1-(3-Dimethylaminopropyl)-2-methyl-2-phenyl-1-indanol and Related Compounds. A New Class of Analgesic Agents[1]

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The syntheses of the two racemates of the title compound and 17 analogs and derivatives are reported. All of these compounds were tested orally for analgesic activity in mice using a tail-flick procedure. Three of these products were more active than codeine sulfate.

2-Methyl-2-phenyl-1-indanone (I)[2,3] was subjected to a variety of chemical reactions and the products were submitted for pharmacological evaluation. The interaction of I with 3-dimethylaminopropylmagnesium chloride (II) in tetrahydrofuran gave a high yield of a mixture of the two racemates of the title compound. After complete separation by selective crystallization, the racemates were converted to hydrochloride salts (designated as α and β forms) and tested orally for analgesic activity in mice using a tail-flick procedure.[4] The α form (**1**) was found to be more active than the β form (**2**) or codeine sulfate by this method.

The infrared spectra (in $CDCl_3$) of these isomers showed a distinct difference in the absorption frequency of the hydroxy group: the α form at 3590 cm^{-1} and the β form at 3556 cm^{-1}. The absorption frequency of the β form indicates that the hydroxyl is bonded to the π electrons of the phenyl group,[5] thus requiring these groups to have a *cis* configuration, whereas the normal nonbonded hydroxyl and phenyl groups of the α form are in a *trans* position. These structural assignments were in agreement with the subsequent nmr studies, the details of which will be the subject of a separate paper.[6]

In order to determine a structure–activity correlation in this class of compounds, 2,3-dimethyl-2-phenyl-1-indanone[3] and 2-methyl-2-phenyl-1-tetralone[7] were treated with II. I was also treated with the Grignard reagents derived from 4-chloro-N-methylpiperidine and 3-(methylphenethylamino)propyl chloride (obtained from the reaction of allyl alcohol with methylphenethylamine, followed by treatment of the resulting propanol with $SOCl_2$). The analog of **1** containing a two-carbon side chain (**10**) was obtained by the treatment of I with α-bromo-N,N-dimethylacetamide in the presence of zinc dust, followed by the $LiAlH_4$ reduction of the amido intermediate. The products of these reactions are listed in Table I. In addition to these carbinols, the related tricyclic compound, 9-(3-dimethylaminopropyl)fluoren-9-ol,[8] was prepared for comparison with **1**. Treatment of the free base of **1** with propionyl chloride in $CHCl_3$ (an attempt to obtain an ester of **1**) yielded the dehydration product (**12**). The latter indanylidene was then hydrogenated to the corresponding indanyl analog (**13**). In a similar manner, the piperidine indanol (**6**) was converted to **14** and **15**.

Treatment of **1** with a mixture of HCl and acetic acid resulted in the conversion to the carbonium ion and subsequent migration of the phenyl group to the 1 position to give 1-phenyl-N,N,2-trimethyl-1-indenepropylamine (**16**). The same migration of the phenyl group took place when the piperidine (**6**) and naphthalene (**9**) analogs were made to react to give **18** and **19**. Hydrogenation of **16** gave the corresponding indanpropylamine (**17**).

All of the compounds of Table I were tested for analgesic activity by the oral route in mice using a tail-flick procedure;[4] three of these (**1**, **3**, and **8**) were more active than codeine sulfate in this test procedure. In a direct comparison, **1** was found to be slightly more active than codeine sulfate in mice when administered by the intraperitoneal route. In each case where two racemates were separated from the reaction, the α form (hydroxyl and phenyl in a *trans* configuration) was more potent than the β form. Neither of the isomers of the piperidine compound (**6** and **7**), or the dehydration product (**14**) showed significant analgesic activity. The latter material exhibited weak antihistaminic and antiserotonin properties. All of the other above-mentioned modifications of **1** showed a lower order of analgesic activity.

Experimental Section

Melting points are corrected. Infrared spectra were recorded on a Perkin-Elmer Model 21 spectrometer and the nmr data ($CDCl_3$) were obtained with a Varian Associates Model A-60, with Me_4Si as an internal reference standard.

1-(3-Dimethylaminopropyl)-2-methyl-2-phenyl-1-indanol Hydrochlorides (1, 2).—A suspension of 48.0 g (2.0 g-atoms) of Mg powder in 180 ml of dry tetrahydrofuran (THF) was treated with about 150 ml of a solution of 240 g (2.0 moles) of 3-dimethylaminopropyl chloride in 720 ml of THF. A few crystals of iodine were added and the mixture was gently heated to about 66°. The reaction became exothermic and was controlled by brief cooling in an ice bath. The mixture was then allowed to reflux during the addition of the remainder of the 3-dimethylaminopropyl chloride solution and continued for an additional 30 min. The external heating was discontinued during the addition (20 min) of a solution of 150 g (0.68 mole) of 2-methyl-2-phenyl-1-indanone[3] in 150 ml of THF, and the resulting mixture was refluxed for 6 hr, cooled, and then added to a cold solution of 900 g of NH_4Cl in 4.5 l. of water. The mixture was extracted several times with ether, the organic phases were combined and dried ($MgSO_4$), and the solvents were removed under reduced pressure

(1) Presented in part before the Division of Medicinal Chemistry, 151st National Meeting of the American Chemical Society, Pittsburgh, Pa., March 1966.

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(3) The authors are indebted to Dr. H. Brison of the Olin Research Laboratories for a supply of this material. A description of a new one-step synthesis of this indanone is disclosed by Olin Mathieson Chemical Corp., Belgian Patent 676,372 (Aug 11, 1966).

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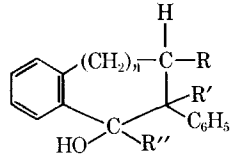
TABLE I

BASICALLY SUBSTITUTED INDANOLS AND RELATED COMPOUNDS



No.	Form	n	R	R′	R″	M.p., °C[a]	Yield, %	Formula	Chlorine, % Calcd	Chlorine, % Found	Nitrogen, % Calcd	Nitrogen, % Found	Analgesic act. in mice (oral) ED_{50}, mg/kg[b,c]
1	α	0	H	CH_3	$(CH_2)_3N(CH_3)_2$	173–175	33	$C_{21}H_{28}ClNO$	10.25	10.06	4.05	4.07	15
2	β	0	H	CH_3	$(CH_2)_3N(CH_3)_2$	173–175	20	$C_{21}H_{28}ClNO$	10.25	10.03	4.05	4.01	63
3	α[d]	0	CH_3	CH_3	$(CH_2)_3N(CH_3)_2$	192–194[e]	60	$C_{22}H_{30}ClNO$	9.85	10.01	3.89	3.82	36
4	α	0	H	CH_3	$(CH_2)_3N(CH_3)(CH_2)_2C_6H_5$	100–102[f]	15	$C_{28}H_{34}ClNO \cdot H_2O$[g]	7.81	8.05	3.09	3.01	92
5	β	0	H	CH_3	$(CH_2)_3N(CH_3)(CH_2)_2C_6H_5$	150–152[f]	15	$C_{28}H_{34}ClNO \cdot H_2O$[g]	7.81	7.96	3.09	3.31	>105
6	α	0	H	CH_3	$C_6H_9NCH_3$[h]	197–199[h]	37	$C_{22}H_{28}ClNO$	9.91	9.73	3.91	3.71	>105
7	β	0	H	CH_3	$C_6H_9NCH_3$[h]	148–150[h]	8	$C_{22}H_{28}ClNO \cdot H_2O$[i]	9.43	9.15	3.73	3.83	>105
8	α	1	H	CH_3	$(CH_2)_3N(CH_3)_2$	155–157[j]	2	$C_{22}H_{30}ClNO$	9.85	9.99	3.89	4.08	21
9	β	1	H	CH_3	$(CH_2)_3N(CH_3)_2$	206–207[j]	50	$C_{22}H_{30}ClNO$	9.85	9.87	3.89	3.85	80
10	α[d]	0	H	CH_3	$(CH_2)_2N(CH_3)_2$	195–197	15	$C_{20}H_{26}ClNO$	10.68	10.65	4.22	4.31	>105
	Related compounds, HCl salts												
11	9-(3-Dimethylaminopropyl)fluoren-9-ol					162–164[k]	54	$C_{20}H_{24}N_2O_4S$			6.27	6.28	>105
12	N,N-Dimethyl-3-(2-methyl-2-phenyl-1-indanylidene)propylamine					83–85	56	$C_{21}H_{26}ClN$[l]	10.81	10.50	4.27	4.42	>105
13	N,N-Dimethyl-3-(2-methyl-2-phenyl-1-indanyl)propylamine					231–233	56	$C_{21}H_{28}ClN$	10.75	10.54	4.25	4.39	m
14	1-Methyl-4(2-methyl-2-phenyl-1-indanylidene)piperidine					243–245	77	$C_{22}H_{26}ClN$	10.43	10.20	4.12	4.18	>105
15	1-Methyl-4-(2-methyl-2-phenyl-1-indanyl)piperidine					216–218	53	$C_{22}H_{28}ClN$	10.37	10.63	4.10	4.28	71
16	1-Phenyl-N,N,2-trimethyl-1-indenepropylamine					142–144	57	$C_{21}H_{26}ClN \cdot 0.5H_2O$[n]	10.52	10.66			>105
17	1-Phenyl-N,N,2-trimethyl-1-indanpropylamine					205–207	39	$C_{21}H_{28}ClN$	10.75	10.83	4.25	4.30	>105
18	1-Methyl-4-(2-methyl-1-phenyl-1-indenyl)piperidine					249–251	65	$C_{22}H_{26}ClN$	10.43	10.37	4.12	3.87	>105
19	1,4-Dihydro-1-phenyl-N,N,2-trimethyl-1-naphthalenepropylamine					206–208	72	$C_{22}H_{28}ClN$	10.37	10.22	4.10	3.91	>105

[a] Crystallization solvents: **1, 10,** and **12** (EtOH–Et_2O); **2, 3, 5, 6,** and **9** (MeOH–Et_2O); **4** ($CHCl_3$–Et_2O–H_2O); **7** ($CHCl_3$–Et_2O); **8** (MeCN–Et_2O); **11** (EtOH); **13–15, 17–19** (MeCN); and **16** (butanone). [b] Test procedure described in ref 4. [c] The ED_{50} for codeine sulfate by this method is 58 mg/kg. Most of the compounds were tested as 0.25% aqueous solutions; the water-insoluble materials (**4** and **5**) were treated as 0.25% suspensions in 0.25% agar. [d] The oral toxicity in mice (mg/kg) of several of these compounds was determined: **1** (500), **2** (660), **3** (575), **6** (510), **7** (260), **9** (440), **13** (215), **15** (485), and **16** (350). [e] Concentration of the hexane mother liquor from which the base was crystallized yielded only a small quantity of residue which contained some of the β form. [f] The base melted at 101–103° (hexane). *Anal.* Calcd for $C_{22}H_{29}NO$: C, 81.69; H, 9.04; N, 4.33. Found: C, 81.81; H, 9.04; N, 4.41. [g] The free bases of these isomers (an oily mixture) yielded a semicrystalline hydrochloride salt. Trituration of this mixture with butanone dissolved **4** and left **5** as a pure crystalline material. Dilution of the butanone with ether yielded **4**. [h] A 50% excess of the Grignard reagent was used in this preparation. [i] *Anal.* Calcd: C, 74.07; H, 7.99. Found (**4**): C, 73.97; H, 7.85. Found (**5**): C, 73.82; H, 8.06. [j] $C_9H_9NCH_3$ = 1-methyl-4-piperidinyl. Melting point of base: **6**, 203–205° (MeCN); **7**, 119–121° (hexane). *Anal.* Calcd for $C_{22}H_{29}NO$: C, 82.20; H, 8.47; N, 4.36. Found (**6**): C, 82.29; H, 8.43; N, 4.50. Found (**7**): C, 82.22; H, 8.47; N, 4.53. [k] A 100% excess of the Grignard reagent was used in this experiment. [l] *Anal.* Calcd: C, 70.29; H, 8.04. Found: C, 70.21; H, 8.03. [m] The free base of **9** crystallized from a hot hexane solution, mp 77–79°. Concentration of the hexane filtrate and subsequent crystallization of the resulting oil from diisopropyl ether yielded the free base of **8**, mp 87–89°. *Anal.* Calcd for $C_{22}H_{29}NO$: C, 81.69; H, 9.04; N, 4.33. Found (**9**): C, 81.96; H, 9.03; N, 4.21. Found (**8**): C, 81.78; H, 9.06. [n] Salt with cyclohexanesulfamic acid. *Anal.* Calcd: S, 7.18. Found: S, 7.08. [o] *Anal.* Calcd: C, 76.92; H, 7.99. Found: C, 76.84; H, 8.13. [p] Analgesic activity uncertain due to excess stimulation caused by this material. [q] *Anal.* Calcd: C, 74.86; H, 8.08. Found: C, 74.69; H, 8.00.

to give 202 g of crystalline residue, mp 93–120°. The latter material was digested with 1.1 l. of hot hexane leaving 24.5 g of insoluble product, mp 125–129°. The solid which separated from the cooled hexane solution weighed 137 g, mp 95–120°. The latter material was pulverized and triturated with 600 ml of ether for 10 min, the insoluble product (42 g, mp 128–131°) was filtered, and the filtrate (combined with the above hexane mother liquor) was evaporated to give 115 g of solid, mp 92–96°. This material was crystallized from 420 ml of hexane to give 91 g of the free base of 1, mp 98–100°.

Anal. Calcd for $C_{21}H_{27}NO$: C, 81.51; H, 8.80; N, 4.53. Found: C, 81.43; H, 8.97; N, 4.50.

A solution of 91.0 g of base in 1.2 l. of ether was treated with an equivalent quantity of ethereal HCl to give 96.5 g of colorless solid, mp 163–165°. This material was dissolved in 600 ml of ethanol at room temperature and diluted with 6 l. of ether to give 78.0 g of crystalline product.

The above higher melting fractions (24.5 and 42.0 g) were combined and crystallized from 320 ml of acetonitrile to give 51.0 g of the free base of **2**, mp 134–136°.

Anal. Calcd for $C_{21}H_{27}NO$: C, 81.51; H, 8.80; N, 4.53. Found: C, 81.32; H, 8.64; N, 4.31.

A solution of this base in 250 ml of $CHCl_3$ was treated with an equivalent quantity of alcoholic HCl and diluted to 2 l. with ether to give 55.0 g of material, mp 170–172°.

A mixture of 1 and **2** (recrystallized products) melted at 162–165°.

One significant difference in the infrared spectra (Nujol mull) of these isomers was apparent; 1 showed a characteristic band at 753 cm^{-1} and **2** at 766 cm^{-1}. In the form of the free bases, these bands were shown at 763 and 772 cm^{-1}, respectively.

1-(2-Dimethylaminoethyl)-2-methyl-2-phenyl-1-indanol Hydrochloride (10).—A solution of 10.0 g (0.045 mole) of 2-methyl-2-phenyl-1-indanone and 9.0 g (0.054 mole) of α-bromo-N,N-dimethylacetamide[9] in 30 ml of benzene was added portionwise to a stirred and refluxing suspension of 3.6 g (0.055 g-atom) of zinc dust in 10 ml of benzene (containing a trace of I_2). This mixture was refluxed for 3 hr, cooled to 5°, and treated portionwise with 25 ml of 10% H_2SO_4. The layers were separated, and the organic phase was washed ($NaHCO_3$, H_2O). After drying ($MgSO_4$), the solvent was evaporated at reduced pressure to give 11.4 g of a semicrystalline mixture of the hydroxy amide and starting ketone. The above material was dissolved in 150 ml of ether and added to a stirred suspension of 5.0 g (0.13 mole) of $LiAlH_4$ in 300 ml of ether, and the mixture was refluxed for 6 hr. The product (10.5 g of syrupy material) was isolated in the usual manner, dissolved in 400 ml of ether, and treated with an equivalent quantity of a solution of maleic acid in ether to give an oily maleic acid salt. The latter was dissolved in 25 ml of butanone and diluted with ether to give 5.0 g of solid, mp 127–130°. An aqueous solution of this salt was treated with excess K_2CO_3, the liberated base was extracted with ether and dried ($MgSO_4$), and the solvent was evaporated to give 3.2 g of base, mp 100–103°. After crystallization from 15 ml of hexane, the material weighed 2.3 g, mp 106–108°.

Anal. Calcd for $C_{24}H_{25}NO$: C, 81.31; H, 8.53; N, 4.74. Found: C, 81.34; H, 8.71; N, 4.60.

The above base gave 2.4 g of the HCl salt.

N,N-Dimethyl-3-(2-methyl-2-phenyl-1-indanylidene)propylamine Hydrochloride (12).—A solution of 10.0 g (0.029 mole) of 1 in 200 ml of $CHCl_3$ was cooled in an ice bath and treated with a solution of 3.2 g (0.035 mole) of propionyl chloride in 75 ml of $CHCl_3$, and the resulting solution was allowed to stand at room temperature for 12 hr. The solvent was removed under reduced pressure and the residue was triturated with 200 ml of ether to give 9.5 g of solid, mp 80–83°. Nmr on the purified material showed a singlet at τ 8.32 (CH_3) and a multiplet centered at 4.17 (olefinic proton of $=CHCH_2$).

N,N-Dimethyl-3-(2-methyl-2-phenyl-1-indanyl)propylamine Hydrochloride (13).—A mixture of 3.6 g (0.11 mole) of **12**, 3.0 g of 5% Pd–C and 100 ml of ethanol was placed on a Parr apparatus under 3 atm of hydrogen at room temperature. The theoretical quantity of hydrogen was consumed in 15 min. The mixture was filtered, the filtrate was concentrated under reduced pressure, and the residue was triturated with 100 ml of ether to give 3.1 g of colorless product, mp 224–226°.

1-Phenyl-N,N,2-trimethyl-1-indenepropylamine Hydrochloride (16).—A mixture of 10.0 g (0.029 mole) of 1, 160 ml of CH_3COOH, and 60 ml of concentrated HCl was heated and the resulting solution was refluxed for 3 hr. The solution was concentrated under reduced pressure and the residue was triturated with a mixture of acetone and ether to give 5.5 g of product, mp 138–140°. Nmr on the purified material showed a doublet centered at τ 8.24 (CH_3 protons of $CH_3C{=}CH$) and a quartet centered at 3.45 (olefinic proton of $CH_3C{=}CH$).

This material was hydrogenated (4-hr period) to give **17** in the manner described for **13**.

3-(N-Methylphenethylamino)-1-propanol.—A stirred mixture of 82 ml (1.2 moles) of allyl alcohol and 16.0 g (0.40 mole) of powdered NaOH was warmed to 65°, treated with 54.0 g (0.40 mole) of N-methylphenethylamine, and then refluxed for 7 hr. Water (200 ml) was added, and the mixture was distilled until 100 ml of distillate was collected. The cooled residue was extracted with 200 ml of $CHCl_3$ (three times), the extracts were combined and dried ($MgSO_4$), and the solvent was evaporated. Fractionation of the residue gave 19.0 g of the starting amine and 30.0 g (60%, based on recovered starting material) of the product, bp 132–136° (2 mm).

Anal. Calcd for $C_{12}H_{19}NO$: N, 7.25. Found: N, 7.37.

N-(3-Chloropropyl)-N-methylphenethylamine.—A solution of 41.0 g (0.21 mole) of the above material in 110 ml of $CHCl_3$ was treated with 33 ml of $SOCl_2$ and refluxed for 2 hr. About 50 ml of liquid was distilled, and the residue was cooled and diluted with 200 ml of ether to give 50.0 g of the hydrochloride, mp 125–128°. The analytical sample was crystallized from acetonitrile, mp 131–133°.

Anal. Calcd for $C_{12}H_{19}Cl_2N$: Cl, 28.25; N, 5.49. Found: Cl, 28.57; N, 5.64.

The hydrochloride was suspended in 75 ml of cold water and treated with a cold solution of 32.0 g of K_2CO_3 in 50 ml of water, and the liberated base was extracted with ether. The ethereal solution was dried ($MgSO_4$), the solvent was evaporated, and the residue was fractionated to give 33.0 g (74%) of product, bp 98–100° (0.3 mm).

Anal. Calcd for $C_{12}H_{18}ClN$: N, 6.62. Found: N, 6.81.

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