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 CH_3I. 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 CH_2N_2 in DMF. The mixture of **18** and **17** was separated by column chromatography on silica gel using $CHCl_3$–MeOH–NH_3 (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% HNO_3 was added to a soln of 3.99 g (0.02 mole) of **18** in 100 ml of AcOH and 50 ml of Ac_2O. 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 $NaHCO_3$ 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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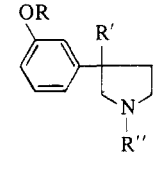
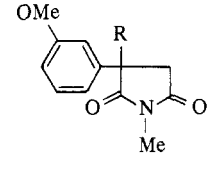
Various *m*-(3-alkyl-1-methyl-3-pyrrolidinyl)phenols and *m*-[3-alkyl-1-(*p*-R-phenethyl)-3-pyrrolidinyl]-phenols were synthesized in order to examine the effects of 3-branched-alkyl substituents on the analgetic activity. In the 1-Me series, going from the earlier 3-*n*-Pr (profadol) to 3-$CHMe_2$, 3-CHEtMe, 3-CH_2CHMe_2, or 3-CH_2CMe_3 increased activity and the activity:toxicity ratio. In the 1-$(CH_2)_2C_6H_4$-*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-$CH_2CH{=}CH_2$, 3-COEt, and 3-CH_2COMe.

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 $(CH_2)_2C_6H_4$-*p*-OH) as determined by the mechanoceptive test in rats employed[1-3] 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.



I



II

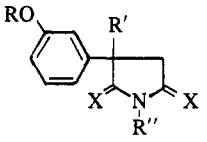
Chemistry. The basic step in the synthesis of several of the compounds with unsaturated or oxygenated groups in the 3 position has been treatment of 2-(*m*-methoxyphenyl)-*N*-methylsuccinimide (II, R = H) with an appropriate halide (*e.g.*, allylbromide) to effect the required 3-substitution (*e.g.*, II, R = $CH_2CH{=}CH_2$). 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

†J. E. Villarreal, personal communication, 1969, 1970; H. W. Kosterlitz and A. J. Watt, personal communication, 1969.

‡A. S. Keats and J. Telford, personal communication, 1968, 1969; T. G. Kanter, E. Laska, A. Sunshine, A. Rudolph, and F. Steinberg, personal communication, 1969; A. Sunshine, E. Laska, and J. Slafta, personal communication, 1970.

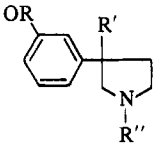
Table I. Pyrrolidine Intermediates



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_2CHMe_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	$(CH_2)_2CHMe_2$	H	H_2	120–125 (0.15)	88	$C_{16}H_{25}NO$	C, H, N
5	Me	$CH_2CHEtMe$	H	H_2	125–128 (0.25)	78	$C_{16}H_{25}NO$	C, H, N
6	Me	CH_2CMe_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_2CHMe_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	$(CH_2)_2CHMe_2$	Me	H_2	120 (0.4)	68	$C_{17}H_{27}NO$	C, H, N
11	Me	$CH_2CHEtMe$	Me	H_2	140–143 (1.5)	81	$C_{17}H_{27}NO$	
12	Me	CH_2CMe_3	Me	H_2	116–124 (0.4)	83	$C_{17}H_{27}NO$	
13	Me	$(CH_2)_3Me$	$(CH_2)_2C_6H_4$-*p*-OMe	H_2	196–202 (0.15)	89	$C_{24}H_{33}NO_2$	C, H, N
14	Me	$CHMe_2$	$(CH_2)_2C_6H_4$-*p*-OMe	H_2	214–217 (0.5)	85	$C_{23}H_{31}NO_2$	C, H, N
15	Me	CH_2CHMe_2	$(CH_2)_2C_6H_4$-*p*-OMe	H_2	202–206 (0.35)	59	$C_{24}H_{33}NO_2$	C, H, N
16	Me	CHEtMe	$(CH_2)_2C_6H_4$-*p*-OMe	H_2	195–198 (0.1)	77	$C_{24}H_{33}NO_2$	C, H, N
17	Me	$(CH_2)_2CHMe_2$	$(CH_2)_2C_6H_4$-*p*-OMe	H_2	192–195 (0.05)	83	$C_{25}H_{35}NO_2$	C,[b] H, N
18	Me	CH_2CMe_3	$(CH_2)_2C_6H_4$-*p*-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	$C_{17}H_{25}NO_2$	
21	Me	$CH_2CH{=}CH_2$	Me	O	168–170 (0.5)	61	$C_{15}H_{17}NO_3$	C, H, N
22	Me	$CH_2C{\equiv}CH$	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

[a]Where no symbols appear, these intermediates were not obtained in a state of analytical purity. [b]C: calcd, 78.7; found, 78.1.

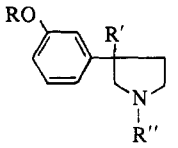
Table II. Pyrrolidines



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	*g*	$C_{14}H_{22}BrNO$	C, H, N
26	H	CH_2CHMe_2	Me	152 (0.6)	A	25	$C_{15}H_{23}NO$	C, H, N
27	H	CH_2CHMe_2	Me	156–157[d]	A	*h*	$C_{15}H_{23}NO\cdot 0.67(C_4H_6O_4)$	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*	$C_{15}H_{24}BrNO$	C, H, N
30[a]	H	$(CH_2)_2CHMe_2$	Me	154–157 (0.5)	A	64	$C_{16}H_{25}NO$	C, H, N[j]
31	H	$CH_2CHEtMe$	Me	164–165 (0.7)	A	42	$C_{16}H_{25}NO$	C, H, N
32[a]	H	CH_2CMe_3	Me	138–143 (0.1)	A	64	$C_{16}H_{25}NO$	C, H, N
33	H	$CH_2CH{=}CH_2$	Me	165–168 (1.5)	A	54	$C_{14}H_{19}NO$	C,[k] H, N
34	H	CH_2CHMe_2	H	145–146[e]	*m*	81	$C_{18}H_{27}NO_5$	C, H, N
35	H	CH_2CHMe_2	$(CH_2)_2C_6H_4$-*p*-NH_2	>150[f] dec	A	93	$C_{22}H_{32}Cl_2N_2O\cdot 1.5H_2O$	C, H, N
36	H	$(CH_2)_3Me$	$(CH_2)_2C_6H_4$-*p*-OH	196–198[f]	A	78	$C_{22}H_{30}ClNO_2$	C, H, N
37	H	$CHMe_2$	$(CH_2)_2C_6H_4$-*p*-OH	94–96[f]	A	38	$C_{21}H_{28}ClNO_2\cdot H_2O$	C, H, N
38	H	CH_2CHMe_2	$(CH_2)_2C_6H_4$-*p*-OH	201–202[f]	A	48	$C_{22}H_{30}ClNO_2\cdot H_2O$	C,[l] H, N
39	H	CHEtMe	$(CH_2)_2C_6H_4$-*p*-OH	105–107[f]	A	65	$C_{22}H_{30}ClNO_2\cdot H_2O$	C, H, N
40	H	$(CH_2)_2CHMe_2$	$(CH_2)_2C_6H_4$-*p*-OH	97–99	A	74	$C_{23}H_{31}NO_2$	C, H, N
41	H	CH_2CMe_3	$(CH_2)_2C_6H_4$-*p*-OH	216–217[f]	A	88	$C_{23}H_{32}ClNO_2$	C, H, N
42	COMe	CH_2CHMe_2	$(CH_2)_2C_6H_4$-*p*-OCOMe	238–240 (0.4)	B	40	$C_{26}H_{33}NO_4$	C, H, N
43	COMe	CH_2CMe_3	$(CH_2)_2C_6H_4$-*p*-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	$C_{14}H_{20}ClNO_2\cdot 0.5H_2O$	C, H, N
46	Me	$CH_2CH{=}CH_2$	Me	117 (0.5)	D	64	$C_{15}H_{21}NO$	C, H, N
47	Me	$CH_2C{\equiv}CH$	Me	106–110 (0.4)	D	72	$C_{15}H_{19}NO$	C, H, N
48[a]	Me	CH_2COMe	Me	122–134 (0.45)	E	54	$C_{15}H_{21}NO_2$	C, H, N
49	Me	$(CH_2)_3OH$	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

[a]Prepared by D. J. Peters. [b]Prepared by P. J. Hattersley. [c]Hydrobromide. [d]Partial succinate. [e]Succinate. [f]Hydrochloride. [g]Rods from EtOH. [h]Prisms from *i*-PrOH. [i]Microcrystalline from EtOH–Et_2O. [j]N: calcd, 5.7; found, 5.1. [k]C: calcd, 77.4; found, 76.9. [l]C: calcd, 67.1; found, 67.6. [m]Ref 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	$(CH_2)_2Me$	2.5	83	1.9
e	$(CH_2)_3Me$	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	CHEtMe	3.2	183	5.4
26	CH_2CHMe_2	2.7	137	3.5
31	$CH_2CHEtMe$	1.5	129	1.8
30	$(CH_2)_2CHMe_2$	1.0	109	1.1
32	CH_2CMe_3	3.8	129	4.6
33	$CH_2CH{=}CH_2$	1.2	61	0.7
45	COEt	1.7	115	1.9
44	COOEt	(0.4)[f]	103	(0.4)
		R = H; R″ = $(CH_2)_2C_6H_4$-*p*-NH_2		
g	$(CH_2)_2Me$	5.8	52	2.8
35	CH_2CHMe_2	5.0	42	2.0
		R = H; R″ = $(CH_2)_2C_6H_4$-*p*-OH		
g	$(CH_2)_2Me$	3.5[h]	117[h]	<3.8[h]
36	$(CH_2)_3Me$	1.0[h,i]	220[h,i]	<2.1[h]
37	$CHMe_2$	1.9[h,i]	210[h,i]	<3.8[h]
39	CHEtMe	1.0[h,i]	178[h,i]	<1.7[h]
38	CH_2CHMe_2	5.2[h,j]	111[h,j]	<5.5[h]
40	$(CH_2)_2CHMe_2$	0.7[h,i]	163[h,i]	<1.0[h]
41	CH_2CMe_3	3.9[h,i]	263[h,i]	<9.6[h]
		R = COMe; R″ = $(CH_2)_2C_6H_4$-*p*-OCOMe		
g	$(CH_2)_2Me$	3.9	137[i]	<5.0[i]
43	CH_2CMe_3	0.5[k]	*ca.* 290[k]	*ca.* 1.4
		R = Me; R″ = Me		
l	$(CH_2)_2Me$	1.3	67	0.8
46	$CH_2CH{=}CH_2$	0.9	61	0.5
47	$CH_2C{\equiv}CH$	(0.4)[f]	54	(0.2)
49	$(CH_2)_3OH$	None[m]	146	
50	CH(OH)Et	(0.2)[f,h]	230[h]	(<0.4)[h]
52	OEt	None[h,m]	259[h]	
48	CH_2COMe	0.8	103[h]	<0.7[h]
51	OCOEt	(0.2)[f,h]	163[h]	(<0.3)[h]

[a] Relative to codeine (base/base) 30 min after treatment. [b] From small numbers of young, male, Sprague–Dawley rats of differing lots. [c] 1,2-Dimethyl-3-phenyl-3-propionoxypyrrolidine (prodilidine) of the earlier ester series is set equal to 1.[19,20] [d] Profadol.[1-18,†,‡] [e] Ref 2. [f] Figures 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. [g] Ref 3. [h] Incomplete solution, especially at lethal dose levels, hence lethal dose and index (last column) probably biased upward and potency sometimes downward. [i] With NaOH. [j] Suspended (partial sol) in aqueous acacia. [k] Base suspended in vegetable oil. [l] Ref 1-3. [m] At 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-$CHMe_2$, 3-CH_2CHMe_2, 3-CHEtMe, or 3-CH_2CMe_3. Less compact branched chains such as 3-$(CH_2)_2CHMe_2$ or 3-$CH_2CHEtMe$ 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-$(CH_2)_2C_6H_4$-*p*-OH for this series of compounds was a poor one, because the varyingly poor solubilities of the resulting diphenols precluded clear quantitative results. There was some suggestion of a favorable influence of 3-CH_2CHMe_2 and 3-CH_2CMe_3 over 3-*n*-Pr, but on going to the highly favorable 1-$(CH_2)_2C_6H_4$-*p*-NH_2, even with complete solubility, there was no evidence of any superiority of 3-CH_2CHMe_2 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-substitution[3] 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-$CH_2CH{=}CH_2$, 3-COEt, and 3-CH_2COMe.

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-$CHMe_2$, 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-CH_2CHMe_2 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-CHEtMe), **32** (3-CH_2CMe_3), or **41** (3-CH_2CMe_3 with 1-$(CH_2)_2C_6H_4$-*p*-OH).

Thus, in neither general manner of improving the antimechanoceptive (agonist) potency and/or potency:toxicity ratio of profadol in rats, *i.e.*, 1-$(CH_2)_2C_6H_4$-*p*-R in place of Me[3] 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. H_2O (400 ml) was added, and the mixture extracted with C_6H_6 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-propionoyl compound obtained on reaction of the succinimide with propionoyl 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 LAH[24] 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 BBr_3.[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 Et_2O, wa basified with 6 *N* NH_3, and the product was extracted into Et_2O.

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 $NaHCO_3$.

3-Substituted-3-(*m*-methoxyphenyl)-1-methylpyrrolidines from Succinimides. Method D. Substituted succinimides in Et_2O 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 $HgSO_4$ (2 g) in 2 *N* H_2SO_4 were stirred at 60° for 1.5 hr. The mixture was basified and extracted with Et_2O, and the dried Et_2O 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) i C_6H_6 (25 ml) was added to NaH (1.9 g, 50% dispersion in oil) in C_6H_6 (100 ml). The mixture was refluxed 2 hr and cooled, EtBr (4.5 ml) was added, and the mixt 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 Johnson[25]) was stirred in 33% $MeNH_2$ 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.* ($C_{11}H_{11}NO_3$) 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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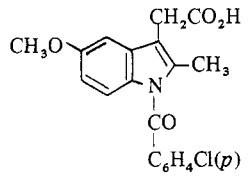
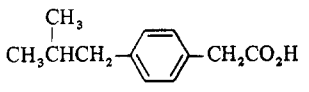
The preparation of a series of 5-substituted-1-indancarboxylic acids is described. These compounds are analogs of the active phenylacetic acids in which the carboxyl group is fixed conformationally. Racemic 5-isopropyl- and 5-cyclohexyl-1-indancarboxylic acid are active in suppressing carrageenin-induced 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 biphenylylacetic 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]



1



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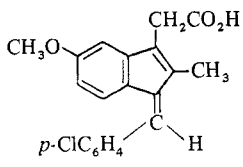

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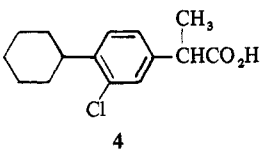
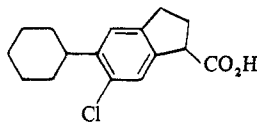


4

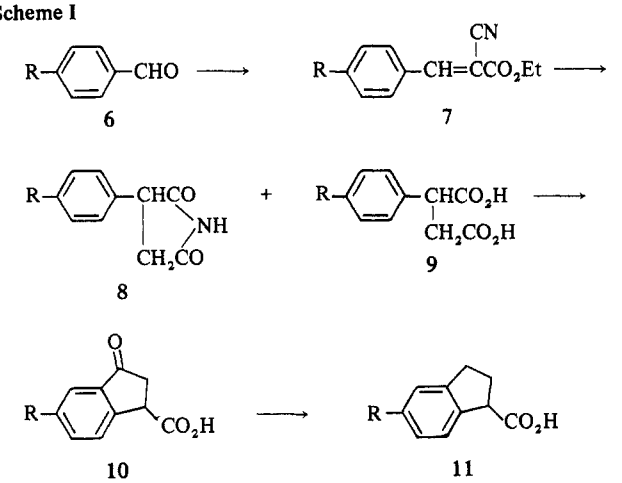
In view of our interest[5,6] in analogs of nonsteroidal antiinflammatory agents in which the carboxylic acid group is fixed conformationally, we have prepared certain 5-alkylindancarboxylic acids for testing as antiinflammatory agents. Independent of our efforts, two other laboratories have prepared 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]



5

The 5-substituted-1-indancarboxylic acids **11** were prepared 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-biphenylylcarboxaldehyde (**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-biphenylylsuccinic acid (**9b**). Application of this sequence to *p*-isopropylbenzaldehyde (**6a**) furnished 56% of acid **9a** without isolation of intermediates.

Scheme I



a, R = *i*-C_3H_7
b, R = C_6H_5
c, R = *c*-C_6H_{11}