3-Alkyl-3-phenylpiperidine Derivatives as Analgesics

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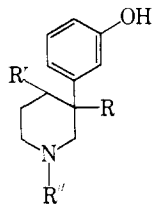
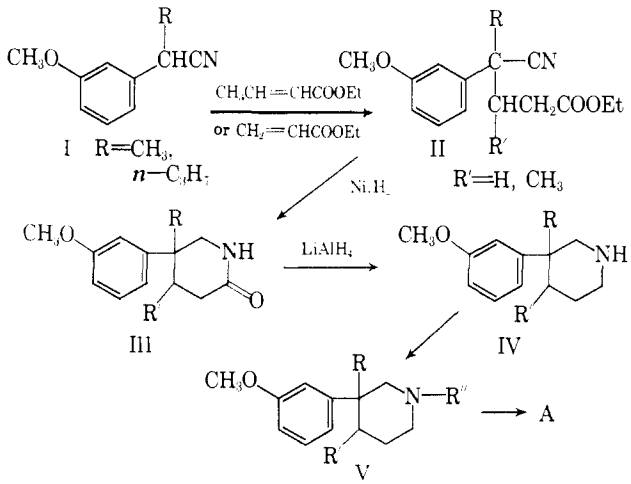
Certain N-substituted 3-alkyl-3-(3-hydroxyphenyl)piperidines and their 4-methyl analogs have been synthesized. The effect on analgesic activity of some modifications on the nitrogen atom, and of the 4-methyl group, was examined.

A recent paper from this laboratory described the synthesis of 1-methyl-3-(3-hydroxyphenyl)-3-methyl-(and ethyl)-piperidines[1] (A, R = CH_3, C_2H_5; R′ = H; R″ = CH_3). In view of the known analgesic activity in mice of the 3-methyl derivative, we undertook the study of certain derivatives of this class of compounds.[2] This paper presents the synthesis and pharmacological study of 1-substituted-3-alkyl-3-(3-hydroxyphenyl)-piperidines and their 4-methyl analogs (A).



A

Chemistry.—The synthesis of 3-alkyl-3-(3-methoxyphenyl)piperidines (IV, R′ = H) followed the reaction sequence and procedures given in the previous report.[1] Reaction of the phenylacetonitriles (I) with ethyl crotonate gave the 3-methyl-4-cyano esters (II, R′ = CH_3). Hydrogenation of II (R′ = CH_3) and



lithium aluminum hydride reduction of the lactams (III, R′ = CH_3) as in the demethyl series afforded the 4-methyl analogs (IV, R′ = CH_3). Introduction of substituents with various halides into IV was carried out in the usual way to give the N-substituted derivatives (V). Because of the *cis-trans* relationship between the 4-methyl and the 3-phenyl group, the 4-methyl derivatives (V, R′ = CH_3) afforded two stereoisomers in each case. The stereochemistry of the methyl group at C-4 in the isomers remains unknown. Tentatively, the designation of α-form to the salt with the higher melting point and β- to that having the lower melting point was made. Demethylation of V with 48% hydrobromic acid afforded the 3′-hydroxyphenyl derivatives (A). A number of N-substituted 3-alkyl-3-(3-methoxyphenyl)piperidines and 3-(3-hydroxyphenyl) derivatives thus synthesized are listed in Table I and II, respectively.

Pharmacology

Methods.—(1) **Analgesic Activity and Toxicity.**—Analgesic effect was measured by the hot-plate method.[3] ED_{50} values were calculated[4] from the pain reaction time of each group of 10 mice on the hot plate at 55°. LD_{50} values were calculated[4] from the mortality of groups of five mice 24 hr. after the subcutaneous administration of the compounds.

(2) **Antagonism Study.**—Groups of 5 to 10 male mice were given subcutaneously analgesic doses of drugs and N-allyl compounds at separate parts of the back. Pain response was tested by Haffner's method[5] 15, 30, 45, 60, and 75 min. after the injection.

(3) **Effect on Rectal Temperature of Rats and Mice** —Male rats weighing 200–250 g. which had a rectal body temperature between 36.7 and 38.5°, or male mice weighing 25 to 30 g. with a rectal body temperature of 37.1–38.7° were injected, subcutaneously, the test compounds dissolved in normal saline. The rectal body temperature was measured after the administration at intervals of 30 min.

(4) **Thiopental Potentiation.**—Groups of 10 mice each were given, subcutaneously, the test compounds in various doses 15 min. prior to the intravenous injection of 25 mg./kg. of thiopental sodium. Prolongation of the sleeping tie was compared with that of control animals.

(5) **Effects on Blood Pressure and Respiration** —A 2.5–3.0 kg. male rabbit was anesthetized with a subcutaneous injection of 1.2 g./kg. of urethane, and the blood pressure and respiration were recorded on a smoked paper by the usual methods. Saline solutions of the compounds were administered intravenously.

Results

The results listed in Table III reveal some structure–activity relationships. The analgesic effect of these derivatives is affected by the type of substituents at positions 1 and 3.

Of compounds **4–21**, the 3-methyl derivatives with a long-chain radical at position 1 exhibited a more potent effect than those with a short-chain radical at position 1, while in the 3-propyl derivatives a reversed structure–activity relationship was found with respect to the substituents at the 1-position. Methylation at position 4 decreased the analgesic effect of the parent compound.

(1) H. Kugita and T. Oine, *Chem. Pharm. Bull. Japan*, **11**, 253 (1963).

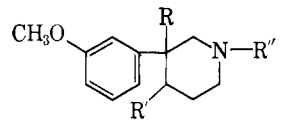
(2) The analogous 1,4-dialkyl-4-phenylpiperidines were prepared by S. M. McElvain and D. H. Clemens, *J. Am. Chem. Soc.*, **80**, 3915 (1958).

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

(4) C. S. Weil, *J. Biometric Soc.*, **8**, 249 (1952).

(5) F. Haffner, *Deut. Med. Wochschr.*, **55**, 731 (1929).

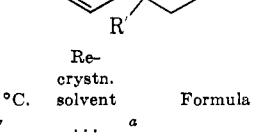
TABLE I



No.	R	R′	R″	Salt	M.p., °C.	Recrystn. solvent	Formula	% Carbon Calcd.	% Carbon Found	% Hydrogen Calcd.	% Hydrogen Found	% Nitrogen Calcd.	% Nitrogen Found
1	CH_3	H	CH_2=$CHCH_2$	HCl	149-150	*a*	$C_{16}H_{24}ClNO$	68.20	68.33	8.58	8.89	4.97	5.00
2	CH_3	H	$C_6H_5CH_2CH_2$	HCl	166–168	*b*	$C_{21}H_{28}ClNO$	72.91	72.76	8.16	8.09	4.08	4.19
3	CH_3	H	$C_6H_5COCH_2$	HBr	183–185	*c*	$C_{21}H_{26}BrNO_2$	62.37	62.31	6.48	6.61	3.46	3.98
4	*n*-C_3H_7	H	CH_3	HBr	203–204	*d*	$C_{16}H_{26}BrNO$	58.53	58.62	7.88	7.73	4.27	4.52
5	*n*-C_3H_7	H	CH_2=$CHCH_2$	HBr	164–165	*a*	$C_{18}H_{28}BrNO$	61.01	61.00	7.96	7.80	3.95	4.02
6	*n*-C_3H_7	H	$C_6H_5CH_2CH_2$	HBr	179–181	*b*	$C_{23}H_{32}BrNO$	66.02	66.04	7.71	7.57	3.34	3.40
7	*n*-C_3H_7	H	$C_6H_5COCH_2$	HBr	177–179	*c*	$C_{23}H_{30}BrNO_2$	63.88	64.11	6.99	7.07	3.24	3.31
8	CH_3	CH_3 (α)	CH_3	HCl	266–268	*d*	$C_{15}H_{24}ClNO$	66.77	66.53	8.97	8.69	5.19	5.23
9	CH_3	CH_3 (β)	CH_3	HCl	234–235	*e*	$C_{15}H_{24}ClNO$	66.77	66.92	8.97	8.85	5.19	5.26
10	*n*-C_3H_7	CH_3 (α)	CH_3	HBr	208–210	*d*	$C_{17}H_{28}BrNO$	59.64	59.39	8.24	8.03	4.32	4.41
11	*n*-C_3H_7	CH_3(β)	CH_3	HBr	183–188	*a*	$C_{17}H_{28}BrNO$	59.64	59.93	8.24	7.95	4.32	4.29
12	*n*-C_3H_7	CH_3(α)	$C_6H_5CH_2CH_2$	HCl	209–211	*b*	$C_{24}H_{34}ClNO$	74.29	74.16	8.84	8.81	3.61	3.65
13	*n*-C_3H_7	CH_3(β)	$C_6H_5CH_2CH_2$	HCl	169–171	*a*	$C_{24}H_{34}ClNO$	74.29	73.90	8.84	8.92	3.61	3.69

[a] Acetone–ether. [b] Acetone. [c] Acetone–ethanol–ether. [d] Ethyl acetate–ethanol. [e] Ethyl acetate–ethanol–ether.

TABLE II



No.	R	R′	R″	Salt	M.p., °C.	Recrystn. solvent	Formula	% Carbon Calcd.	% Carbon Found	% Hydrogen Calcd.	% Hydrogen Found	% Nitrogen Calcd.	% Nitrogen Found
14	CH_3	H	CH_3	HBr	215–217	...	[a]						
15	CH_3	H	CH_2=$CHCH_2$	HCl	170–173	*b*	$C_{18}H_{22}ClNO$	67.27	67.06	7.28	8.21	5.22	5.18
16	CH_3	H	$C_6H_5CH_2CH_2$	$(COOH)_2$	138–142	*c*	$C_{22}H_{27}NO_5$	68.55	68.84	7.06	7.35	3.63	4.24
17	CH_3	H	$C_6H_5COCH_2$	HCl	227–229	*b*	$C_{20}H_{24}ClNO_2$	69.45	69.45	6.99	7.03	4.04	4.08
18	C_2H_5	H	CH_3	HCl	223–225	...	[a]						
19	*n*-C_3H_7	H	CH_3	HCl	222–224	*b*	$C_{16}H_{24}ClNO$	66.76	66.88	8.97	8.83	5.19	5.37
20	*n*-C_3H_7	H	CH_2=$CHCH_2$	HCl	158–160 dec.	*d*	$C_{17}H_{26}ClNO \cdot 0.5H_2O$	66.97	67.22	8.92	8.81	4.59	4.72
21	*n*-C_3H_7	H	$C_6H_5CH_2CH_2$	HCl	181–183	*b*	$C_{22}H_{30}ClNO$	73.41	72.86	8.40	8.29	3.89	4.02
22	CH_3	CH_3 (α)[g]	CH_3	HCl	259–260	*b*	$C_{14}H_{22}ClNO$	65.73	65.77	8.67	8.47	5.48	5.48
23	CH_3	CH_3 (β)	CH_3	HCl	199–200	*b*	$C_{14}H_{22}ClNO$	65.73	65.45	8.67	8.77	5.48	5.51
24	*n*-C_3H_7	CH_3 (α)	CH_3	HCl	129–130 dec.	*b*	$C_{16}H_{27}ClNO \cdot H_2O$	63.66	64.28	9.35	9.62	4.64	4.50
25	*n*-C_3H_7	CH_3 (β)	CH_3	HCl	270–274	*e*	$C_{16}H_{27}ClNO$	67.70	67.55	9.23	8.84	4.94	4.94
26	*n*-C_3H_7	CH_3 (α)	$C_6H_5CH_2CH_2$	HCl	232–235	*f*	$C_{23}H_{32}ClNO$	67.38	73.29	8.63	8.67	3.75	3.70
27	*n*-C_3H_7	CH_3 (β)	$C_6H_5CH_2CH_2$	$(COOH)_2$	191–193 dec.	*c*	$C_{25}H_{33}NO_5 \cdot H_2O$	69.90	69.61	8.21	7.85	3.26	3.43

[a] See ref. 1. [b] Acetone–ethanol–ether. [c] Ethanol. [d] Ethyl acetate–ethanol. [e] Ethanol–ether. [f] Ethanol–acetone. [g] The isomers (**22–27**) were assigned α and β so as to parallel the preceding methoxy derivatives.

Elimination of the 3-hydroxyl group diminished the activity. The highest analgesic activity of this series of compounds was observed with **17**. Its activity was equal to that of meperidine and twice that of codeine, but the duration of its activity was shorter than that of codeine or morphine. Compounds of comparatively high potency produced the Straub reaction, mydriasis, and the increase in spontaneous activity and muscle tone (Table III).

The analgesic effect of **17** and morphine was antagonized by the simultaneous injection of nalorphine or **15** in 0.2–0.1 the dose of both analgesic drugs. This observation seems to be interesting in view of the reported failure of N-allylnormeperidine to produce antagonism.[6] However, **20** did not antagonize, but enhanced the effect of both drugs. This is probably due to an analgesic activity of its own.

A subcutaneous injection of **17**, **19**, **20**, and **16** decreased the rectal body temperature of mice and caused a rise of the rectal body temperature of rats. The effects of these compounds were weaker than that of morphine (Fig. 1).

(6) P. J. Costa, and D. D. Bonnycastle, *J. Pharmacol. Exptl. Therap.*, **113**, 310 (1955).

When administered 15 min. prior to the injection of thiopental sodium, **17** increased the effect of the barbiturate more than morphine did (Table V).

The intravenous administration of **17** to rabbits caused depression of respiratory frequency in doses greater than 0.5 mg./kg. Two mg./kg. of **17** produced respiratory depression and a temporary fall of carotid blood pressure (about 25–30 mm.) for **1** min. followed by continuous rise (about 20–25 mm.) for 6 min. This effect was the same as that of morphine.

Experimental[7]

Ethyl 3-Methyl-4-cyano-4-(3-methoxyphenyl)pentanoate (II, **R** = CH_3, **R′** = CH_3).—To a solution of sodium (1.45 g.) in ethanol (26.5 ml.) was added over a period of 20 min. a mixture of 2-(3-methoxyphenyl)propionitrile (I, R = CH_3) (10 g.) and ethyl crotonate (8.1 g.) at 25–29°. The mixture was refluxed for 10 hr., then neutralized with dilute acetic acid and extracted with ether. Evaporation of ether and distillation of the residue gave a colorless liquid, b.p. 156–158° (0.7 mm.); yield, 11 g. (64.5%).

Anal. Calcd. for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.76; H, 7.40; N, 5.20.

Ethyl 3-*n*-Propyl-4-cyano-4-(3-methoxyphenyl)pentanoate (II, **R** = *n*-C_3H_7, **R′** = CH_3).—Reaction of I (R = *n*-C_3H_7) with

(7) Melting points are corrected.

TABLE III

ANALGESIC EFFECT AND TOXICITY OF 3-ALKYL-3-PHENYLPIPERIDINE DERIVATIVES IN MICE (SUBCUTANEOUS INJECTION)

Compd.	Analgesic ED_{50}, mg./kg.	Toxicity LD_{50}, mg./kg.	LD_{50}/ED_{50}	Symptoms to dose: Dose, mg./kg.	Observation
14	50.6	367.4	7.2	100	*a*
15	*ca.* 60	265.0	4.4	100	*b, c*
16	24.4	207.7	8.5	100	*b, d, c*
17	12.1	368.0	30.4	100	*b, d, f, g*
18	*ca.* 100	175.0	1.7	100	*b, d*
19	24.0	137.5	5.6	100	*d, f*
20	22.5	175.3	7.8	100	*b, f, b*
21	53.2	450.0	*ca.* 10.0	300	*d, f, c*
22	None	225.0	...	100	*g*
23	*ca.* 66	137.0	2.0	100	*b*
24	None	...	...	100	*f, c, a*
25	None	265.0	...		
26	138.0	265.0	1.9	100	*d*
27	104.0	208.1	2.0	100	*i, c*
Meperidine	12.5	273.5	21.9		Not observed.
Codeine	24.3	231.2	9.5		

[a] Salivation. [b] Straubtail. [c] ↓ Spontaneous activity. [d] ↑ Spontaneous activity. [e] Tremor. [f] Mydriasis. [g] ↑ Muscle tone. [h] Convulsion. [i] ↓ Muscle tone.

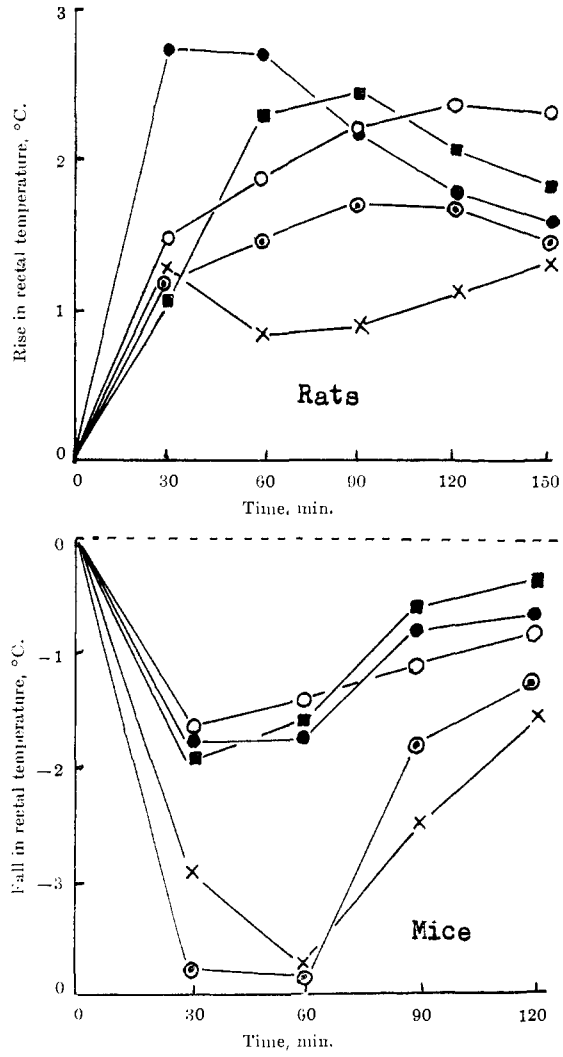


Fig. 1.—The effects of morphine and 3-phenylpiperidine derivatives on the rectal temperature of rats and mice; ×, 16; ⊙, 17; ○, 19; ●, 20; ■, morphine.

ethyl crotonate as mentioned previously gave 60.5% yield of II (R = *n*-C_3H_7, R′ = CH_3), colorless liquid, b.p. 148–149° (0.4 mm.).

Anal. Calcd. for $C_{18}H_{25}NO_3$: C, 71.25; H, 8.31; N, 4.62. Found: C, 71.22; H, 8.10; N, 4.63.

TABLE IV

EFFECT OF THE N-ALLYL DERIVATIVES AND NALORPHINE ON THE ANALGESIC EFFECT OF COMPOUND 17 AND MORPHINE

Antagonist added	Antagonist dosage, mg./kg.	% Animals in analgesia: 15 min.	30 min.	45 min.	60 min.	90 min.	120 min.
Compound 17 (80 mg./kg.)							
None	...	100	100	20	20	5	0
N-allyl 15	16	0	0	0	0	0	0
	8	10	40	40	15	0	0
N-allyl 20	16	100	100	60	40	10	0
	8	100	100	80	40	5	0
Nalorphine	16	0	0	0	0	0	0
	8	0	0	0	0	0	0
Morphine (20 mg./kg.)							
None	...	40	80	70	60	40	10
N-allyl 15	4	0	0	0	10	10	0
	2	0	0	0	20	10	0
N-allyl 20	4	40	90	80	70	40	10
	2	30	80	70	60	40	10
Nalorphine	4	0	0	0	0	0	0
	2	0	0	0	0	0	0

TABLE V

THE EFFECT OF 17 AND MORPHINE ON THE SLEEPING TIMES OF MICE TREATED WITH THIOPENTAL (25 MG./KG.)

Compound added	Dosage, mg./kg.	Sleeping time, sec.
None	...	152.0 ± 17.2
17	2.5	194.8 ± 23.0
	5.0	396.4 ± 48.1
	10.0	1395.0 ± 112.3
Morphine	10.0	185.1 ± 35.0
	20.0	223.7 ± 56.1
	40.0	374.1 ± 65.2

2-Oxo-(3-methoxyphenyl)-3,4-dimethylpiperidine (III, R = R′ = CH_3).—II (R = R′ = CH_3) (10 g.) was dissolved in 10% ethanolic ammonia (52 ml.) and hydrogenated in an autoclave with Raney nickel as catalyst. Absorption of hydrogen took place at 150–160°. The catalyst was removed by filtration and the solvent was distilled. A small portion of ether was added to the crystalline residue and insoluble material was filtered yielding 3.5 g. Recrystallization from ligroin–ethyl acetate gave an analytical sample, colorless needles, m.p. 146.5–148.5°.

Anal. Calcd. for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 71.97; H, 8.01; N, 5.91.

The ethereal filtrate was evaporated to give an isomer (3 g.), m.p. 101–105°; analytical sample crystallized from ligroin, m.p. 106–109°.

Anal. Calcd. for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 71.75; H, 8.14; N, 6.03.

Hydrogenation of II (R = n-C_3H_7, R′ = CH_3) (24.2 g.) by the previously described method yielded a mixture of two isomers (21 g.) which failed to crystallize and was used in the crude state in the next step.

3-Alkyl-3-(3-methoxyphenyl)-4-methylpiperidines (IV). (**R = R′ = CH_3**).—A solution of III (R = R′ = CH_3, m.p. 146.5–148.5°) (3.5 g) in dioxane (38 ml.) was added dropwise to a solution of lithium aluminum hydride (1.7 g.) in ether (85 ml.) and refluxed for 22 hr. The reaction mixture was worked up in the usual way to give a colorless liquid, b.p. 147–149° (1 mm.); yield, 2.3 g. (70%); hydrochloride, colorless rectangles (ethanol–ether), m.p. 184–185°.

Anal. Calcd. for $C_{14}H_{21}NO \cdot HCl$: C, 65.73; H, 8.67; N, 5.48. Found: C, 65.81; H, 8.48; N, 5.48.

Reduction of III (R = R′ = CH_3, m.p. 106–109°) as above yielded 2.1 g. (80%) of colorless liquid, b.p. 150–152° (1 mm.); hydrochloride, colorless needles (ethanol–ether), m.p. 182–183°.

Anal. Calcd. for $C_{14}H_{21}NO \cdot HCl$: C, 65.73; H, 8.67; N, 5.48. Found: C, 65.57; H, 8.60; N, 5.58.

R = n-C_3H_7, R′ = CH_3.—A solution of III (R = n-C_3H_7, R′ = CH_3, mixture of isomers) (21 g.) in dioxane (150 ml.) was reduced with lithium aluminum hydride (9 g.) in ether (450 ml.) as previously mentioned. A colorless liquid, b.p. 152–154° (1 mm.) was obtained; yield, 11.6 g. The hydrochloride, hydrobromide, and picrate all failed to crystallize. The oxalate crystallized after standing for 1 week and this apparently consisted of two different salts, one of which was separated in analytically pure form after repeated recrystallizations; colorless needles (ethanol–ether), m.p. 180–182°.

Anal. Calcd. for $C_{16}H_{20}NO \cdot C_2H_2O_4$: C, 64.07 H, 8.06; N, 4.15. Found: C, 63.79; H, 7.94; N, 4.56.

3-(3-Methoxyphenyl)-3-propylpiperidine (IV, R = n-C_3H_7, R′ = H).—The synthesis of this compound followed the reaction sequence employed in the synthesis of the 3-methyl and 3-ethyl analogs.[1] Starting material was 2-(3-methoxyphenyl)valeronitrile (I, R = n-C_3H_7). The picrate gave yellow needles from benzene, m.p. 129.5–131°.

Anal. Calcd. for $C_{21}H_{26}N_4O_8$: C, 54.54; H, 5.67; N, 12.12. Found: C, 54.49; H, 5.51; N, 11.59.

N-Substitution of IV. Synthesis of V (R″ = CH_3) (Table I, 4, 8, 9, 10, and 11).—As a representative example, the synthesis of 1-methyl-3-(3-methoxyphenyl)-3-n-propylpiperidine (Table I, **4**) is presented.

A mixture of IV (R = n-C_3H_7, R′ = H) (2.0 g.), 37% formalin (0.86 ml.), and 50% ethanol (40 ml.) was warmed in a water bath at 50–60° for 30 min., then hydrogenated with 10% Pd–C as catalyst. Hydrogen (210 ml.) was absorbed. The catalyst was filtered, the filtrate was concentrated, extracted with ether, and dried. The ethereal solution was treated with 22% hydrogen chloride–methanol, the hydrochloride was filtered and recrystallized from ethyl acetate–ethanol to give colorless plates (2.0 g.), m.p. 203–204° (Table I, 4).

R″ = CH_2=$CHCH_2$ (Table I, 1, 5).—The general procedure is illustrated as follows: A mixture of IV (R = CH_3, R′ = H)[1] (2.0 g.) allyl bromide (1.2 g.), potassium carbonate (1.5 g.), and acetone (30 ml.) was refluxed for 9 hr., inorganic material was filtered, the solvent was distilled, and acetic anhydride (1 ml.) was added to the residue. After heating in a water bath for 1 hr. the mixture was poured into water, made basic with potassium carbonate, and extracted with ether. The ethereal solution was extracted with 5% hydrochloric acid, made basic with potassium carbonate, and extracted with ether. Evaporation of the ether and distillation of the residue gave 1.8 g. (80%) of colorless liquid, b.p. 168° (2 mm.); hydrochloride, colorless plates (acetone–ether), m.p. 149–150° (Table I, 1).

R″ = $C_6H_5COCH_2$ (Table I, 3, 7).—A mixture of IV (R = CH_3, R′ = H) (2 g.), phenacyl bromide (2 g.), potassium carbonate (1.5 g.), and ethanol (30 ml.) was refluxed for 2 hr. in a water bath. The solvent was distilled, water was added to the residue, and the separated base was extracted with ether and dried. The ethereal solution was treated with 26% ethanolic hydrogen bromide. The hydrobromide was filtered and recrystallized from acetone–ethanol–ether as colorless needles, m.p. 183–185°; yield, 2.5 g. (Table I, **3**).

R″ = $C_6H_5CH_2CH_2$ (Table I, 2, 6, 12, 13).—To a stirred mixture of IV (R = CH_3, R′ = H) (2.0 g.), potassium carbonate (2.0 g.), methanol (35 ml.), and water (10 ml.) was added dropwise, at 5–10°, phenylacetyl chloride (2.0 g.). The mixture was stirred at that temperature for 30 min., then at room temperature for 1.5 hr. The methanol was distilled under reduced pressure and the separated oil was extracted with ether. The extract was washed with dilute hydrochloric acid, aqueous sodium bicarbonate, and water, dried and evaporated. The crude N-phenylacetyl derivative (3.3 g.), was added to a solution of lithium aluminium hydride (1.5 g.) in ether (80 ml.) and refluxed for 15 hr. Working up in the usual way yielded an oily base (2.9 g.) which was converted to the hydrochloride. Recrystallization of the salt from acetone gave colorless prisms, m.p. 166–168°; yield, 3.0 g. (Table I, **2**). The procedure described here applied to the synthesis of other N-phenethyl derivatives listed in Table I.

In the manner illustrated, IV (R = n-C_3H_7, R′ = CH_3, mixture of two isomers) gave two products when an appropriate salt of the N-substituted derivative was recrystallized from an appropriate solvent system. The higher melting isomer separated first from the solution, and the lower melting isomer was obtained from the mother liquor by concentration. Analytical data confirmed the isomerism. Tentatively, α was assigned to the higher melting isomer, and β to the lower melting one.

Synthesis of A (Table II).—The 3-methoxyphenyl derivatives (V) were refluxed with 48% hydrobromic acid for 20–40 min. The hydrobromic acid was distilled under reduced pressure, and the residue was dissolved in water, made basic with aqueous ammonia, extracted with appropriate solvents, dried, and evaporated. The crude base was converted to the salt and recrystallized.

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