3-Alkyl-3-phenylpiperidine Derivatives as Analgesics. II

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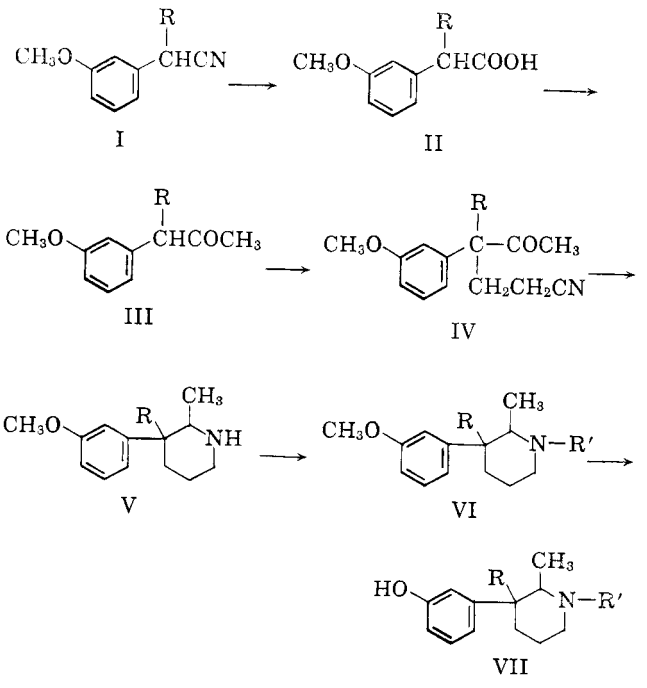
Received November 14, 1965

2-Methyl analogs of certain 3-alkyl-3-phenylpiperidine derivatives have been synthesized and tested for analgesic activity. 1-Phenacyl derivative of the 2,3-dimethyl compound (**11**) was shown to have a potent analgesic activity and low toxicity in mice. The 1-allyl derivative (**12**) antagonized analgesia produced by **11** and morphine. The spatial relationship between the 2-methyl and the 3-alkyl groups is discussed based on n.m.r. spectroscopy.

In the continuation of our earlier work on 3-alkyl-3-phenylpiperidine derivatives as analgesics,[1b] introduction of an alkyl group into the 2-position of the piperidine ring has been accomplished in the hope of obtaining analogs of higher activity. This paper describes the synthesis and physiological evaluation of a series of 3-alkyl-2-methyl-3-phenylpiperidine derivatives.

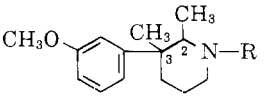
Chemistry.—2-Substituted 2-(3-methoxyphenyl)acetonitriles (I, R = CH_3, n-C_3H_7, $C_6H_5CH_2$) were hydrolyzed by heating with sulfuric acid in acetic acid[2] to give the carboxylic acids (II). Reaction of II with methyllithium[3] gave the methyl ketones (III) which were converted into the ketonitriles (IV) by reaction with acrylonitrile. Hydrogenation of IV with Raney nickel at elevated temperature afforded the 3-alkyl-2-methyl-3-(3-methoxyphenyl)piperidines (V). This reductive cyclization of IV (R = CH_3) afforded only one diastereoisomer as shown by gas chromatographic analysis. In our earlier work on an analogous case, in which the two alkyl groups of the piperidine ring of V were connected through a carbon chain with the formation of a six-membered ring, one isomer was obtained by a similar reductive cyclization of 2-cyanoethyl-2-(3-methoxyphenyl)cyclohexanone. The *trans*-decahydroquinoline structure was assigned to this isomer[4,5] on the assumption that addition of hydrogen to the C=N linkage of the intermediary imino compound would occur from the side opposite to the phenyl group. A *trans* relationship between the two methyl groups of V (R = CH_3) was considered likewise feasible as in the previous case, and the n.m.r. spectra[6] of V (R = CH_3) and its N-acetyl derivative supported this hypothesis (Table I).



The spectrum of V shows resonance signals of a secondary methyl, a doublet centered at δ 0.93 (J = 6.5 c.p.s.), and a tertiary methyl singlet at δ 1.33, in conformity with the given structure. The spectrum of the N-acetyl derivative, measured at room temperature, shows signals of secondary and tertiary methyls as well as that of the acetyl, each peak of the normally observed doublet for >CH–CH_3 and singlets for >C–CH_3 and CO–CH_3 all being divided into two components of roughly equal intensity. This phenomenon suggested the presence of two conformers A and B due to a restricted rotation[7] of the acetyl group around C-1–N linkage. When taken at 69°, the twin peaks were integrated into single peaks in conformity with the structure.

In the ground state, as shown by A and B, the carbonyl group of the acetyl derivative is considered to be

TABLE I
N.M.R. DATA OF V (R = CH_3) AND ITS N-ACETYL DERIVATIVE



	Chemical shifts, p.p.m. (J, c.p.s.)		
		R = $COCH_3$	
Protons	R = H	at 22°	at 69°
2-CH_3	0.93 (6.5)	0.84 (6.4)	0.77 (6.5)
		0.74 (6.5)	
3-CH_3	1.33	1.31	1.28
		1.26	
CO-CH_3	...	2.15	2.01
		2.10	

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(2) *Cf.* A. Campbell and J. Kenyon, *J. Chem. Soc.*, 25 (1946).

(3) K. Mislow and C. L. Hamermesh, *J. Am. Chem. Soc.*, **77**, 1590 (1955).

(4) N. Sugimoto, H. Kugita, and T. Fujita, *J. Pharm. Soc. Japan*, **75**, 177 (1955).

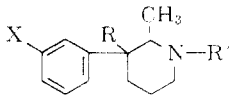
(5) N. Sugimoto and H. Kugita, *Pharm. Bull.* (Tokyo), **5**, 378 (1957).

(6) The n.m.r. spectra were measured on a high-resolution n.m.r. spectrometer (Japan Electron Optics Co., JNMC-60) at 60 Mc.p.s. with tetramethylsilane as internal standard. The authors thank Dr. K. Kotera of this laboratory for the measurement of the spectra and useful discussion.

(7) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p. 365.

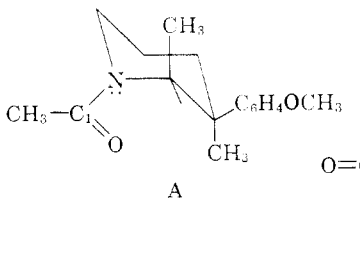
TABLE II

3-ALKYL-2-METHYL-3-ARYLPIPERIDINES

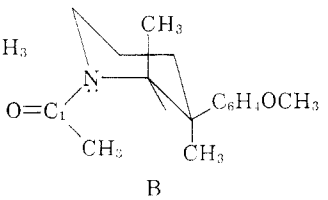


No.	X	R	R'	Salt	M.p., °C.	Formula	% Carbon Calcd.	% Carbon Found	% Hydrogen Calcd.	% Hydrogen Found	% Nitrogen Calcd.	% Nitrogen Found
1	CH_3O	CH_3	CH_3	HCl[a]	240–242	$C_{15}H_{24}ClNO$	66.78	66.82	8.96	8.63	5.19	5.51
2	CH_3O	CH_3	$C_6H_5CH_2CH_2$	$(COOH)_2$[b]	225–227	$C_{24}H_{31}NO_5$	69.71	69.71	7.56	7.25	3.39	3.62
3	CH_3O	CH_3	$C_6H_5COCH_2$	HBr[a]	203–205	$C_{22}H_{28}BrNO_2$	63.15	63.46	6.75	6.58	3.35	3.46
4	CH_3O	CH_3	CH_2=$CHCH_2$	HCl[c]	161–163	$C_{17}H_{26}ClNO$	69.06	69.48	8.86	8.72	4.74	4.84
5	CH_3O	n-C_3H_7	$C_6H_5COCH_2$	HCl[d]	188–190	$C_{24}H_{32}ClNO_2 \cdot 0.5H_2O$	70.30	70.64	8.11	7.94	3.41	3.37
6	CH_3O	n-C_3H_7	CH_2=$CHCH_2$	HBr[e]	167–169	$C_{19}H_{30}BrNO$	61.95	62.09	8.21	8.39	3.80	3.87
7	CH_3O	$C_6H_5CH_2$	$C_6H_5COCH_2$	HCl[c]	143–145	$C_{28}H_{32}ClNO_2 \cdot H_2O$	71.85	71.66	7.30	7.03	2.99	3.00
8	CH_3O	$C_6H_5CH_2$	CH_2=$CHCH_2$	HCl[d]	221–222	$C_{23}H_{30}ClNO$	74.27	74.10	8.13	8.12	3.77	3.77
9	HO	CH_3	CH_3	HBr[a]	226–228	$C_{14}H_{22}BrNO$	56.00	56.21	7.39	7.07	4.66	4.85
10	HO	CH_3	$C_6H_5CH_2CH_2$	HBr[a]	224–226	$C_{21}H_{28}BrNO$	64.61	64.87	7.23	6.96	3.59	3.76
11	HO	CH_3	$C_6H_5COCH_2$	HBr[a]	225–227	$C_{21}H_{26}BrNO_2$	62.37	62.41	6.48	6.21	3.46	3.55
12	HO	CH_3	CH_2=$CHCH_2$	HBr[f]	213–214	$C_{16}H_{24}BrNO$	58.89	59.18	7.41	7.15	4.29	4.52
13	HO	n-C_3H_7	$C_6H_5COCH_2$	HCl[d]	219–221	$C_{23}H_{30}ClNO_2$	71.21	71.16	7.80	7.51	3.61	3.68
14	HO	n-C_3H_7	CH_2=$CHCH_2$	$(COOH)_2$[a]	207–210	$C_{19}H_{29}NO_3$	71.67	71.42	8.86	8.47	4.40	4.45
15	HO	$C_6H_5CH_2$	$C_6H_5COCH_2$	HBr[g]	186–188	$C_{27}H_{30}BrNO_2 \cdot 0.5H_2O$	66.25	66.60	6.38	6.14	2.86	2.78
16	HO	$C_6H_5CH_2$	CH_2=$CHCH_2$	HCl[d]	251–253	$C_{22}H_{28}ClNO$	73.80	73.80	7.88	7.69	3.94	3.89

[a] Recrystallized from EtOH. [b] Recrystallized from MeOH–water. [c] Recrystallized from Me_2CO. [d] Recrystallized from Me_2CO–MeOH–Et_2O. [e] Recrystallized from Me_2CO–Et_2O. [f] Recrystallized from water. [g] Recrystallized from Me_2CO–MeOH.



A



B

situated in a geometry so as to be coplanar with the nitrogen and two carbon atoms adjacent to the nitrogen with the double-bond character of the C-1–N linkage. The protons of the 2-methyl were expected to be shifted upward when located axially, *i.e.*, perpendicular to the carbonyl, by the shielding effect of the latter, and if located equatorially, a deshielding effect of the carbonyl may cause a downward shift of the methyl protons. The spectrum measured at room temperature showed an upward shift of the 2-methyl protons by 0.19 and 0.09 p.p.m. in the two conformers, respectively, implying that the 2-methyl is axial. A similar, but far smaller upward shift (0.07 and 0.02 p.p.m., respectively) was observed also with the signal of the 3-methyl; this means, coupled with the probability that the phenyl group occupies an equatorial direction, that the 3-methyl is most conceivably axial, *i.e.*, *trans* to the 2-methyl.

The reductive cyclization of IV, in the case of R = n-C_3H_7, gave two products, both analyzing for the molecular formula corresponding to structure V (R = n-C_3H_7). The major product was assigned tentatively the *trans*-dialkyl structure on the ground that the phenyl group might be bulkier than propyl, while the minor product was given the *cis*-dialkyl structure. Substitution at the 1-position of V in the usual way and final O-demethylation of the product VI afforded VII (Table II).

Pharmacological Results.—The analgesic activities of VII were measured by the hot-plate method.[8] ED_{50} and LD_{50} values (in mice) were calculated as previously described.[1] The analgesic effect of these 3-alkyl-2-methyl-3-phenylpiperidine derivatives varied significantly according to the substituents both at positions 1 and 3. In the 3-methyl analogs analgesic activity was found only for the N-phenethyl **10** and the N-phenacyl derivative **11**, the latter being more potent than the former. Acute toxicity was greatly lowered in **11**, again demonstrating the superior therapeutic index of the N-phenacyl group in this series of piperidine analgesics.[1] Substitution of a n-propyl or a benzyl group for the methyl group at the 3-position resulted in such a marked fall in the activity that it was almost undetectable even at a toxic dose (Table III).

TABLE III

ANALGESIC ACTIVITIES AND TOXICITIES OF 3-ALKYL-2-METHYL-3-PHENYLPIPERIDINE DERIVATIVES IN MICE (S.C.)

Compd.	ED_{50}, mg./kg.	LD_{50}, mg./kg.	Symptoms: Dose, mg./kg.	Symptoms: Obsn.
9	...	161	100	*a*, *b*, *c*
10	9.77	155	100	*b*, *d*–*g*
11[h]	7.15	>800	800	*d*, *e*, *g*
12[h]	...	182	100	*b*, *i*
13	...	171	100	*b*, *d*, *g*
14[h]	...	268	100	*b*, *c*, *d*, *g*
15[i]	...	>400	400	...
16[i]	...	>400	400	*b*, *g*
Morphine	4.2	407	...	...

[a] ↓ spontaneous activity. [b] Convulsion. [c] ↓ muscle tone. [d] ↑ spontaneous activity. [e] Straub tail. [f] Twitch. [g] ↑ pupil size. [h] Tested with HCl salt. [i] Tremor. [j] Tested by intraperitoneal injection.

The N-allyl derivative **12** antagonized the analgesic effect of morphine and **11** at 1/10 to 2/10 the dose of the analgesic when tested according to the previously described method.[1] However, **12** failed to show analgesic activity contrary to the fact reported in the previous paper that the 2-demethyl analog appeared to be

(8) N. B. Eddy and D. Leimbach, *J. Pharmacol. Exptl. Therap.*, **107**, 385 (1953).

analgesic in mice while being an antagonist. The allyl derivatives of the 3-*n*-propyl and 3-benzyl analogs (**14** and **16**) were ineffective in antagonizing morphine analgesia when tested in the same way. Compound **11** was tested for its ability to suppress morphine abstinence syndrome in monkeys.[9] No physical dependence capacity has been shown in the dose range of 2–16 mg./kg.[10]

Experimental[11]

2-(3-Methoxyphenyl)propionic Acid (II, R = CH_3).—2-(3-Methoxyphenyl)propionitrile (I, R = CH_3) (50 g.) was added to a mixture of sulfuric acid (36 ml.), acetic acid (33 ml.), and water (28 ml.) at room temperature. The mixture was heated at 90–100° for 3.5 hr. with stirring and at 130° for 40 min., cooled, diluted with water, and extracted with ether. The ethereal solution was extracted with 10% sodium carbonate, the alkaline solution was neutralized with concentrated hydrochloric acid and extracted with ether. Evaporation of the dried solution and distillation of the residue gave a main fraction (33 g.) distilling at 145–147° (1 mm.) and a fraction (15 g.) distilling at 148–170° (1 mm.). As the latter was shown to contain a considerable amount of phenolic compounds, it was treated with dimethyl sulfate and sodium hydroxide to give additional amount of II (12 g.), b.p. 145–147° (1 mm.).

Anal. Calcd. for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.54; H, 6.56.

2-(3-Methoxyphenyl)valeric Acid (II, R = *n*-C_3H_7).—I (R = *n*-C_3H_7) was hydrolyzed in a way similar to that mentioned above; colorless oil, b.p. 139–144° (0.4 mm.), yield 76%. An analytical sample distilled at 152–153° (0.3 mm.).

Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 68.86; H, 7.54.

2-(3-Methoxyphenyl)-3-phenylpropionic Acid (II, R = $C_6H_5CH_2$).—I (R = $C_6H_5CH_2$)[12] was hydrolyzed in the same way to give a colorless oil, b.p. 175–185° (0.4 mm.), yield 83.5%. The oil crystallized upon standing. Recrystallization from ether–petroleum ether (b.p. 30–70°) gave colorless prisms, m.p. 65–66°.

Anal. Calcd. for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 74.78; H, 6.11.

3-(3-Methoxyphenyl)-2-butanone (III, R = CH_3).—This was prepared according to the procedure described by Mislow and Hamermesh.[3] To a methyllithium solution prepared from lithium (4.65 g.) and methyl iodide (47.5 g.) in ether (200 ml.) was added at 0–5° a solution of II (R = CH_3) (15 g.) in ether (30 ml.) over a period of 25 min., after which the mixture was stirred at 5–10° for 30 min. and poured into ice–water containing ammonium chloride. The organic layer was separated, washed with 10% sodium carbonate and water, dried, and evaporated. The residue was distilled to give a colorless oil (14.2 g.), b.p. 135–140° (15 mm.), which was added to a solution of semicarbazide hydrochloride (11.2 g.) and sodium acetate (13.6 g.) in ethanol (45 ml.) and water (20 ml.) and allowed to stand overnight at room temperature. The semicarbazone was filtered, washed with ethanol, and dried, m.p. 149–152°, yield 14 g. (70% from III). An analytical sample crystallized from ethanol in colorless prisms, m.p. 152.5–154.5°.

Anal. Calcd. for $C_{12}H_{17}N_3O_2$: C, 61.25; H, 7.28; N, 17.86. Found: C, 61.44; H, 7.19; N, 17.61.

The semicarbazone (13.7 g.) was added to a mixture of 10% HCl (28 ml.) and petroleum ether (50–90°) (28 ml.) and refluxed for 1 hr. Ether was added to the mixture and the separated organic layer was washed with water, dried, and evaporated. The residue was distilled to give a colorless oil (9.3 g.), b.p. 136–138° (16 mm.).

3-(3-Methoxyphenyl)-2-hexanone (III, R = *n*-C_3H_7).—Reaction of II (R = *n*-C_3H_7) with methyllithium in the same way as described previously gave the semicarbazone of III (R = *n*-C_3H_7) in 65% yield. Colorless needles (ethanol–water), m.p. 118–120°.

Anal. Calcd. for $C_{14}H_{21}N_3O_2$: C, 63.85; H, 8.04; N, 15.96. Found: C, 63.82; H, 7.96; N, 15.88.

The semicarbazone was refluxed with 10% HCl in petroleum ether as described before. Compound III (R = *n*-C_3H_7) was obtained as a colorless oil, b.p. 127–130° (3 mm.).

3-(3-Methoxyphenyl)-4-phenyl-2-butanone (III, R = $C_6H_5CH_2$).—Reaction of II (R = $C_6H_5CH_2$) with methyllithium gave likewise the semicarbazone of III in 64.7% yield; colorless needles (ethanol–water), m.p. 115.5–117°.

Anal. Calcd. for $C_{18}H_{21}N_3O_2$: C, 69.43; H, 6.80; N, 13.50. Found: C, 69.61; H, 6.53; N, 13.28.

The ketone distilled at 134–136° (0.3 mm.).

Cyanoethylation of III.—As a representative example the synthesis of 3-cyanoethyl-3-(3-methoxyphenyl)-2-butanone (IV, R = CH_3) is presented. A solution of acrylonitrile (6.1 g.) in dioxane (15 ml.) was added to a mixture of III (R = CH_3) (15.7 g.), dioxane (70 ml.), and Triton B (2 ml.) at a rate to maintain the internal temperature at 30–40°. After the addition was completed the mixture was stirred at 45–50° for 30 min., dioxane was distilled under reduced pressure, and the residue was dissolved in ether, washed with water, and dried. Evaporation of the ether and distillation of the residue gave a colorless oil (16.6 g.), b.p. 140–145° (0.1 mm.). An analytical sample distilled at 140–141° (0.1 mm.).

Anal. Calcd. for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.78; H, 7.36; N, 6.33.

Compound IV (**R** = *n*-C_3H_7) was isolated as a colorless oil, b.p. 153–154° (0.3 mm.).

Anal. Calcd. for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 73.50; H, 7.53; N, 5.38.

Compound IV (**R** = $C_6H_5CH_2$) was isolated as colorless prisms (benzene), m.p. 120–122°.

Anal. Calcd. for $C_{20}H_{21}NO_2$: C, 78.14; H, 6.89; N, 4.56. Found: C, 78.27; H, 6.73; N, 4.64.

Reductive Cyclization of IV. A. R = CH_3.—A mixture of IV (R = CH_3) (15 g.), Raney nickel (10 g.), and methanol (80 ml.) was hydrogenated in an autoclave with an initial hydrogen pressure of 90 kg./cm.^{2}. Three molar equivalents of hydrogen was absorbed at 120–130° in 2 hr. The catalyst was filtered, methanol was distilled, and the residue was dissolved in ether and extracted with 10% HCl. The acid solution was basified with ammonia, extracted with ether, dried, and evaporated. Distillation of the residue gave a colorless oil (12 g.), b.p. 138–140° (4 mm.), which was converted to the hydrochloride and recrystallized from ethanol as colorless prisms, m.p. 232–234°, yield 12.7 g.

Anal. Calcd. for $C_{14}H_{22}ClNO$: C, 65.74; H, 8.67; N, 5.48. Found: C, 65.87; H, 8.57; N, 5.44.

B. R = *n*-C_3H_7.—IV (R = *n*-C_3H_7) (11 g.) was hydrogenated in a way similar to that described above. There was obtained a colorless oil (10.1 g.), b.p. 159–164° (3 mm.). The hydrochloride gave two fractions by recrystallization from ethanol. Each fraction was recrystalized repeatedly from ethanol to give colorless prisms (5.3 g.), m.p. 226–228° (A), and colorless rectangular plates (1.1 g.), m.p. 191.5–193.5° (B).

Anal. Calcd. for $C_{16}H_{26}ClNO$: C, 67.70; H, 9.23; N, 4.94. Found for A: C, 67.87; H, 9.12; N, 4.90. Found for B: C, 67.85; H, 8.98; N, 4.78.

C. R = $C_6H_5CH_2$.—IV (R = $C_6H_5CH_2$) was hydrogenated likewise to give the basic product (12.9 g.), b.p. 163–168° (0.3 mm.), which was converted to the oxalate and recrystallized from methanol. There were obtained two portions of oxalate, a crystalline portion (9.8 g.), m.p. 190–192° dec., and a noncrystalline portion (7.0 g.). The former was dissolved in water and basified with ammonia, the free base was taken into ether, dried, and evaporated, and the residue was treated with perchloric acid. The perchlorate was recrystallized from acetone–ether as colorless plates, m.p. 187–189°, yield 8.4 g.

Anal. Calcd. for $C_{20}H_{26}ClNO_5$: C, 60.68; H, 6.62; N, 3.54. Found: C, 61.00; H, 6.54; N, 3.50.

Similarly the noncrystalline oxalate gave the perchlorate (2.7 g.), m.p. 170–174°. An analytical sample was crystallized from methanol in colorless plates, m.p. 173.5–175.5°. The infrared spectrum suggested a ketimine structure by its absorption at 1685 cm.$^{-1}$.

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

(10) Private communication from Dr. E. L. May. We are also informed by Dr. May that compound **11** (NIH 8173) has a subcutaneous ED_{50} of 1.51 mg./kg. (SE limits 1.30–1.77).

(11) Microanalyses were done by Mrs. F. Hisamichi and Messrs. T. Kono and N. Takeda whom the authors thank. Melting points (Yamoto Scientific Co., Ltd., apparatus) are corrected.

(12) I (R = $C_6H_5CH_2$) was prepared from 2-(3-methoxyphenyl)acetonitrile by alkylation with sodamide and benzyl chloride in an analogous way to that used for the synthesis of I (R = *n*-C_3H_7).[1]

Anal. Calcd. for $C_{20}H_{24}ClNO_5$: C, 61.01; H, 6.14; N, 3.55. Found: C, 61.05; H, 6.49; N, 3.56.

Spatial relationships between the benzyl and 2-methyl derivatives remain uncertain.

N-Substitution of V.—Introduction of substituents into 1-position of V followed typical procedures described in the previous paper.[1] Products are presented in Table II (**1–8**).

Synthesis of VII.—VI was refluxed with 48% HBr for 20–30 min. and worked up in the usual way. The products are presented in Table II (**9–16**).

1-Acetyl-2,3-dimethyl-3-(3-methoxyphenyl)piperidine.—Acetyl chloride (0.59 g.) in acetone (3 ml.) was added to a mixture of V (R = CH_3) (1.1 g.), K_2CO_3 (1 g.), and acetone (20 ml.) at 2–4° over a period of 20 min. The mixture was stirred at 2–4° for 1 hr., at room temperature for 3 hr., then allowed to stand overnight at room temperature and filtered. Acetone was removed by distillation and the residue was dissolved in ether, washed with water, dried, and evaporated. Distillation of the residue gave a colorless oil (1 g.), b.p. 160–161° (0.35 mm.).

Anal. Calcd. for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.65; H, 8.72; N, 5.36.

Acknowledgment.—The authors wish to thank Drs. Everette L. May and Nathan B. Eddy for the aid in arranging some of the compounds described here and previously for the monkey test of addiction liability at the University of Michigan.

Analgetics Based on the Pyrrolidine Ring. IV

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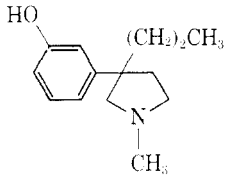
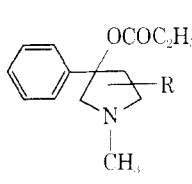
Received September 19, 1964

Following the discovery of the meperidine level of analgetic activity in the pyrrolidinylphenol (I), over seventy additional compounds of this type have been synthesized. The chosen routes to these compounds provide, in some instances, novel aspects of synthetic pyrrolidine chemistry. Pharmacologically, few, if any, of the additional compounds prepared had activity as great as the original I; the activity of I itself was found to be distributed between its *d* and *l* optical isomers in a ratio of 1:2.

In earlier work on pyrrolidine analgetics[1] we showed that the inclusion of a further alkyl substituent in the pyrrolidine ring changed a compound of sub-codeine activity (II, R = H) into one having clear analgetic activity [II, R = 2- or 4-CH_3 or 2,5-$(CH_3)_2$]. When, therefore, we found a meperidine level of action in the pyrrolidinylphenol (I),[2] we decided to effect substitutions in the free positions of the ring; from this we were led to effect changes in other parts of the molecule.



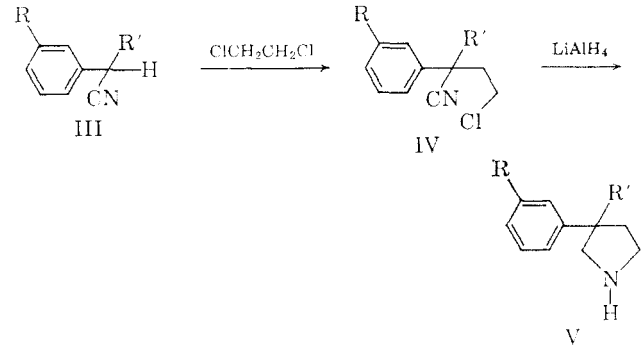
I



II

Chemistry.—While the 3,3-diarylpyrrolidines have been fairly extensively examined, the 3-alkyl-3-aryl and the 3,(2, 4, or 5)-dialkyl-3-arylpyrrolidines have received little attention.[3]

The major intermediate in our work was the chloronitrile IV, prepared by alkylating the appropriate benzyl cyanide with sodamide and an alkyl bromide, then treating the product III with more sodamide and 1,2-dichloroethane. Reduction of the chloronitrile IV with lithium aluminum hydride gave, in excellent yield, the 3,3-disubstituted pyrrolidine V. Other chemical reducing agents found to be inactive were potassium borohydride–aluminum chloride in ether, stannous chloride, sodium metabisulfite, and thiourea dioxide. Catalytic hydrogenation followed by cyclization was also unsuccessful. Probably the nitrile group is so hindered that reductive dehalogenation precedes reduction of the nitrile.



To prepare the 2-substituted pyrrolidines, the chloronitrile IV was allowed to react with a Grignard reagent in dibutyl ether when, on boiling, the Grignard complex VI cyclized spontaneously to the pyrroline VII.[4] It was found preferable to isolate the pyrroline at this stage, even if only in an impure state, then reduce with lithium aluminum hydride to the pyrrolidine VIII rather than add the crude reaction mixture directly to the hydride. Catalytic hydrogenation with a variety of catalysts (Raney nickel alone and with ammonia,

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(2) J. F. Cavalla, R. Jones, M. Welford, J. Wax, and C. V. Winder, *ibid.*, **7**, 412 (1964).

(3) P. J. A. Demoen and P. A. J. Janssen, *J. Am. Chem. Soc.*, **81**, 6281 (1959).

(4) L. C. Craig, H. Balbrook, and R. M. Hixon, *ibid.*, **53**, 1831 (1931).