

pH adjusted to 5–6 with 20% NaOH. The precipitate was collected by filtration to yield 1.7 g (89%) of 17, mp 252–254°.

1-Methyl-4-nitro-2,2'-biimidazole (18). Method A. To a solution of 1.79 g (0.01 mole) of 8 in 50 ml of DMF and 5 ml of 2*N* NaOH was added, dropwise and at room temp, 0.63 ml (0.011 mole) of CH₃I. The soln was kept at 60° for 15 hr, then evaporated to dryness. The residue was crystd from dioxane and recrystd from MeOH to give 0.58 g (30%) of the product, mp 252–253°.

Method B. Compound 18 (20%) together with compound 17 (40%) was obtained by treating 8 with a stoichiometric amount of CH₂N₂ in DMF. The mixture of 18 and 17 was separated by column chromatography on silica gel using CHCl₃-MeOH-NH₃ (190:10:1).

4,4'-Dinitro-1-methyl-2,2'-biimidazole (19). While stirring and heating to 70°, 1.25 ml (0.03 mole) of 99% HNO₃ was added to a soln of 3.99 g (0.02 mole) of 18 in 100 ml of AcOH and 50 ml of Ac₂O. The temp was raised to 85° and maintained for 8 hr. The soln was then evaporated to dryness and the solid crystd from a satd aqueous soln of NaHCO₃ to give 2.6 (50%) of the Na salt of 19. On acidifying 19 was obtained, mp 283–293°.

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Analgetics Based on the Pyrrolidine Ring. 6

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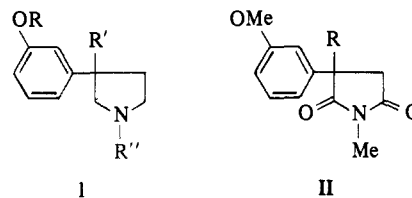
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Various *m*-(3-alkyl-1-methyl-3-pyrrolidinyl)phenols and *m*-[3-alkyl-1-(*p*-R-phenethyl)-3-pyrrolidinyl]-phenols were synthesized in order to examine the effects of 3-branched-alkyl substituents on the analgetic activity. In the 1-Me series, going from the earlier 3-*n*-Pr (profadol) to 3-CHMe₂, 3-CH₂CHMe₂, or 3-CH₂CMe₃ increased activity and the activity:toxicity ratio. In the 1-(CH₂)₂C₆H₄-*p*-R series superiority of such branched 3-substitutions was not clear. Various *m*-(1-methyl-3-pyrrolidinyl)-phenols and 3-(*m*-methoxyphenyl)-1-methylpyrrolidines were synthesized to study the effects of unsaturated and variously oxygenated groups in place of the earlier 3-*n*-Pr. All were deleterious, albeit clear activity was shown with 3-CH₂CH=CH₂, 3-COEt, and 3-CH₂COMe.

In previous papers of this series we have described numerous, variously substituted pyrrolidines of the general formula I, some relationships between structure and analgetic (antimechanoceptive) activity in rats, and some evidence of varying degrees of separation of narcotic-like, physical-dependence liability from analgetic action.¹⁻³ Of these structures, profadol (I, R = H; R' = Pr; R'' = Me) and its enantiomers have been studied extensively in animals^{4-12,†} and the racemate has been evaluated in man.^{13-18,‡}

One purpose of this paper is to report the effect of substitution of certain branched chains in the 3 position (I, R') on the agonist activity of profadol and related compounds (e.g., I, R'' = Me or (CH₂)₂C₆H₄-*p*-OH) as determined by the mechanoceptive test in rats employed¹⁻³ heretofore. A second purpose of the paper is to describe the preparation and analgetic (antimechanoceptive) activities of a limited number of pyrrolidines with unsaturated or oxygenated groups in the 3 position.



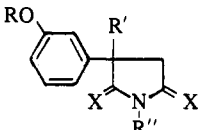
Chemistry. The basic step in the synthesis of several of the compounds with unsaturated or oxygenated groups in the 3 position has been treatment of 2-(*m*-methoxyphenyl)-*N*-methylsuccinimide (II, R = H) with an appropriate halide (e.g., allylbromide) to effect the required 3-substitution (e.g., II, R = CH₂CH=CH₂). Subsequent reduction with lithium aluminum hydride afforded the pyrrolidine. Otherwise the synthetic procedures used are for the most part based on those described in the preceding papers. The physical properties of the compounds prepared are listed in Tables I and II and details of the methods used are given below.

Pharmacology. Acute lethal toxicities and analgetic (antimechanoceptive) potencies were estimated in young male rats by the intraperitoneal route as described earlier.¹⁹ The antinociceptive potencies are based reciprocally on

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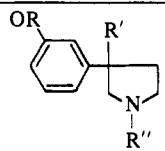
Table I. Pyrrolidine Intermediates



Compd	R	R'	R''	X	Bp (mm), °C	Yield, %	Formula	Analyses ^a
1	Me	CHMe ₂	H	H ₂	114-122 (0.5)	77	C ₁₄ H ₂₁ NO	
2	Me	CH ₂ CHMe ₂	H	H ₂	120-124 (1.0)	88	C ₁₅ H ₂₃ NO	
3	Me	CHEtMe	H	H ₂	122-124 (0.5)	67	C ₁₅ H ₂₃ NO	
4	Me	(CH ₂) ₂ CHMe ₂	H	H ₂	120-125 (0.15)	88	C ₁₆ H ₂₅ NO	C, H, N
5	Me	CH ₂ CHEtMe	H	H ₂	125-128 (0.25)	78	C ₁₆ H ₂₅ NO	C, H, N
6	Me	CH ₂ CMe ₃	H	H ₂	128-130 (0.7)	87	C ₁₆ H ₂₅ NO	
7	Me	CHMe ₂	Me	H ₂	102-104 (0.2)	60	C ₁₅ H ₂₃ NO	
8	Me	CH ₂ CHMe ₂	Me	H ₂	118-120 (0.8)	78	C ₁₆ H ₂₅ NO	
9	Me	CHEtMe	Me	H ₂	120-122 (1.0)	78	C ₁₆ H ₂₅ NO	C, H, N
10	Me	(CH ₂) ₂ CHMe ₂	Me	H ₂	120 (0.4)	68	C ₁₇ H ₂₇ NO	C, H, N
11	Me	CH ₂ CHEtMe	Me	H ₂	140-143 (1.5)	81	C ₁₇ H ₂₇ NO	
12	Me	CH ₂ CMe ₃	Me	H ₂	116-124 (0.4)	83	C ₁₇ H ₂₇ NO	
13	Me	(CH ₂) ₃ Me	(CH ₂) ₂ C ₆ H ₄ - <i>p</i> -OMe	H ₂	196-202 (0.15)	89	C ₂₄ H ₃₃ NO ₂	C, H, N
14	Me	CHMe ₂	(CH ₂) ₂ C ₆ H ₄ - <i>p</i> -OMe	H ₂	214-217 (0.5)	85	C ₂₃ H ₃₁ NO ₂	C, H, N
15	Me	CH ₂ CHMe ₂	(CH ₂) ₂ C ₆ H ₄ - <i>p</i> -OMe	H ₂	202-206 (0.35)	59	C ₂₄ H ₃₃ NO ₂	C, H, N
16	Me	CHEtMe	(CH ₂) ₂ C ₆ H ₄ - <i>p</i> -OMe	H ₂	195-198 (0.1)	77	C ₂₄ H ₃₃ NO ₂	C, H, N
17	Me	(CH ₂) ₂ CHMe ₂	(CH ₂) ₂ C ₆ H ₄ - <i>p</i> -OMe	H ₂	192-195 (0.05)	83	C ₂₅ H ₃₅ NO ₂	C, ^b H, N
18	Me	CH ₂ CMe ₃	(CH ₂) ₂ C ₆ H ₄ - <i>p</i> -OMe	H ₂	218-222 (0.7)	88	C ₂₅ H ₃₅ NO ₂	C, H, N
19	CHMe ₂	COOEt	Me	H ₂	115-120 (0.2)	52	C ₁₇ H ₂₅ NO ₃	
20	CHMe ₂	COEt	Me	H ₂	146-151 (0.8)	64	C ₁₇ H ₂₅ NO ₃	
21	Me	CH ₂ CH=CH ₂	Me	O	168-170 (0.5)	61	C ₁₅ H ₁₇ NO ₃	C, H, N
22	Me	CH ₂ C≡CH	Me	O	166-171 (0.6)	67	C ₁₅ H ₁₅ NO ₃	C, H, N
23	Me	OH	Me	O	115-117 (0.4)	70	C ₁₂ H ₁₇ NO ₂	C, H, N

^aWhere no symbols appear, these intermediates were not obtained in a state of analytical purity. ^bC: calcd, 78.7; found, 78.1.

Table II. Pyrrolidines



Compd	R	R'	R''	Mp or bp (mm), °C	Method	Yield, %	Formula	Analyses
24	H	CHMe ₂	Me	142-144	A	37	C ₁₄ H ₂₁ NO	C, H, N
25	H	CHMe ₂	Me	181-183 ^c	A	<i>g</i>	C ₁₄ H ₂₂ BrNO	C, H, N
26	H	CH ₂ CHMe ₂	Me	152 (0.6)	A	25	C ₁₅ H ₂₃ NO	C, H, N
27	H	CH ₂ CHMe ₂	Me	156-157 ^d	A	<i>h</i>	C ₁₅ H ₂₃ NO · 0.67(C ₄ H ₆ O ₄)	C, H, N
28	H	CHEtMe	Me	162 (0.6)	A	25	C ₁₅ H ₂₃ NO	C, H, N
29	H	CHEtMe	Me	179-180 ^c	A	<i>i</i>	C ₁₅ H ₂₄ BrNO	C, H, N
30 ^a	H	(CH ₂) ₂ CHMe ₂	Me	154-157 (0.5)	A	64	C ₁₆ H ₂₅ NO	C, H, N
31	H	CH ₂ CHEtMe	Me	164-165 (0.7)	A	42	C ₁₆ H ₂₅ NO	C, H, N
32 ^a	H	CH ₂ CMe ₃	Me	138-143 (0.1)	A	64	C ₁₆ H ₂₅ NO	C, H, N
33	H	CH ₂ CH=CH ₂	Me	165-168 (1.5)	A	54	C ₁₄ H ₁₉ NO	C, ^k H, N
34	H	CH ₂ CHMe ₂	H	145-146 ^e	<i>m</i>	81	C ₁₈ H ₂₇ NO ₅	C, H, N
35	H	CH ₂ CHMe ₂	(CH ₂) ₂ C ₆ H ₄ - <i>p</i> -NH ₂	>150 ^f dec	A	93	C ₂₂ H ₃₂ Cl ₂ N ₂ O · 1.5H ₂ O	C, H, N
36	H	(CH ₂) ₃ Me	(CH ₂) ₂ C ₆ H ₄ - <i>p</i> -OH	196-198 ^f	A	78	C ₂₂ H ₃₀ ClNO ₂	C, H, N
37	H	CHMe ₂	(CH ₂) ₂ C ₆ H ₄ - <i>p</i> -OH	94-96 ^f	A	38	C ₂₁ H ₂₈ ClNO ₂ · H ₂ O	C, H, N
38	H	CH ₂ CHMe ₂	(CH ₂) ₂ C ₆ H ₄ - <i>p</i> -OH	201-202 ^f	A	48	C ₂₂ H ₃₀ ClNO ₂ · H ₂ O	C, ^l H, N
39	H	CHEtMe	(CH ₂) ₂ C ₆ H ₄ - <i>p</i> -OH	105-107 ^f	A	65	C ₂₂ H ₃₀ ClNO ₂ · H ₂ O	C, H, N
40	H	(CH ₂) ₂ CHMe ₂	(CH ₂) ₂ C ₆ H ₄ - <i>p</i> -OH	97-99	A	74	C ₂₃ H ₃₁ NO ₂	C, H, N
41	H	CH ₂ CMe ₃	(CH ₂) ₂ C ₆ H ₄ - <i>p</i> -OH	216-217 ^f	A	88	C ₂₃ H ₃₂ ClNO ₂	C, H, N
42	COMe	CH ₂ CHMe ₂	(CH ₂) ₂ C ₆ H ₄ - <i>p</i> -OCOME	238-240 (0.4)	B	40	C ₂₆ H ₃₅ NO ₄	C, H, N
43	COMe	CH ₂ CMe ₃	(CH ₂) ₂ C ₆ H ₄ - <i>p</i> -OCOME	245-246 (0.8)	B	57	C ₂₇ H ₃₅ NO ₄	C, H, N
44	H	COOEt	Me	101.5-103	C	56	C ₁₄ H ₁₉ NO ₃	C, H, N
45	H	COEt	Me	167-169 ^f	C	70	C ₁₄ H ₂₀ ClNO ₂ · 0.5H ₂ O	C, H, N
46	Me	CH ₂ CH=CH ₂	Me	117 (0.5)	D	64	C ₁₅ H ₂₁ NO	C, H, N
47	Me	CH ₂ C≡CH	Me	106-110 (0.4)	D	72	C ₁₅ H ₁₉ NO	C, H, N
48 ^a	Me	CH ₂ COMe	Me	122-134 (0.45)	E	54	C ₁₅ H ₂₁ NO ₂	C, H, N
49	Me	(CH ₂) ₃ OH	Me	138-142 (0.25)	D	45	C ₁₅ H ₂₃ NO ₂	C, H, N
50 ^b	Me	CH(OH)Et	Me	150-155 (0.4)	D	15	C ₁₅ H ₂₃ NO ₂	C, H, N
51	Me	OCOEt	Me	119-121 (0.4)	F	81	C ₁₅ H ₂₁ NO ₃	C, H, N
52	Me	OEt	Me	166-169 (11.0)	G	67	C ₁₄ H ₂₁ NO ₂	C, H, N

^aPrepared by D. J. Peters. ^bPrepared by P. J. Hattersley. ^cHydrobromide. ^dPartial succinate. ^eSuccinate. ^fHydrochloride. ^gRods from EtOH. ^hPrisms from *i*-PrOH. ⁱMicrocrystalline from EtOH-Et₂O. ^jN: calcd, 5.7; found, 5.1. ^kC: calcd, 77.4; found, 76.9. ^lC: calcd, 67.1; found, 67.6. ^mRef 2.

Table III. Variations in 3-Substitution

No.	R'	Estd ip potency ^a	Estd av ip lethal dose, mg of base/kg ^b	Potency × [lethal dose ^c / (0.8 × 133)]
R = H; R'' = Me				
d	(CH ₂) ₂ Me	2.5	83	1.9
e	(CH ₂) ₃ Me	1.7	81	1.3
e	Et	1.0	65	0.6
e	Me	(0.2) ^f	122	(0.2)
24	CHMe ₂	3.0	173	4.8
28	CH ₂ CHMe	3.2	183	5.4
26	CH ₂ CHMe ₂	2.7	137	3.5
31	CH ₂ CH ₂ CHMe	1.5	129	1.8
30	(CH ₂) ₂ CHMe ₂	1.0	109	1.1
32	CH ₂ CMe ₃	3.8	129	4.6
33	CH ₂ CH=CH ₂	1.2	61	0.7
45	COEt	1.7	115	1.9
44	COOEt	(0.4) ^f	103	(0.4)
R = H; R'' = (CH ₂) ₂ C ₆ H ₄ -p-NH ₂				
g	(CH ₂) ₂ Me	5.8	52	2.8
35	CH ₂ CHMe ₂	5.0	42	2.0
R = H; R'' = (CH ₂) ₂ C ₆ H ₄ -p-OH				
g	(CH ₂) ₂ Me	3.5 ^h	117 ^h	< 3.8 ^h
36	(CH ₂) ₃ Me	1.0 ^{h,i}	220 ^{h,i}	< 2.1 ^h
37	CHMe ₂	1.9 ^{h,i}	210 ^{h,i}	< 3.8 ^h
39	CH ₂ CHMe	1.0 ^{h,i}	178 ^{h,i}	< 1.7 ^h
38	CH ₂ CHMe ₂	5.2 ^{h,j}	111 ^{h,j}	< 5.5 ^h
40	(CH ₂) ₂ CHMe ₂	0.7 ^{h,i}	163 ^{h,i}	< 1.0 ^h
41	CH ₂ CMe ₃	3.9 ^{h,i}	263 ^{h,i}	< 9.6 ^h
R = COMe; R'' = (CH ₂) ₂ C ₆ H ₄ -p-OCOMe				
g	(CH ₂) ₂ Me	3.9	137 ⁱ	< 5.0 ⁱ
43	CH ₂ CMe ₃	0.5 ^k	ca. 290 ^k	ca. 1.4
R = Me; R'' = Me				
l	(CH ₂) ₂ Me	1.3	67	0.8
46	CH ₂ CH=CH ₂	0.9	61	0.5
47	CH ₂ C≡CH	(0.4) ^f	54	(0.2)
49	(CH ₂) ₃ OH	None ^m	146	
50	CH(OH)Et	(0.2) ^{f,h}	230 ^h	(< 0.4) ^h
52	OE _t	None ^{h,m}	259 ^h	
48	CH ₂ COMe	0.8	103 ^h	< 0.7 ^h
51	OCOEt	(0.2) ^{f,h}	163 ^h	(< 0.3) ^h

^aRelative to codeine (base/base) 30 min after treatment. ^bFrom small numbers of young, male, Sprague-Dawley rats of differing lots. ^c1,2-Dimethyl-3-phenyl-3-propionoxypyrrolidine (prodilidine) of the earlier ester series is set equal to 1.^{19,20} ^dProfadol.^{1-18,†,‡} ^eRef 2. ^fFigures in parentheses were 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. ^gRef 3. ^hIncomplete solution, especially at lethal dose levels, hence lethal dose and index (last column) probably biased upward and potency sometimes downward. ⁱWith NaOH. ^jSuspended (partial sol) in aqueous acacia. ^kBase suspended in vegetable oil. ^lRef 1-3. ^mAt 0.25 the estd lethal dose.

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.⁴

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

poorly soluble hydrochlorides of phenolic compounds which we attempted, with little success, to convert to a more soluble, opposite, ionic form with NaOH. The small quantities available of 34 and 42 precluded biological evaluation.

Results are set out in Table III.

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

Of 3-*n*-alkyl substituents (I, R'), 3-*n*-Pr has appeared optimal in terms of traditional (agonist type) antinociceptive action in rats (e.g., profadol, 1, R = H; R' = *n*-Pr; R'' = Me),² as reviewed in Table III. Now, maintaining N-methylation as in profadol (1, R'' = Me), it is found that the best straight chain, *n*-Pr, is not actually optimal in the 3 position, but that branching within certain apparent limits of compactness increases potency and/or decreases acute lethal toxicity as in 3-CHMe₂, 3-CH₂CHMe₂, 3-CH₂CHMe, or 3-CH₂CMe₃. Less compact branched chains such as 3-(CH₂)₂CHMe₂ or 3-CH₂CH₂CHMe are deleterious, though still providing good antinociceptive agents, and this is reminiscent of going from 3-*n*-Pr to 3-*n*-Bu in the straight-chain series (reviewed in Table III).

It had been found that substituting phenethyl (with or without certain para substituents) for methyl on the nitrogen of profadol improved potency and the potency:toxicity ratio, as reviewed in Table III.³ It was therefore of interest to study the effect of branching the 3-alkyl chain in the presence of such a favorable N substituent. Unfortunately, the choice of 1-(CH₂)₂C₆H₄-p-OH for this series of compounds was a poor one, because the varying poor solubilities of the resulting diphenols precluded clear quantitative results. There was some suggestion of a favorable influence of 3-CH₂CHMe₂ and 3-CH₂CMe₃ over 3-*n*-Pr, but on going to the highly favorable 1-(CH₂)₂C₆H₄-p-NH₂, even with complete solubility, there was no evidence of any superiority of 3-CH₂CHMe₂ over 3-*n*-Pr.

It is thus evident that a broadly favorable effect on agonist potency of certain compact branchings of the 3-alkyl group in profadol is more limited or is absent in the presence of certain more favorable N substituents; i.e., that there is an interaction between 3 and N substituents in their influences on potency. Such interactions were found earlier between O-methylation (I, R) and N-substitution³ and between O-methylation and 2-alkylation.²

Varying unsaturation or oxidation of the 3 substituent, with or without O-methylation, was unfavorable to activity and, generally, to the activity:toxicity ratio. However, clear activity could be shown with 3-CH₂CH=CH₂, 3-COEt, and 3-CH₂COMe.

Compounds 24, 26, 28, 32, and 41 were submitted to preliminary tests for suppression and/or precipitation of abstinence in chronically and heavily morphinized rhesus monkeys (3 mg of sulfate/kg per 6 hr) by Dr. J. Villarreal at the University of Michigan. A rather surprising gradation of morphine-like (fractional agonist?) quality (in the area of pharmacoreceptors involved in the expression of physical dependence in the monkey) emerged among the five compounds. At the one extreme, with 3-CHMe₂, compound 24 resembled profadol (3-*n*-Pr) in clearly precipitating abstinence in a graded fashion in the dose range 2.9-12 mg of base/kg. At the other extreme, compound 26 with

3-CH₂CHMe₂ clearly suppressed abstinence, almost completely at 12 mg of base/kg and thus roughly equivalently to 2.3 mg of morphine base/kg. In an intermediate manner, clear evidence of neither suppression nor precipitation was obtained with compounds 28 (3-CH₂EtMe), 32 (3-CH₂CMe₃), or 41 (3-CH₂CMe₃ with 1-(CH₂)₂C₆H₄-*p*-OH).

Thus, in neither general manner of improving the anti-mechanoceptive (agonist) potency and/or potency:toxicity ratio of profadol in rats, *i.e.*, 1-(CH₂)₂C₆H₄-*p*-R in place of Me³ or branching the 3-alkyl, have we achieved evidence of even as low a level of physical-dependence liability as that reflected in monkeys, with the possible exception of compound 24.

Experimental Section §

3-Alkyl-3-(*m*-methoxyphenyl)pyrrolidines (Table I). These compounds were prepared by the method previously described.² They were converted to 3-alkyl-3-(*m*-methoxyphenyl)-1-methylpyrrolidines by the action of formic acid-formaldehyde. Since they were intermediates, they were not always purified completely. Available data are given in Table I, but the analyses are omitted where analytically pure products were not obtained.

3-Alkyl-1-(*p*-methoxyphenethyl)-3-(*m*-methoxyphenyl)pyrrolidines (Table I). 3-Alkyl-3-(*m*-methoxyphenyl)pyrrolidines were allowed to react with *p*-(methoxyphenyl)acetyl chloride, and the resultant crude amides were reduced with LAH as previously described.³

1-(*p*-Aminophenethyl)-3-isobutyl-3-(*m*-methoxyphenyl)pyrrolidine. 3-Isobutyl-3-(*m*-methoxyphenyl)-1-(*p*-nitrophenethyl)pyrrolidine was prepared by condensation of *p*-nitrophenethyl bromide with the appropriate pyrrolidine as described previously.²⁰ Hydrogenation of the crude nitro compound in EtOH containing 1 equiv of HCl in the presence of Pd/C afforded 1-(*p*-aminophenethyl)-3-isobutyl-3-(*m*-methoxyphenyl)pyrrolidine which was not characterized but was converted to the corresponding 3-pyrrolidinylphenol (method A).

3-(*m*-Isopropoxyphenyl)-1-methyl-3-pyrrolidinecarboxylic Acid Ethyl Ester (Table I). This was prepared by catalytic hydrogenation of ethyl 2-cyano-4-(benzylmethylamino)-2-(*m*-isopropoxyphenyl)butyrate using a method similar to that reported by Bergel, *et al.*²¹

1-[3-(*m*-Isopropoxyphenyl)-1-methyl-3-pyrrolidinyl]-1-propanone (Table I). This compound was prepared by the action of EtMgI on the foregoing 3-(*m*-isopropoxyphenyl)-1-methyl-3-pyrrolidinecarboxylic acid ethyl ester using a method similar to that of Avison and Morrison.²² The product [bp 146–151° (0.8 mm)], obtained in 64% yield, was not further characterized but was converted to the phenol (method C).

2-Substituted-2-(*m*-methoxyphenyl)-*N*-methylsuccinimides (Table I). 2-(*m*-Methoxyphenyl)-*N*-methylsuccinimide (43 g) in dry DMF (100 ml) was added to NaH (5 g) in DMF (100 ml) at 65–75° over 2 hr. After cooling to 35°, allyl bromide (26 ml) was added portionwise over 15 min. The temperature was maintained at 60° for 40 min. The mixture was filtered, and the filtrate evaporated to half-volume. H₂O (400 ml) was added, and the mixture extracted with C₆H₆ from which 2-allyl-2-(*m*-methoxyphenyl)-*N*-methylsuccinimide was obtained after distillation *in vacuo*.

The 3-(2-propynyl) analog was prepared by a similar procedure.

Reaction of 2-(*m*-methoxyphenyl)-*N*-methylsuccinimide with ethyl 3-bromopropionate under similar conditions afforded an oil that was not characterized but was used directly, as was the 3-propionyl compound obtained on reaction of the succinimide with propionyl chloride.

3-(*m*-Methoxyphenyl)-1-methyl-3-pyrrolidinol (Table I). 3-Hydroxy-3-(*m*-methoxyphenyl)-1-pyrrolidinecarboxylic acid ethyl ester was prepared by a method analogous to that previously reported by Wu, *et al.*²³ Reduction of the resulting urethane with LAH²⁴ afforded the required 1-methylpyrrolidine analog.

***m*-(3-Alkyl-1-methyl-3-pyrrolidinyl)phenols, *m*-[3-Alkyl-1-(*p*-hydroxyphenethyl)-3-pyrrolidinyl]phenols, etc. (Table II).** Method

A. Methyl ethers were converted to the corresponding phenols using BBr₃.³

1-(*p*-Acetoxyphenethyl)-3-alkyl-3-(*m*-acetoxyphenyl)pyrrolidines (Table II). Method B. Acetylation of the dihydroxy compounds was carried out as described previously.³

1-[3-(*m*-Hydroxyphenyl)-1-methyl-3-pyrrolidinyl]-1-propanone Hydrochloride (Table II). Method C. The corresponding *m*-isopropoxyphenyl analog (20, Table I) was refluxed with 6 *N* HCl for 17 hr. The acid was concentrated and, after extracting with Et₂O, was basified with 6 *N* NH₃, and the product was extracted into Et₂O.

Similar treatment of 3-(*m*-isopropoxyphenyl)-1-methyl-3-pyrrolidinecarboxylic acid ethyl ester afforded a crude product that was essentially 3-(*m*-hydroxyphenyl)-1-methyl-3-pyrrolidinecarboxylic acid. This was refluxed with ethanolic HCl overnight, the solution evaporated, and 3-(*m*-hydroxyphenyl)-1-methyl-3-pyrrolidinecarboxylic acid ethyl ester isolated by extraction from NaHCO₃.

3-Substituted-3-(*m*-methoxyphenyl)-1-methylpyrrolidines from Succinimides. Method D. Substituted succinimides in Et₂O were reduced to pyrrolidines with LAH.

1-[3-(*m*-Methoxyphenyl)-1-methyl-3-pyrrolidinyl]-2-propanone. Method E. 3-(*m*-Methoxyphenyl)-1-methyl-3-(2-propynyl)pyrrolidine (24 g) and HgSO₄ (2 g) in 2 *N* H₂SO₄ were stirred at 60° for 1.5 hr. The mixture was basified and extracted with Et₂O, and the dried Et₂O extracts were evaporated. The mixture was distilled *in vacuo*.

3-(*m*-Methoxyphenyl)-1-methyl-3-pyrrolidinol Propionate Ester (Table II). Method F. 3-(*m*-Methoxyphenyl)-1-methyl-3-pyrrolidinol was acylated with propionic anhydride in the presence of pyridine.

3-Ethoxy-3-(*m*-methoxyphenyl)-1-methylpyrrolidine (Table II). Method G. 3-(*m*-Methoxyphenyl)-1-methyl-3-pyrrolidinol (12.4 g) in C₆H₆ (25 ml) was added to NaH (1.9 g, 50% dispersion in oil) in C₆H₆ (100 ml). The mixture was refluxed 2 hr and cooled, EtBr (4.5 ml) was added, and the mixture was refluxed 3 hr. The mixture was poured onto ice and the product extracted into benzene and purified by distillation *in vacuo*.

2-(*m*-Methoxyphenyl)-*N*-methylsuccinimide. (*m*-Methoxyphenyl)succinic acid (225 g, prepared by a method similar to that of Allen and Johnson²⁵) was stirred in 33% MeNH₂ in EtOH (490 ml) for 30 min. Solvent was removed on the steam bath and the oily residue heated *in vacuo* (*ca.* 10 mm) for 1.5 hr at 160° and 0.5 hr at 200°. The product was recrystallized from EtOH as cubes, mp 73–75°. *Anal.* (C₁₁H₁₁NO₃) C, H, N.

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§ 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.

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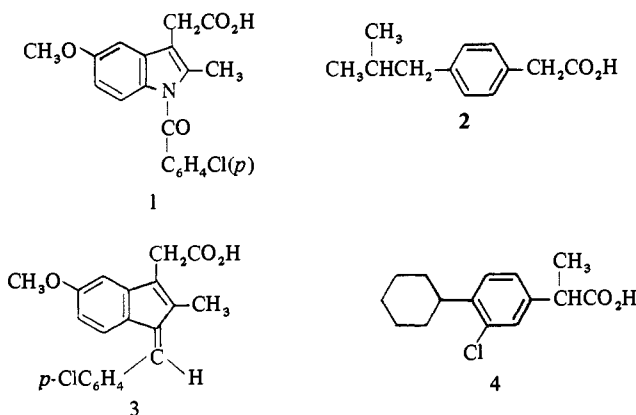
5-Substituted-1-indancarboxylic Acids as Potential Antiinflammatory Agents

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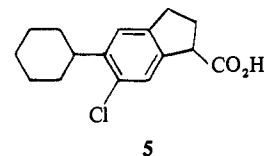
The preparation of a series of 5-substituted-1-indancarboxylic acids is described. These compounds are analogs of the active phenylacetic acids in which the carboxyl group is fixed conformationally. Racemic 5-isopropyl- and 5-cyclohexyl-1-indancarboxylic acid are active in suppressing carrageenin-induced paw edema in the rat and uv-induced erythema in the guinea pig. However, they appear less potent than indomethacin in these systems. None of the indancarboxylic acids significantly suppressed adjuvant-induced arthritis or promoted weight gain in the rat.

The reports on the utility of 1-(*p*-chlorobenzoyl)-5-methoxy-2-methyl-3-indolylacetic acid (**1**)¹ and *p*-isobutylphenylacetic acid (**2**)² as antiinflammatory agents stimulated an intense search for other such compounds within the heterocyclic and arylalkanoic acid series. The clinical utility of the former substance added impetus to this effort, and early investigations focused upon a series of indenacetic acids, as exemplified by the *cis* isomer **3**.³ The activity of **3** indicated that the indomethacin-like potency was not restricted to indole derivatives, and the preparation of other arylacetic acids was undertaken. These investigations culminated in the preparation of a series of biphenylacetic acids and *p*-alkyl- and *p*-cycloalkylphenylacetic acids.⁴ One member of the last series, the dextrorotatory isomer of 2-(4-cyclohexyl-3-chlorophenyl)propionic acid (**4**), was reputed to be the most potent nonsteroidal antiinflammatory agent known at that time.⁴



In view of our interest^{5,6} in analogs of nonsteroidal antiinflammatory agents in which the carboxylic acid group is fixed conformationally, we have prepared certain 5-alkylindancarboxylic acids for testing as antiinflammatory agents. Independent of our efforts, two other laboratories have prepared the most apparent analog of this type, *i.e.*, 6-chloro-5-cyclohexylindan-1-carboxylic acid (**5**), and reported on its antiinflammatory properties.^{7,8}

The 5-substituted-1-indancarboxylic acids **11** were pre-



pared by Clemmensen reduction of the corresponding 3-indanone derivatives **10** (see Scheme I), which were obtained by Friedel-Crafts closure with hydrogen fluoride of a substituted phenylsuccinic acid **9**. The last substances were synthesized by a modification of the procedure of Baker and Lapworth.^{9,10} Thus, allowing 4-biphenylcarboxaldehyde (**6b**) and 4-cyclohexylbenzaldehyde (**6c**) to react with ethyl cyanoacetate gave the corresponding unsaturated esters **7**. Michael addition of cyanide to these α -cyanocinnamates and acid hydrolysis of the intermediate dinitriles gave the substituted succinic acids **9** in good yield. Considerable succinimide **8b** was formed in the preparation of 4-biphenylsuccinic acid (**9b**). Application of this sequence to *p*-isopropylbenzaldehyde (**6a**) furnished 56% of acid **9a** without isolation of intermediates.

Scheme I

