

the extract washed with H₂O and dried (Na₂SO₄). Concentration of the Et₂O extract left a colorless solid which was recrystallized from Me₂CO to give **5** (400 mg, 72%) as a colorless solid: mp 124°; ir and nmr as expected. Anal. (C₂₃H₃₆O) C, H.

19-Iodositost-5-en-3 β -ol-¹²⁵I. A solution of **5** (50 mg) and Na¹²⁵I (3.8 mCi) in Me₂CO (4 ml) was heated to gentle reflux for 4 hr. The solution was allowed to cool and cold H₂O was added slowly when a solid separated. The solid was collected by filtration and recrystallized from Me₂CO to give 32 mg of 19-iodo- β -sitosterol-¹²⁵I with a specific activity of 66.0 μ Ci/mg (55% exchange). Tlc using CHCl₃-EtOH (1:1) (*R_f* 0.64) or C₆H₆-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 μ Ci 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 H₂O in the case of liver and 3 ml of H₂O 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% H₂O₂ solution were added. Ten milliliters of thixotropic liquid-counting system¹⁰ 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 ¹²⁵I-quench standards curves.

References

- G. N. Holcomb, C. M. Boyd, R. E. Counsell, W. H. Beierwaltes, R. A. Szczesniak, D. R. Murty, and G. A. Bruno, *J. Pharm. Sci.*, **60**, 390 (1971).
- (a) R. E. Counsell, V. V. Ranade, R. J. Blair, W. H. Beierwaltes, and P. A. Weinhold, *Steroids*, **16**, 318 (1970); (b) R. J. Blair, W. H. Beierwaltes, L. M. Lieberman, C. N. Boyd, R. E. Counsell, P. A. Weinhold, and V. M. Varma, *J. Nucl. Med.*, **12**, 176 (1971).
- L. M. Lieberman, W. H. Beierwaltes, J. W. Conn, A. N. Ansari, and H. Nishiyama, *N. Engl. J. Med.*, **285**, 1387 (1971).
- J. W. Conn, R. Morita, E. L. Cohen, W. H. Beierwaltes, W. J. McDonald, and K. Herwig, *Arch. Int. Med.*, **129**, 417 (1972).
- W. H. Beierwaltes, L. M. Lieberman, A. N. Ansari, and H. Nishiyama, *J. Amer. Med. Ass.*, **216**, 275 (1971).
- R. Morita, L. M. Lieberman, W. H. Beierwaltes, J. W. Conn, A. N. Ansari, and H. Nishiyama, *J. Clin. Endocrinol. Metab.*, **34**, 36 (1972).
- T. Nagai, B. A. Solio, and C. S. Koh, *J. Nucl. Med.*, **9**, 576 (1968).
- E. Denot, C. Casas-Campilio, and P. Crabbe, *Eur. J. Steroids*, **2**, 495 (1967).
- A. Bowers, R. Villotti, J. A. Edwards, E. Denot, and D. Halpern, *J. Amer. Chem. Soc.*, **84**, 3204 (1962).
- E. P. Frenkel, B. E. Whalley, C. T. Knorp, and D. R. Korst, *J. Lab. Clin. Med.*, **59**, 174 (1962).

Substituted Tetralines. 5. Analgesic Properties of Some Diastereoisomeric *N,N*-Dimethyl-4-phenyl-1,2,3,4-tetrahydro-2-naphthylamines¹

E. M. Kandeel and A. R. Martin*

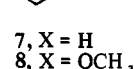
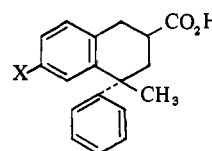
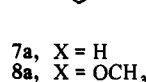
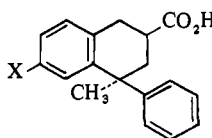
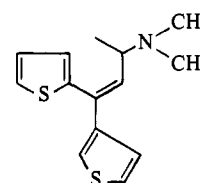
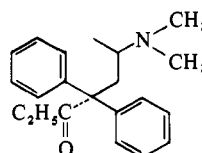
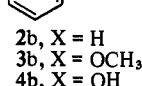
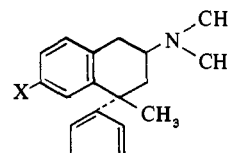
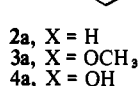
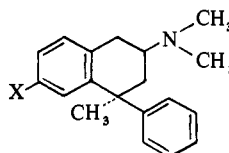
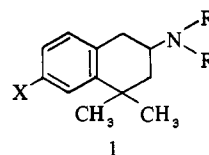
College of Pharmacy, Washington State University, Pullman, Washington 99163. Received March 1, 1973

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 struc-

ture-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-methoxy and 6-hydroxyl derivatives **3a,b** and **4a,b**, respectively, were prepared and tested for analgesic activity.

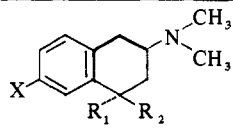
Substitution of a phenyl group for methyl in **1** provides analogs of the diaryl analgesics, e.g., methadone (**5**) and thiambutene (**6**), wherein the conformation of one of the phenyl rings is partially restricted. If it is assumed that the tetralin ring system (present in virtually all potent analgesics having rigid structures⁵) 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 methylation⁸ 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.



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 ₆ H ₅	0.058 (0.042-0.080)
2b	H	C ₆ H ₅	CH ₃	0.052 (0.035-0.068)
3a	OCH ₃	CH ₃	C ₆ H ₅	0.102 (0.078-0.151)
3b	OCH ₃	C ₆ H ₅	CH ₃	0.078 (0.062-0.098)
4a	OH	CH ₃	C ₆ H ₅	0.042 (0.030-0.064)
4b	OH	C ₆ H ₅	CH ₃	0.029 (0.021-0.044)
Meperidine				0.052 (0.044-0.070)
Morphine				0.0049 (0.0041-0.0059)

^aExpressed as mmol/kg.

saline control was administered intraperitoneally. Relative potencies, expressed as the AD₅₀ (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-methoxy 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 benzomorphan¹⁴ types. The observed minimal conformational/configurational requirements for these compounds may be rationalized in terms of different modes of interaction of analgesic agents with receptors¹⁵ 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 SOCl₂ was refluxed 4 hr. The excess SOCl₂ was removed *in vacuo* (aspirator) leaving the acid chloride [ν_{\max} (CHCl₃) 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 NaN₃ in 6 ml of H₂O was added over a period of 1 min. The mixture was stirred for 45 min, then 100 ml of cold H₂O 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 Mg₂SO₄. 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 N₂ was in evidence for a period of about 3 hr. The vacuum was then removed, the flask fitted with a reflux condenser, and the solution heated to the boiling point. Xylene was then distilled off *in vacuo* yielding the isocyanate [ν_{\max} (CHCl₃) 2272 cm⁻¹]. The nmr spectrum exhibited a single CH₃ 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 H₂O 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 Et₂O. The ether extracts

[†]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.

were combined and dried over anhydrous K₂CO₃ and the Et₂O 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 Et₂O. The Et₂O extracts were combined, dried over anhydrous K₂CO₃, and decanted to a dry flask. Dry ethereal HCl was added to the dry Et₂O solution of the amine causing 4.0 g (45%) of the HCl salt **2a** to precipitate as yellowish white needles, mp 243-245° [from CHCl₃-(CH₃CH₂)₂O]. *Anal.* (C₁₉H₂₄ClN) 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 CHCl₃-(CH₃CH₂)₂O]. *Anal.* (C₁₉H₂₄ClN) 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} (CHCl₃) 1792 cm⁻¹] and thence to the azide, which was then rearranged to the isocyanate [ν_{\max} (CHCl₃) 2260 cm⁻¹]. The isocyanate was hydrolyzed in 90% HCOOH (concentrated HCl appeared to cause some cleavage of the methoxy 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 [CHCl₃-(CH₃CH₂)₂O]. *Anal.* (C₂₀H₂₆ClNO) 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 [CHCl₃-(CH₃CH₂)₂O]. *Anal.* (C₂₀H₂₆ClNO) 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 N₂ until evolution of CH₃Br (as evidenced by a cloudy appearance to the N₂ stream) ceased. After about 1 hr of reflux, H₂O 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.* (C₁₉H₂₄BrNO) 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.* (C₁₉H₂₄BrNO) C, H, N; C: calcd, 62.98; found, 63.22.

Acknowledgment. Support of this work by Grants NBO2054 and MH21009 from the National Institutes of Health is gratefully acknowledged.

References

- Presented in part at the 163rd National Meeting of the American Chemical Society, Boston, Mass., April 1972.
- A. R. Martin, A. P. Parulkar, D. J. Gusseck, L. J. Anderson, G. L. Grunewald, and A. I. White, *J. Pharm. Sci.*, **58**, 340 (1969).
- D. E. Green, A. R. Martin, and A. I. White, *ibid.*, **59**, 526 (1970).
- V. S. Pai, A. P. Parulkar, A. R. Martin, and A. I. White, *ibid.*, **60**, 201 (1971).
- A. H. Beckett and A. F. Casy, *Progr. Med. Chem.*, **4**, 171 (1965).
- A. H. Beckett and A. F. Casy, *J. Pharm. Pharmacol.*, **6**, 986 (1954).
- P. A. Smith, "Organic Reactions," Collect. Vol. III, Wiley, New York, N. Y., 1946, p 337.
- A. Burger and W. Yost, *J. Amer. Chem. Soc.*, **70**, 2198 (1948).
- E. M. Kandeel, L. J. Anderson, J. H. Block, A. I. White, and A. R. Martin, *J. Pharm. Sci.*, **61**, 1231 (1972).
- N. B. Eddy and D. Leimbach, *J. Pharmacol. Exp. Ther.*, **107**, 385 (1953).
- J. T. Litchfield, Jr., and F. Wilcoxon, *ibid.*, **96**, 99 (1949).
- P. S. Portoghese, A. A. Mikhail, and H. J. Kupferberg, *J. Med. Chem.*, **11**, 219 (1968).
- E. E. Smisson and M. J. Steinman, *ibid.*, **9**, 455 (1966).
- A. E. Jacobson and E. L. May, *ibid.*, **7**, 409 (1964).
- P. S. Portoghese, *ibid.*, **8**, 147 (1965).
- S. Archer and L. S. Harris, *Progr. Drug Res.*, **8**, 262 (1965).