was prepared from the colorless oil and recrystallized several times from acetone–ether; m.p. 234–235°.

Anal. Calcd. for $C_{17}H_{26}ClN$: C, 72.96; H, 9.37. Found: C, 73.11; H, 9.71.

A **picrate** was prepared and recrystallized several times from ethanol; m.p. 209–210°.

Anal. Calcd. for $C_{23}H_{28}N_4O_7$: C, 58.46; H, 5.97. Found: C, 58.67; H, 5.97.

β-5,9-Diethyl-2′-hydroxy-2-methyl-6,7-benzomorphan (X).[11]—The benzomorphan IX was converted *via* the 2′-nitro and 2′-amino derivatives to the known 2′-hydroxy X according to the general procedure of May and Fry.[8] The 2′-hydroxy compound was found to be identical with the known compound[11] in its melting point, mixture melting point (no depression), infrared spectrum, and thin layer chromatography.[15]

Vapor Phase Chromatography.—A Research Specialties vapor phase chromatograph was used with a 1.83-m. glass column, 6.3 mm. in diameter, silanized and packed with 1.5% SE 30 on 100–140 Chromosorb W. It was equipped with a flame ionization detector. The α-5,9-diethyl-2-methyl-6,7-benzomorphan hydrochloride (VI), β-5,9-diethyl-2-methyl-6,7-benzomorphan hydrochloride (IX), and β-5,9-diethyl-2′-hydroxy-2-methyl-6,7-benzomorphan (X) could be identified. A 9:1 mixture of α-VI and β-IX was identifiable. The reverse was not true. At least 25% of VI is needed in the mixture to discern it. The chromatograph was run isothermally at a column temperature of 132° for VI and IX. The α-benzomorphan VI had a somewhat longer retention time (21 min.) on the column than the β-IX (16 min.) and therefore gave a broader, more widespread band. No attempt was made to sharpen the peak since the two compounds could be easily differentiated. The 2′-hydroxybenzomorphan X was chromatographed using a column temperature of 190°. The retention time for this compound was 4 min.

Rate Studies.—The general procedure of Fullerton, May, and Becker[12] was used. In Table II are given the results which show that the reaction of VI with methyl iodide is ten times faster than the reaction of IX with this reagent, and leaves no doubt about the stereochemistry of VI and IX.

(15) All of the products from the various reactions were examined by thin layer chromatography, using the general method of J. Cochin and J. W. Daly [*Experientia*, **18**, 294 (1962)]. The plates were coated with silica gel G (Merck, Darmstadt). The solvent system consisted of ethanol–dioxane–benzene–ammonium hydroxide, 5:40:50:5. The products were detected by spraying with potassium iodoplatinate reagent. In the case of VI and IX it was found that β-compound IX ran faster than α-compound VI. The R_f values were 0.81 for IX and 0.58 for VI, compared with 0.85 for a simultaneously chromatographed standard test mixture provided by the Brinkmann Instrument Co. (a mixture of 0.01% each of 4-dimethylaminobenzene, indophenol, and sudan red G in benzene).

TABLE II

RATES OF REACTION OF METHYL IODIDE WITH BENZOMORPHANS

Compound	Reaction time, hr.	% Benzomorphan converted to methiodide
α-5,9-Diethyl-2-methyl-6,7-benzomorphan (VI)	2.5	29.8
	5.0	55.9
β-5,9-Diethyl-2-methyl-6,7-benzomorphan (IX)	2.5	3.8
	5.0	4.3
	24.0	9.7

Analgetics Based on the Pyrrolidine Ring. III.

J. F. CAVALLA, R. JONES,

Parke, Davis & Company, Hounslow, Middlesex, England

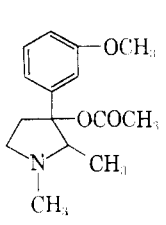
M. WELFORD, J. WAX, AND C. V. WINDER

Parke, Davis & Company, Ann Arbor, Michigan

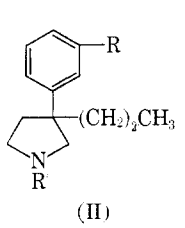
Received January 8, 1964

The pyrrolidine analgetic, *m*-(1-methyl-3-propyl-3-pyrrolidinyl)phenol (II, R = OH; R′ = CH_3), is described, having activity superior to meperidine by a parenteral route in rats and with no morphine-like addiction liability in monkeys. Various analogs and congeners have been synthesized.

In continuance of our work on pyrrolidines of possible value as analgetics we have prepared a series of 3,3-disubstituted pyrrolidines (II, R′ = CH_3; R = OCH_3, OH, and $OCOCH_3$) which are more active than the 1,2-dimethyl-3-phenyl-3-propionoxypyrrolidine (I) described earlier.[1]



(I)



(II)

Chemistry.—The 3,3-disubstituted pyrrolidines (II) were prepared by chemical reduction of the corresponding succinimides. *m*-Methoxybutyrophenone was prepared by the reaction of *m*-methoxybenzoyl chloride with dipropylcadmium (a method we found more convenient than that described by McElvain[2]) and treated with ethyl cyanoacetate to give the substituted ethyl cinnamate (III), following the conditions given by Cope[3] and Cragoe.[4] Potassium cyanide readily added across the olefinic linkage in this molecule to give the succinonitrile (IV) which on acid hydrolysis was converted into the succinic acid (V). With methylamine, this furnished the succinimide[5] (VI) which, with lithium aluminum hydride, gave the pyrrolidine (II, R = OCH_3; R′ = CH_3).

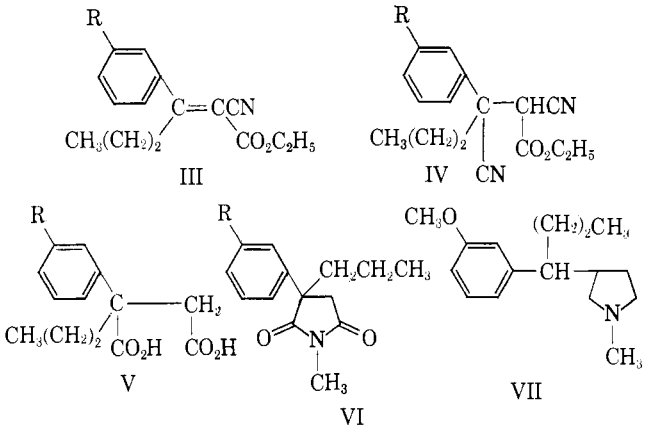
(1) J. F. Cavalla, R. A. Selway, J. Wax, L. Scotti, and C. V. Winder, *J. Med. Pharm. Chem.*, **5**, 441 (1962).

(2) S. M. McElvain and D. H. Clemens, *J. Am. Chem. Soc.*, **80**, 3915 (1958).

(3) A. C. Cope, C. M. Hofmann, C. Wyckoff, and E. Hardenbergh, *ibid.*, **63**, 3452 (1941).

(4) E. J. Cragoe, Jr., C. M. Robb, and J. M. Sprague, *J. Org. Chem.*, **15**, 381 (1950).

(5) C. A. Miller and L. M. Long, *J. Am. Chem. Soc.*, **75**, 6265 (1953).



In the initial stages, the synthesis was tried using the unsubstituted butyrophenone and only when the experimental conditions had been refined was the less accessible *m*-methoxybutyrophenone put at hazard.

When benzylamine was substituted for methylamine the resulting 1-benzylpyrrolidine was hydrogenated to give the secondary base (II, R = OCH_3; R′ = H). This was used as an intermediate in the preparation of analogs of II where the nitrogen substituent was ethyl, propargyl, or propyl.

On refluxing the methoxy compounds with hydrobromic acid, the corresponding phenols (II, R = OH) were obtained and these in turn, with acetic anhydride, gave the acetates (II, R = $OCOCH_3$).

The introduction of a further carbon atom between the basic center and the methoxyphenylpropyl grouping to give VII was accomplished, as before, by reducing the corresponding succinimide. In this case the required acid was prepared by condensing *m*-methoxybutyrophenone with diethyl succinate[6] and hydrogenating the resulting substituted itaconic acid.

Pharmacology.—Average lethal single doses (7-day observation period) and antinociceptive activities were estimated in young male rats as described in more detail earlier.[7] Compounds were dissolved in 0.9% saline solution as soluble hydrochloride or monotartrate salts, or with addition of an equivalent of hydrochloric acid, except that the less soluble hydrochloride of II (R = OCH_3; R′ = $C_6H_5CH_2$) was partly dissolved and the remainder finely suspended with the aid of acacia.

In principle, estimation of antinociceptive potencies relative to codeine depended on reading the amount of uniformly increasing mechanical pressure on the rat's tail required just to elicit squeaking, 30 min. after administration of a dose. Varying compounds at varying doses, no greater than one-fourth the estimate of the average lethal dose, were included in randomized-group experiments along with vehicle and reference doses of codeine phosphate (11.3 mg. of base/kg.) and aminopyrine (84 mg./kg.). Linear plots of [(mean log threshold pressure with experimental treatment) − (mean log threshold pressure with codeine)] against [(log dose of experimental agent) − (log dose of codeine)] afforded the estimate of relative potency. In the case of compounds of which as much as one-fourth the average lethal dose failed to yield a mean log threshold as great as that with the reference dose of codeine, the line was extrapolated to the level of codeine equivalency by reference to slopes with more effective compounds.

All 15 **pyrrolidines** described were so studied except VII, which was converted to the corresponding phenol and acetate. Results are summarized in Table I.

Requirements for clear activity in this series were sharp. All but three of the compounds showed a subcodeine grade of antinociceptive efficacy, if any, at one-fourth their respective average lethal doses; only one of these significantly exceeded the aminopyrine grade. For some time there has been reason to believe that such subcodeine grades of antinociceptive efficacy are not predictive of clinical analgesia without some adjunctive pharmacological property such as an antiinflammatory effect.[8]

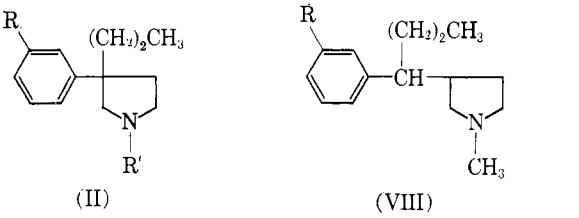
Three compounds of structure II, however, did clearly exhibit a codeine-like grade of antinociceptive action. By comparison with the less clearly active or inactive compounds they indicate that substitution on the phenyl ring (*e.g.*, *m*-HO, CH_3CO_2, or CH_3O) and N-methylation are required. These requirements contrast with those in the series of 3-phenyl-3-propionoxypyrrolidines,[1,7] where substitution on the phenyl was deleterious, where there was broader latitude in N-substitution, and where 2- or 4-substitution was required on the pyrrolidine ring in addition to the substituents at positions 1 and 3.

Inasmuch as the base contents of codeine and meperidine are of substantially equivalent potency by the procedure and route employed in the antinociceptive evaluations, potencies relative to meperidine (base) approximate those listed relative to codeine (base).

The optimal compound (II, R = OH; R′ = CH_3) was studied for its ability to alleviate the morphine abstinence syndrome in monkeys. Completely nega-

TABLE I

PYRROLIDINES STUDIED PHARMACOLOGICALLY



Structure	R	R′	Estimate of i.p. potency[a]	Est. of av. i.p. lethal dose,[b] mg. of base/kg.	Potency × lethal dose[c] 0.8 × 133
II	H	CH_3	None[d]	65	...
II	HO	H	None[d]	119	...
II	HO	CH_3	2.5	83	1.9
II	HO	*n*-C_3H_7	None[d]	60	...
II	CH_3CO_2	CH_3	1.7	97	1.5
II	CH_3CO_2	*n*-C_3H_7	None[d]	59	...
II	CH_3O	H	None[d]	68	...
II	CH_3O	CH_3	1.3	67	0.8
II	CH_3O	C_2H_5	(0.4)[e]	64	(0.3)
II	CH_3O	*n*-C_3H_7	(0.3)[e]	84	(0.2)
II	CH_3O	$CH{:}CCH_2$	(0.2)[f]	168	(0.3)
II	CH_3O	$C_6H_5CH_2$	(0.1)[e]	189	(0.2)
VIII	HO	...	None[d]	99	...
VIII	CH_3CO_2	...	(0.2)[e]	109	(0.2)

[a] Relative to codeine (base/base). [b] From small numbers of young, male, Sprague–Dawley rats of differing logs. [c] 2-Dimethyl-3-phenyl-3-propionoxypyrrolidine (prodilidine) of the earlier series[7] thus assigned unity. [d] Less effect, if any, at one-fourth the estimated average lethal dose than with 84 mg. of aminopyrine/kg. [e] By extrapolation. Effect equivalent to 11.3 mg. of codeine base/kg. not actually attained at a dose one-fourth the estimated average lethal dose; effect approximated that of 84 mg. of aminopyrine/kg. or less. [f] By extrapolation. Efficacy at one-fourth the average lethal dose between those of reference doses of aminopyrine and codeine.

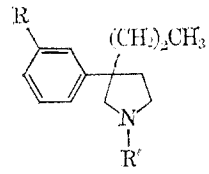
(6) G. H. Daub and W. S. Johnson, *J. Am. Chem. Soc.*, **70**, 418 (1948).

(7) 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).

(8) C. V. Winder, *Nature*, **184**, 494 (1959).

TABLE II

3,3-DISUBSTITUTED PYRROLIDINES



R	R′	Method	Yield, %	B.p. °C.	B.p. mm.	$n^{20}D$	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
H	CH_3	A	70	131–132[a]		[b]	$C_{14}H_{22}ClN$	70.1	9.3	5.8	70.2	9.0	6.1
CH_3O	$C_6H_5CH_2$	A	60	182–186	0.7	1.5604	$C_{21}H_{27}NO$	81.5	8.8	4.5	81.2	8.7	5.0
CH_3O	$C_6H_5CH_2$			144–146[a]		[b]	$C_{21}H_{28}ClNO$	72.9	8.2	4.1	72.8	7.9	4.2
CH_3O	n-C_3H_7	B	75	121	0.3	1.5161	$C_{17}H_{27}NO$	78.1	10.4	5.4	77.6	10.6	5.8
CH_3O	n-C_3H_7			112–118[a]		[b]	$C_{17}H_{28}ClNO \cdot 0.25H_2O$	67.5	9.4	4.6	67.1	9.4	5.1
CH_3O	$CH{:}CCH_2$	B	80	145–147	1.2	1.5348	$C_{17}H_{23}NO$	79.3	9.0	5.4	79.3	9.0	5.4
HO	H	C	72	184–189	0.9	[c]	$C_{13}H_{19}NO$	76.1	9.3	6.8	76.1	9.1	6.9
HO	n-C_3H_7	C	76	146–149	0.4	[c]	$C_{16}H_{25}NO$	77.7	10.2	5.7	77.2	10.0	5.4
CH_3CO_2	n-C_3H_7	D	78	146–147	0.5	1.5080	$C_{18}H_{27}NO_2$	74.7	9.4	4.8	74.4	9.3	4.8

[a] Melting point. [b] Hydrochloride. [c] Material too viscous for measurement.

tive results indicated no morphine-like addiction liability.[9]

Experimental[10]

***m*-Methoxybutyrophenone.**—To a stirred solution of *n*-propylmagnesium bromide (from 24 g. of magnesium and 135 g. of *n*-propyl bromide) in ether (500 ml.) was added anhydrous cadmium chloride (91.7 g.) and the mixture was heated under reflux until a test probe gave a negative Gilman test[11] (15 min.). The solution was distilled with stirring, while adding dry benzene to maintain the volume, until the still-head temperature reached 78°, then cooled to 10°, and treated with a solution of *m*-methoxybenzoyl chloride (110 g.) in dry benzene (200 ml.). When addition was complete the temperature was allowed to rise to 45° and held there for 3 hr. The mixture was stirred overnight at room temperature, then poured onto crushed ice (0.5 kg.) and 10 *N* sulfuric acid (200 ml.) and the organic layer isolated. Removal of the benzene gave an oil which was freed from unreacted *m*-methoxybenzoyl chloride by shaking vigorously with 5 *N* sodium hydroxide, then isolated with benzene and distilled, b.p. 105–110° (2 mm.), $n^{20}D$ 1.5253; yield 90 g. (78%); lit,[2] b.p. 142–146° (11 mm.), $n^{25}D$ 1.5235.

α-(*m*-Methoxyphenyl)-N-methyl-α-propylsuccinimide (VI, R = OCH_3).—Potassium cyanide was made to react with III (R = OCH_3)[2] in the manner described by Miller and Long[5]; the resulting dinitrile was not purified but hydrolyzed directly to the acid, obtained as a crude undistillable oil. This was added to aqueous methylamine (1.2 moles) and the solution heated until the internal temperature reached 190°. The mixture was held at this temperature for 30 min., then cooled slightly and distilled to give a colorless oil, b.p. 160–170° (0.6 mm.), $n^{20}D$ 1.5475; yield 50–60%.

Anal. Calcd. for $C_{15}H_{19}NO_3$: C, 68.9; H, 7.3; N, 5.4. Found: C, 68.8; H, 7.1; N, 5.0.

N-Methyl-α-phenyl-α-propylsuccinimide prepared as above had b.p. 141–142° (0.7 mm.), $n^{20}D$ 1.5438.

Anal. Calcd. for $C_{14}H_{17}NO_2$: C, 72.7; H, 7.4; N, 6.1. Found: C, 72.9; H, 7.7; N, 6.2.

N-Benzyl-α-(*m*-methoxyphenyl)-α-propylsuccinimide had b.p. 220–226° (0.7 mm.).

Anal. Calcd. for $C_{21}H_{23}NO_3$: C, 74.8; H, 6.9; N, 4.2. Found: C, 74.9; H, 6.5; N, 4.5.

3-(*m*-Methoxyphenyl)-1-methyl-3-*n*-propylpyrrolidine (II, R = OCH_3; R′ = CH_3). A.—The succinimide (VI, R = OCH_3) was reduced with lithium aluminum hydride in dry ether to give the pyrrolidine, b.p. 119–121° (0.8 mm.), $n^{20}D$ 1.5218, in 70% yield.

Anal. Calcd. for $C_{15}H_{23}NO$: C, 77.2; H, 9.9; N, 6.0. Found: C, 77.1; H, 10.2; N, 6.1.

The **hydrochloride** had m.p. 135–136°.

Anal. Calcd. for $C_{15}H_{24}ClNO$: C, 66.8; H, 9.0; N, 5.2. Found: C, 66.7; H, 8.9; N, 5.1.

3-(*m*-Methoxyphenyl)-3-propylpyrrolidine (II, R = OCH_3; R′ = H).—1-Benzyl-3-(*m*-methoxyphenyl)-3-propylpyrrolidine (46.3 g.) in ethanol (250 ml.) was treated with palladium-on-charcoal (1 g., 10%) and shaken in an atmosphere of hydrogen when the theoretical absorption (3.4 l.) occurred in 1 hr. The catalyst was removed, and the solution was concentrated and distilled to give the secondary amine (25.3 g.), b.p. 125–129° (1.0 mm.), $n^{20}D$ 1.5388.

Anal. Calcd. for $C_{14}H_{21}NO$: C, 76.7; H, 9.7; N, 6.4; Found: C, 76.9; H, 9.3; N, 6.2.

1-Ethyl-3-(*m*-methoxyphenyl)-3-propylpyrrolidine (II, R = OCH_3; R′ = C_2H_5). B.—The preceding secondary amine (11 g.) in dimethylformamide (50 ml.) was stirred with potassium carbonate (6 g.) and ethyl bromide (6.4 g.) for 22 hr. at room temperature. The mixture was poured into water (250 ml.) and the product isolated as an oil (10.2 g.) with ether. This oil gave a solid hydrochloride (9.5 g.) which crystallized from isopropanol-ether mixtures as small needles, m.p. 149–150°.

Anal. Calcd. for $C_{16}H_{26}ClNO$: C, 67.7; H, 9.2; N, 4.9. Found: C, 67.7; H, 9.0; N, 4.9.

***m*-(1-Methyl-3-propyl-3-pyrrolidinyl)phenol (II, R = OH; R′ = CH_3). C.**—3-(*m*-Methoxyphenyl)-1-methyl-3-propylpyrrolidine (21.4 g.) was refluxed in constant-boiling hydrobromic acid (90 ml.) for 90 min. The solution was concentrated under reduced pressure, dissolved in water (200 ml.) saturated with potassium bicarbonate, and exhaustively extracted with a mixture of benzene and ether (1:1). Removal of the solvents gave a viscous oil which was isolated as the hydrochloride, m.p. 146–147°; yield 18.5 g.

Anal. Calcd. for $C_{14}H_{22}ClNO$: C, 65.7; H, 8.7; Cl, 13.9. Found: C, 65.9; H, 8.7; Cl, 13.6.

***m*-(1-Methyl-3-propylpyrrolidinyl)phenyl Acetate (II, R = CH_3CO_2; R′ = CH_3). D.**—The above phenol (8 g.) was held at 95° for 3 hr. with acetic anhydride (40 ml.) and pyridine (10 ml.) then concentrated and distilled to give the ester (6 g.), b.p. 136–138° (0.7 mm.), $n^{20}D$ 1.5228.

Anal. Calcd. for $C_{16}H_{23}NO$: C, 73.5; H, 8.9; N, 5.4. Found: C, 73.5; H, 9.1; N, 5.7.

3-[1′-(*m*-Methoxyphenyl)-*n*-butyl]-1-methylpyrrolidine (VII).—*m*-Methoxybutyrophenone (49 g.) and diethyl succinate (144 g.) were condensed using sodium hydride[6] (13.2 g.). The crude product in ethanol (400 ml.) was shaken in an atmosphere of hydrogen with palladium-on-charcoal (1.0 g., 10%) when 4 l. (theory 6.2 l.) of hydrogen was absorbed. The catalyst was removed, and the residue was treated with aqueous methylamine (1.2 moles) and slowly heated until the internal temperature reached 190° where it was held for 30 min. The product was cooled, dissolved in

(9) We are indebted for this study to Dr. G. A. Deneau of the University of Michigan.

(10) Melting points were determined in a capillary tube and are uncorrected. This work was completed before the announcement of the requirement for corrected melting points by the journals of the American Chemical Society.

(11) H. Gilman and F. Schulze, *J. Am. Chem. Soc.*, **47**, 2002 (1925).

dry ether, and reacted with lithium aluminum hydride (20 g.) in dry ether to give the pyrrolidine as a colorless oil, b.p. 130–132° (0.8 mm.), $n^{20}D$ 1.5216; yield 20 g., 29%.

Anal. Calcd. for $C_{16}H_{25}NO$: C, 77.7; H, 10.2; N, 5.7. Found: C, 77.7; H, 10.1; N, 5.8.

m-[1'-(1-**Methyl-3-pyrrolidinyl**)**butyl**]**phenol**.—This was prepared following method C and isolated as a hygroscopic (+)-tartrate, m.p. 70° (sealed tube).

Anal. Calcd. for $C_{19}H_{29}NO_7$: C, 59.5; H, 7.6; N, 3.7. Found: C, 59.5; H, 7.9; N, 4.0.

m-[**1'-(1-Methyl-3-pyrrolidinyl)butyl**]**phenyl Acetate.**—This was prepared from the above following method D and isolated as a colorless oil, b.p. 134–136° (0.8 mm.), $n^{20}D$ 1.5158.

Anal. Calcd. for $C_{17}N_{25}NO_2$: C, 74.1; H, 9.2; N, 5.1. Found: C, 74.3; H, 9.0; N, 5.3.

Acknowledgment.—The authors thank Dr. R. E. Bowman for helpful discussions, Mr. F. H. Oliver for the microanalyses, and Miss Sue Ketchum, Mrs. S. Stanat, and Mrs. J. Grant for help in the pharmacological work.

Synthesis and Pharmacological Activity of 3-(2-Pyrrolidinyl)indoles

GILBERT A. YOUNGDALE, DOUGLAS G. ANGER, WILLIAM C. ANTHONY, JOHN P. DAVANZO, MARGARET E. GREIG, RICHARD V. HEINZELMAN, HUGH H. KEASLING, AND JACOB SZMUSZKOVICZ

Research Laboratories of The Upjohn Company, Kalamazoo, Michigan

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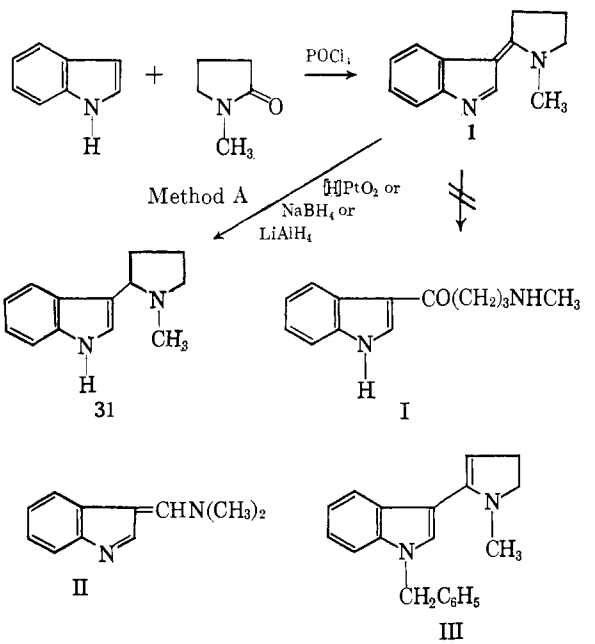
A number of 3-(2-pyrrolidinyl)indoles have been synthesized by several methods. These compounds and numerous intermediates showed various types of interesting central nervous system activity in mice and rats.

We have reported recently[1] the preparation of indole-3-C^{14}-carboxaldehyde by the method of Smith[2] involving the reaction of indole with dimethylformamide in the presence of phosphorus oxychloride. In subsequent attempts to avoid the inefficient use of excess radioactive dimethylformamide as the reaction solvent the latter was replaced by 1-methyl-2-pyrrolidinone as solvent. It was soon observed that the pyrrolidinone participated in the reaction. Consequently, indole was allowed to react with the complex formed from 1-methyl-2-pyrrolidinone and phosphorus oxychloride with the expectation that the amino ketone I would be produced.[3] Instead the product isolated had the structure **1**[4] which is reminiscent of the unstable intermediate II isolated by Smith[2] from the reaction of indole, dimethylformamide, and phosphorus oxychloride. However, whereas II was readily hydrolyzed by hot water to give indole-3-carboxaldehyde, **1** was resistant to hydrolysis to the amino ketone I. The reduction of **1** was accomplished readily by several methods to yield 3-(1-methyl-2-pyrrolidinyl)indole (**31**). The only 3-(2-pyrrolidinyl)-indole compound reported to date is the parent member of this class prepared by Fuhlhage and VanderWerf[5a,b] from indole and 1-pyrroline.



The method of preparation of **1** proved to be of general utility. A variety of substituted indoles and 2-pyrrolidinones was employed. The compounds prepared by method A are listed in Table I. Their ultraviolet spectra are similar to those reported for II[2] and other related 3H-indole derivatives,[6] and all have a band at 336–361 mμ with an extinction coefficient of 7800–20,700. Additional support for the 3H-indole over the 3-(2-pyrrolin-2-yl)indole structure is provided by the absence of an NH band in the infrared spectrum of **1** in both a Nujol mull and chloroform solution. In the case of 1-benzylindole which could not lead to the 3H-indole structure, the spectral data (see Experimental section) suggested that the product was a mixture which could contain the enamine III. Catalytic reduction of this mixture produced 1-benzyl-3-(1-methyl-2-pyrrolidinyl)indole.

The 3-(2-pyrrolidinylidene)-3H-indoles of type **1** were reduced by catalytic hydrogenation (method B), sodium borohydride (method C), or lithium aluminum hydride (method D) to the 3-(2-pyrrolidinyl)indoles listed in Tables II and III.

Another method (E) for the synthesis of 3-(2-pyrrolidinyl)indoles was developed employing Mannich bases derived from 3-acetylindoles.[7] The Mannich bases were allowed to react with a nitroalkane using a catalytic amount of sodium methoxide to produce the 3-indolyl nitro ketones (Table IV) in fair to good yield. Hydrogenation oft hese nitro ketones employing Raney nickel catalyst gave the corresponding 1-pyrrolines in

(1) J. Szmuszkovicz and R. C. Thomas, *J. Org. Chem.*, **26**, 960 (1961).

(2) G. F. Smith, *J. Chem. Soc.*, 3842 (1954).

(3) W. C. Anthony, *J. Org. Chem.*, **25**, 2049 (1960).

(4) Roman numerals refer to compounds mentioned only in the text, while Arabic numerals refer to compounds in the tables.

(5) (a) D. W. Fuhlhage and C. A. VanderWerf, *J. Am. Chem. Soc.*, **80**, 6249 (1958). (b) After this manuscript had been submitted for publication, the preparation of compound **43** by an alternate route was reported by F. Haglid and I. Wellings, *Acta Chem. Scand.*, **17**, 1743 (1963).

(6) E. Wenkert, J. H. Udelhofen, and N. K. Bhattacharyya, *J. Am. Chem. Soc.*, **81**, 3763 (1959).

(7) J. Szmuszkovicz, *ibid.*, **82**, 1180 (1960).