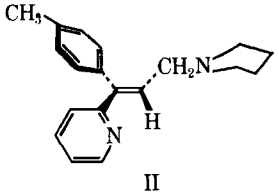
Assignment of Absolute Configurations to Receptor Sites and Drugs

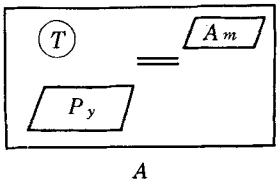
Sir:

Based on the facts that racemic 9-(1′-[2′-dimethylamino]propyl) - 10 - thia - 1,9 - diazaanthracene, isothipendyl (I) is antihistaminically active and that the antihistaminically more active geometric isomer of 1-(2′-pyridyl)-1-(*p*-methylphenyl)-3-pyrrolidinoprop-1-ene, triprolidine (II) has the *trans*-configuration and exhibits an ultraviolet spectrum characteristic of vinyl pyridine and not styrene, Barlow (1) proposed *A* as the hypothetical antihistaminic receptor to which II, in the conformation written (1) presents its lower face. However, the equally probable mirror image receptor configuration (*B*) may be deduced upon adsorption by the opposite face of II.

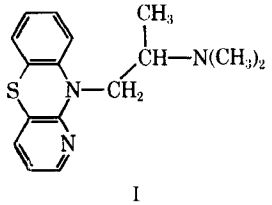
Nevertheless, assuming that *A* is the receptor configuration, Barlow's conclusion (1) that (+)-1 - (2′ - pyridyl) - 1 - (*p* - chlorophenyl) - 3 - dimethylaminopropane, (+)-chlorpheniramine, the antihistaminically more active antipode, has the (R)-configuration (III) is unwarranted since III



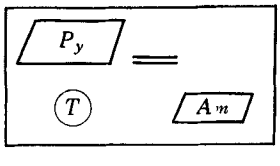
II



A

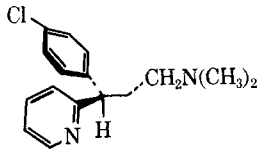


I



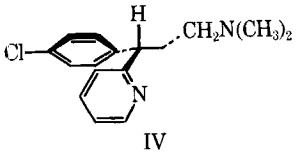
B

(R)



III

(S)



IV

(complementary to *A*) with the methine hydrogen toward the receptor surface, presents the same receptor pattern (*A*) as IV, the (S)-configuration with the hydrogen away from the receptor surface. The adsorption of (+)-chlorpheniramine with the hydrogen toward the receptor is clearly arbitrary. Thus, even if one knew the absolute configuration of the (+)-pheniramines to be (R) there would be no justification for assigning *A* as the absolute configuration of the hypothetical antihistaminic receptor since presentation of the upper face of III (methine hydrogen away from the receptor surface) affords the receptor pattern *B*.

Any argument based upon steric considerations, for example, that the receptor should adsorb to the bottom face of III since this represents the sterically less hindered approach to the molecule, is equally arbitrary and is not in keeping with current concepts regarding the conformational mobility and adaptability of proteins (2, 3) or with the related duality of conformational (4) and configurational (5) requirements of analogs of model drugs presumably acting on the same receptors.

The topography and configuration of the receptor, or more likely, the drug-bound receptor, may be deduced only for the selected case where one face of a conformationally rigid molecule, presenting the requisite configuration and pharmacophoric array, is accessible for binding. Indeed, conclusions based upon such models need not be valid for conformationally less restrained systems or for systems exhibiting chemical and spatial differences in peripheral groups. Assuming involvement of the same receptor and possible accessory binding or hindering moieties, these peripheral groups may modify the receptor–drug interaction and result not only in different modes of attachment to the receptor (4) but also in inversion of optical specificity (5). Since the

topography of the hypothetical antihistaminic receptor and/or drug-bound receptor is unknown, *A* and *B* should only be looked upon as highly schematized two-dimensional representations of a three-dimensional pattern for the bound receptor. In addition, the structures presented here are not necessarily uniformly representative of the conformations of the bound drug. There is no evidence to suggest that the conformationally mobile antihistamines are bound in their most stable conformations nor is there any evidence to suggest that I, II, and IV bind to the hypothetical receptor in the same way.

Finally, it is clear that Barlow's (1) rationalization leading to assignment of the (S)-configuration for the antihistaminically more active antipode of isothipendyl (I) is subject to the same objections already discussed. Accordingly, this assignment of configuration, if correct, is only fortuitously so. While the α-methyl may sterically inhibit the drug receptor binding as apparently suggested (1), it may instead contribute to and thus re-enforce the other drug–receptor interactions through hydrophobic and more highly distant specific van der Waals interactions with the receptor. The latter possibility would lead to selection of the (R)-configuration as the more active antipode. Neither observation is necessarily productive of sound configuration-activity relationships without data on the desmethyl analog as well.

The finding (6) that the absolute configuration of all the (+)-pheniramines is (S) and not (R) as proposed by Barlow (1) does not affect this critique, and we obviously defer assignment of configuration to the hypothetical antihistaminic receptor until more definitive experiments, now in progress, are completed.

(1) Barlow, R. B., "Introduction to Chemical Pharmacology," 2nd ed., John Wiley & Sons, Inc., New York, N. Y., 1964, pp. 371–374, and references cited therein.
(2) Koshland, D. E., Jr., "Proceedings of the First International Pharmacological Meeting," Stockholm, 1961, vol. 7, Pergamon Press Ltd., London, 1963, p. 161, and reference cited.
(3) Belleau, B., and Lacasse, *J. Med. Chem.*, **7**, 768(1964); Belleau, B., *ibid.*, **7**, 776(1964).
(4) Smissman, E. E., and Steinman, M., *ibid.*, **9**, 455 (1966); Portoghese, P. S., Abstracts of the 153rd Meeting of the American Chemical Society, Medicinal Chemist Section, April 1967, Miami Beach, Fla., M/14.
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(6) Shafi'ee, A., and Hite, G., Abstracts of the 153rd Meeting of the American Chemical Society, Medicinal Chemistry Section, April 1967, Miami Beach, Fla., M/48.

G. HITE*
A. SHAFI'EE

Division of Pharmaceutical Chemistry
Department of Pharmaceutical Sciences
Columbia University
New York, NY 10023

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* To whom inquiries should be addressed.

Tumor Localizing Agents III. Radioiodinated Quinoline Derivatives

Sir:

For several years we have been interested in developing an agent which would be useful for the diagnostic localization and treatment of melanotic tumors. Our approach to this problem has involved the synthesis of radiolabeled compounds which would selectively localize in these tumors much like radioiodine localizes in the thyroid. In order to achieve this tumor selectivity, the initial selection of compounds for radiolabeling has fallen into two categories, namely: (*a*) precursors of melanin and (*b*) compounds which are known to interact with melanin. Previous publications (1, 2) from this laboratory described the results with several radiolabeled melanin precursors.

In recent years, several reports have appeared indicating that chloroquine has a marked affinity for melanin and is only slowly released from pigmented tissues (3–5). This information prompted us to synthesize a number of radioiodinated analogs of chloroquine and study their distribution in mice with transplanted melanomas. This report describes initial results with one of these radioiodinated analogs.

The general procedure of Price and Roberts (6) was employed to obtain the key intermediate 4-chloro-7-iodoquinoline (V). (Scheme I.)

Ethoxymethylenemalonic ester was condensed with 3-iodoaniline to give ethyl α-carbethoxy-β-(3-iodophenylamino)acrylate (I) in 77% yield, m.p. 88–89°.

Anal.—Calcd. for $C_{14}H_{16}INO_4$: C, 43.21; H, 4.14. Found: C, 43.34; H, 4.11.

The addition of I to refluxing diphenylether afforded 3-carbethoxy-4-hydroxy-7-iodoquinoline (II) in 94% yield. Recrystallization from pyridine gave an analytical sample which starts to sublime at 255°.