the extract washed with H_2O and dried (Na_2SO_4). Concentration of the Et_2O extract left a colorless solid which was recrystallized from Me_2CO to give **5** (400 mg, 72%) as a colorless solid: mp 124°; ir and nmr as expected. *Anal.* ($C_{29}H_{49}IO$) C, H.

19-Iodositost-5-en-3β-ol-^{125}I. A solution of **5** (50 mg) and $Na^{125}I$ (3.8 mCi) in Me_2CO (4 ml) was heated to gentle reflux for 4 hr. The solution was allowed to cool and cold H_2O was added slowly when a solid separated. The solid was collected by filtration and recrystallized from Me_2CO to give 32 mg of 19-iodo-β-sitosterol-^{125}I with a specific activity of 66.0 μCi/mg (55% exchange). Tlc using $CHCl_3$-EtOH (1:1) (R_f 0.64) or C_6H_6-EtOAc (1:1) (R_f 0.43) showed a single spot coincident with a single radioactive peak appearing on the radiochromatogram scan.

Tissue Distribution Studies. Radioiodinated steroids were given by intraperitoneal injection to immature male Sprague-Dawley albino rats weighing 175-200 g. The dose administered was approximately 50 μCi per rat and the vehicle used was 90% EtOH (0.2-0.3 ml). Groups of two animals were killed by exsanguination through the ventricle 24, 48, 96, and 144 hr after the injection. The major organs such as liver and kidney were excised, weighed, and homogenized. These organs were washed thoroughly with isotonic saline to remove blood, dried, and minced with scissors. Minced tissue was then placed in a homogenizer tube containing 20 ml of H_2O in the case of liver and 3 ml of H_2O in the case of kidney. Homogenates were not prepared for small organs such as adrenal and thyroid. Liver and kidney homogenates and entire adrenal, thyroid, and several heparinized blood samples were placed in scintillation counting vials. To each vial 0.5 ml of 10% NaOH solution was added and left overnight and then heated for at least 10 min at 60° in a water bath to complete digestion. The vials were allowed to cool and 5 drops each of glacial HOAc and 30% H_2O_2 solution were added. Ten milliliters of thixotropic liquid-counting system[10] was then added to each vial and the contents were shaken using a vortex mixer. The vials were kept in a cool dark place for at least 4 hr before counting. Radioactivity was assayed in a Beckman LS-200 liquid scintillation spectrometer. Sufficient counts were accumulated to reduce the probable error of counting to less than 5%. All counts were corrected for quench by using ^{125}I-quench standards curves.

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Substituted Tetralines. 5. Analgesic Properties of Some Diastereoisomeric *N,N*-Dimethyl-4-phenyl-1,2,3,4-tetrahydro-2-naphthylamines[1]

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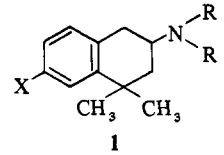
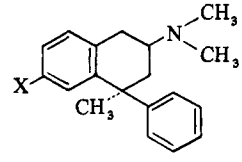
In a series of recent publications the synthesis and analgesic potency of some derivatives of general structure **1** were reported.[2-4] As part of a continuing study of structure-activity relationships directed toward the investigation of the effect of 4 substitutions in this system, the diastereoisomeric *N,N*-dimethyl-4-phenyl-1,2,3,4-tetrahydro-2-naphthylamines **2a** and **2b** and their 6-methoxyl and 6-hydroxyl derivatives **3a,b** and **4a,b**, respectively, were prepared and tested for analgesic activity.

Substitution of a phenyl group for methyl in **1** provides analogs of the diaryl analgesics, *e.g.*, methadone **(5)** and thiambutene **(6)**, wherein the conformation of one of the phenyl rings is partially restricted. If it is assumed that the tetralin ring system (present in virtually all potent analgesics having rigid structures[5]) serves in the role as a determinant of analgesic potency proposed by Beckett and Casy,[6] then 4-phenyl-substituted tetralins might be useful for investigating the importance of the second phenyl group of diaryl analgesics.

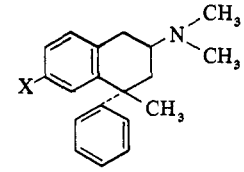
Chemistry. The amines **2a, 2b, 3a,** and **3b** were prepared from the corresponding 4-methyl-4-phenyl-1,2,3,4-tetrahydro-2-naphthoic acids **7a, 7b, 8a,** and **8b** by means of a modified Curtius procedure,[7] followed by Eshweiler-Clarke methylation[8] of the primary amines. The synthesis, separation, and proof of stereostructure of the diastereoisomeric acids, **7** and **8**, have been reported previously.[9] Treatment of the *N,N*-dimethyl-6-methoxy-4-methyl-4-phenyl-1,2,3,4-tetrahydro-2-naphthylamines **3a** and **3b** with 48% HBr gave **4a** and **4b**, respectively.



1



2a, X = H
3a, X = OCH_3
4a, X = OH



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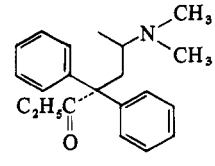
4b, X = OH



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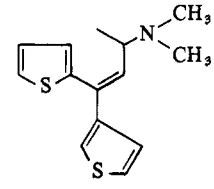

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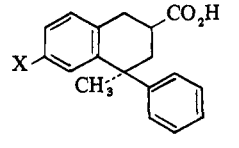
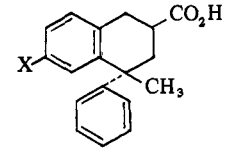


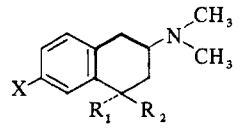
7a, X = H
8a, X = OCH_3



7, X = H
8, X = OCH_3

Biological Results. The analgesic potencies of the amines were determined in white albino mice (Carnworth Farm CF No. 1 strain) by the hot-plate procedure of Eddy and Leimbach.[10] In the complete assay procedure for each compound, five groups of six mice each were screened at dosage levels of 0.025, 0.050, 0.075, and 0.100 mmol/kg and a normal

Table I. Analgesic Potencies of Tetrahydro-2 naphthylamines



Compd	X	R_1	R_2	AD_{50}[a] (95% confidence interval)
2a	H	CH_3	C_6H_5	0.058 (0.042–0.080)
2b	H	C_6H_5	CH_3	0.052 (0.035–0.068)
3a	OCH_3	CH_3	C_6H_5	0.102 (0.078–0.151)
3b	OCH_3	C_6H_5	CH_3	0.078 (0.062–0.098)
4a	OH	CH_3	C_6H_5	0.042 (0.030–0.064)
4b	OH	C_6H_5	CH_3	0.029 (0.021–0.044)
Meperidine				0.052 (0.044–0.070)
Morphine				0.0049 (0.0041–0.0059)

[a]Expressed as mmol/kg.

saline control was administered intraperitoneally. Relative potencies, expressed as the AD_{50} (the dose of compound that doubled the normal reaction time in 50% of the mice tested), were calculated by the method of Litchfield and Wilcoxon.[11] From the data (Table I) it is seen that compounds **2a** and **2b** are comparable in potency to meperidine in mice. Substitution of a 6-hydroxy group (**4a** and **4b**), corresponding to the 3-hydroxy in morphine, increases potency, whereas 6-methoxyl substitution (**3a** and **3b**) decreases potency.

The lack of significant differences in activity between any of the diastereoisomeric (cis and trans) pairs of amines (**2**, **3**, or **4**) indicated that analgesic activity is apparently not dependent on a single specific conformation/configuration of the 4-phenyl group of these compounds. This result is paralleled in previous studies of conformationally restricted analgesics of the meperidine,[12] prodine,[13] and benzomorphan[14] types. The observed minimal conformational/configurational requirements for these compounds may be rationalized in terms of different modes of interaction of analgesic agents with receptors[15] and/or multiple receptors with different structural specifications.[16]

Experimental Section†

cis-N,N-**Dimethyl-4-methyl-4-phenyl-1,2,3,4-tetrahydro-2-naphthylamine Hydrochloride (2a).** A mixture of 8 g (0.03 mol) of **7a**[9] and freshly distilled $SOCl_2$ was refluxed 4 hr. The excess $SOCl_2$ was removed *in vacuo* (aspirator) leaving the acid chloride [ν_{max} ($CHCl_3$) 1802 cm^{-1}]. The acid chloride was dissolved in 50 ml of dry reagent grade acetone. The solution was chilled in an ice bath and, with vigorous stirring, a chilled solution of 2 g (0.03 mol) of NaN_3 in 6 ml of H_2O was added over a period of 1 min. The mixture was stirred for 45 min, then 100 ml of cold H_2O was added, and the crude azide was extracted with dry xylene. The extract was washed once with saturated NaCl solution and then filtered through anhydrous Mg_2SO_4. Rearrangement of the azide to the isocyanate was accomplished by applying vacuum (aspirator) to the xylene solution contained in a 500-ml flask and stirring vigorously with a magnetic stirrer The evolution of N_2 was in evidence for a period of about 3 hr. The vacuum was then removed, the flask fitted with a reflux condensor, and the solution heated to the boiling point. Xylene was then distilled off *in vacuo* yielding the isocyanate [ν_{max} ($CHCl_3$) 2272 cm^{-1}]. The nmr spectrum exhibited a single CH_3 absorption of δ 1.72 ppm, indicating that no epimerization had taken place. Concentrated HCl (50 ml) was cautiously added to the isocyanate and, after the exothermic reaction subsided, the brownish solution was refluxed overnight. Distilled H_2O was then added and the solution extracted with ether. The acidic aqueous solution was then evaporated and the residue dissolved in 10% KOH solution and extracted twice with Et_2O. The ether extracts were combined and dried over anhydrous K_2CO_3 and the Et_2O was distilled to yield the primary amine. The crude primary amine was then dissolved in 10 ml (0.2 mol) of 90% HCOOH, 10 ml of 37% HCHO was then added, and the mixture refluxed for 12 hr. After the mixture cooled, 5 ml of concentrated HCl was added and the mixture evaporated *in vacuo* (aspirator) to dryness. To the residue was added 10% KOH and the mixture was extracted twice with Et_2O. The Et_2O extracts were combined, dried over anhydrous K_2CO_3, and decanted to a dry flask. Dry ethereal HCl was added to the dry Et_2O solution of the amine causing 4.0 g (45%) of the HCl salt **2a** to precipitate as yellowish white needles, mp 243–245° [from $CHCl_3$–$(CH_3CH_2)_2O$]. *Anal.* ($C_{19}H_{24}ClN$) C, H, N.

trans-N,N-**Dimethyl-4-methyl-4-phenyl-1,2,3,4-tetrahydro-2-naphthylamine Hydrochloride (2b).** Following the same procedure employed for the preparation of **2a**, 8 g of **7b**[9] gave 3.8 g (45%) of **2b** as yellowish white needles, mp 246–248° [from $CHCl_3$–$(CH_3CH_2)_2O$]. *Anal.* ($C_{19}H_{24}ClN$) C, H, N.

cis-N,N-**Dimethyl-6-methoxy-4-methyl-4-phenyl-1,2,3,4-tetrahydro-2-naphthylamine Hydrochloride (3a).** Similar procedures employed for the synthesis of **2a** and **2b** were used to prepare **3a** and **3b**. Thus, 8.5 g (0.02 mol) of **8a**[9] was converted to the acid chloride [ν_{max} ($CHCl_3$) 1792 cm^{-1}] and thence to the azide, which was then rearranged to the isocyanate [ν_{max} ($CHCl_3$) 2260 cm^{-1}]. The isocyanate was hydrolyzed in 90% HCOOH (concentrated HCl appeared to cause some cleavage of the methoxyl group in a previous reaction) to a primary amine which was then N,N-dimethylated and converted to the HCl salt, giving 4.0 g (40%) of **3a**, mp 188–189° (sealed tube) following recrystallization [$CHCl_3$–$(CH_3CH_2)_2O$] *Anal.* ($C_{20}H_{26}ClNO$) C, H, N.

trans-N,N-**Dimethyl-6-methoxy-4-methyl-4-phenyl-1,2,3,4-tetrahydro-2-naphthylamine Hydrochloride (3b).** Following procedures for the synthesis of **3a**, 8.5 g (0.025 mol) of **8b**[9] gave 4.0 g (40%) of **3b**, mp 223° (sealed tube) following recrystallization [$CHCl_3$–$(CH_3CH_2)_2O$]. *Anal.* ($C_{20}H_{26}ClNO$) C, H, N.

cis-N,N-**Dimethyl-6-hydroxy-4-methyl-4-phenyl-1,2,3,4-tetrahydro-2-naphthylamine Hydrobromide (4a).** A solution of 1.65 g (0.005 mol) of **3a** in 15 ml of 48% HBr was refluxed under a stream of N_2 until evolution of CH_3Br (as evidenced by a cloudy appearance to the N_2 stream) ceased. After about 1 hr of reflux, H_2O and excess HBr were removed *in vacuo* (aspirator) and the residue was recrystallized (EtOH–EtOAc) giving a nearly quantitative yield of **4a** as colorless needles, mp 293°. *Anal.* ($C_{19}H_{24}BrNO$) C, H, N.

trans-N,N-**Dimethyl-6-hydroxy-4-methyl-4 phenyl-1,2,3,4-tetrahydro-2-naphthylamine Hydrobromide (4b).** Following the procedure for the synthesis of **4a**, 1.65 g (0.005 mol) of **3b** gave a quantitative yield of **4b** as pale yellow needles, mp 318°. *Anal.* ($C_{19}H_{24}BrNO$) C, H, N; C: calcd, 62.98; found, 63.22.

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†Melting points (uncorrected) were determined on a Fisher-Johns melting block. Microanalyses were performed by the Galbraith Laboratories, Knoxville, Tenn., and by the Weiler and Strauss Microanalytical Laboratory, Oxford, England. Ir spectra were obtained on Beckman IR-5 and IR-33 spectrophotometers. Nmr spectra were obtained with a Varian T-60 spectrometer.