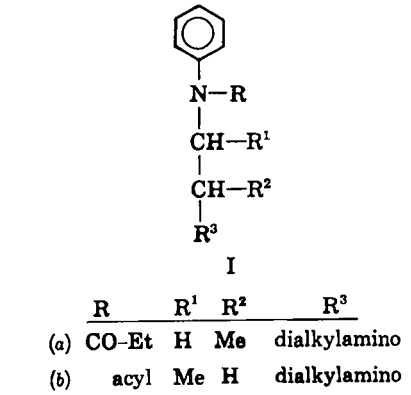
Resolution and Absolute Configuration of (+)-α-Anilinopropionic Acid

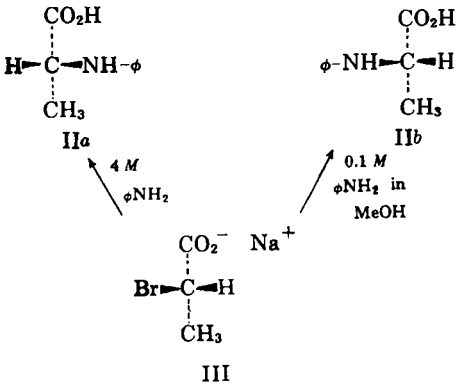
Sir:

We have previously reported (1, 2) the absolute configuration of certain basic anilide analgesics of type I*a* (3, 4). As a continuation of our interest in this area, we wished to determine further the configuration of various analgesics represented by formula I*b* (3–6). Since these compounds (I*b*) contain an anilino moiety attached to an asymmetric carbon atom, a configurational correlation could be accomplished by relating such compounds to a configurationally known α-anilino structure. There are, however, no structures possessing features of I*b* whose absolute stereochemistry is known. A compound which conceivably can be transformed into structures of type I*b* is α-anilinopropionic acid (7) (II). We wish to describe its optical resolution and configurational assignment.



I

	R	R¹	R²	R³
(*a*)	CO–Et	H	Me	dialkylamino
(*b*)	acyl	Me	H	dialkylamino



III

The resolution of II*a* was accomplished by crystallization of its quinine salt from acetone-methanol. Large triclinic crystals, m.p. 199–201°, $[\alpha]_D^{22°}$ − 126° (*c* 2% in water), were formed after the solution stood for 24 hours at 25°. Two subsequent recrystallizations produced crystals which showed no change in rotation or melting point.

Anal.—Calcd. for $C_{29}H_{35}N_3O_4$: C, 71.21; H, 7.21; N, 8.58. Found: C, 71.11; H, 7.33; N, 8.90.

Treatment of the quinine salt with aqueous 1 *N* sodium hydroxide followed by extraction with chloroform and acidification of the aqueous solution to pH 4 afforded the resolved (+)-amino acid (II*a*), m.p. 149–150°, $[\alpha]_D^{23°}$ +71° (*c* 2% in ethanol). The solid state infrared spectrum of II*a* is very similar to racemic II (7).

Our configurational assignment of II*a* is based upon the conclusions of Cowdrey, Hughes, and Ingold (8), who have rigorously established the mechanism and steric course of displacement reactions on optically active sodium α-bromopropionate. L-(−)-α-Bromopropionic acid was prepared according to the procedure of Greenstein (9) and converted to the sodium salt by titration with methanolic sodium hydroxide or sodium methoxide. Removal of solvent resulted in a quantitative yield of the sodium salt (III), $[\alpha]_D^{25°}$ +6.0° (*c* 5% in water). When III was heated in pure aniline, partially racemic II*a*, $[\alpha]_D^{22°}$ +28.5° (*c* 4% in ethanol), was produced. Carrying out the reaction of 0.1 *M* III in 4 *M* methanolic aniline likewise afforded II*a*, $[\alpha]_D^{23°}$ +7.0° (*c* 4% in ethanol). When the concentration of aniline was reduced to 0.1 *M*, the enantiomeric product (II*b*), $[\alpha]_D^{23°}$ −9.0° (*c* 4% in ethanol), was formed.

The aforementioned results are consistent with the established stereochemical course of displacement reactions of III (8). In both pure or 4 *M* aniline the net effect is inversion due to S_N2 attack by aniline. However, in 0.1 *M* aniline there is net retention of configuration due to neighboring carboxylate anion participation (8). Since III is known to have the L-configuration (10), an S_N2 displacement by aniline should afford a product in the D-series. Thus, (+)-α-anilinopropionic acid is represented by projection formula II*a* and possesses the D-configuration.

REFERENCES

(1) Portoghese, P. S., and Larson, D. L., THIS JOURNAL, 51, 1115(1962).
(2) Portoghese, P. S., *ibid.*, 51, 1197(1962).
(3) Wright, W. B., Jr., Brabander, H. J., and Hardy, R. A., Jr., *J. Org. Chem.*, 26, 476(1961).
(4) Wright, W. B., Jr., Brabander, H. J., and Hardy, R. A., Jr., *ibid.*, 26, 485(1961).
(5) Kigasawa, K., Sugahara, H., Hiiragi, M., and Fukawa, K., *J. Pharm. Soc. Japan*, 83, 696(1963).
(6) Kigasawa, K., Sugahara, H., and Hiiragi, M., *ibid.*, 83, 689(1963).
(7) Tiemann, H., *Ber.*, 15, 2034(1882).
(8) Cowdrey, W. A., Hughes, E. D., and Ingold, C. K., *J. Chem. Soc.*, 1937, 1208.
(9) Fu, S. J., Birnbaum, S. M., and Greenstein, J. P., *J. Am. Chem. Soc.*, 76, 6054(1954).
(10) Greenstein, J. P., and Winitz, M., "Chemistry of the Amino Acids," Vol. 1, John Wiley and Sons, Inc., New York, N. Y., 1961, p. 165.

PHILIP S. PORTOGHESE

Department of Pharmaceutical Chemistry
College of Pharmacy
University of Minnesota,
Minneapolis.

Received October 30, 1963.
Accepted for publication December 18, 1963.

Books

REVIEWS

A Bibliography of the Tabletting of Medicinal Substances. Compiled by A. J. EVANS and D. TRAIN. The Pharmaceutical Press, 17 Bloomsbury Square, W.C. 1, England, 1963. 159 pp. 14 × 18.5 cm.

A comprehensive bibliography of publications on medicinal tabletting is presented classified into five main groups: general, tablets, tabletting practice (with subdivisions for granulation, compression, coating, standardization and variation, packaging and storage), materials, and fundamentals. In all, it contains about 900 references from the 1945–1961 period as well as references to fundamental papers published since 1935. The authors explain that they hope to supplement the volume with additional references as well as publications appearing since 1961. Author and subject indexes are provided.

Human Aging. Edited by J. E. BIRREN, R. N. BUTLER, S. W. GREEHOUSE, L. SILOLOFF, and M. R. YARROW. Public Health Service, National Institutes of Health, Bethesda, Md. Available from the Superintendent of Documents, U. S. Government Printing Office, Washington 25, D. C. 1963. xi + 328 pp. 17 × 25 cm. Price $3.

The efforts of 22 investigators from the National Institutes of Mental Health toward elucidating the biological and behavioral aspects of the human aging process are presented. The entire volume deals with the study of 47 aged males, and the authors note that the study should be considered a pilot rather than a definitive study. Some 15 phases of the study are described in detail.

The Clinical Chemistry of Monoamines. Edited by H. VARLEY and A. H. GOWENLOCK. Elsevier Publishing Company, Inc., 52 Vanderbilt Ave., New York 17, N. Y., 1963. xvi + 242 pp. 16.5 × 24 cm. Price $11.

The volume reports a symposium organized around three major topics: the clinical chemistry of catecholamines, the clinical chemistry of 5-hydroxyindoles, and pharmacological and toxicological aspects of monoamines. The volume will be of general interest and utility to pharmaceutical scientists particularly the papers covering the determination of catecholamines in biological materials, the determination of metabolites of catecholamines by chromatographic and other techniques, thin-layer chromatography in the diagnosis of phaeochromocytoma and malignant argentaffinoma, the formation and metabolism of hydroxyindoles, and the toxicology of monoamine oxidase inhibitors and tranquilizers. A subject index is appended.

Analysis Instrumentation, 1963. Edited by L. J. FOWLER, R. D. EANES, and T. J. KEHOE. Plenum Press, Inc., 227 West 17th St., New York 11, N. Y., 1963. x + 261 pp. 21.5 × 28 cm. Price $12.50.

A survey of analytical automation is presented in this volume which reports the proceedings of an annual symposia sponsored by the Instrument Society of America. Among the papers presented were those on methods of calibrating the process gas chromatograph, sampling systems and methods for precise analyzer pressure control, polymer molecular weight distribution measurement by liquid chromatography, potentiometric determination of chloride impurity in various salts, continuous measurement of moisture in flowing solids, and quantitative analysis by charged particle bombardment. The papers are well illustrated with pictures, figures, and graphs. Only an author index is provided.

Medical Mycology. By C. W. EMMONS, C. H. BINFORD, and J. P. UTZ. Lea & Febiger, 600 S. Washington Square, Philadelphia 6, Pa., 1963. 380 pp. 17.5 × 26 cm. Price $14.

A general introduction to general mycology is presented with detailed descriptions, clinical descriptions, diagnostic clues, directions for diagnostic laboratory procedures, and information about environmental sources of infection. The first seven chapters introduce the reader to mycology, medical mycology, and some of the general problems presented by mycoses. The remaining chapters are devoted to specific mycoses or groups of closely related mycoses. Appendices present information on culture