Med. Chem., **19**, 615 (1976).
(9) D. Henry, J. H. Block, J. L. Anderson, and G. R. Carlson, *ibid.*, **19**, 619 (1976).
(10) R. A. Scherrer and S. M. Howard, *ibid.*, **20**, 53 (1977).
(11) C. Horváth, W. Melander, and I. Molnár, *Anal. Chem.*, **49**, 142 (1977).
(12) W. E. Deming, "Statistical Adjustment of Data," Dover, New York, N.Y., 1943, p. 45.

ACKNOWLEDGMENTS

The authors thank Dr. David Johnson, Dr. Richard Runkel, and Dr. David Robertson for permission to cite their pKa determinations on naproxen and Dr. Richard Jones for access to his NLNMRQ modification of Metzler's (Upjohn) NONLIN program.

This paper is contribution 500 from the Syntex Institute of Organic Chemistry.

Substituted Tetralins VI: Tentative Assignment of Absolute Stereochemistry of 1-Methyl-1-phenyl-1,2,3,4-tetrahydro-3-naphthoic Acid and *N,N*,1-Trimethyl-1-phenyl-1,2,3,4-tetrahydro-3-naphthylamine Isomers

D. R. GALPIN, E. M. KANDEEL, and A. R. MARTIN *x

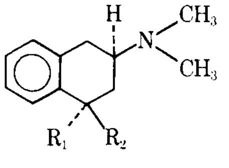
Received November 21, 1977, from the *College of Pharmacy, Washington State University, Pullman, WA 99164.* Accepted for publication January 31, 1978. *Present address: Department of Pharmaceutical Sciences, College of Pharmacy, University of Arizona, Tucson, AZ 85721.

Abstract ☐ The absolute configurations of the enantiomers of *N,N*,1-trimethyl-*cis*- and *trans*-1-phenyl-1,2,3,4-tetrahydro-3-naphthylamines (I*a* and I*b*) were assigned tentatively from the circular dichroism spectrum of a bridged ketone derived by cyclization of optically active 1-methyl-*cis*-1-phenyl-1,2,3,4-tetrahydro-3-naphthoic acid (II*a*). Thus, (−)-II*a* and the corresponding amine, (−)-I*a*, were assigned the (2*S*, 4*R*)-configuration. Epimerization of (−)-II*a* through its methyl ester yielded the *trans*-acid, (−)-II*b*, which established the absolute configuration of (−)-II*b* and the corresponding amine, (−)-I*b*, as (2*R*, 4*R*).

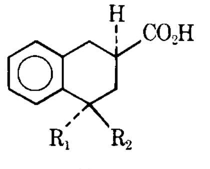
Keyphrases ☐ Tetralins, substituted—absolute configurations of enantiomers of 1-methyl-1-phenyl-1,2,3,4-tetrahydro-3-naphthoic acid and *N,N*,1-trimethyl-1-phenyl-1,2,3,4-tetrahydro-3-naphthylamine assigned ☐ Naphthoic acids and naphthylamines, substituted—absolute configurations of enantiomers assigned ☐ Stereochemistry—substituted naphthoic acids and naphthylamines, absolute configurations assigned

Previous publications described the synthesis of racemic *N,N*,1-trimethyl-1-phenyl-1,2,3,4-tetrahydro-3-naphthylamine diastereoisomers (I*a* and I*b*) (1) and the precursors 1-methyl-1-phenyl-1,2,3,4-tetrahydro-3-naphthoic acids (II*a* and II*b*) (2). Since various aminotetralin structures (1) exhibit analgesic (3–5) and/or analgesic antagonist (6) properties in animals, it was desirable to resolve some of the more active racemic compounds and to establish the absolute configuration of the enantiomers. Moreover, the precursor acids are potentially stereoselective anti-inflammatory analgesics.

This report describes the resolution of the diastereoisomeric acids (±)-II*a* and (±)-II*b*, the stereospecific conversion of each enantiomer to the corresponding *N,N*-dimethylamino derivatives, and the tentative assignment of absolute stereochemistry of the acids and amines.



I*a*: $R_1 = CH_3$, $R_2 = C_6H_5$
I*b*: $R_1 = C_6H_5$, $R_2 = CH_3$



II*a*: $R_1 = CH_3$, $R_2 = C_6H_5$
II*b*: $R_1 = C_6H_5$, $R_2 = CH_3$

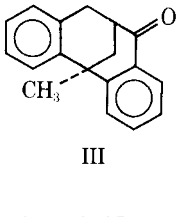
DISCUSSION

Stereochemical relationships among stereoisomers I*a*–I*b* and II*a*–II*b* were elucidated by resolution of the acids and stereospecific conversion of II*a* and II*b* to the corresponding amines. Thus, racemic II*a* and II*b* were resolved by fractional recrystallization of their (+)-dehydroabietylamine salts. Each enantiomer was converted to the corresponding primary amine *via* the Curtius reaction. Subsequent Eschweiler–Clarke methylation afforded the tertiary amines. In this manner, (−)-I*a* was obtained from (−)-II*a*, (−)-I*b* was obtained from (−)-II*b*, *etc.*

The absolute configurations of the enantiomeric *cis*-acids, (−)-II*a* and (+)-II*a*, were determined by investigating the spectral properties of the bridged ketone (+)-7,12-dihydro-12-methyl-6,12-methanodibenzo[*a,d*]cycloocten-5(6*H*)-one [(+)-III], prepared by cyclization of (−)-II*a* in anhydrous hydrogen fluoride. This cyclization previously was employed to assign the relative stereochemistry of racemic II*a* and II*b* (2).

The absolute configuration of (+)-III was determined from its circular dichroism spectrum (Fig. 1), which exhibited a strong positive Cotton effect for the carbonyl $n \rightarrow \pi^*$ transition. The assignment was made on the basis of the octant rule for aryl ketones developed by Snatzke (7). The aryl ketone chirality rule is an extension of the chirality rules for conjugated enones (7, 8), wherein conjugation of the π-bonds of the aromatic ring with the carbonyl group is formally considered to comprise a combination of both *cisoid*- and *transoid*-enone contributions. In aryl ketones, the *cisoid*- and *transoid*-enone contributions predict the same sign of their Cotton effects and thus reinforce each other.

The aryl ketone chirality rule was employed to predict successfully the sign of the $n \rightarrow \pi^*$ Cotton effect for a wide variety of aryl ketones for which absolute configurations were established independently by chemical synthesis and/or X-ray crystallography. The rule was shown to hold for flavanones (9, 10), α-tetralones (11, 12), respirones and related 9,9′-spirobifluorenone derivatives (13), 1-oxo[2.2]*p*-cyclophanes (14), and 1-oxo[2.2]*m*-cyclophanes (15). In fact, a literature search through August 1977 revealed only one partial exception to the rule, a series of 6-bromo-7-oxoditerpenoids containing an aromatic C-ring (16) for which



III

0022-3549/78/1000-1367$01.00/0

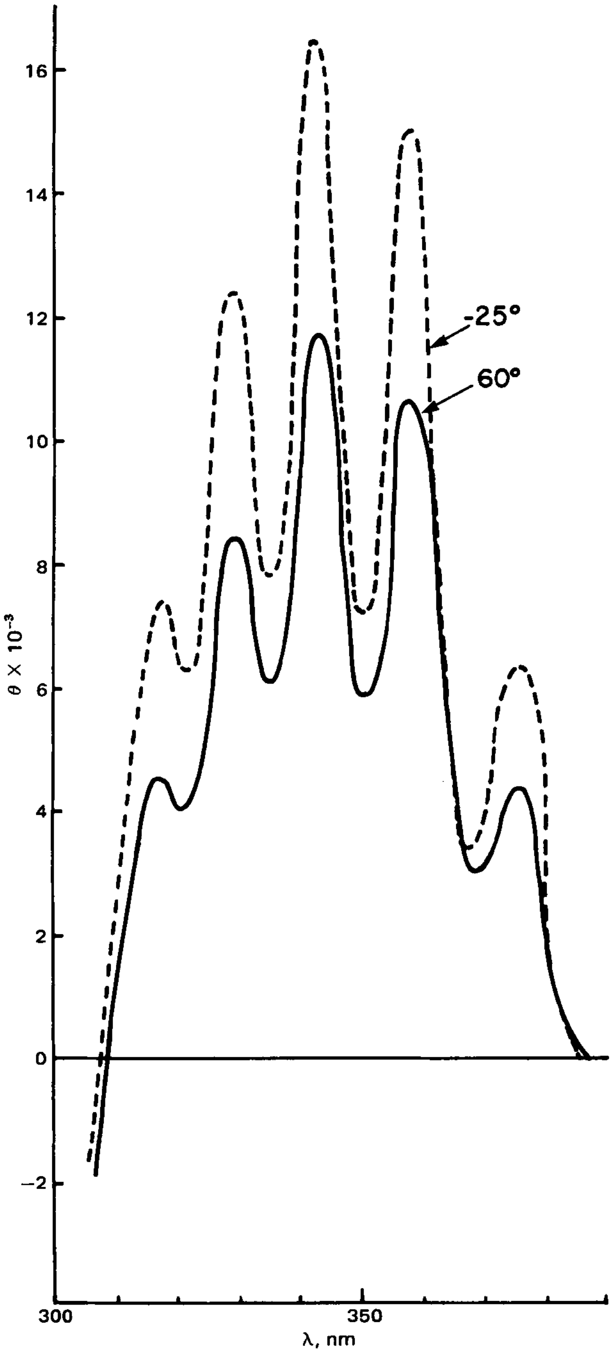


Figure 1—*Circular dichroism curves (isooctane) of (+)-(III) at 60° (—) and at −25° (- - -).*

the rule predicts the correct sign of the Cotton effect of the $n \rightarrow \pi^*$ transition but fails to provide a reliable guide to the orientation of the α-bromo substituent.

An examination of a Dreiding model of III reveals that the preferred conformation of this molecule is one where both nonaromatic rings are in half-chair conformations with all vicinal hydrogen atoms staggered. Deviation from this conformation leads to the eclipsing of several bonds. In this preferred conformation, the octant rule for aryl ketones predicts the absolute configuration of (+)-III to be (6*S*, 12*S*). Furthermore, the nonconjugated aromatic ring is oriented in a pseudoaxial conformation with respect to the aryl ketone system and thus lies in a positive octant to reinforce the positive Cotton effect. Comparative depictions are shown in Fig. 2. Since (+)-III was derived from (−)-II*a* with retention of the configuration (1), the absolute configuration of (−)-II*a* is (2*S*, 4*R*).

Because some conformational mobility is possible for (+)-III, it was necessary to establish that the fully staggered conformation dominated the sign of the Cotton effect. A temperature study in isooctane at three

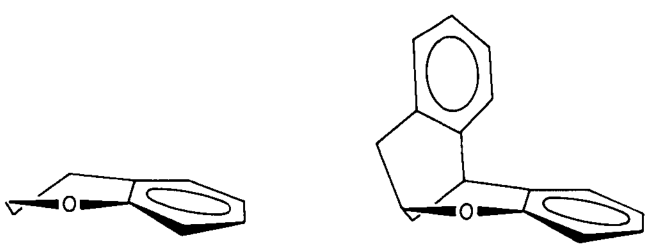


Figure 2—*Projection drawing showing a conformation of aryl ketones which produces a (+)-Cotton effect [after Snatzke (8)] and (+)-III in the preferred conformation.*

different temperatures supported this conclusion. The high- and low-temperature circular dichroism curves are shown in Fig. 1. (An intermediate curve at 25°, which lies between those presented, was omitted for clarity. The data, however, are given under *Experimental*.)

Inspection of the curves reveals that the Cotton effect increases as the temperature is decreased, which is consistent with the argument that the preferred conformation is determining the sign. This result could also be interpreted on the basis of increased solvation (17), where the more solvated species gives rise to a positive Cotton effect. However, the lack of a hypsochromic shift and the more prominent fine structure observed with decreasing temperature suggest that solvation effects are minimal over the temperature range examined (17). A similar enhancement of the carbonyl Cotton effect and its fine structure in 1-tetralone compounds upon lowering the temperature also was attributed to changes in conformer populations (18). By comparison, a slight blue shift is accompanied by a loss of fine structure when the solvent is changed from isooctane to methanol (see *Experimental*).

Separate equilibrations of the methyl esters of both (−)-II*a* and (−)-II*b* with sodium methoxide in refluxing methanol yielded identical results. The equilibrium mixture of esters had a *cis* to *trans* ratio of approximately 40:60, as judged from the optical rotation of the mixture and integration of the signals of the nonequivalent ester methyl groups in the NMR spectrum. The optical rotation of the mixture indicated that the (−)-*cis*-ester epimerized to the (−)-*trans*-isomer. This configurational relationship was confirmed with the isolation of (−)-II*b* from the mixture of acids obtained following hydrolysis of the equilibrium products of the ester of (−)-II*a*. Thus, the absolute configuration of (−)-II*b* and the stereochemically related amine (−)-I*b* is (2*R*, 4*R*).

An X-ray crystallographic investigation of the hydrobromide salt of (+)-I*b* is in progress. Also in progress is the synthesis of sufficient quantities of I*a* and I*b* enantiomers for analgesic and analgesic antagonist evaluation.

EXPERIMENTAL

Melting points were obtained on a melting block and are uncorrected. Elemental analyses were within ±0.4% of theory. NMR spectra were obtained[1] in carbon tetrachloride with tetramethylsilane as an internal reference. Optical rotations were measured in a 1-dcm cell in a half-shade polarimeter[2] at ambient temperatures and are probably accurate to 3°. The diastereoisomeric salts were subjected to differential thermal analysis to establish purity.

(+)-Dehydroabietylamine—Crude (+)-dehydroabietylamine was purified by its conversion to the acetate salt, which was recrystallized to a constant melting point according to the literature procedure (19), mp 45° [lit. (19) mp 44–45°].

(−)-1-Methyl-*trans*-1-phenyl-1,2,3,4-tetrahydro-3-naphthoic Acid [(−)-II*b*]—To a solution of 2.50 g (9 mmoles) of (+)-dehydroabietylamine (19) dissolved in 210 ml of boiling ethanol was added 2.40 g (9 mmoles) of II*b*. The solution was chilled, and the precipitate was collected and dried to give 4.8 g of a mixture of the diastereomeric salts. Fractional recrystallization from 95% ethanol yielded 2.0 g of white needles, mp 186.5–187°.

The dehydroabietylamine salt was shaken gently with a mixture of 40 ml of 10% sodium carbonate and 100 ml of ether until the solid had dis-

---

[1] Varian T-60 spectrometer.

[2] Dubosq-Pellin precision model. Although this instrument is graduated to 0.01° (using the vernier scale), inability to perceive a difference in the halves covered a range as high as 0.20°. If it is assumed that the midpoint of this range could be estimated with an accuracy of 0.05°, specific rotations would be in error by 2.5° at the lowest concentrations employed.

solved. The aqueous layer was separated and extracted twice with small portions of ether. After acidification, the aqueous phase was extracted twice with ether; the combined ether extracts were washed once with water and dried over anhydrous sodium sulfate. Solvent removal gave crystals of (−)-II*b*, which were recrystallized from 95% ethanol, mp 177.5–178.5°, $[\alpha]_D^{26}$ −100° (c 5, carbon tetrachloride).

(+)-1-Methyl-*trans*-1-phenyl-1,2,3,4-tetrahydro-3-naphthoic Acid [(+)-II*b*]—The mother liquors remaining from the isolation of the dehydroabietylamine salt of (−)-II*b* were diluted intermittently with water over several days; each addition generated the formation of crystals. When a sufficient quantity accumulated, it was isolated and recrystallized from 95% ethanol to give 1.5 g of white crystals, mp 162°. The free acid was recovered in the same manner as described for the (−)-isomer, producing 0.7 g of white needles, mp 175–176°, $[\alpha]_D^{27}$ +96° (c 5, carbon tetrachloride).

(−)-1-Methyl-*cis*-1-phenyl-1,2,3,4-tetrahydro-3-naphthoic Acid [(−)-II*a*]—A mixture of diastereomeric dehydroabietylamine salts of II*a* was obtained and resolved in the same manner as described for II*b*. The first salt isolated and purified had a melting point of 184–186° and yielded (−)-II*a* as an amorphous powder, mp 94–105°, $[\alpha]_D^{25}$ −33° (c 3, carbon tetrachloride).

(+)-1-Methyl-*cis*-1-phenyl-1,2,3,4-tetrahydro-3-naphthoic Acid [(+)-II*a*]—The second salt obtained from the mother liquors of the isolation of (−)-II*a* was purified by recrystallization (ethanol) to yield white needles, mp 167–168°. Liberation of the free acid gave (+)-II*a* as an amorphous powder, mp 95–105°, $[\alpha]_D^{27}$ +30° (c 3, carbon tetrachloride).

(+)- and (−)-7,12-Dihydro-12-methyl-6,12-methanodibenzo[*a,d*]cycloocten-5(6*H*)-one [(+)- and (−)-III]—The cyclization of 0.3 g of (−)-II*a* in 20 g of anhydrous hydrogen fluoride in a procedure identical to that described previously (2) for the synthesis of racemic ketone III yielded 0.25 g of (+)-III as colorless crystals, mp 145–146°, $[\alpha]_D^{27}$ +96° (c 2, methanol). Compound (−)-III was prepared in an identical fashion from (+)-II*a*, mp 145–146°, $[\alpha]_D^{26}$ −97° (c 3, carbon tetrachloride).

Epimerization of (−)-II*a*—This method was employed to isomerize both (−)-II*a* and (−)-II*b* and yielded the same results in each case. The procedure for (−)-II*a* is described.

A solution of 0.3 g of (−)-II*a* in 30 ml of absolute methanol containing 1 ml of sulfuric acid was refluxed overnight. The reaction solution was diluted with cold water and extracted twice with small portions of carbon tetrachloride. The combined extracts were washed once with 5% sodium bicarbonate and once with water and dried over anhydrous sodium sulfate. Removal of solvent yielded a viscous oil, $[\alpha]_D^{25}$ −20° (c 5, carbon tetrachloride). The NMR spectrum exhibited a methyl group signal at δ 3.60 ppm; no signal for an acid proton was detected. The methyl ester of (−)-II*b* prepared in a similar fashion showed an NMR signal for the ester methyl group at δ 3.55 ppm, $[\alpha]_D^{26}$ −94° (c 4, carbon tetrachloride).

The ester was dissolved in 25 ml of a solution of sodium methoxide (prepared by adding a small piece of sodium metal to freshly distilled, magnesium-dried methanol) and refluxed for 10 hr. The resulting mixture of esters of (−)-II*a* and (−)-II*b* was isolated as described for the ester of (−)-II*a*. The NMR spectrum of this mixture displayed nonequivalent signals of the methyl groups for the two isomers for both the ester and C-4 methyl functions. Integration of the ester methyl signals indicated an isomer composition of approximately 60% *trans*–40% *cis*. The specific rotation ($[\alpha]_D^{26}$ −60.2°) of the crude reaction workup was also consistent with this isomer ratio.

This mixture of esters was hydrolyzed by refluxing for 2 hr in a basic solution of methanol–water. The system was cooled, acidified to pH 2, and extracted three times with small portions of carbon tetrachloride. The combined extracts were washed twice with water and dried over anhydrous sodium sulfate. After removing the solvent, the white solid residue was dissolved in a minimal quantity of boiling ether, diluted with an equal amount of petroleum ether, and chilled. The colorless crystals of (−)-II*b*, which deposited, had a melting point of 174–177° and $[\alpha]_D^{26}$ −93.3° (c 2, carbon tetrachloride). The NMR spectrum showed essentially pure *trans*-acid; no *cis*-isomer was detected.

Circular Dichroism Spectra of (+)-III—The circular dichroism spectra were obtained on a recording spectropolarimeter[3] in spectrograde solvents. The room temperature spectra were measured in 1.0–0.010-cm cells at 0.5 mg/ml. The temperature study was conducted in a 5.0-cm jacketed cell connected to a thermostated bath regulated to ±0.1°; concentrations ranged from 0.1 to 0.01 mg/ml. Data are expressed in values of $[\theta] \times 10^{-3}$ for the maxima (λ) and the points of inflection (λ_i).

With methanol at 25°, c = 0.506: 382.5 (0), 375i (+1.42), 355i (8.39), 339 (+13.3), 328 (+13.0), 307.5 (0), 290 (−4.41), 283 (0), 262 (+42.6), 247 (0), and 215 (123).

With isooctane at 25°, c = 0.53: 387.5 (0), 376 (+4.92), 367.5 (+2.90), 358.5 (+11.6), 350.5 (+5.90), 344 (+12.7), 335 (+6.10), 329 (+9.08), 321 (+4.03), 317.5 (+4.64), 308.5 (0), 290 (−9.18), 277.5 (0), 264–260 (+43.5) (shoulder), 254 (+57.6), 242 (0), 224 (−89.8), 218 (−70.2), and 215 (−84.3).

With isooctane at 60°, c = 0.106: 388 (0), 376 (+4.45), 367.5 (+2.95), 358.5 (+10.7), 350.5 (+5.95), 343 (+11.8), 335 (+6.09), 329.5 (+8.57), 320 (+4.07), 317 (+4.35), 308 (0), 290 (−8.24), 277.5 (0), 264 (+40.8) (shoulder), 254 (+55.8), and 250 (+44.4).

With isooctane at −25°, c = 0.0106: 388 (0), 376 (+6.41), 367.5 (+3.42), 358.4 (+15.1), 350.5 (+7.16), 343 (+16.6), 335 (+7.77), 329 (+12.5), 321.5 (+6.18), 317 (+7.49), 308 (0), 291.5 (−6.74), 277.5 (0), and 275 (+9.83).

(−)-*N,N*,1-Trimethyl-*trans*-1-phenyl-1,2,3,4-tetrahydro-3-naphthylamine Hydrochloride [(−)-I*b*]—A mixture of 0.8 g (3 mmoles) of (−)-II*b* and 1 ml of freshly distilled thionyl chloride was refluxed 4 hr. The excess thionyl chloride was removed *in vacuo* (aspirator), leaving the acid chloride. Then the acid chloride was dissolved in 5 ml of dry reagent grade acetone. The solution was chilled in an ice bath and, with vigorous stirring, a chilled solution of 0.2 g (3 mmoles) of sodium azide in 1 ml of water was added over 1 min. The mixture was stirred for 10 min, 10 ml of cold water was added, and the crude azide was extracted into dry xylene. The extract was washed with saturated sodium chloride solution and then filtered through anhydrous magnesium sulfate.

Rearrangement of the azide to the isocyanate was accomplished by applying vacuum (aspirator) to the xylene solution contained in a 50-ml flask and stirring vigorously with a magnetic stirrer. The evolution of nitrogen was in evidence for about 2 hr. The vacuum was then removed, the flask was fitted with a reflux condenser, and the solution was heated to the boiling point. Xylene was then distilled off *in vacuo*, yielding the isocyanate. Concentrated hydrochloric acid (5 ml) was added cautiously to the isocyanate; after the exothermic reaction subsided, the brownish solution was refluxed overnight. Distilled water was then added, and the solution was extracted with ether. The acidic aqueous solution was then evaporated, and the residue was dissolved in 10% KOH and extracted twice with ether.

The ether extracts were combined and dried over anhydrous potassium carbonate, and the ether was distilled to yield the primary amine. The crude amine was dissolved in 1 ml (2 mmoles) of 90% formic acid, 1 ml of 37% formaldehyde was then added, and the mixture was refluxed for 8 hr. After the mixture cooled, 0.5 ml of concentrated hydrochloric acid was added, and the mixture was evaporated *in vacuo* (aspirator) to dryness. To the residue was added 10% KOH, and the mixture was extracted twice with ether.

The ether extracts were combined, dried over anhydrous potassium carbonate, and decanted to a dry flask. Dry ethereal hydrogen chloride was added to the dry ether solution of the amine, causing 0.4 g (45%) of the hydrochloride salt (−)-I*b* to precipitate as yellowish-white needles, mp 221–223° (from chloroform–ether), $[\alpha]_D^{27}$ −104° (c 3, methanol).

Anal.—Calc. for $C_{19}H_{24}ClN$: C, 75.60; H, 8.01; N, 4.64. Found: C, 75.15; H, 7.85; N, 4.82.

(+)-*N,N*,1-Trimethyl-*trans*-1-phenyl-1,2,3,4-tetrahydro-3-naphthylamine Hydrochloride [(+)-I*b*]—With the same procedure employed for the preparation of (−)-I*b*, 0.8 g (29 mmoles) of (+)-II*b* gave 0.4 g (45%) of (+)-I*b* as yellowish-white needles, mp 220–222° (from chloroform–ether), $[\alpha]_D^{27}$ +106° (c 3, methanol).

Anal.—Calc. for $C_{19}H_{24}ClN$: C, 75.60; H, 8.01; N, 4.64. Found: C, 75.56; H, 7.88; N, 4.43.

(−)-*N,N*,1-Trimethyl-*cis*-1-phenyl-1,2,3,4-tetrahydro-3-naphthylamine Hydrochloride [(−)-I*a*]—Treatment of 0.78 g (28 mmoles) of (−)-II*a* by the same procedure used to prepare (−)-I*b* gave 0.39 g (45%) of (−)-I*a*, mp 252–255° (chloroform–ether), $[\alpha]_D^{27}$ −99.5° (c 3, methanol).

Anal.—Calc. for $C_{19}H_{24}ClN$: C, 75.60; H, 8.01; N, 4.64. Found: C, 75.28; H, 8.14; N, 4.56.

(+)-*N,N*,1-Trimethyl-*cis*-1-phenyl-1,2,3,4-tetrahydro-3-naphthylamine Hydrochloride [(+)-I*a*]—Treatment of 0.72 g (26 mmoles) of (+)-II*a* by the same procedure used to prepare (−)-I*b* gave 0.31 g (44%) of (+)-I*a*, mp 252–255° (from chloroform–ether), $[\alpha]_D^{27}$ +101° (c 3, methanol).

Anal.—Calc. for $C_{19}H_{24}ClN$: C, 75.60; H, 8.01; N, 4.64. Found: C, 75.42; H, 8.06; N, 4.61.

---

[3] Cary 60, equipped with a 6001 CD attachment.

REFERENCES

(1) E. M. Kandeel and A. R. Martin, *J. Med. Chem.*, **16,** 947 (1973).

(2) E. M. Kandeel, J. L. Anderson, J. H. Block, A. I. White, and A. R. Martin, *J. Pharm. Sci.*, **61,** 1231 (1972).

(3) A. R. Martin, A. P. Parulkar, D. J. Gusseck, L. J. Anderson, G. L. Grunewald, and A. I. White, *ibid.*, **58,** 340 (1969). V. S. Pai, A. P. Parulkar, A. R. Martin, and A. I. White, *ibid.*, **60,** 201 (1971).

(4) J. Maillard, M. Langlois, P. Delaunay, T. V. Van, J. Chenu, R. Morin, M. Benharkate, C. Manuel, and F. Motosso, *J. Med. Chem.*, **15,** 1123 (1972).

(5) M. E. Freed, J. R. Potoski, E. H. Freed, G. L. Conklin, and J. L. Malis, *ibid.*, **16,** 595 (1973). M. E. Freed, J. R. Potoski, E. H. Freed, G. L. Conklin, and S. C. Bell, *ibid.*, **19,** 476 (1976).

(6) D. S. Fries and D. J. Bertelli, MEDI 24, presented at the 174th ACS National Meeting, Chicago, Ill., Aug. 1977.

(7) G. Snatzke, *Tetrahedron*, **21,** 439 (1965).

(8) *Ibid.*, **21,** 413 (1965).

(9) W. Gaffield and A. C. Weiss, Jr., *Chem. Commun.*, **1968,** 29.

(10) W. Gaffield, *Tetrahedron*, **26,** 4093 (1970).

(11) F. Zymalkowski and E. Dornhege, *Justus Liebigs Ann. Chem.*, **728,** 144 (1969).

(12) J. M. Luche, A. Marquet, and G. Snatzke, *Tetrahedron*, **28,** 1677 (1972).

(13) G. Haas, P. B. Hulbert, W. Klyne, V. Prélog, and G. Snatzke, *Helv. Chim. Acta*, **54,** 491 (1971).

(14) H. Falk, P. Reich-Rohrwig, and K. Schlögl, *Tetrahedron*, **26,** 511 (1970).

(15) K. Mislow, M. Brzechffa, H. W. Gschwend, and R. T. Puckett, *J. Am. Chem. Soc.*, **95,** 621 (1973).

(16) R. C. Cambie, D. R. Crump, W. A. Denny, and T. J. Fullerton, *Aust. J. Chem.*, **24,** 1237 (1971).

(17) K. M. Wellman, P. H. A. Laur, W. S. Briggs, A. Moscowitz, and C. Djerassi, *J. Am. Chem. Soc.*, **87,** 66 (1965).

(18) J. Barry, H.-B. Kagan, and G. Snatzke, *Tetrahedron*, **27,** 4737 (1971).

(19) W. J. Gottstein and L. C. Cheney, *J. Org. Chem.*, **30,** 2072 (1965).

ACKNOWLEDGMENTS

Presented in part at the 167th ACS National Meeting, Los Angeles, Calif., March 1974, MEDI 45. At that time, the stereochemistry of (−)-*Ib* was erroneously assigned as (2*S*, 4*S*).

Abstracted in part from the thesis submitted by E. M. Kandeel to Washington State University in partial fulfillment of the Doctor of Philosophy degree requirements.

Supported by Grants MH21009 from the National Institute of Mental Health and DA00117 from the National Institute on Drug Abuse.

Pharmacokinetics of Drug Permeation through Human Skin

S. K. CHANDRASEKARAN ˣ, W. BAYNE, and J. E. SHAW

Received August 8, 1977, from *Alza Research, Palo Alto, CA 94304.* Accepted for publication January 30, 1978.

Abstract ☐ Based on sorption and permeation characteristics of scopolamine in human skin *in vitro* and drug elimination kinetics obtained from pharmacokinetic studies, a mathematical model was developed for estimating and optimizing the temporal pattern of scopolamine delivery from a transdermal therapeutic system through human skin *in vivo.* Experimentally measured scopolamine delivery *in vivo* conformed to this model.

Keyphrases ☐ Permeation, cutaneous—scopolamine, mathematical model for pharmacokinetics in human skin ☐ Scopolamine—cutaneous permeation, mathematical model for pharmacokinetics in human skin ☐ Pharmacokinetics—cutaneous permeation of scopolamine, mathematical model for human skin ☐ Dosage forms—transdermal therapeutic system for scopolamine delivery, mathematical model for pharmacokinetics ☐ Anticholinergics—scopolamine, cutaneous permeation, mathematical model for pharmacokinetics in human skin

Considerable attention has been focused on drug permeation through skin *in vitro* (1–3). The principal resistance to drug permeation through intact human skin resides within the stratum corneum, which is comprised of dead, partially desiccated, keratinized epidermal cells (3). Transdermal permeation of drugs occurs by Fickian diffusion, with most of the gradient in drug concentration across the entire skin being localized within the stratum corneum (3). There is an experimentally observed disparity between the steady-state diffusivity of the drug in skin and the unsteady-state value computed from transient (time-lag) permeation measurements. This discrepancy can be reconciled using the dual-sorption model, which invokes the coexistence of dissolved and mobile sorbed molecules in equilibrium with site-bound and immobile molecules within the skin (4).

Little effort has been directed to a quantitative understanding of drug permeation through skin *in vivo,* correlation with *in vitro* skin permeation, and a quantitatively understood application of transdermal drug permeation principles to systemic drug administration. The purpose of this study was to examine the kinetics of scopolamine sorption and permeation in human skin to achieve predictable transdermal drug delivery under clinical conditions.

THEORY

***In Vitro* Skin Permeation**—Previously (4), the basic validity of the dual-mode sorption model was demonstrated in the analysis of the permeation characteristics of scopolamine through human skin *in vitro.* The model postulates that sorption occurs by two mechanisms, the first mechanism being a simple dissolution producing mobile and freely diffusible molecules and the second being an adsorption process producing nonmobile molecules that do not participate in the diffusion process. If it is assumed that exchange between mobile and immobile species is rapid compared with the diffusion process and, thus, that a local equilibrium exists between the mobile and immobilized species, the drug concentration in the skin is governed by (4):

$$\left[1 + \frac{C_I{}^*b^*/k_D}{(1 + C_Db^*/k_D)^2}\right]\frac{\partial C_D}{\partial t} = D\frac{\partial^2 C_D}{\partial x^2} \qquad \text{(Eq. 1)}$$

where the second term within brackets on the left-hand side arises as a consequence of drug immobilization.

Pharmacokinetics—*Oral*—For scopolamine administered orally, the plasma concentration can be represented adequately by a two-compartment pharmacokinetic model after the completion of absorption (5):

$$C_p = Ae^{-at} + Be^{-bt} \qquad \text{(Eq. 2)}$$

0022-3549/ 78/ 1000-1370$01.00/ 0