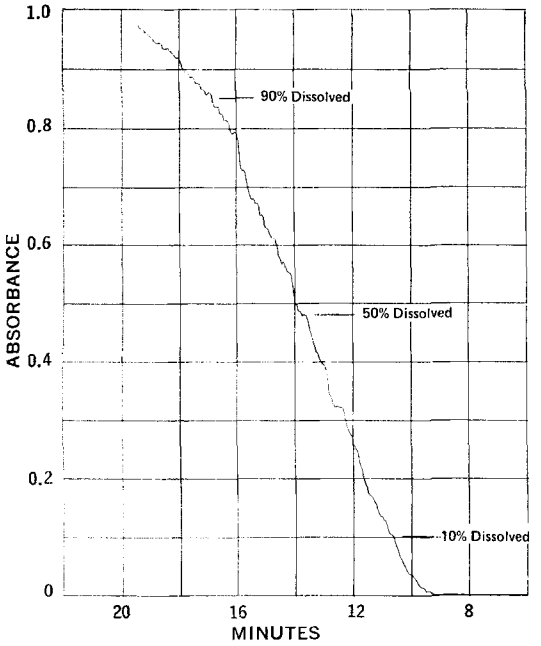


Figure 7—*Absorbance* versus *time: 300-mg. film-coated tablets of Drug A in simulated gastric solution (without pepsin); 0.2-cm. flow-cell at 391 nm.; 100% label claim concentration = 0.950 absorbance units.*

Values for *y*-intercepts appear to approach a limiting value of 9999+. This value is the highest number obtainable on the multipot dial. Although these numbers are arbitrary, 9999+ is analogous to 100% transmittance since the ordinate represents infinite dilution or 0% concentration.

In addition to monitoring concentration dynamics during a dissolution or kinetic study, the concentration converter allows for rapid analysis of solutions assayed by colorimetric or spectrophotometric methods. Samples can be quickly pumped through the flow-cell; their concentrations can be read directly from the chart rather than converting an absorbance value to concentration by means of absorptivity calculations or working curves.

While the primary advantage of the concentration converter in this study was direct display of a concentration parameter, the instrument also permits the presentation of absorbance and percent transmittance data on a recording chart simply by switching the multirange switch on the converter.

REFERENCES

(1) L. C. Schroeter, J. E. Tingstad, E. J. Knoechel, and J. G. Wagner, *J. Pharm. Sci.*, **51**, 865(1962).

(2) G. Levy, J. R. Leonards, and J. A. Procknal, *ibid.*, **54**, 1719 (1965).

(3) E. Nelson, *J. Amer. Pharm. Ass., Sci. Ed.*, **48**, 96(1959).

(4) J. A. Hersey, *Mfg. Chem. Aerosol News*, **Feb. 1969**, 32.

(5) H. Macdonald, F. Pisano, J. Burger, A. Dornbush, and E. Pelcak, *Clin. Med.*, **76** (12), 30(1969).

ACKNOWLEDGMENTS AND ADDRESSES

Received July 24, 1970, from the *Pharmaceutical Product Development Department, Lederle Laboratories, American Cyanamid Company, Pearl River, NY 10965*

Accepted for publication September 17, 1970.

The authors acknowledge the technical assistance of Mrs. Jane Davis and Mr. Michael O'Dowd.

NOTES

Absolute Configuration of (+)-*trans*-2-*o*-Tolyl-*trans*-5-hydroxycyclohexanol: Metabolite of Racemic *trans*-2-*o*-Tolylcyclohexanol

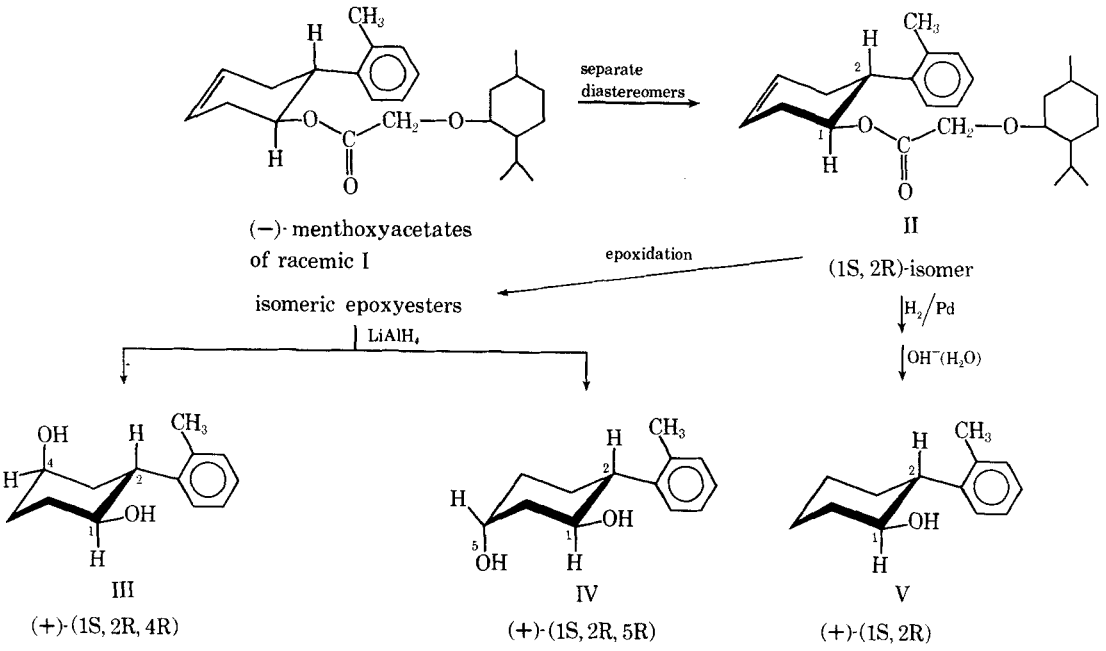
ALAIN C. HUITRIC, N. PETER McGRAW*, and BETTY R. LOWRY

Abstract □ The absolute configuration of the urinary metabolite (+)-*trans*-2-*o*-tolyl-*trans*-5-hydroxycyclohexanol, isolated after administration of racemic *trans*-2-*o*-tolylcyclohexanol in male Holtzman rats, was established by relating it chemically to (1S,2R)-(+)-*trans*-2-*o*-tolylcyclohexanol of known absolute configuration. The results give unequivocal proof that the original tentative assignment of (1S,2R,5R)-(+)-*trans*-2-*o*-tolyl-*trans*-5-hydroxycyclohexanol is correct.

Keyphrases □ (+)-*trans*-2-*o*-Tolyl-*trans*-5-hydroxycyclohexanol, urinary metabolite—absolute configuration □ Urinary metabolites—absolute configuration of (+)-*trans*-2-*o*-tolyl-*trans*-5-hydroxycyclohexanol

In an earlier publication (1), the authors reported the characterization of a major rat urinary metabolite of racemic *trans*-2-*o*-tolylcyclohexanol as the dextrorotatory axial C-5 ring hydroxylated product *trans*-2-*o*-tolyl-*trans*-5-hydroxycyclohexanol (IV). The characterization was done by NMR and by comparison with authentic racemic IV previously synthesized in this laboratory (2). In the same publication, a tentative assignment of absolute configuration of the metabolite was made by comparison of its ORD curve with that of (1S,2R)-(+)-*trans*-2-*o*-tolylcyclohexanol (V) (3). The assignment was tentative because of the lack of direct information on the effect of the remote hydroxyl group at C-5 on the Cotton effects of the aromatic chromophore at C-2.

Unequivocal proof is now presented that the original assignment of (1S,2R,5R) is correct. The proof of absolute configuration was obtained by relating (+)-*trans*-2-*o*-tolyl-*trans*-5-hydroxycyclohexanol (IV) chemically to (1S,2R)-(+)-*trans*-2-*o*-tolylcyclohexanol (V), the absolute configuration of which was previously reported (3) and recently confirmed by single crystal X-ray



Scheme I

diffraction analysis of its 3-nitro-4-bromobenzoate derivative (4).

EXPERIMENTAL AND DISCUSSION

(+)-*trans*-2-*o*-Tolyl-*trans*-5-hydroxycyclohexanol (IV) was related chemically to V by the procedure depicted in Scheme I.

Known racemic *trans*-5-*o*-tolylcyclohexen-4-ol (I) (2) was converted to the diastereomeric (−)-menthoxyacetate esters by a known method (4). The diastereomeric esters were separated by crystallization, and the separation was monitored by NMR (5). Isomer II {m.p. 73–74°, $[\alpha]_D^{27}$ −25.2° (c 4.3, chloroform)} yielded (+)-(1S, 2R)-2-*o*-tolylcyclohexanol (V) upon hydrogenation of the double bond followed by basic hydrolysis of the ester.[1] Since the absolute configuration of V has been established as (1S,2R) with certainty (4), this also establishes the absolute configuration on carbons 1 and 2 of II as (1S,2R). The introduction of the axial hydroxyl group at position 4 or 5 through epoxidation of the double bond in II, followed by lithium aluminum hydride reduction of the epoxy esters, does not cause any change in the configuration at carbons 1 and 2. Therefore, the optically active diols, III and IV, also have the (1S,2R) configurations. Diols III and IV were separated by chromatography and characterized by comparison of their NMR spectra with those of the known racemic compounds (2). (1S,2R,-5R)-(+)-*trans*-2-*o*-Tolyl-*trans*-5-hydroxycyclohexanol (IV) obtained by Scheme I has $[\alpha]_D^{25}$ + 44.8°, and its ORD curve is qualitatively the same as that reported for the metabolite (1). The metabolite was not purified sufficiently to permit assignment of its optical purity with certainty.

Since metabolite IV, obtained from racemic V, has the absolute configuration (1S,2R,5R), it seems logical to deduce that it has resulted from a stereoselective hydroxylation of the (1S,2R) enantiomer V. This means that the (1R,2S) enantiomer (the mirror image of V) is not metabolized by the same pathway.

[1] The product is identical to authentic V in specific rotation and rotatory dispersion.

REFERENCES

(1) D. R. Galpin, T. G. Cochran, and A. C. Huitric, *Biochem. Pharmacol.*, **18**, 979(1969).

(2) J. B. Carr and A. C. Huitric, *J. Org. Chem.*, **29**, 2506(1964).

(3) D. R. Galpin and A. C. Huitric, *J. Pharm. Sci.*, **57**, 447(1968).

(4) A. Camerman, L. H. Jensen, T. G. Cochran, and A. C. Huitric, to be published.

(5) D. R. Galpin and A. C. Huitric, *J. Org. Chem.*, **33**, 921(1968).

ACKNOWLEDGMENTS AND ADDRESSES

Received July 30, 1970, from the *College of Pharmacy, University of Washington, Seattle, WA 98105*

Accepted for publication August 27, 1970.

This investigation was supported in part by Research Grant MH 12204 from the National Institute of Mental Health, U. S. Public Health Service.

* NSF Undergraduate Research Participant; Recipient of the 1970 Lunsford Richardson Regional Honorable Mention award for a manuscript based in part on this research.