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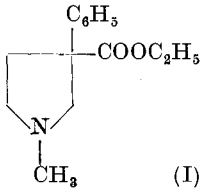
Analgetics Based on the Pyrrolidine Ring

J. F. CAVALLA, J. DAVOLL, (MRS.) M. J. DEAN, C. S. FRANKLIN and (MRS.) D. M. TEMPLE, *Parke, Davis and Company, Hounslow, Middlesex, England*

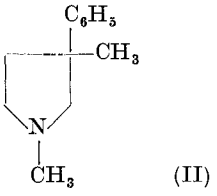
and

(MISS) J. WAX and C. V. WINDER, *Parke, Davis and Company, Ann Arbor, Michigan, U.S.A.*

The pyrrolidine ring, unlike that of piperidine, has attracted only slight attention as a likely framework for compounds possessing analgetic activity. Apart from the early work of Bergel,[1,2] and to a lesser extent that of Woods,[3] little appears to have been reported; the compounds of these workers, (I) and (II) respectively, both proved inactive and possibly acted as a disincentive to further study.



(I)



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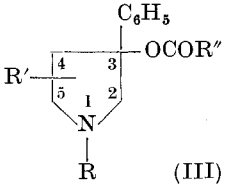

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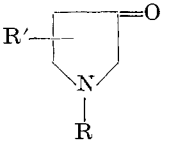

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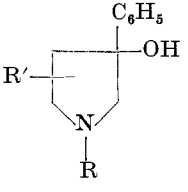

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We have prepared a number of substituted 3-acyloxy-3-phenylpyrrolidines (III) by reacting the pyrrolidones (IV) with phenylmetallo complexes to give the phenylpyrrolidinols (V), and subsequent acylation. Several of these compounds have been found to exhibit an interesting degree of activity similar to that of codeine.

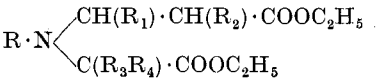
Chemistry

Although several singly substituted 3-pyrrolidones (IV; R′ = H) have been prepared,[4–7] the polyalkyl compounds have been only superficially examined.[5,6,8] The most satisfactory method for their preparation is the Dieckmann cyclization of the appropriate iminodicarboxylate diester (VI) to the pyrrolidone carboxylate ester (VII), which on hydrolysis and decarboxylation gives the pyrrolidone. The method is limited since only moderately substituted pyrrolidones can be prepared: when $R_2 = R_3 = CH_3$ then R_4 must be H for cyclization to occur.

The iminodicarboxylate diesters (VI) were prepared by condensation of the substituted β-aminopropionic ester or nitrile (VIII; $X = COOC_2H_5$ or CN) with a substituted α-bromoacetic acid ester (IX). This condensation proceeded well in all cases tried except in that where $R_3 = R_4 = CH_3$. In this case, part of the ethyl α-bromoisobutyrate was dehydrobrominated to ethyl methacrylate which then reacted with the amino acid ester to give a product isomeric to that required. Using this mixture in the later steps of the synthesis led to a product shown to consist[9] of almost equal parts of 1,3-dimethyl-4-piperidone and 1,2,2-trimethyl-3-pyrrolidone, which were separated by fractional crystallization of the mixed tartrates.

Preparation of the compound (III; R = H, R′ = 2-CH_3) was effected by using a protective benzyl group on the nitrogen atom and making its removal by catalytic hydrogenation the last stage of the synthesis, a reaction sequence which proceeded well, in contradistinction to work on the corresponding piperidines.[10]

Ease of reaction of the pyrrolidones with phenylmagnesium bromide depended upon their degree of substitution. In the simplest case (IV; $R = CH_3$, R′ = H), the reaction gave good yields of the required pyrrolidinol. In the case of IV ($R = CH_3$, R′ = 2-CH_3), however, a complex reaction occurred to give a



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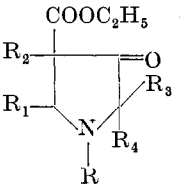


(VII)

(VIII)

(IX)

product from which the required phenylpyrrolidinol could be obtained only with greater difficulty and in lower yields. By substituting phenyllithium for phenylmagnesium bromide good yields of the required product were obtained with no evidence of the complex reactions obtained using the former reagent. Possibly similar results were found by Ziering[11] in his work on the prodines; in this case phenyllithium is used without mention of failure with phenylmagnesium bromide, although Jenson[12] in his original work on the simple 1-methyl-4-piperidone had found the reaction with phenylmagnesium bromide to be quite satisfactory.

Nazarov,[13] in synthesizing promedol, used phenyllithium without explanation but later[14] stated that 'γ-piperidones react with Grignard reagents predominantly as the enolic form'; considering the work of Jenson,[12] it might probably be more accurate to say that it is substituted piperidones which act in this way. This, however, would not seem to provide the complete explanation for the anomalous reactions in the case of substituted pyrrolidones, for besides enolization some evidence of ring opening was apparent.

The ease of propionation of the phenylpyrrolidinols also depended to a large extent on the degree of substitution of the pyrrolidine ring. Thus with V ($R = CH_3$, $R' = H$) reaction with propionyl chloride in ether gave good yields of the propionate but with V [$R = CH_3$, $R' = 2,5\text{-}(CH_3)_2$] long heating of the alcohol with propionic anhydride was found necessary to obtain equivalent yields.

Resolution of one of the more active compounds (III; $R = CH_3$, $R' = 2\text{-}CH_3$) was effected smoothly by fractional crystallization of the tartrates of the corresponding alcohol.

Synthesis

Ethyl β-methylaminobutyrate,[15] methyl β-methylaminoisobutyrate,[16] ethyl α-methylaminomethylbutyrate,[12] ethyl 2-methylaminomethyl-4-pentenoate,[17] β-ethylaminopropionitrile,[18] β-allylaminopropionitrile,[19] β-isopropylaminopropionitrile[20] and β-benzylaminopropionitrile[21] were prepared using the literature methods.

Condensation of β-Methylaminopropionitrile with Ethyl α-bromopropionate. A stirred mixture of β-methylaminopropionitrile[18] (84 g) and anhydrous potassium carbonate (138 g) in methyl ethyl ketone (250 ml) was treated slowly under reflux with ethyl α-bromopropionate (181 g) during 2 h. After addition, reflux and stirring was continued for 6 h; the mixture was cooled, filtered, concentrated and distilled to give *N*-(β-cyanoethyl)-*N*-(α-ethoxycarbonylethyl)methylamine (147 g, 80 per cent), b.p. 94–102°/0·8 mm, n_D^{20} 1·4446.

Anal. Calcd. for $C_9H_{16}N_2O_2$: C, 58·7; H, 8·8; N, 15·2. Found: C, 58·7; H, 8·6; N, 14·9.

Using this general method, the iminoester nitriles and iminodiesters listed in Table I-(*i*) were prepared.

Ethanolysis of Iminoester Nitriles. (*a*) *Using concentrated* H_2SO_4. *N*-(β-Cyanoethyl)-*N*-(ethoxycarbonylmethyl)methylamine (89·6 g) in absolute ethanol (280 ml) was treated cautiously with concentrated sulphuric acid (194 g) and the mixture refluxed gently for 18 h. The solution was cooled, diluted with water (600 ml) and basified with aqueous potassium carbonate (20 per cent). The liberated diester was isolated with ether and distilled, b.p. 110°/1·5 mm, n_D^{20} 1·4356. Prill and McElvain[4] give b.p. 124–125°/10 mm, n_D^{20} 1·4350.

(*b*) *Using HCl gas.* *N*-(β-Cyanoethyl)-*N*-(α-ethoxycarbonylethyl)allylamine (255 g) in absolute ethanol (1 l.) was saturated with hydrogen chloride and refluxed for 3 h, when ammonium chloride separated. The mixture was left overnight at room temperature, filtered, concentrated, dissolved in water (500 ml) and basified with aqueous potassium carbonate (20 per cent). The oil was extracted with ether, dried (Na_2SO_4) and distilled to give *N*-(α-ethoxycarbonylethyl)-*N*-(β-ethoxycarbonylethyl)allylamine (221 g, 71 per cent), b.p. 103°/0·4 mm, n_D^{20} 1·4483.

Anal. Calcd. for $C_{13}H_{23}NO_4$: C, 60·7; H, 9·0; N, 5·4. Found: C, 60·8; H, 9·2; N, 5·6.

Using these two methods, the diesters listed in Table I-(*ii*) were prepared.

1,2-Dimethyl-3-pyrrolidone. *N*-(α-Ethoxycarbonylethyl)-*N*-(β-ethoxycarbonylethyl)methylamine (140 g) in dry benzene (700 ml) was added to 'foamed' sodium ethoxide [made from sodium (14 g) and absolute ethanol (300 ml)] and the mixture stirred and refluxed, passing the vapour through a 12-in. Fenske column. The alcohol was removed as its azeotrope with benzene (*ca.* 230 ml) over 5 h and the solution cooled and treated with concentrated hydrochloric acid (200 ml). The aqueous layer was separated and the benzene solution washed with 6N hydrochloric acid (2 × 100 ml). The bulked aqueous layers were refluxed for 3 h, concentrated to a solid *in vacuo*, dissolved in water (50 ml) and basified with 10N sodium hydroxide, filtered and the pyrrolidone (41 g, 60 per cent) isolated with ether and distilled, b.p. 55°/22 mm, n_D^{20} 1·4452.

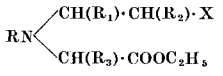
Anal. Calcd. for $C_6H_{11}NO$: C, 63·7; H, 9·8; N, 12·4. Found: C, 63·8; H, 9·8; N, 12·3. The *pyrrolidone hydrochloride* had m.p. 179–182°.

Anal. Calcd. for $C_6H_{11}NO \cdot HCl$: C, 48·2; H, 8·1; N, 9·4. Found: C, 48·2; H, 8·4; N, 9·4.

Using this method, the pyrrolidones listed in Table II were prepared.

1,2,2-Trimethyl-2-pyrrolidone. β-Methylaminopropionitrile (291 g, 2 moles) was kept at 85° for 48 h with ethyl α-bromoisobutyrate (334 g, 1 mole), then cooled, treated with ether and the ether-soluble material separated and washed. Concentration and distillation gave a mixture (115 g, 34 per cent), b.p. 105–110°/1·0 mm of *N*-(β-cyanoethyl)-*N*-(α-ethoxycarbonyl-α-methylethyl)methylamine and *N*-(β-cyanoethyl)-*N*-(β-ethoxycarbonylpropyl)methylamine which could not be resolved. The mixture was ethanolysed using method (*b*) above to give an inseparable mixture of diesters (106 g, 74 per cent), b.p. 105/1·5 mm. Cyclization of this mixture following the above procedure gave a mixture (34 g, 63 per cent) of 1,2,2-trimethyl-3-pyrrolidone and 1,3-dimethyl-4-piperidone. The infrared spectrum of this mixture showed peaks at both 1715 and 1754 cm^{-1} indicative of a six- and a five-membered ring ketone[9]

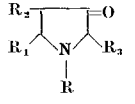
Table I. Imino-ester nitriles and imino-diesters



	R	R_1	R_2	R_3	X	b.p., °C (mm)	n_D^{20}	% Yield	Formula	Analysis, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
(*i*)	CH_3	H	H	H	CN	110 (0·9)	1·4440	70	[d]						
	CH_3	CH_3	H	H	$COOC_2H_5$	103 (1·0)	1·4402	78	$C_{11}H_{21}NO_4$	57·1	9·2	6·1	56·8	9·0	6·2
	CH_3	H	CH_3	H	$COOCH_3$	87 (1·0)	1·4362	79	$C_{10}H_{19}NO_4$	55·3	8·8	6·5	55·2	8·7	6·4
	CH_3	H	CH_3	CH_3	$COOCH_3$	89–94 (1·0)	1·4370	77	$C_{11}H_{21}NO_4$	57·1	9·2	6·1	56·9	9·3	6·8
	CH_3	CH_3	H	CH_3	$COOC_2H_5$	103 (1·0)	1·4397	75	$C_{12}H_{23}NO_4$	58·8	9·5	5·7	58·4	9·3	5·6
	CH_3	H	H	CH_3	CN	110–111 (1·0)	1·4435	73	$C_{10}H_{18}N_2O_2$	60·6	9·2	14·1	60·5	9·1	13·9
	CH_3	H	C_2H_5	H	$COOC_2H_5$	96-100 (1·0)	1·4363	75	$C_{12}H_{23}NO_4$	58·8	9·5	—	58·4	9·4	—
	CH_3	H	CH_2–$CHCH_2$	H	$COOC_2H_5$	103–107 (1·0)	1·4458	82	$C_{13}H_{23}NO_4$	60·7	9·0	—	60·6	9·1	—
	CH_3	H	H	CH_3	CN	98–102 (0·8)	1·4428	62	$C_{10}H_{18}N_2O_2$	60·6	9·2	14·1	59·8	9·3	14·2
	CH_2=$CHCH_2$	H	H	CH_3	CN	118 (1·0)	1·4545	54	$C_{11}H_{18}N_2O_2$	62·8	8·6	13·3	62·6	8·8	14·0
	i-C_3H_7	H	H	CH_3	CN	92–97 (0·1)	1·4456	38[a]	$C_{11}H_{20}N_2O_2$	62·2	9·5	13·2	62·5	9·6	13·7
	$C_6H_5CH_2$	H	H	CH_3	CN	157 (1·0)	1·5032	56	$C_{15}H_{20}N_2O_2$	69·2	7·7	—	69·5	8·1	—
	CH_3	H	H	C_6H_5	$COOC_2H_5$	162–164 (1·5)	1·4941	63	$C_{16}H_{23}NO_4$	65·5	7·9	4·8	65·1	8·0	4·8
(*ii*)	CH_3	H	H	CH_3	$COOC_2H_5$	95 (1·1)	1·4410	65[b]	$C_{11}H_{21}NO_4$	57·1	9·2	6·1	57·4	9·2	6·0
	CH_3	H	H	C_2H_5	$COOC_2H_5$	106 (1·5)	1·4378	68[b]	$C_{12}H_{23}NO_4$	58·8	9·5	5·7	58·6	9·4	6·0
	C_2H_5	H	H	CH_3	$COOC_2H_5$	100 (1·0)	1·4380	65[b]	$C_{12}H_{23}NO_4$	58·8	9·5	5·7	58·7	9·4	5·8
	i-C_3H_7	H	H	CH_3	$COOC_2H_5$	93–97 (0·3)	1·4397	60[c]	$C_{13}H_{25}NO_4$	60·2	9·7	5·4	59·6	9·8	5·4
	$C_6H_5CH_2$	H	H	CH_3	$COOC_2H_5$	137 (0·3)	1·4901	35[c]	$C_{17}H_{25}NO_4$	66·4	8·2	—	66·4	8·5	—

[a] This compound was prepared by heating the amine (2 moles) with the bromo ester (1 mole) in the absence of solvent at 100° for 24 h; using the standard reaction gave negligible yields of product. [b] H_2SO_4/C_2H_5OH. [c] HCl/C_2H_5OH. [d] Reference 17.

Table II. Substituted 3-pyrrolidones



R	R_1	R_2	R_3	b.p., °C (mm)	n_D^{20}	% Yield	Formula	Analysis, %					
								Calcd.			Found		
								C	H	N	C	H	N
CH_3	H	H	H	77–79 (78)	1·4450	64	C_5H_9NO	60·6	9·2	14·3	60·0	9·6	13·7
CH_3	CH_3	H	H	70 (39)	1·4417	70	$C_6H_{11}NO$	63·7	9·8	12·4	63·9	9·9	12·1
CH_3	H	CH_3	H	38 (8)	1·4403	63	$C_6H_{11}NO$	63·7	9·8	—	63·7	9·7	—
CH_3	H	CH_3	CH_3	72–76 (14)	1·4407	12	$C_7H_{13}NO$	66·1	10·3	11·1	65·7	10·5	10·9
CH_3	CH_3	H	CH_3	72 (37)	1·4450	54	$C_7H_{13}NO$	66·1	10·3	11·1	66·0	10·1	10·7
CH_3	H	H	C_2H_5	76 (35)	1·4468	22	$C_7H_{13}NO$	66·1	10·3	11·1	65·8	10·1	11·0
CH_3	H	C_2H_5	H	51·5 (9)	1·4436	53	$C_7H_{13}NO$	66·1	10·3	—	65·8	10·2	—
CH_3	H	CH_2=$CHCH_2$	H	65 (6)	1·4641	35	$C_8H_{13}NO$	69·0	9·4	—	69·0	9·7	—
C_2H_5	H	H	CH_3	85 (50)	1·4480	38	$C_7H_{13}NO$	66·1	10·3	11·1	65·9	10·2	11·0
CH_2=$CHCH_2$	H	H	CH_3	79 (18)	1·4622	70	$C_8H_{13}NO$	69·0	9·4	10·1	68·6	9·6	10·2
i-C_3H_7	H	H	CH_3	79 (12)	1·4539	60	$C_8H_{15}NO$	—	—	9·9	—	—	10·0
$C_6H_5CH_2$	H	H	CH_3	101–103 (0·8)	1·5276	66	$C_{12}H_{15}NO$	76·2	8·0	7·4	76·5	8·2	7·2
CH_3	H	H	C_6H_5	106–108 (1·2)	—	56	$C_{11}H_{12}NO$	75·4	7·5	8·0	74·7	7·6	8·1

in the approximate proportions of 1 : 2. After some difficulty, a crude salt of this mixture was obtained with (+)-tartaric acid which on repeated crystallization from absolute ethanol gave 1,2,2-trimethyl-3-pyrrolidone (+)-tartrate monohydrate, m.p. 79–82°.

Anal. Calcd. for $C_7H_{13}NO \cdot C_4H_6O_6 \cdot H_2O$: C, 44·7; H, 7·2; N, 4·7. Found: C, 44·8; H, 7·1; N, 4·5. Conversion of this salt to the base gave *1,2,2-trimethyl-3-pyrrolidone*, b.p. 59–60°/17 mm, n_D^{20} 1·4477.

Anal. Calcd. for $C_7H_{13}NO$: C, 66·1; H, 10·3; N, 11·0. Found: C, 66·2; H, 10·5; N, 11·0.

1,2-Dimethyl-3-phenyl-3-pyrrolidinol. (*a*) *Using phenylmagnesium bromide.* Phenylmagnesium bromide (1·5 mole), [prepared from magnesium (10·0 g) and bromobenzene (71 g)], in ether (250 ml) was treated with an ethereal solution of 1,2-dimethyl-3-pyrrolidone (30·3 g, 1·0 mole) and refluxed for 2 h. Addition of 2N hydrochloric acid (200 ml), followed by removal of the organic layer and basification of the acid solution, gave an oil which was isolated with ether and distilled to give a *mixture*, (21 g, 41 per cent) b.p. 104–108°/1 mm which set to a solid, m.p. 47–50°. Infrared examination of this material suggested that it contains three separate hydroxy compounds along with traces of unsaturation. (Found: C, 72·7; H, 9·0; N, 8·4.) By refluxing the material (1·5 g) in ethanol (10 ml) with methyl iodide (3 ml) a solid (0·7 g, 30 per cent) m.p. 180° was obtained, which after three crystallizations from ethanol–ether mixtures gave *3-hydroxy-3-phenyl-1,1,2-trimethylpyrrolidinium iodide*, m.p. 200–202°.

Anal. Calcd. for $C_{13}H_{20}INO$: C, 46·9; H, 6·1; N, 4·2; I, 38·1. Found: C, 46·9; H, 6·2; N, 4·7; I, 38·2.

(*b*) *Using phenyllithium.* 1,2-Dimethyl-3-pyrrolidone (116·5 g) in dry ether (200 ml) was added cautiously to a stirred solution of phenyllithium (1·75 moles) prepared from lithium wire (21·5 g) and bromobenzene (242 g) in dry ether (700 ml). The mixture was refluxed for 2 h, cooled, then treated with water (25 ml) followed by 6N hydrochloric acid (500 ml), the aqueous layer separated, basified with aqueous potassium hydroxide and the precipitated oil isolated with chloroform. Removal of the chloroform gave a solid which on crystallizing twice from light petroleum (40–60°) gave yellow prisms (137 g, 76 per cent) of *1,2-dimethyl-3-phenyl-3-pyrrolidinol*, m.p. 83–84°.

Anal. Calcd. for $C_{12}H_{17}NO$: C, 75·4; H, 9·0; N, 7·3. Found: C, 75·3; H, 8·8; N, 7·5.

With acetone-methyl iodide, this product gave the quaternary salt in 96 per cent yield, m.p. 203°, undepressed on admixture with the material obtained above.

Using this latter method the pyrrolidinols listed in Table III were prepared.

Acylation of Pyrrolidinols. (*a*) *Using acyl chloride.* The pyrrolidinol (1 mole) in dry ether or methylene chloride was treated with the acyl chloride (5 moles) and the mixture refluxed for 2 h. The solvent was removed by distillation and the residue dissolved in water, basified with aqueous potassium carbonate and the ester isolated with ether and distilled *in vacuo*.

(*b*) *Using acid anhydride.* The pyrrolidinol (1 mole) in pyridine (1 mole) was treated with the acid anhydride (5 moles) and kept overnight at 100°. The mixture was evaporated *in vacuo*, xylene added, and re-evaporated, repeating this to remove all traces of pyridine. The resulting oil was either distilled *in vacuo* or dissolved in ether and isolated as a salt with an appropriate acid.

The esters prepared using these methods are given in Table IV.

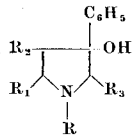
The *diethylcarbamate ester* was made, with some difficulty, by the reaction of the pyrrolidinol in benzene with sodium hydride followed by the addition of diethylcarbamoyl chloride.

2-Methyl-3-phenyl-3-propionoxypyrrolidine. 1-Benzyl-2-methyl-3-phenyl-3-propionoxypyrrolidine hydrochloride (15 g) in ethanol (100 ml) was shaken with palladized charcoal (1 g, 5 per cent) at 50–60° in an atmosphere of hydrogen, when 1·06 l. hydrogen (theory: 0·94 l.) was absorbed during 1·5 h. The solution was filtered, concentrated to low bulk and treated with ether to give a white solid (9 g). Crystallization of this from ethanol–ether mixtures gave small needles (7·8 g, 70 per cent) of *2-methyl-3-phenyl-3-propionoxypyrrolidine hydrochloride*, m.p. 219–222°.

Anal. Calcd. for $C_{14}H_{19}NO_2 \cdot HCl$: C, 62·3; H, 7·5. Found: C, 62·1; H, 7·8. This is compound number 17 in Table VII.

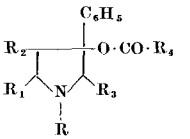
Resolution of 1,2-Dimethyl-3-phenyl-3-pyrrolidinol. Treatment of the pyrrolidinol (9·55 g) in warm ethanol (30 ml) with (+)-tartaric acid (7·5 g) in warm ethanol (70 ml) gave, on cooling, a product (8 g) which, after four recrystallizations from ethanol, afforded (−)-*1,2-dimethyl-3-phenyl-3-pyrrolidinol* (+)-*tartrate*

Table III. Substituted 3-phenyl-3-pyrrolidinols



R	R_1	R_2	R_3	b.p., °C (mm)	n_D^{20}	% Yield	Formula	Analysis, %					
								Calcd.			Found		
								C	H	N	C	H	N
CH_3	CH_3	H	H	70–71[a]	—	87	$C_{12}H_{17}NO$	75·4	9·0	7·3	75·7	8·8	7·3
CH_3	CH_3	H	H	254–255[a]	—	—	$C_{13}H_{20}INO$[d]	46·9	6·1	4·2	46·9	5·9	4·0
CH_3	H	CH_3	H	74–76[a, e]	—	38	$C_{12}H_{17}NO$	75·4	9·0	7·3	75·5	8·5	7·6
CH_3	H	CH_3	H	107 (0·7)[c]	1·5387	26	$C_{12}H_{17}NO$	75·4	9·0	—	74·9	9·1	—
CH_3	H	H	CH_3	84–86[a]	—	80	$C_{12}H_{17}NO$	75·4	9·0	7·3	75·3	8·8	7·5
CH_3	H	H	CH_3	202–203[a]	—	—	$C_{13}H_{20}INO$[d]	46·9	6·1	4·2	47·3	5·9	3·8
CH_3	H	CH_3	CH_3	75–77[a]	—	76	$C_{13}H_{19}NO$	76·1	9·3	6·8	75·8	9·3	7·1
CH_3	CH_3	H	CH_3	55–57[a]	—	81	$C_{13}H_{19}NO$	76·1	9·3	6·8	75·7	9·2	6·7
CH_3	H	H	C_2H_5	100–103[a]	—	86	$C_{13}H_{19}NO$	76·1	9·3	6·8	75·5	9·1	6·8
CH_3	H	C_2H_5	H	96 (0·4)	1·5333	70	$C_{13}H_{19}NO$	76·1	9·3	—	76·1	9·3	—
CH_3	H	CH_2=$CHCH_2$	H	111 (0·6)	1·5407	56	$C_{14}H_{19}NO$	77·4	8·4	—	77·0	9·3	—
C_2H_5	H	H	CH_3	63–65[a]	—	67	$C_{13}H_{19}NO$	76·1	9·3	6·8	76·1	9·3	6·5
CH_2=$CHCH_2$	H	H	CH_3	118 (0·9)	1·5420	84	$C_{14}H_{19}NO$	77·4	8·8	6·5	77·3	9·2	6·1
n-C_3H_7	H	H	CH_3	94 (0·2)	1·5308	68	$C_{14}H_{21}NO$	76·7	9·7	6·4	76·8	10·1	6·3
$C_6H_5CH_2$	H	H	CH_3	79–80[a]	—	70	$C_{18}H_{21}NO$	—	—	5·2	—	—	5·2
$C_6H_5CH_2$	H	H	CH_3	217[a]	—	—	$C_{18}H_{22}ClNO$[b]	71·1	7·3	—	70·8	7·5	—
CH_3	H	H	C_6H_5	130 (0·4)	—	68	$C_{17}H_{19}NO$	80·6	7·6	5·5	81·1	8·0	5·4
CH_3	H	H	$(CH_3)_2$	98–100 (0·6)	1·5331	52	$C_{13}H_{19}NO$	76·1	9·3	6·8	75·3	9·6	7·4
CH_3	H	H	$(CH_3)_2$	205[a]	—	—	$C_{20}H_{25}NO_4$[c]	70·0	7·3	4·1	70·2	7·6	3·9

[a] m.p. [b] Hydrochloride. [c] Salicylate. [d] Methyl iodide. [e] This compound was obtained in two possibly stereoisomeric forms.



No.	R	R_1	R_2	R_3	R_4	Form	b.p., °C (mm)	n_D^{20}	% Yield	Formula	Analysis					
											Calcd.			Found		
											C	H	N	C	H	N
5	CH_3	H	H	H	C_2H_5	Base	107–109 (0·7)	1·5150	60[b]	$C_{14}H_{19}NO_2$	72·1	8·2	6·0	72·2	8·1	5·8
	CH_3	H	H	CH_3	C_2H_5	Base	126–128 (1·1)	1·5164	77[b]	$C_{15}H_{21}NO_2$	72·8	8·6	5·7	72·9	8·8	5·7
1	CH_3	H	H	CH_3	C_2H_5	HCl[e]	194–195[a]	—	—	$C_{15}H_{22}ClNO_2$	63·5	7·8	4·9	63·4	8·0	5·1
	CH_3	H	H	CH_3	C_2H_5	Salicylate	132–134[a]	—	—	$C_{22}H_{27}NO_5$	68·6	7·1	—	68·3	7·2	—
	CH_3	H	H	CH_3	C_2H_5	Sulphamate	80–82[a]	—	—	$C_{15}H_{24}N_2O_5S.H_2O$	49·7	7·2	—	50·0	7·2	—
	CH_3	H	H	CH_3	C_2H_5	Malate	137–138[a]	—	—	$C_{19}H_{27}NO_7$	59·8	7·1	—	59·8	7·4	—
	CH_3	H	H	CH_3	C_2H_5	Tartrate	173–175[a]	—	—	$C_{19}H_{27}NO_8$	57·4	6·9	—	57·2	6·9	—
23	CH_3	H	H	CH_3	C_2H_5	Methyl iodide	170–171[a]	—	—	$C_{16}H_{24}INO_2$	49·4	6·2	32·6[d]	49·5	6·2	32·4[d]
13	CH_3	H	H	CH_3	CH_3	HCl[e]	184–185[a]	—	80[c]	$C_{14}H_{20}ClNO_2$	62·3	7·5	—	61·9	7·9	—
14	CH_3	H	H	CH_3	n-C_3H_7	HCl	178–179[a]	—	79[c]	$C_{16}H_{24}ClNO_2$	64·5	8·1	4·7	64·3	8·4	4·6
	CH_3	H	H	CH_3	i-C_3H_7	Base	129–130 (1·4)	1·5100	40[b]	$C_{16}H_{23}NO_2$	73·5	8·9	5·4	73·9	9·3	5·1
15	CH_3	H	H	CH_3	i-C_3H_7	HCl	209–210[a]	—	—	$C_{16}H_{24}ClNO$	64·5	8·1	4·7	64·1	8·5	4·6
16[i]	CH_3	H	H	CH_3	$N(C_2H_5)_2$	HCl	161–163[a]	—	30	$C_{17}H_{27}ClN_2O_2$	62·5	8·3	8·6	63·3	8·8	7·9
6	CH_3	CH_3	H	H	C_2H_5	Base	127–130 (1·2)	1·5109	70[c]	$C_{15}H_{21}NO_2$	72·8	8·6	5·7	73·2	8·6	5·7
24	CH_3	CH_3	H	H	C_2H_5	Methyl iodide	211–212[a]	—	—	$C_{16}H_{24}INO_2$	49·4	6·2	3·6	49·5	5·9	3·8
	CH_3	H	CH_3	H	C_2H_5	Base[j]	114 (1·5)	1·5115	75[b]	$C_{15}H_{21}NO_2$	72·8	8·6	5·7	72·7	8·5	5·8
7	CH_3	H	CH_3	H	C_2H_5	HCl	167–168[a]	—	—	$C_{15}H_{22}ClNO_2$	63·5	7·8	—	62·9	7·8	—
25	CH_3	H	CH_3	H	C_2H_5	Methyl iodide	204–205[a]	—	—	$C_{16}H_{24}INO_2$	49·4	6·2	3·6	49·3	6·1	3·1
11	CH_3	H	CH_3	CH_3	C_2H_5	Base	110–117 (0·5)	1·5141	44[b]	$C_{16}H_{23}NO_2$	73·5	8·9	5·4	73·1	8·8	5·4
12	CH_3	CH_3	H	CH_3	C_2H_5	HCl	161–163[a]	—	35[c]	$C_{16}H_{24}ClNO_2$	64·5	8·1	4·7	64·3	8·4	4·7
	CH_3	H	H	C_2H_5	C_2H_5	Base	137 (0·9)	1·5145	82[c]	$C_{16}H_{23}NO_2$	73·5	8·9	5·4	74·3	9·0	5·5
3	CH_3	H	H	C_2H_5	C_2H_5	HCl	179–181[a]	—	—	$C_{16}H_{24}ClNO_2$	64·5	8·1	4·7	64·1	8·3	4·8
	CH_3	H	C_2H_5	H	C_2H_5	Base	101 (0·1)	1·5084	80[c]	$C_{16}H_{23}NO_2$	73·5	8·9	—	73·0	8·6	—
8	CH_3	H	C_2H_5	H	C_2H_5	HCl	157[a]	—	—	$C_{16}H_{24}ClNO_2$	64·5	8·1	—	63·8	8·2	—
	CH_3	H	$CH_2{=}CHCH_2$	H	C_2H_5	Base	123 (0·6)	1·5159	80[c]	$C_{17}H_{23}NO_2$	74·7	8·5	—	74·4	8·8	—
10	CH_3	H	$CH_2{=}CHCH_2$	H	C_2H_5	HCl	118–120[a]	—	—	$C_{17}H_{24}ClNO_2$	65·7	7·8	—	65·6	8·0	—
9	CH_3	H	n-C_3H_7	H	C_2H_5	HCl	141–142[a]	—	50[f]	$C_{17}H_{26}ClNO_2$	65·3	8·4	—	65·1	8·8	—
	C_2H_5	H	H	CH_3	C_2H_5	Base	125–128 (0·5)	1·5130	83[c]	$C_{16}H_{23}NO_2$	73·5	8·9	5·4	73·4	9·2	5·4
18	C_2H_5	H	H	CH_3	C_2H_5	HCl	213·5–214[a]	—	—	$C_{16}H_{24}ClNO_2$	64·5	8·1	4·7	64·6	8·2	4·6
	$CH_2{=}CHCH_2$	H	H	CH_3	C_2H_5	Base	140–142 (1·8)[g]	1·5289	76	$C_{17}H_{23}NO_2$	74·7	8·5	5·1	74·4	8·7	5·1
21	$CH_2{=}CHCH_2$	H	H	CH_3	C_2H_5	HCl	189–191[a]	—	—	$C_{17}H_{24}ClNO_2$	65·9	7·8	4·5	65·5	8·0	4·8
19	n-C_3H_7	H	H	CH_3	C_2H_5	HCl	201–203[a]	—	40[f]	$C_{17}H_{26}ClNO_2$	65·5	8·4	4·5	65·0	8·6	4·6
	i-C_3H_7	H	H	CH_3	C_2H_5	Base	123 (0·3)	1·5130	82[c]	$C_{17}H_{25}NO_2$	74·1	9·2	5·1	74·0	9·1	5·2
20	i-C_3H_7	H	H	CH_3	C_2H_5	Tartrate	112 and 130[h]	—	—	$C_{21}H_{31}NO_9.H_2O$	56·9	7·5	3·2	56·7	7·7	3·3
22	$C_6H_5CH_2$	H	H	CH_3	C_2H_5	HCl	174–175[a]	—	78[c]	$C_{21}H_{26}ClNO_2$	70·1	7·3	—	69·8	7·4	—
4	CH_3	H	H	C_6H_5	C_2H_5	Base	152–155 (0·5)	—	80[c]	$C_{20}H_{23}NO_2$	77·6	7·5	4·5	77·6	7·6	4·4
2	CH_3	H	H	diCH_3	C_2H_5	HCl[e]	177–179[a]	—	62[c]	$C_{15}H_{24}ClNO_2$	64·5	8·1	4·7	64·8	8·2	4·7

[a] m.p. [b] Method (*a*). [c] Method (*b*). [d] Iodine determination. [e] Hygroscopic. [f] By catalytic hydrogenation of corresponding allyl. [g] m.p. 58–61 ex light petroleum (40–60). [h] Double m.p. [i] Could not be obtained completely pure. [j] Prepared from corresponding alcohol m.p. 74–76°.

(3·45 g) m.p. 166–167°. Evaporation of the combined mother-liquors, basification of an aqueous solution of the residue, and extraction with ether afforded crude pyrrolidinol (6·7 g), which was converted to (+)-*1,2-dimethyl-3-phenyl-3-pyrrolidinol* (−)-*tartrate* (4·67 g), m.p. 166–168°, by treatment with (−)-tartaric acid (5·2 g) in ethanol followed by three recrystallizations of the product.

Treatment of an aqueous solution of its tartrate with sodium hydroxide, followed by ether extraction, gave (−)-*1,2-dimethyl-3-phenyl-3-pyrrolidinol* (100 per cent), as a waxy solid, m.p. 35–45°, $[\alpha]_D^{24}$ −7° (*c*, 3·14 per cent in C_2H_5OH). (Found: C, 75·7; H, 9·3; N, 7·5.) Similarly prepared, (+)-*1,2-dimethyl-3-phenyl-3-pyrrolidinol* had m.p. 35–43°, $[\alpha]_D^{25}$ +8° (*c*, 3·13 per cent in C_2H_5OH). A mixture of equal weights of the enantiomorphs crystallized from ethanol as the racemate, m.p. 79–81°.

(+) *and* (−)-*1,2-Dimethyl-3-phenyl-3-propionoxypyrrolidines.* These were prepared as described above and isolated as (+)-tartrates without distillation. (+)-*1,2-Dimethyl-3-phenyl-3-propionoxypyrrolidine* (+)-*tartrate* formed rods (from ethanol), m.p. 94–98°, $[\alpha]_D^{24}$ +60° (*c*, 3·07 per cent in H_2O).

Anal. Calcd. for $C_{15}H_{21}NO_2 \cdot C_4H_6O_6 \cdot 3H_2O$: C, 50·8; H, 7·0; N, 3·1. Found: C, 50·5; H, 7·4; N, 3·1. This is compound No. 26 in Table IX.

(−)-*1,2-Dimethyl-3-phenyl-3-propionoxypyrrolidine* (+)-*tartrate* formed rods (from ethanol), m.p. 172–174°, $[\alpha]_D^{24}$ −38° (*c*, 3·24 per cent in H_2O).

Anal. Calcd. for $C_{15}H_{21}NO_2 \cdot C_4H_6O_6 \cdot H_2O$: C, 54·9; H, 7·0; N, 3·4. Found: C, 54·7; H, 6·7; N, 3·1. This is compound No. 27 in the Table IX. Crystallization of a mixture of equimolar amounts from ethanol gave the racemic (+)-tartrate with m.p. and mixed m.p. 174–176°.

Pharmacology

Methods

We used Sprague–Dawley albino rats at about four weeks of age for both the acute toxicity and the antinociceptive potency evaluations.

For the toxicity studies, groups of 3 or 6 rats were injected

intraperitoneally at log-dose intervals of 0·075 or 0·150, depending on the amount of compound available, and deaths counted for 7 days thereafter. The various doses of the various compounds fell in a semisystematic manner on to varying lots of animals, and the mean lethal dose was computed by the 'moving average' method.[22] The 95 per cent precision of the estimates, strictly applicable only as approximations to the respective confounds of compound and animal lot, varied usually from × or ÷ 1·06 to × or ÷ 1·25, with a few cases as wide as 1·38 to 1·92 (compound No. 9, Table V).

For the antinociceptive studies, we used a modification described elsewhere[23] of the method of Green *et al.*[24] for determining a measure of the mechanical pressure on the tail at which squeaking occurs. The compound was administered intraperitoneally, 30 min before measuring. Starting at one-fourth the estimated mean lethal dose, or no higher than 400 mg/kg, in successive experiments we repeated or halved doses of any compound(s) until the elevation of squeak threshold, if any, was reliably less than that associated with a standard dose of aminopyrine. In all experiments a constant reference dose of codeine phosphate (11·3 mg of base per kg) and vehicle was included.

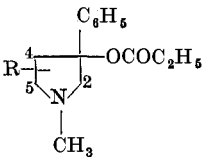
The experimental design and analysis was of the randomized group type. Customarily, 15 groups provided 15 replicates; i.e. 15 animals per treatment group. The observer was unaware of any individual animal's treatment. We converted threshold pressures for squeaking to their logarithms before arithmetical manipulation. Occasional threshold values exceeding the range of the apparatus were recorded as the limit of the range; for purposes at hand, this did not seriously bias estimates.

We estimated antinociceptive potencies relative to that of codeine by plotting the mean log threshold with experimental treatment reduced by the mean log threshold with codeine, against the log experimental dose reduced by the log codeine dose. Formal confidence limits cannot be computed from such data, but we estimated from the scatter in such plots and the numbers of points, that the relative potency figures, within the meaning of the technique used, are usually precise to within about two integers in the first decimal place. (The percentage uncertainty increased as the fewness of sub-toxic dose points at which activity occurred,

hence usually as potency decreased, in such a manner as to maintain a fairly constant uncertainty on the arithmetical potency scale.)

The last column of Tables V to IX shows the ratio of potency to toxicity referred to that of compound No. 1 as unity, and includes the greater uncertainty of both biological estimates.

Table V. Substitution in the ring

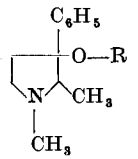


Compound no.	R	Estimate of i.p. potency[a]	Est. of average i.p. lethal dose,[b] mg base/kg	(Potency) × (Lethal dose)[c] / 0·8 × 133
1	2-CH_3	0·8	133	1·0
2	2,2-$(CH_3)_2$	(0·3)[d]	117	(0·3)[d]
3	2-C_2H_5	(<0·3)	181	(<0·3)
4	2-C_6H_5	0·4	154	0·5
5	H	(<0·3)	133	(0·3)
6	5-CH_3	(<0·3)	146	(<0·3)
7	4-CH_3	0·5	131	0·6
8	4-C_2H_5	0·4	160	0·6
9	4-n-C_3H_7	(<0·3)	99	(<0·3)
10	4-CH_2=CH—CH_2	(<0·3)	121	(0·3)
11	2,4-$(CH_3)_2$	(<0·3)	154	(0·3)
12	2,5-$(CH_3)_2$	0·6	156	0·9

[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 assigned unity.
[d] Figures in parentheses obtained by extrapolation. Effect equivalent to 11·3 mg codeine (base) per kg not actually attained at ¼ lethal dose.

All computations are in terms of base contents. All doses were carried as their salts in 1·0 ml of 0·9 per cent NaCl, except in a few cases where the material was only partially soluble and a suspension was used. These solubility exceptions are indicated in the tables.

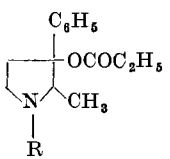
Table VI. Substitution on the hydroxyl



Compound no.	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	COC_2H_5	0·8	133	1·0
13	$COCH_3$	0·3	281	0·9
14	CO-*n*-C_3H_7	0·4	152	0·5
15	CO-*i*-C_3H_7	0·7	102	0·7
16	$CON(C_2H_5)_2$	None[e]	102	—

[a–c] See footnotes to Table V.
[e] At ¼ the 'average lethal dose'.

Table VII. Substitution on the nitrogen atom



Compound no.	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
17	H	(0·8)[d]	39	(0·3)[d]
18	C_2H_5	0·6	118	0·6
19	*n*-C_3H_7	0·9	94	0·8
20	*i*-C_3H_7	(<0·3)	199	(<0·3)
21	$CH_2{=}CH{-}CH_2$	0·8	93	0·7
22	$C_6H_5CH_2$	0·3	318	0·9

[a–d] See footnotes to Table V.

Table VIII. Methiodides

Compound no.	Methiodide of	Estimate of i.p. potency[a]	Est. of average i.p. lethal dose,[b] mg base/kg	(Potency) × (Lethal dose)[c] / 0·8 × 133
23	Comp. no. 1	(< 0·3)[d]	160	(< 0·3)[d]
24	Comp. no. 6	None[e,f]	127	—
25	Comp. no. 7	None[e,f]	160	—

[a–d] See footnotes to Table V.
[e] See footnote to Table VI.
[f] Partially suspended.

Table IX. Optical isomers of compound no. 1

Compound no.	Isomer	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	*d, l-*	0·8	133	1·0
26	*d-*	1·1	103	1·0
27	*l-*	0·5	173	0·9

[a–c] See footnotes to Table V.

Results and Discussion

Antinociceptive results (Tables V to IX) less than that of the reference dose of codeine obtained at a fourth the respective compounds' average lethal doses (results in parentheses) are of questionable specificity.[25]

Optimal conditions among the 3-phenylpyrrolidines described here were methyl substitution at the 2-position in the ring (Table V), propionoxy esterification at the 3-position (Table VI), and one-, two- or three-carbon (*normal*) alkyl substitution on the nitrogen (Table VII). Substitution at the 2- or 4-position on the ring converted a compound of low activity (No. 5) to one of higher and clearly specific potency (No. 1 or No. 7). Esterification of alcohols was found essential for clear-cut antinociceptive activity (other molecular circumstances being favourable), though the sharpness of the optimum at propionoxy was less apparent (Table VI) than

in the more potent *N*-methyl series.[27–29] Carbamate formation destroyed activity. Tertiary nitrogen substitution was clearly important. The latitude in *N*-alkyl chain length was greater than experience with prior (more potent) series might lead one to expect, and there was a sharp drop in activity with branching of the chain in isopropyl, a condition once of some positive interest in a more potent series.[26]

Further, in the area of ring substitution (Table V), it was interesting to note that 5-methylation, either alone or in the presence of 2-methylation, had relatively little influence. By contrast, while either 2- or 4-substitution alone was favourable, both together resulted in a misfit, as though they might function vicariously but not simultaneously at receptor sites. Another suggestion of misfit resulting from supernumerary groupings at critical sites was found in the 2,2-dimethyl substituent. Increasing the substituent from methyl to ethyl at the more critical 2-position was much more sharply deleterious than such change at the less critical 4-position. Re-emergence of a good quality of activity with 2-phenyl substitution challenges the imagination.

In accord with constantly broadening experience with agents acting at higher CNS levels, quaternization of the nitrogen was deleterious (Table VIII).

The dextro-rotatory enantiomorph of compound No. 1 is about twice as potent (intraperitoneally administered) as the laevo-rotatory (Table IX), a relationship identical to that between the enantiomorphs of betaprodine.[30] These two situations, along with that of the thiambutenes,[31] are exceptions to the general rule that, among analgetic racemates, the antinociceptive (and analgetic) activity resides substantially in only one enantiomorph. The relationship between activity and (lethal) toxicity of the enantiomorphs of compound No. 1 suggested no important therapeutic utility in resolution. Extended studies on the racemate presently suggest the presence of a moderate grade of clinical analgesia, and the absence of many morphine-like side effects. It is quite conjectural whether the relative freedom from morphine-like properties be associated more with a general reduction in receptor affinity (codeine-like potency), or more with a differential influence of the pyrrolidine nucleus. The general synthetic area is being explored further.

Summary. A series of 3-phenyl-3-acyloxypyrrolidines has been prepared and their antinociceptive properties compared. The activities of several of the compounds approximate that of codeine. Several substituent influences differ from those among previously known anaelgetics. 1,2-Dimethyl-3-phenyl·3-propionoxypyrrolidine is being investigated as a clinical analgetic.

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