was converted to the base as described above, freed from the benzene used for extraction, dissolved in dimethylformamide (50 ml.) and added to a mixture of sodium carbonate (3.9 g.) and trimethyl-β-benzoylethylammonium iodide (13 g.) in dimethylformamide (100 ml.). The solution was then stirred at room temperature for 4 hr. while passing a stream of nitrogen to remove the liberated trimethylamine; water (500 ml.) was then added and the solution cooled and filtered to give the crude product, 12.5 g. (94%), m.p. 82–83°. Crystallization from light petroleum (60–80°) gave plates, m.p. 85°.

Anal. Calcd. for $C_{23}H_{27}NO_3$: C, 75.6; H, 7.5; N, 3.8. Found: C, 75.8; H, 7.5; N, 3.8.

The *hydrochloride* was obtained as fine needles, m.p. 170°.

Anal. Calcd. for $C_{23}H_{27}NO_3 \cdot HCl$: C, 68.7; H, 7.0; N, 3.5. Found: C, 68.9; H, 7.2; N, 3.5.

1 - (3 - Hydroxy - 3 - phenylpropyl) - 2 - methyl - 3 - phenyl - 3 - propionoxypyrrolidine (18).—The preceding ketone (3.65 g.) in ethanol (150 ml.) was treated with a solution of potassium borohydride (0.54 g.) in water (30 ml.) and stirred for 3 hr. The solution was concentrated *in vacuo*, poured into ice-water and extracted with benzene. Removal of the benzene gave an oil which could not be solidified. Treatment with ethereal hydrogen chloride gave the hydrochloride, 3.7 g. (90%), m.p. 100–120°. Crystallization from 2-propanol-ether mixtures gave the pure compound as fine needles, m.p. 162–166°.

Anal. Calcd. for $C_{23}H_{29}NO_3 \cdot HCl$: C, 68.4; H, 7.5; Cl, 8.8. Found: C, 68.5; H, 7.4; Cl, 8.8.

1 - (3 - Hydroxy - 3 - phenylpropyl) - 2 - methyl - 3 - phenyl - 3 - pyrrolidinol.—1-(2-Benzoylethyl)-2-methyl-3-phenyl-3-propionoxypyrrolidine (10 g.) in dry ether (100 ml.) was added to a suspension of lithium aluminum hydride (5 g.) in dry ether (150 ml.). The mixture was stirred and refluxed for 4 hr., cooled, treated cautiously with water (20 ml.), filtered, concentrated to an oil and the residue crystallized from a benzene–light petroleum (60–80°) mixture as clusters of needles, 8.9 g. (93%), m.p. 107–110°.

Anal. Calcd. for $C_{20}H_{25}NO_2$: C, 77.1; H, 8.1; N, 4.5. Found: C, 77.4; H, 7.9; N, 4.5.

1 - (3 - Phenyl - 3 - propionoxypropyl) - 2 - methyl - 3 - phenyl - 3 - propionoxypyrrolidine (19).—Propionylation of either of the preceding compounds with propionic anhydride and pyridine at 110° for 16 hr. gave the required compound, isolated as the (+)-tartrate, m.p. 118–121°.

Anal. Calcd. for $C_{26}H_{33}NO_4 \cdot C_4H_6O_6$: C, 62.8; H, 6.9; N, 2.4. Found: C, 62.6; H, 6.9; N, 2.8.

2-Methyl-3-phenyl-3-propionoxy-1-succinylpyrrolidine (20).—2-Methyl-3-phenyl-3-propionoxypyrrolidine hydrochloride (10 g.) was converted to the base as described above and dissolved in a mixture of tetrahydrofuran (60 ml.) and ether (140 ml.). The resulting solution was refluxed for 4 hr. in a Soxhlet apparatus and the condensed vapors of the solvent caused to pass through a thimble containing succinic anhydride (6 g.). The solution was concentrated to a solid and dissolved in aqueous sodium bicarbonate removing the small quantity of insoluble starting material by extracting with ether. Acidification of the basic solution gave a white solid which was crystallized from an ethyl acetate–ether mixture to give the pure acid as small plates, 10 g. (81%), m.p. 129–131°.

Anal. Calcd. for $C_{18}H_{23}NO_5$: C, 64.9; H, 7.0; N, 4.2. Found: C, 65.1; H, 7.1; N, 4.2.

1,2-Dimethyl-3-*o*-tolyl-3-pyrrolidinol.—Following the experimental details given previously[1] 1,2-dimethyl-3-pyrrolidone (46 g.) was treated with *o*-tolyllithium (from 70 g. *o*-bromotoluene and 5.8 g. lithium) to give a solid, 27 g. (32%), m.p. 89–92°, crystallizing as plates from light petroleum (40–60°).

Anal. Calcd. for $C_{13}H_{19}NO$: C, 76.1; H, 9.3; N, 6.8. Found: C, 76.4; H, 9.4; N, 6.6.

Substituting the appropriate lithium derivative for the *o*-tolyllithium in the above experiment the following alcohols were prepared: *1,2-Dimethyl-3-p-tolyl-3-pyrrolidinol* (88%) plates, m.p. 111–113°.

Anal. Calcd. for $C_{13}H_{19}NO$: C, 76.1; H, 9.3; N, 6.8. Found: C, 76.0; H, 9.5; N, 6.6.

1,2-Dimethyl-3-m-trifluoromethylphenyl-3-pyrrolidinol (69%) m.p. 69–70° (the preparation of the lithium derivative is recorded[9]).

Anal. Calcd. for $C_{13}H_{16}F_3NO$: N, 5.4; F, 22.0. Found: N, 5.3; F, 21.6.

1,2-Dimethyl-3-(2-pyridyl)-3-pyrrolidinol.—Following the procedure given by Gilman and Spatz[10] 2-pyridyllithium was prepared from lithium (2.45 g.), butyl chloride (16.3 g.) and 2-bromopyridine (22.8 g.) and the resulting ethereal solution (300 ml.) was treated at −15° with a solution of 1,2-dimethyl-3-pyrrolidone (16.3 g.) in dry ether (50 ml.), stirred from 30 min., then allowed slowly to regain room temperature. The solution was treated with saturated aqueous ammonium chloride (100 ml.), the layers were separated, the ethereal layer was washed with water (100 ml.), then extracted three times with 70 ml. of 2 *N* aqueous hydrochloric acid. Basification of the acid extracts gave an oil which on extraction with chloroform and distillation gave the required pyrrolidinol, 3.0 g. (11%), b.p. 102–104° (0.8 mm.), which solidified on standing.

Anal. Calcd. for $C_{11}H_{16}N_2O$: C, 68.7; H, 8.4; N, 14.6. Found: C, 68.6; H, 8.3; N, 14.3.

3-*m*-Anisyl-1,2-dimethyl-3-pyrrolidinol.—A Grignard reagent was prepared in the usual way from *m*-bromoanisole (65 g.) and magnesium (8.4 g.) in ether (250 ml.) and the solution treated at −40° with 1,2-dimethylpyrrolidone (39 g.) in ether (150 ml.). The mixture was stirred at this temperature for 1 hr. then allowed to regain room temperature. A mixture of concentrated hydrochloric acid (70 ml.) and water (170 ml.) was added and the aqueous layer separated, basified and the precipitated oil extracted with chloroform (3 × 100 ml.) and distilled: b.p. 125–127° (0.7 mm.), 22 g. (29%). This was then repeatedly crystallized from light petroleum (40–60°) to give the pyrrolidinol as small cubes, 4 g. (5%) m.p. 89°.

Anal. Calcd. for $C_{13}H_{19}NO_2$: C, 70.6; H, 8.7; N, 6.3. Found: C, 70.7; H, 8.7; N, 6.6.

Propionylation of the above alcohols with propionic anhydride-pyridine mixtures at 100–110° for 16 hr. gave the propionates listed in Table II, isolated either as the free base, by distillation or as an appropriate salt, by crystallization.

1-Benzyl-3,x-diphenyl-2-methyl-3-pyrrolidinol.—Reaction of phenyllithium with 1-benzyl-2-methyl-3-pyrrolidone[1] gave a product, m.p. 70–74° (73%), which was fairly pure 1-benzyl-2-methyl-3-phenyl-3-pyrrolidinol. Examination of the mother liquors from this product showed the presence of a high melting material which, when isolated and recrystallized from ether, had m.p. 118–120° (5%). This was the diphenylated compound of unknown structure; ultraviolet spectrum: λ_{max} 258 and 264 mμ, ε 946 and 735 in ethanol.

Anal. Calcd. for $C_{24}H_{25}NO$: C, 83.9: H, 7.3; N, 4.1. Found: C, 84.0; H, 7.3; N, 3.9.

2-Methyl-3-phenyl-3-pyrrolidinol.—Pure 1-benzyl-2-methyl-3-phenyl-3-pyrrolidinol (m.p. 79–80°, 13.4 g.) in ethanol (200 ml.) was hydrogenated with palladized charcoal (10%; 1 g.) at 50° and atmospheric pressure. After the theoretical quantity (1.3 l.) of hydrogen had been absorbed (2 hr.) the catalyst was filtered, the filtrate concentrated and the residue crystallized from benzene–light petroleum (40–60°) mixtures. The product was obtained as rods, 8.3 g. (93%), m.p. 102–104°, which retained solvent tenaciously.

(9) H. Gilman and L. A. Woods, *J. Am. Chem. Soc.*, **66**, 1981 (1944).
(10) H. Gilman and S. M. Spatz, *J. Org. Chem.*, **16**, 1485 (1951).

Anal. Calcd. for $C_{11}H_{15}NO$: C, 74.5; H, 8.5; N, 7.9. Found: C, 74.6; H, 8.5; N, 8.0.

The *pyrrolidinol hydrochloride* had m.p. 193–195°.

Anal. Calcd. for $C_{11}H_{15}NO \cdot HCl$: C, 61.8; H, 7.5; N, 6.6. Found: C, 61.7; H, 7.6; N, 6.6.

3,x-Diphenyl-2-methyl-3-pyrrolidinol.—Pure 1-benzyl-3,x-diphenyl-2-methyl-3-pyrrolidinol (m.p. 116–119°, 10 g.) was hydrogenated as described above to give a solid, crystallizing from a mixture of benzene–light petroleum (40–60°) as rods, m.p. 104–106°, 6.7 g. (91%): ultraviolet spectrum: λ_{max} 259 and 265 mμ, ε 682 and 530 in ethanol.

Anal. Calcd. for $C_{17}H_{19}NO$: C, 80.6; H, 7.6; N, 5.5. Found: C, 80.5; H, 7.8; N, 5.3.

Molecular Compound of 2-Methyl-3-phenyl-3-pyrrolidinol with 3,x-Diphenyl-2-methyl-3-pyrrolidinol.—Impure 1-benzyl-2-methyl-3-phenyl-3-pyrrolidinol (m. p. 70–74°, 100 g.) was hydrogenated as above and the resulting solid crystallized from benzene (150 ml.)–light petroleum (40–60°, 500 ml.) to give felting needles, 34 g., m.p. 134–138°. Treatment of the mother liquor with more light petroleum gave 2-methyl-3-phenyl-3-pyrrolidinol, 25 g., m.p. 100–102°. The larger fraction was recrystallized twice from benzene to give the molecular compound, 14 g., m.p. 144–145°.

Anal. Calcd. for $C_{11}H_{15}NO \cdot C_{17}H_{19}NO$: C, 78.1; H, 8.0; N, 6.5. Found: C, 78.1, 78.2; H, 7.9, 8.0; N, 6.3, 6.3.

Methylation of the Molecular Compound.—The compound (3.5 g.) was added to a mixture of formic acid (5.5 ml.) and aqueous formaldehyde (40%, 4.8 ml.) and the whole held at 95° for 6 hr. The solution then was basified cautiously with sodium carbonate (2 *N*) when a solid (1.8 g.) precipitated, m.p. 135–138°. Addition of more sodium carbonate (4 *N*) gave more solid (1.1 g.), m.p. 72–73°. Separate crystallization of these two solids from light petroleum (40–60°) gave: prisms, m.p. 141–143° and rhombs, m.p. 82–83°. The first of these was *1,2-dimethyl-3,x-diphenyl-3-pyrrolidinol.*

Anal. Calcd. for $C_{18}H_{21}NO$: C, 80.9; H, 7.9; N, 5.2. Found: C, 80.9; H, 7.8; N, 5.4.

The second product was shown (m.p. and mixture m.p.) to be 1,2-dimethyl-3-phenyl-3-pyrrolidinol.[1] These two compounds did not form a molecular compound: an equimolar mixture had m.p. 74–115°.

Acyl Migration in 2-Methyl-3-phenyl-3-propionoxypyrrolidine.—2-Methyl-3-phenyl-3-propionoxypyrrolidine hydrochloride (10 g.) in water was basified with caustic soda (50 ml., 2 *N*) and the liberated base extracted with ether. Removal of the ether left an oil which was held at 95° for 30 min. dissolved in ether (20 ml.) and diluted with light petroleum (40–60°, 80 ml.) to give *2-methyl-3-phenyl-1-propionyl-3-pyrrolidinol* as rods, 3.7 g., m.p. 112–114°.

Anal. Calcd. for $C_{14}H_{19}NO_2$: C, 72.1; H, 8.2; N, 6.0. Found: C, 72.2; H, 8.2; N, 5.6.

The *hydrochloride*, from dry ether, had m.p. 146–148°, p*K* 2.9. It was decomposed by water.

Anal. Calcd. for $C_{14}H_{19}NO_2 \cdot HCl$: C, 62.3; H, 7.5; N, 5.2; Cl, 13.1. Found: C, 61.8; H, 7.6; N, 5.2; Cl, 13.2.

Pharmacology.—The methods used for the estimation of the lethal doses and potencies of these compounds in rats have been described

in our earlier paper.[1] The results obtained are listed in Tables III and IV. Increasing the size of the substituent on the nitrogen atom resulted, in selected cases, in compounds having good potency. Compound (12), where *p*-aminophenethyl replaces methyl, has activity significantly greater than the reference compound. The *p*-nitrophenethyl compound (11), an intermediate in the synthesis of the *p*-aminophenethyl analog, would appear to be of interest with regard to its apparently low toxicity compared with other compounds in the series; with its retention of analgetic activity this gives the compound the highest rating in the potency–toxicity column of the tables. However, it is likely that full inherent toxicity was not manifest because of incomplete solution of the compound particularly at toxic dose levels. A strongly basic side chain (10), or an acidic one (20) effectively destroyed activity. None of the compounds with oxygenated side-chains (5,6,13,14,15,16,17,18) showed activity superior to the N-methyl compound. Isosteric replacement of the phenyl group at position 3 with *o*-pyridyl had an unsatisfactory result, while insertion of a methyl, methoxy or trifluoromethyl group effectively abolished activity.

Structure–Activity Relationships in a Series of Anticonvulsant and Hypnotic Bicyclic Carboxamides

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A series of stereoisomeric 5-substituted 2-norbornene-5-carboxamides was synthesized. The effect of alkyl, alkenyl, dialkylaminoalkyl, aryl and aralkyl substitution in the 5-position, halogenation, and N-alkylation upon electroshock- and pentylenetetrazol-induced convulsions and upon hypnotic activity is discussed. The norbornene derivatives are compared with their positional isomers, with bicyclo[2.2.2]oct-2-ene homologs and with several saturated and unsaturated monocyclic analogs.

Central nervous system depression is a characteristic pharmacodynamic response commonly observed upon administration of

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