Histamine II and Anti-Histaminics

Chemistry, Metabolism and Physiological and Pharmacological Actions

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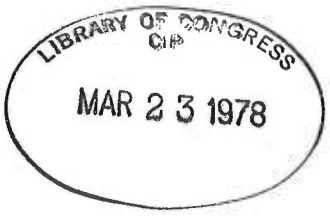

With 92 Figures

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CHAPTER II

Chemistry and Structure-Activity Relationships of Synthetic Anti-Histaminics

SECTION A

Chemistry of Anti-H_1 Histamine Antagonists

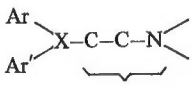
A. F. CASY

With 2 Figures

I. Introduction

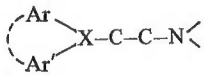
In this Chapter a survey and discussion of the chemistry of compounds which antagonize the effects of histamine at H_1 receptors are presented. ELLIS (1969) has compiled an extensive list of reviews on histamine, 5-hydroxytryptamine, and their antagonists, several of which include some account of the chemical aspects of antihistaminics. Here, attention is drawn in particular to the reviews of WITIAK (1970), DOERGE (1971), and MELVILLE (1973); an extensive review of earlier work is available in Czech (PROTIVA, 1955). Developments in the field are presented periodically in *Annual Reports in Medicinal Chemistry* sponsored by the Division of Medicinal Chemistry of the American Chemical Society, e.g. TOZZI (1972).

Most compounds that are effective at low dose levels in antagonizing histamine at H_1 receptor sites (ASH and SCHILD, 1966) may be described by the general structure (1) where Ar is aryl (including phenyl), substituted phenyl and heteroaryl groups such as 2-pyridyl, and Ar′ is arylmethyl ($ArCH_2$) or a second aryl group. The unit X may be nitrogen, saturated (sp^3) carbon-oxygen (i.e., an ether C–O linkage), or



β-aminoethyl side chain

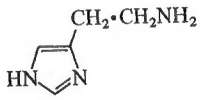
(1)



(2)

a saturated carbon linked directly to the β-aminoethyl side chain; X–C in (1) may also be replaced by a pair of alkenic (sp^2) carbon atoms, i.e., a carbon-carbon double bond. The terminal nitrogen is part of a tertiary acyclic or alicyclic basic grouping, most commonly dimethylamino ($-NMe_2$) or 1-pyrrolidino ($-N$⬡). Tricyclic derivatives (2) in which the two aromatic rings are bridged are also encountered and these do not differ essentially from the general structure.

It is clear, therefore, that most H_1 antagonists have structures which comprise a double-aromatic unit linked by a two or three atom chain to a tertiary amino basic group. Histamine (3) itself is likewise a molecule of the aryl-saturated chain-basic



(3)

amino group type, but differs from its antagonists in possessing only a single aromatic feature (imidazole) and having a primary ($-NH_2$) basic feature. Remarkably little investigation has been made of the antihistaminic properties of molecules of type (1) with primary aminoethyl side chains.

Most antihistaminics are chemically stable, no members contain labile ester or amide functionalities, and aryl substituents that facilitate oxidation such as phenolic hydroxyl and amino are absent. The phenothiazine group of which promethazine is the prime example is the one most likely to suffer oxidative change through attack at the ring sulphur atom (SCHENKER and HERBST, 1963).

The most important physical property of antihistaminic drugs is that of equilibrium between the base and its conjugate acid, as measured by the pK_a (ALBERT and SERJEANT, 1971). MARSHALL (1955) has measured

$$R_3\overset{+}{N}H \rightleftharpoons R_3N + H^+$$

$$K_a = \frac{[R_3N]\,[H^+]}{[R_3\overset{+}{N}H]}$$

$$-\log K_a = pK_a$$

the pK_a values of a wide range of antihistaminic drugs; some of his results are given in Table 1 and are representative of almost all classes of antihistaminic drugs in clinical use.

Magnitudes found are such that all the compounds will be extensively protonated (90% or greater) at physiologic pH. Thus, application of formula (3a) (ALBERT and SERJEANT, 1971) and taking body pH as 7.2,

$$\text{percent ionized} = \frac{100}{1 + \text{antilog}\,(pH - pK_a)} \qquad (3a)$$

shows that mepyramine will be about 97.8 and chlorpheniramine about 98.9% in the cationic species. In derivatives with a second basic nitrogen, e.g., mepyramine (an ethylene diamine) and triprolidine (a 2-pyridyl derivative), protonation of the nitrogen additional to that which is part of the tertiary-aminoethyl chain is insignificant at pH values close to 7. It is doubtful whether any correlation exists between potency and extent of ionization for antihistaminic bases with pK_a values greater than 8.

Because of their basic properties, antihistamine drugs may be administered orally in the form of water-soluble salts which remain in solution in the gastro-intestinal

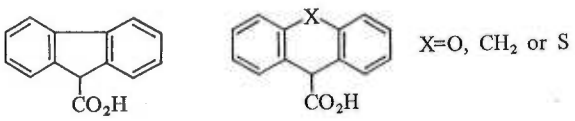
Table 1. pK_a values of some clinically used antihistaminic agents (MARSHALL, 1955)[a]

Name	Section and formula number		pK_a
Mepyramine	B	(9a)	8.85
Tripelennamine	B	(9b)	8.95
Methapyrilene	B	(10, R=H)	8.85
Chloropyrilene	B	(10, R=Cl)	8.70
Bromopyrilene	B	(10, R=Br)	8.63
Antazoline	B	(14)	10.00
Diphenhydramine	C	(21)	8.98
Chlorcyclizine	C	(31b)	8.15
Cyclizine	C	(31a)	8.16
Pheniramine	F	(59a)	9.23
Chlorpheniramine	F	(59b)	9.16
Promethazine	G	(72a)	9.08
Pyrathiazine	G	(72b)	8.91
Phenindamine	I	(103)	8.98

[a] Values are for water as solvent and have been corrected in cases where ethanol was required to keep the base in solution during the pK_a determination.

tract, a factor which facilitates absorption. Hydrochloride and maleate salts are the most popular but salts formed with citric, succinic, and phosphoric acid are also used. Fully ionized quaternary ammonium salts of antihistaminics are less effective, in general, than salts formed with acids, probably as a result of inferior absorption after oral administration and adverse differences in distribution after entry into the blood. However, there are examples of quaternary nitrogen compounds that are effective antihistaminic agents, e.g., *Aprobit* (p. 197) and methohalides of diphenhydramine (p. 182). Such forms are less prone to have central effects (e.g., sedation) due most likely to their difficulty in penetrating the CNS; the enhanced ability of quaternary forms to antagonize acetylcholine, however, may make them clinically unacceptable.

Little information on the partition of antihistaminics between water and lipids is available. An additivity principle has been used to calculate 1-octanol:H_2O partition coefficients of a series of aryl-substituted diphenhydramines relative to the parent (KUTTER and HANSCH, 1969), while direct measurements as well as calculations have been used to establish the same parameters of a series of basic esters of the acids (4) (BOWDEN and YOUNG, 1970).



(4)

Some studies have also been made of the ability of antihistaminics and their metabolites to bind to plasma and tissue proteins—a factor that may have an important bearing upon their levels and duration of action. From spin-spin relaxation rate

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