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3,5-Propanopiperidine Derivatives as Potential Analgesics

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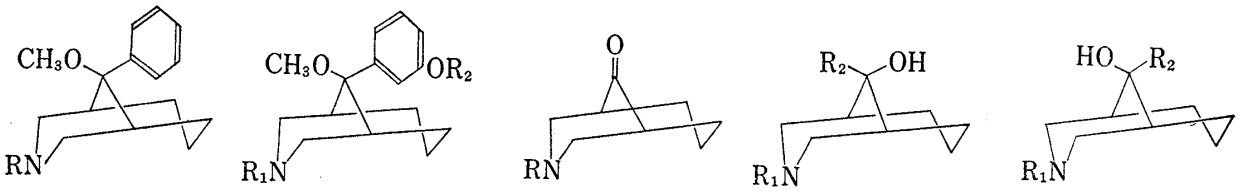
4β-Methoxy-4α-phenyl-3α,5α-propanopiperidine derivatives were prepared and tested biologically. Introduction of a *m*-hydroxy substituent into the phenyl group of these derivatives results in radical potentiation of analgesic and antitussive activities. Also, some N-carbamates of these derivatives exhibit appreciable anti-inflammatory effects with analgesic activity.

In a previous paper of this series,[2] we reported that 4-alkoxy-4-phenylpiperidine derivatives with a trimethylene bridge between the 3 and 5 positions of the piperidine ring exhibited promising analgesic activities and one of the more potent derivatives, 4β-methoxy-1-methyl-4α-phenyl-3α,5α-propanopiperidine (**1a**), was selected for extensive pharmacological tests[3] and clinical trials. This paper also describes a supplementary study in this series.

As previously shown among many modifications of the structure of **1a**,[2] and introduction of *p*-substituents into the phenyl ring of **1a** resulted in lowering of analgesic potency. On the other hand, it is known that a phenolic hydroxyl group at the *m*-position is an important



1a,b **2a–f** **3a,b** **4a–d** **5a–d**

1a: R=CH_3
1b: R=CH_2CH_2-

3a: R=CH_3
3b: R=CH_2CH_2-

2a: R_1=CH_3 R_2=H
2b: R_1=CH_3 R_2=CH_3
2c: R_1=CH_2CH_2- R_2=H
2d: R_1=CH_2CH_2- R_2=CH_3
2e: R_1=$COOCH_2CCl_3$ R_2=CH_3
2f: R_1=H R_2=CH_3

4a: R_1=CH_3 R_2=-OCH_2OCH_3
4b: R_1=CH_3 R_2=-OCH_3
4c: R_1=CH_2CH_2- R_2=-
4d: R_1=CH_2CH_2- R_2=-OCH_3

5a: R_1=CH_3 R_2=-OCH_2OCH_3
5b: R_1=CH_3 R_2=-OCH_3
5c: R_1=CH_2CH_2- R_2=-
5d: R_1=CH_2CH_2- R_2=-OCH_3

Chart 1

1) Location: *Hiromachi, Shinagawa-ku, Tokyo.*
2) E. Ohki, S. Oida, Y. Ohashi, H. Takagi, and I. Iwai, *Chem. Pharm. Bull.* (Tokyo), **18**, 2050 (1970).
3) S. Kobayashi, K. Hasegawa, T. Ohshima, and H. Takagi, *Toxicol. Appl. Pharmacol.*, **17**, 344 (1970).

feature of analgesics based on morphine, morphinan and benzomorphan; consequently, a synthesis of the *m*-hydroxy analog of **1a** (**2a**) was undertaken with expectation of obtaining a high-potent analgesic.

Treatment of 1-methyl-3,5-propanopiperidone-4[4] (**3a**) with the Grignard reagent prepared from 3-bromo-1-methoxymethoxy-benzene gave an isomeric mixture of 4-piperidinol derivatives (**4a** and **5a**) whose etherification with acidic methanol yielded the desired compound (**2a**), mp 158—160°, along with removal of the protecting group. Alternately, **2a** was also synthesized by treatment of **3a** with *m*-methoxyphenylmagnesium bromide, successive treatment of the formed piperidinols (**4b** and **5b**) in acidic methanol and demethylation of the resulting methyl ether of **2a** (**2b**) in the presence of thioethoxide.[5] As discussed in our preceding paper,[2] this acid-catalysed etherification proceeds stereospecifically and the resulting ethers (**2a** and **2b**) have a 4β-methoxy-4α-phenyl configuration. This was suggested by their nuclear magnetic resonance spectra (NMR) by consideration of the House's illustration[4] wherein the N-methyl proton signal in the 4β-hydroxy-4α-phenyl compounds falls at 2.20—2.24 ppm and that of the 4α-hydroxy-4β-phenyl isomers shifts to a higher field by about 0.2 ppm under the influence of the benzene ring current. Activities of these *m*-hydroxy analogs (**2a** and **2b**) will be discussed later.

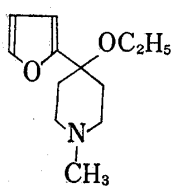
In the preceding paper,[2] we also reported that an N-(β-phenylethyl) analog of **1a** (**1b**) was shown to be highly potent as compared to the parent compound (**1a**) (See Table I). Accordingly, we next conducted the synthesis of the corresponding *m*-hydroxy analog of **1b** (**2c**).

Similar to the preparation of the N-methyl ketone (**3a**),[4] treatment of β-phenylethylamine with cyclohexanone and formalin gave 1-(β-phenylethyl)-3,5-propano-4-piperidone (**3b**), mp 45—46°, which formed a crystalline *p*-toluenesulfonate, mp 204—207°. Prior to the synthesis of the objective compound (**2c**), an alternate synthesis of the parent compound (**1b**) from **3b** was attempted, since the reported procedure[2] for **1b** including the replacement of the N-methyl group of the parent compound (**1a**) has too many steps to prepare the material in quantity.

Treatment of the piperidone (**3b**) obtained as above with phenyllithium yielded a phenylpiperidinol (**4c**), mp 82—83°, along with a small amount of its isomer (**5c**), mp 108°. The former piperidinol (**4c**) was easily isomerized into the latter (**5c**) with acid. Treatment of **4c** with acidic methanol gave 4β-methoxy-4α-phenylpiperidine (**1b**), whose structure is well-established.[2] These results were just parallel with the case of the N-methyl series described previously.[2] This suggests that the piperidinol (**4c**) has a 4α-hydroxy configuration and the 4β-hydroxy isomer (**5c**) is predominant in acidic medium due to hydrogen bonding between nitrogen and hydroxy group.[2,4]

In the same way, treatment of the N-phenylethylketone (**3b**) with 3-methoxyphenylmagnesium bromide gave 4α-hydroxypiperidine (**4d**) as a syrup, along with a small amount of 4β-hydroxypiperidine (**5d**), mp 83—84°. The former (**4d**) was also isomerized into **5d** on treatment with acid. Refluxing **4d** in acidic methanol afforded 4β-methoxypiperidine (**2d**) as a syrup whose demethylation with thioethoxide gave the desired *m*-hydroxy analog (**2c**), mp 119°. The 4β-methoxy structures of **2c** and **2d** thus obtained were also synthetically confirmed by the replacement of the N-methyl group of the parent compound (**2b**) in the following way. On treatment with β,β,β-trichloroethyl chloroformate, **2b** was converted into 1-(β,β,β-trichloroethoxycarbonyl)piperidine (**2e**). Removal of the N-substituent of **2e** was carried out with zinc in methanol and the resulting secondary amine (**2f**) was alkylated with β-phenylethylbromide to give **2d**.

4) H.O. House and W.M. Bryant, III, *J. Org. Chem.*, **30**, 3623 (1965).
5) G.I. Feutrill and R.N. Mirrington, *Tetrahedron Letters*, **1970**, 1327.



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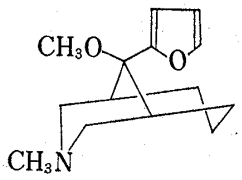

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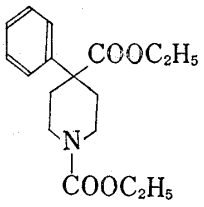

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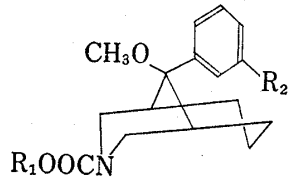


9a—f

9a: $R_1=CH_3$ $R_2=H$
9b: $R_1=CH_2CH_3$ $R_2=H$
9c: $R_1=CH(CH_3)_2$ $R_2=H$
9d: $R_1=CH_2CH_2CH_2CH_3$ $R_2=H$
9e: $R_1=$ $R_2=H$
9f: $R_1=CH_2CH_3$ $R_2=OCH_3$

Chart 2

Additionally, we attempted an isosteric replacement of the phenyl group of the parent compound (**1a**) with a 2-furyl group on the basis that Beckett, *et al.*[6] reported the high activity of a 2-furyl derivative like **6** as an analog of meperidine. Treatment of the N-methyl ketone (**3a**) with furyllithium followed by treatment with acidic methanol gave a syrupy methoxypiperidine (**7**) which formed a crystalline citrate, mp 185—188° (decomp.). The assignment of the 4β-methoxy structure as shown in the chart is tentative and based on analogous examples.

Considering the hypothesis that a N-demethylation metabolic process of meperidine into normeperidine has an important pharmacologic significance in analgesic action, Kupchan, *et al.*[7] prepared some labile amides of normeperidine and reported a potential activity of its ethylcarbamate (**8**). Consequently, we also synthesized the corresponding analogs (**9a, b, c, d, e, f**) in this series by treatment of the parent compound (**1a** or **2b**) with several chloroformates and submitted to these pharmacological tests.

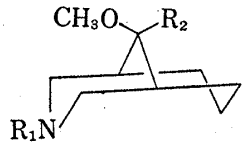
Pharmacological Evaluation

These *m*-hydroxy analogs (**2a** and **2c**) and their methyl ethers (**2b** and **2d**) thus synthesized were assayed by the Haffner's tail pinch method[8] for analgesic activity and by the method of Takagi, *et al.*[10] for antitussive action. These materials were administrated subcutaneously as their hydrogen citrates (in 0.85% saline solution). The results are illustrated in Table I along with the acute toxicities[11] in comparison with the corresponding data of morphine hydrochloride and codeine phosphate.

6) A.H. Beckett, A.F. Casy, and P.M. Phillips, *J. Med. Pharm. Chem.*, **2**, 245 (1960); A.F. Casy, A.H. Bekett, G.H. Hall, and P.K. Vallance, *ibid.*, **4**, 535 (1961).
7) S.M. Kupchan and A.C. Isenberg, *J. Med. Chem.*, **10**, 960 (1967).
8) The analgesic effect was measured by the method of Haffner (F. Haffner, *Deut. Med. Wochschr.*, **55**, 731 (1929)). Male mice of ddY strain weighing about 20 g were used. The criterion for analgesia was the absence of an attempt of the animal to bite a bulldog artery clip when applied for 10 sec to the base of the tail. The animals were selected prior to the test on the basis of making repeated attempts to bite the clip within 5 sec. Analgesic effects were determined 15—30 min after drug injection.[9]
9) ED_{50} and LD_{50} shown in the tables were calculated by the method of Litchfield and Wilcoxon (J.T. Litchfield and F. Wilcoxon, *J. Pharmacol. Exp. Therap.*, **96**, 99 (1949)).
10) The antitussive activity was tested by the method of Takagi, *et al.* (K. Takagi, H. Fukuda, and K. Yano, *Yakugaku Zasshi*, **80**, 1497 (1960)) in guinea pigs weighing 250—350 g. A guinea pig was anesthetized by an intraperitoneal injection of 15 mg/kg of sodium pentobarbital and fixed in a dorsal position. The trachea was exposed and a small incision was made at a distance of 1.5 cm from the clavicle. A stimulating hair was inserted into the incision as deep as 3 cm. The stimuli were applied two times before, and 15, 30, 45, 60, 90, and 120 min after drug administration. When no coughing occurred in 3 or more out of 12 trials after dosage, the dose was considered effective.[9]
11) Acute toxicity was determined in ddY strain mice weighing about 20 g. Five animals were used at each dose level. The Materials were administered subcutaneously and mortality was recorded 1 week later.[9]

In the case of the N-methyl series, the *m*-hydroxy analog (**2a**) and its methyl ether (**2b**) were found to be about 400 times and 35 times as active as the parent compound (**1a**) respectively. This fact also indicates the importance of the *m*-hydroxy function whose removal

Table I. Analgesic and Antitussive Effects of N-Alkyl-3,5-propanopiperidine Derivatives



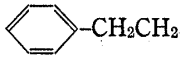
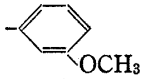
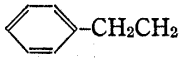
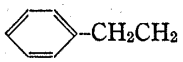
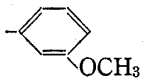
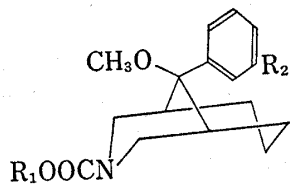
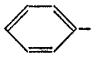
Substance	R_1	R_2	Analgesic activity ED_{50} mg/kg,*s.c.*	Antitussive activity ED_{50} mg/kg,*s.c.*	Acute toxicity LD_{50} mg/kg,*s.c.*
1a	CH_3		4.1	8.1	200
1b			1.25	0.65	>400
2a	CH_3		0.01	0.01	88
2b	CH_3		0.12	0.34	39
2c			0.003	0.001	200
2d			0.12	0.16	>200
7	CH_3		9.5	59.0	>200
Morphine hydrochloride			5.0	6.0	560
Codeine phosphate			25.0	13.5	275

Table II. Analgesic and Anti-inflammatory Effects of N-Alkoxycarbonyl-3,5-propanopiperidine Derivatives



Substance	R_1	R_2	Analgesic activity ED_{50} mg/kg, *p.o.*	Anti-inflammatory activity		Acute toxicity LD_{50} mg/kg, *p.o.*
				Dose mg/kg *p.o.*	Inhibition %	
9a	CH_3	H	17.5	100	42.0	280
9b	CH_3CH_2	H	35.5	100	34.0	920
9c	$(CH_3)_2CH$	H	890.0	100	19.0	>1000
9d	$CH_3(CH_2)_3$	H	360.0	100	22.0	>1000
9e		H	500.0	100	12.0	>1000
9f	CH_3CH_2	OCH_3	94.0	100	7.0	470
Mefenamic acid			80.0	100	64.0	630
Aminopyrine			118.0	100	26.0	470

or masking by methylation results in a sharp fall in potency. Moreover, a faster onset and shorter duration of action was especially observed in the case of the *m*-hydroxy analog (**2a**). In addition, **2a** and its methyl ether (**2b**) exhibit highly potent antitussive activities, 1350 times and 40 times as active as codeine phosphate respectively. The *m*-hydroxy analog (**2c**) in the N-phenylethyl series also showed a strong analgesic activity which was more than 400 times active than that of the parent compound (**1b**). This activity almost corresponds to more than 1600 times of that of morphine hydrochloride. Also **2c** exhibits a strong antitussive action along with a low toxicity. The methyl ether of **2c** (**2d**) has the same potency either as an analgesic or as an antitussive action as the corresponding methyl ether (**2b**) in the N-methyl series, but with a lower toxicity. As shown in the case of **7** (See Table I), the replacement of the phenyl group with a furyl group in the parent compound (**1a**) did not result in an favorable enhancement of pharmacological activity. These compounds having a *m*-hydroxy group exhibit typical morphine-like symptoms, namely, Straub tails, mydriasis and constipation in mice.

Comparative bioassay of the N-alkylcarbamates (**9a, b, c, d, e, f**) synthesized as above was carried out in both analgesic[12] and anti-edema[13] activities in comparison with mefenamic acid and aminopyrine. These compounds were administered as a suspension or solution in olive oil orally. These results are shown in Table II along with their acute toxicities.[11] The analgesic effects of the methylcarbamate (**9a**) and of the ethylcarbamate (**9b**) were shown to be stronger than those of mefenamic acid and aminopyrine. The anti-inflammatory effects of these compounds were almost the same as that of aminopyrine, but less effective than that of mefenamic acid. The methylcarbamate (**9a**) was more toxic than either aminopyrine or mefenamic acid; and toxic symptoms produced by **9a** were excitation and tail-up reaction similar to that of morphine. The ethylcarbamate (**9b**) did not show these symptoms and was not antagonized by nalorphine. The higher analogs (**9c, d, e**) with isopropyl, butyl, or phenyl group have radically lower potencies than those of the methyl or ethyl derivative (**9a** or **9b**). As shown in the case of **9f**, the introduction of a methoxy group at the *m*-position of the phenyl group of **9b** did not result in any appreciable potentiation of the pharmacological activities.

Experimental

Melting points are not corrected. Infrared (IR) spectra were determined on a Perkin-Elmer Model 221 or Perkin-Elmer Infracord, and nuclear magnetic resonance spectra on a Varian A-60 spectrometer. The abbreviations used are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad.

3-Bromo-1-methoxymethoxybenzene——After being washed twice with *n*-hexane, 5.1 g of 50% NaH mineral oil suspension was suspended in 50 ml of dimethoxymethane and a solution of 17.5 g of bromophenol in 50 ml of dimethoxymethane was added dropwise with stirring and ice-cooling under N_2 atmosphere. After 30 min stirring, 9.0 g of chloromethyl methylether was added dropwise and the mixture was stirred further for 1 hr. The reaction mixture was poured into ice-water and extracted three times with benzene. The extract was dried and evaporated to give 20 g of 3-bromo-1-methoxymethoxybenzene as a colorless syrup, which was purified by distillation, bp_7 125—130°. IR $\nu_{max}^{liq.}$ cm^{-1}: 1500, 1578, 1478, 1155, 1000. NMR

12) Analgesic actions were determined by the acetic acid-induced writhing method in mice, following the method of Whittle (B.A. Whittle, *Brit. J. Pharmacol.*, 22, 246 (1964)). Five male mice, ddY strain, weighing 20 to 25 g were used at each dose level. At 30 min after oral administration of the test materials, 0.2 ml of a 0.6% acetic acid was injected intraperitoneally. Writhing was checked from 5 to 15 min after acetic acid injection.[9]

13) Anti-carrageenin edema effect was determined by the method of Winter, *et al.* (C.A. Winter, E.A. Risley, G.W. Nuss, *J. Pharmacol. Exp. Therap.*, **141**, 369 (1963)) using Wistar-Imamichi strain male rats weighing 120 to 150 g. Five animals were used per group. The test compounds were administered orally 30 min before injection of 0.5 mg of carrageenin suspended in 0.05 ml of 0.85% saline solution. The carrageenin was injected subcutaneously into the right hind paw. Paw edema was measured volumetrically just before and 3 hr after the injection of carrageenin. The mean % inhibition of edema formation as compared with that of the control group was calculated.

($CDCl_3$) δ ppm: 6.80—7.30 (4H, m), 5.05 (2H, s), 3.38 (3H, s). *Anal.* Calcd. for $C_8H_9O_2Br$: C, 44.27; H, 4.18; Br, 36.81. Found: C, 44.41; H, 4.18; Br, 36.73.

4α-Hydroxy-4β-(3′-methoxymethoxyphenyl)-1-methyl-3α,5α-propanopiperidine (4a) and Its Isomer (5a)—To a solution of 3-methoxymethoxyphenylmagnesium bromide prepared from 1.2 g of magnesium and 10 g of 3-bromo-1-methoxymethoxybenzene in 50 ml of ether in a usual manner was added dropwise a solution of 5 g of 1-methyl-3,5-propanopiperidone-4[4] (**3a**) in 30 ml of dry ether over a period of 30 min with stirring and cooling. After 30 min stirring, the mixture was decomposed by a careful addition of conc. ammonia. The ether layer was collected and the aqueous layer was extracted three times with ether. The combined organic layer and extracts were dried and evaporated, giving 8.3 g of a mixture of **4a** and **5a** as a syrup. IR $\nu_{max}^{liq.}$ cm^{-1}: 3430, 1600, 1487, 1239, 1150, 1076, 1026, 1003. NMR ($CDCl_3$) δ ppm: 6.80—7.32 (4H, m), 5.15 (2H, s), 3.47 (3H, s), 2.22 (3H, s), 1.83 (3H, s).

An analytical sample was not obtained and the crude product of these compounds was used for the next reaction.

4α-Hydroxy-4β-(3′-methoxyphenyl)-1-methyl-3α,5α-propanopiperidine (4b) and Its Isomer (5b)——To an ice-cold solution of *m*-methoxyphenylmagnesium bromide prepared from 6.3 g of magnesium and 48.4 g of *m*-bromoanisole in 230 ml of dry ether in a usual manner was added dropwise a solution of 31.6 g of the ketone (**3a**) in 150 ml of ether over a period of 1 hr with stirring. Then, the mixture was stirred for 1 hr at room temperature and poured into ice-water. The ether layer was collected and the aqueous layer was extracted with ether four times. The combined extracts were extracted with dil. H_2SO_4 and the extract was made alkaline with aq. NaOH and extracted again with ether. The extract was washed with H_2O and dried, then, evaporated to give 52.25 g of a mixture of **4b** and **5b** as a crude syrup. IR $\nu_{max}^{liq.}$ cm^{-1}: 3450, 1600, 1584, 1039, 708. NMR ($CDCl_3$) δ ppm: 2.00 and 2.23 (singlets, with areas of 2: 1, 3H), 3.80 (3H, s).

4β-Methoxy-4α-(3′-methoxyphenyl)-1-methyl-3α,5α-propanopiperidine (2b)——A mixture of 1.022 g of a crude mixture of **4b** and **5b** obtained as above, 40 ml of absolute MeOH and 4 ml of conc. H_2SO_4 was refluxed for 8 hr and, after being made basic by an addition of aq. ammonia, the mixture was concentrated and diluted with H_2O. The mixture was extracted with $CHCl_3$ three times and the combined extracts were washed with H_2O and dried. Removal of the solvent gave crystalline residue which were recrystallized from hexane to give 430 mg of **2b** as needles, mp 82—83°. The mother liquor from the recrystallization was concentrated and chromatographed over 40 g of alumina and fractions eluted with hexane–$CHCl_3$ (8:1, v/v) were evaporated to give 220 mg of the second crop, mp 80—82.5°. Total yield was 59%. IR ν_{max}^{Nujol} cm^{-1}: 1602, 1579, 1070, 792. NMR ($CDCl_3$) δ ppm: 7.55—6.75 (4H, m), 3.85 (3H, s), 2.28 (3H, s), 2.23 (3H, s). *Anal.* Calcd. for $C_{17}H_{25}O_2N$: C, 74.14; H, 9.15; N, 5.09. Found: C, 74.43; H, 9.23; N, 5.21.

The hydrogen citrate of **2b** was obtained as amorphous powder by adding a solution of an equivalent amount of citric acid in MeOH to a solution of **2b** in ether.

4β-Methoxy-4α-(3′-hydroxyphenyl)-1-methyl-3α,5α-propanopiperidine (2a)——(i) To a cooled solution of 10.0 g of a crude mixture of **4a** and **5a** in 200 ml of MeOH was added 30 ml of conc. H_2SO_4. The mixture was refluxed for 4 hr and the cooled mixture was diluted with ice-water and extracted with benzene after being made basic with Na_2CO_3 (solid). The extract was dried and evaporated to give 6.9 g of a crystalline mass which was recrystallized from benzene–hexane to give 3.0 g of **2a** as prisms, mp 158—160°. IR ν_{max}^{Nujol} cm^{-1}: 3280, 1601, 1500, 1466, 1445, 1280, 1217, 1058. NMR ($CDCl_3$) δ ppm: 6.05—7.40 (4H, m), 5.28 (1H, s), 2.83 (3H, s), 2.23 (3H, s). *Anal.* Calcd. for $C_{16}H_{23}O_2N$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.58; H, 8.77; N, 5.20.

The hydrogen citrate of **2a** was also obtained as amorphous powder.

(ii) A mixture of 212 mg of **2b**, 5 ml of dimethylformamide, and 400 mg of $NaSC_2H_5$ was refluxed for 2 hr under N_2 atmosphere and the cold mixture was poured into a mixture of $CHCl_3$ and H_2O. After neutralizing with 2 N HCl, the mixture was extracted with $CHCl_3$ three times. The combined extracts were dried and evaporated to give 196 mg of crystals which were recrystallized from hexane–benzene, giving 94 mg of **2a**, mp 158—160°, which was identified with the sample obtained as above by mixed mp and infrared spectrometry.

1-(β-Phenylethyl)-3,5-propano-4-piperidone (3b)——A mixture of 500 g of β-phenylethylamine, 350 ml of conc. HCl, 350 ml of cyclohexanone, 820 ml of 37% formalin, and 5000 ml of AcOH was heated on a steam bath for 1¾ hr and, after an addition of 350 ml of conc. HCl, the mixture was evaporated under a reduced pressure below 50°. The residue was diluted with a 2-fold amount of H_2O and washed with ether. The aqueous layer was made alkaline with Na_2CO_3 (solid) and extracted with $CHCl_3$ three times. The combined extracts were evaporated and diluted with 1000 ml of EtOH. To the alcoholic solution was added gradually 300 ml of Ac_2O and the mixture was left standing for 15 min, then, after addition of 350 ml of conc. HCl, the mixture was concentrated under a reduced pressure. The mixture was diluted again with a 2-fold volume of H_2O and washed with $CHCl_3$ and, after being made basic with Na_2CO_3 (solid), extracted with $CHCl_3$ three times. The combined extracts were dried and evaporated, and the residue was distilled to give 290 g of a syrup, $bp_{1,5}$ 160—180°, which crystallized on standing in a refrigerator. Trituration with acetone in a Dry-Ice bath and collection of the crystals gave 110 g of **3b**, mp 40—43°. The analytical sample was obtained by recrystallization from *n*-hexane as needles, mp 45—46°. IR ν_{max}^{Nujol} cm^{-1}: 1735, 1712, 1600, 1498, 1140,

743, 700. NMR ($CDCl_3$) δ ppm: 7.21 (5H, s), 3.3—1.0 (16H, m). *Anal.* Calcd. for $C_{16}H_{21}ON$: C, 78.97; H, 8.70; N, 5.76. Found: C, 78.65; H, 8.62; N, 5.79.

The mother liquor left by collection of the first crop was concentrated and dissolved in EtOH. To the solution was added in portions 35.0 g of *p*-toluenesulfonic acid and the precipitates obtained by dilution with ether were collected. Thus, 40 g of the *p*-toluenesulfonate, mp 204—207° (decomp.), were obtained. IR ν_{max}^{Nujol} cm^{-1}: 3300, 3090, 1600, 1225, 1180, 1121, 1080, 700, 683. *Anal.* Calcd. for $C_{23}H_{29}O_4NS \cdot 1/2H_2O$: C, 65.07; H, 7.12; N, 3.30; S, 7.55. Found: C, 65.04; H, 7.37; N, 3.28; S, 7.54.

The sulfonate thus obtained (40 g) was dissolved in H_2O and made alkaline with Na_2CO_3, then extracted with $CHCl_3$. Thus, removal of the solvent gave 15 g of the second crop. Total yield was 12.5%.

The ketone (**3b**) was easily converted into a 4,4-dialkyl ketal on treatment with acidified alcohol. A mixture of 0.5 g of **3b**, 0.1 g of *p*-toluenesulfonic acid, 3 ml of MeOH was refluxed on a steam bath for 4 hr. The cooled mixture was diluted with H_2O and made alkaline with Na_2CO_3 (solid) and extracted with $CHCl_3$. The extract was dried and evaporated and the residue was distilled to give 0.3 g of 4,4-dimethyl ketal of **3b** as a colorless syrup, bp_1 160—170° (bath temp.). IR $\nu_{max}^{liq.}$ cm^{-1}: 1600, 1498, 1450, 1110, 1059, 949, 740, 700. NMR ($CDCl_3$) δ ppm: 7.19 (5H, s), 3.13 (6H, s), 3.1—1.0 (16H, m). *Anal.* Calcd. for $C_{18}H_{27}O_2N$: C, 74.70; H, 9.40; N, 4.84. Found: C, 74.57; H, 9.59; N, 5.31.

4α-Hydroxy-4β-phenyl-1-(β-phenylethyl)-3α,5α-propanopiperidine (4c) and Its Isomer (5c)——To an ice-cold and stirred solution of phenyllithium prepared from 0.72 g of lithium and 8.2 g of bromobenzene in 35 ml of ether in a usual manner was added dropwise a solution of 5.0 g of **3b** in 10 ml of ether and the mixture was further stirred for 20 min with cooling. The mixture was poured onto ice-water and acidified with dil. HCl, then, washed with ether. The aqueous layer was made alkaline with Na_2CO_3 (solid) and extracted with $CHCl_3$. The combined extracts were dried and evaporated, leaving 4.1 g of a crystalline mass which was recrystallized from *n*-hexane, giving 3 g of **4c** as needles, mp 70—75°. The analytical sample of mp 82—83° was obtained by further recrystallization. IR ν_{max}^{Nujol} cm^{-1}: 3550, 3410, 1600, 1499, 1055, 1010, 761, 740, 700. NMR ($CDCl_3$) δ ppm: 7.6—7.0 (10H, m), 3.1—1.0 (17H, m). *Anal.* Calcd. for $C_{22}H_{27}ON$: C, 82.20; H, 8.47; N, 4.36. Found: C, 82.76; H, 8.48; N, 4.42.

The 4α-hydroxypiperidine (**4c**, 1.2 g) thus obtained was dissolved in 80 ml of 10% HCl and the mixture was refluxed for 4 hr with stirring. The cooled mixture was made alkaline and extracted with $CHCl_3$ twice. The extract was evaporated to give 0.8 g of the isomeric 4β-hydroxypiperidine (**5c**) as prisms, mp 108° (from *n*-hexane). IR ν_{max}^{Nujol} cm^{-1}: 3450, 1600, 1498; 1030, 762, 740, 700. NMR ($CDCl_3$) δ ppm: 7.7—7.1 (10H, m), 3.3—1.0 (17H, m). *Anal.* Calcd. for $C_{22}H_{27}ON$: C, 82.20; H, 8.47; N, 4.36. Found: C, 82.21; H, 8.61; N, 4.58.

4β-Methoxy-4α-phenyl-1-(β-phenylethyl)-3α,5α-propanopiperidine (1b)——A mixture of 0.1 g of **4c**, 1 ml of H_2SO_4, and 10 ml of MeOH was refluxed for 5 hr. Then, the mixture was poured onto ice-water and extracted with $CHCl_3$ after making basic with Na_2CO_3 (solid). The extract was dried and evaporated, leaving 80 mg of **1b** as a syrup which was identified with the authentic sample by thin-layer chromatography and infrared spectrometry.

4α-Hydroxy-4β-(3′-methoxyphenyl)-1-(β-phenylethyl)-3α,5α-propanopiperidine (4d) and Its Isomer (5d)——To a Grignard solution prepared from 2.0 g of magnesium and 27 g of 3-bromoanisole in 20 ml of tetrahydrofuran was added dropwise a solution of 10 g of **3b** in tetrahydrofuran at 3—5° with ice-cooling and stirring in N_2 atmosphere and the mixture was further stirred at room temperature for 20 min. The mixture was diluted with saturated aq. NH_4Cl and extracted with $CHCl_3$ three times. The combined extracts were dried and evaporated to give 8.5 g of a syrup whose thin-layer chromatogram revealed the prominent formation of **4d** contaminated with a small amount of the isomer (**5d**). IR $\nu_{max}^{liq.}$ cm^{-1}: 3450, 1600, 1580, 1481, 1450, 1228, 1250, 1100. NMR ($CDCl_3$) δ ppm: 7.5—6.7 (9H, m), 3.77 (3H, s), 3.2—1.0 (17H, m). *Anal.* Calcd. for $C_{23}H_{29}O_2N$: C, 78.59; H, 8.32; N, 3.99. Found: C, 78.30; H, 8.36; N, 4.14.

The crude 4α-hydroxypiperidine (**4d**, 2.0 g) was dissolved into 20 ml of dil. HCl (10%) and the mixture was refluxed for 5 hr. The cooled mixture was made alkaline with Na_2CO_3 and extracted with $CHCl_3$. Then, the extract was dried and evaporated, giving a syrup which crystallized on standing in a refrigerator. Recrystallization from *n*-hexane gave 1.3 g of the 4β-hydroxy isomer (**5d**), prisms, mp 83—84°. IR ν_{max}^{Nujol} cm^{-1}: 3540, 3400, 1599, 1485, 1380, 1262, 780, 740, 700. NMR ($CDCl_3$) δ ppm: 7.5—6.7 (9H, m), 3.79 (3H, s), 3.2—1.0 (17H, m). *Anal.* Calcd. for $C_{23}H_{29}O_2N$: C, 78.59; H, 8.32; N, 3.99. Found: C, 78.68; H, 8.48; N, 4.37.

4α-Methoxy-4α-(3′-methoxyphenyl)-3α,5α-propanopiperidine (2f)——A mixture of 0.63 g of **2b**, 1.2 g of β,β,β-trichloroethyl chloroformate, and 6 ml of CH_2Cl_2 was left standing at room temperature for 1 day with stirring. The mixture was concentrated and chromatographed over 20 g of silica gel. Elution with $CHCl_3$ containing gradient amounts of AcOEt and removal of the solvent gave 1.049 g of 4β-methoxy-4α-(3′-methoxyphenyl)-1-(β,β,β-trichloroethoxycarbonyl)-3α,5α-propanopiperidine (**2e**) as a colorless syrup. IR $\nu_{max}^{liq.}$ cm^{-1}: 1714, 1602, 1583, 1240, 1130. NMR ($CDCl_3$) δ ppm: 4.98 (1H, d, J=12 Hz), 4.73 (1H, d, J=12 Hz), 3.86 (3H, s), 2.85 (3H, s), 2.75—2.0 (2H, m), 2.4—2.0 (6H, m).

A mixture of 840 mg of the carbamate (**2e**) obtained as above, 840 mg of zinc powder, and 15 ml of EtOH was refluxed for 3 hr with stirring. The solid was filtered and washed with $CHCl_3$. The filtrate and washings were combined and acidified with dil. HCl, then the mixture was concentrated to dryness. The residue was

washed with $CHCl_3$ several times and the washings were dried and evaporated, giving 349 mg of a crude crop of **2f**, which was recrystallized from hexane–$CHCl_3$ to yield needles, mp 207—209° (decomp.). IR ν_{max}^{Nujol} cm^{-1}: 3140, 2650, 1588, 1060. NMR ($CDCl_3$) δ ppm: 9.1 (br., disappeared with an addition of D_2O), 3.85 (3H, s), 2.78 (3H, s). *Anal.* Calcd. for $C_{16}H_{23}O_2N \cdot HCl$: C, 64.53; H, 8.12; N, 4.70; Cl, 11.91. Found: C, 64.74; H, 8.09; N, 5.01; Cl, 12.06.

4β-Methoxy-4α-(3′-methoxyphenyl)-1-(β-phenylethyl)-3α,5α-propanopiperidine (2d)——(i) A mixture of 600 mg of **4d**, 20 ml of absolute MeOH, and 2 ml of conc. H_2SO_4 was refluxed for 8 hr and the mixture was poured into ice-water and extracted with $CHCl_3$ after being made basic with Na_2CO_3. The extract was dried and evaporated to give 0.4 g of **2d**, as a syrup. IR $\nu_{max}^{liq.}$ cm^{-1}: 1600, 1580, 1488, 1260, 1078, 1058, 700. NMR ($CDCl_3$) δ ppm: 3.80 (3H, s), 2.80 (3H, s). 3.2—1.0 (16H, m). *Anal.* Calcd. for $C_{24}H_{31}O_2N \cdot H_2O$: C, 75.16; H, 8.67; N, 3.65. Found: C, 74.74; H, 8.54; N, 3.54.

(ii) A mixture of 245 mg of the hydrochloride of **2f** obtained as above, 260 mg of β-phenylethylbromide, 1 g of K_2CO_3, and 10 ml of *sec*-BuOH was refluxed for 2 hr with stirring. The cooled mixture was filtered and the filtrate was evaporated to dryness. The residue was purified by chromatography, giving 230 mg of **2d** which was identified with the sample obtained as above by infrared spectrometry and by thin-layer chromatography.

4β-Methoxy-4α-(3′-hydroxyphenyl)-1-(β-phenylethyl)-3α,5α-propanopiperidine (2c)——A mixture of 2.0 g of **2d**, 2.0 g of $NaSC_2H_5$, and 80 ml of dimethylformamide was refluxed for 3 hr and then the solvent was evaporated under a reduced pressure. The residue was diluted with saturated aq. NH_4Cl and extracted with $CHCl_3$ three times. The extracts were dried and evaporated to leave 2 g of a crystalline mass which was recrystallized from *n*-hexane, giving 540 mg of **2c**, as prisms, mp 119°. IR ν_{max}^{Nujol} cm^{-1}: 3300, 3200, 1600, 1500, 1380, 1280, 1060, 787, 709, 698. NMR ($CDCl_3$) δ ppm: 7.4—6.7 (9H, m), 5.00 (1H, s), 2.83 (3H, s), 3.0—1.0 (16H, m). *Anal.* Calcd. for $C_{23}H_{29}O_2N$: C, 78.59; H, 8.32; N, 3.99. Found: C, 78.78; H, 8.19; N, 4.19.

The hydrogen citrate of **2c** was also obtained as amorphous powder.

4α-(2-Furyl)-4β-methoxy-1-methyl-3α,5α-propanopiperidine (7)——To an etheral solution containing 0.025 mole of furyllithium prepared in a usual manner was added dropwise a solution of 3.038 g of **3a** in 25 ml of ether at 5—10° with stirring under N_2 atmosphere. Then, the mixture was kept at room temperature for 2 hr. The mixture was poured into ice-water and extracted with $CHCl_3$ several times. The combined extracts were dried and evaporated, leaving 4.12 g of a syrup, whose thin-layer chromatogram revealed 2 spots (MeOH–$CHCl_3$ 1 : 10, v/v, silica gel). IR $\nu_{max}^{liq.}$ cm^{-1}: 3330, 3110, 1496, 1040, 738. NMR ($CDCl_3$) δ ppm: 7.50—7.20 (1H, m), 6.50—6.20 (2H, m), 2.26 and 2.02 (3H, singlets with areas of 3 : 1).

To an ice-cold solution of 1 g of the product thus obtained in 20 ml of absolute MeOH was added 2 ml of conc. H_2SO_4 with stirring and the resulting mixture was kept at room temperature for 2 hr. After making basic by addition of aq. ammonia, the mixture was diluted with H_2O and extracted with $CHCl_3$ three times. The combined extracts were dried and evaporated under a reduced pressure to give a crude sample of **7** which was distilled to afford a colorless syrup, bp_3 105—110° (bath temp.). The thin-layer chromatogram revealed contamination of an amount of the isomeric compound. IR $\nu_{max}^{liq.}$ cm^{-1}: 3100, 1490, 1078, 738. NMR ($CDCl_3$) δ ppm: 7.56—7.40 (1H, m), 6.53—6.33 (2H, m), 2.96 (3H, s), 2.10 (3H, s).

This syrup of **7** formed a crystalline citrate, needles, mp 185—188° (decomp.) (from MeOH–ether). *Anal.* Calcd. for $C_{20}H_{29}O_9N$: C, 56.20; H, 6.84; N, 3.28. Found: C, 56.17; H, 6.85; N, 3.48.

1-Alkoxycarbonyl- or 1-Phenoxycarbonyl-4β-methoxy-4α-phenyl-3α,5α-propanopiperidine (9a—f)——A solution of 0.01 mole of **1a** (or **2b**), 0.011 mole of alkyl or phenyl chloroformate in 25 ml of CH_2Cl_2 was refluxed for 5 hr. The cooled mixture was washed with dil. HCl, and H_2O, dried and evaporated, giving a syrupy product, which was purified by distillation or by chromatography. 1-Methoxycarbonyl compound (**9a**, $R_1=CH_3$, $R_2=H$): prisms, mp 91—93° (from hexane). $bp_{0.02}$ 170—175° (bath temp.). NMR ($CDCl_3$) δ ppm: 7.42 (5H, m), 3.76 (3H, s), 2.81 (3H, s). *Anal.* Calcd. for $C_{17}H_{23}O_3N$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.52; H, 7.94; N, 4.84. 1-Ethoxycarbonyl compound (**9b**, $R_1=C_2H_5$, $R_2=H$): $bp_{0.02}$ 175—180° (bath temp.). NMR ($CDCl_3$) δ ppm: 7.42 (5H, m), 4.20 (2H, q, $J=7$ Hz), 2.81 (3H, s), 1.29 (3H, t, $J=7$ Hz). *Anal.* Calcd. for $C_{18}H_{25}O_3N$: C, 71.25; H, 8.31; N, 4.62. Found: C, 71.35; H, 8.53; N, 4.50. 1-Isopropoxycarbonyl compound (**9c**, $R_1=C_3H_7$, $R_2=N$): prisms, mp 91—92.5° (from hexane). NMR ($CDCl_3$) δ ppm: 7.42 (5H, m), 4.99 (1H, m, $J=6.2$ Hz), 2.81 (3H, s), 1.28 (6H, d, $J=6.2$ Hz). *Anal.* Calcd. for $C_{19}H_{27}O_3N$: C, 71.89; H, 8.57; N, 4.41. Found: C, 72.08; H, 8.73; N, 4.38. 1-*n*-Butoxycarbonyl compound (**9d**, $R_1=n\text{-}C_4H_9$, $R_2=H$): syrup. NMR ($CDCl_3$) δ ppm: 7.42 (5H, m), 4.08 (2H, q, $J=6$ Hz), 2.80 (3H, s), 0.96 (3H, m). *Anal.* Calcd. for $C_{20}H_{29}O_3N$: C, 72.47; H, 8.82; N, 4.23. Found: C, 72.37; H, 8.69; N, 4.99. 1-Phenoxycarbonyl compound (**9e**, $R_1=C_6H_5$, $R_2=H$): prisms, mp 97—98° (from hexane.) NMR ($CDCl_3$) δ ppm: 7.6—7.0 (10H, m), 2.83 (3H, s). *Anal.* Calcd. for $C_{22}H_{25}O_3N$: C, 75.18; H, 7.17; N, 3.99. Found: C, 75.42; H, 7.26; N, 3.83. 1-(Ethoxycarbonyl)-4β-(3′-methoxyphenyl) compound (**9f**, $R_1=C_2H_5$, $R_2=CH_3O$): syrup. NMR ($CDCl_3$) δ ppm: 4.20 (2H, q), 3.85 (3H, s), 2.85 (3H, s), 1.25 (3H, t). *Anal.* Calcd. for $C_{19}H_{27}O_4N$: C, 68.44; H, 8.16; N, 4.20. Found: C, 68.16; H, 7.91; N, 4.10.

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