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Conformation of Histamine Derivatives. 5. Molecular Orbital Calculation of the H_1-Receptor "Essential" Conformation of Histamine[1]

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Conformational energies of histamine and 4-methylhistamine monocations are calculated using the EHT molecular orbital procedure; the results are expressed as potential energy surfaces in which bond rotations (θ_1 for ring–C_β, θ_2 for C_β–C_α) are measured along the axes, and energy variation is indicated by contours. Using the classical Boltzmann partition function and Simpson's rule for normalization, corresponding probability surfaces are generated which take account of the potential surface entropy. Comparing the two surfaces provides regions which are within a given probability contour of histamine but outside this contour for 4-methylhistamine. Thus, at the 99% probability level, three conformational regions defined by the bond rotation angles are indicated as possible "H_1-essential" conformations of histamine: viz. trans (θ_1 = 290–330°, θ_2 = 150–210°) and gauche (θ_1 = 260–280°, θ_2 = 30–90° and θ_1 = 290–320°, θ_2 = 270–320°). This procedure provides a quantitative basis for comparison with other histamine derivatives and may have a general value for studying relationships between conformation and biological activity of closely related small molecules.

Two types of histamine receptor, H_1 and H_2, have recently been characterized by using selective histamine-like stimulants (agonists) and selective histamine-blocking agents (antagonists).[2] A selective agonist of considerable interest is 4-methylhistamine [4-methyl-5-(2-aminoethyl)-imidazole]; it has about half the activity of histamine at H_2 receptors but only $\frac{1}{500}$th of the activity at H_1 receptors. This marked effect of a 4-methyl substituent on H_1-receptor agonist activity poses an intriguing medicinal chemical problem and provides an opportunity to identify chemical properties of histamine likely to be involved in H_1-receptor stimulation.

We have previously shown[3] by EHT calculation that 4-methylhistamine may differ from histamine in its conformational properties. The calculations suggested that the methyl substituent influences the orientation of the imidazole ring with respect to the side chain and introduces a measure of rigidity through restricting ring rotation. We do not know whether these changes account for the observed biological difference but we can explore this as a possibility. If 4-methylhistamine is ineffective as an H_1-receptor stimulant because of restricted rotation or of its inability to assume a necessary conformation then we can define for histamine the "H_1-essential" conformations, i.e., conformations essential to drug activity which have to be adopted by drug molecules at some stage during productive interaction at the H_1-receptor site. To do this we must find those conformations which are *accessible* to histamine but *inaccessible* to 4-methylhistamine. We have previously argued this in a qualitative manner;[4] in the present paper we make it more quantitative.

Calculations were performed on histamine and 4-methylhistamine monocations in their N_3–H (N^τ–H)[6] tautomeric forms (Figure 1) using the nomenclature and geometry previously given.[5] As before, the conformation is described by the two torsion angles θ_1 and θ_2 which, respectively, represent rotation of the imidazole ring about the bond C_5–C_β, and rotation within the side chain about the bond C_β–C_α. The symmetrical ammonium group was held in a staggered position (θ_3 = 60°) with respect to C_α. In 4-methylhistamine the symmetrical methyl substituent was rotated to minimize the energy for given values of θ_1 and θ_2; for most of the surface the orientation θ_4 = 120° is most favorable, but as θ_1 approaches 0°, θ_4 tends toward 75°, and similarly as θ_1 approaches 360°, θ_4 tends toward 165°.

The total internal molecular energies were calculated

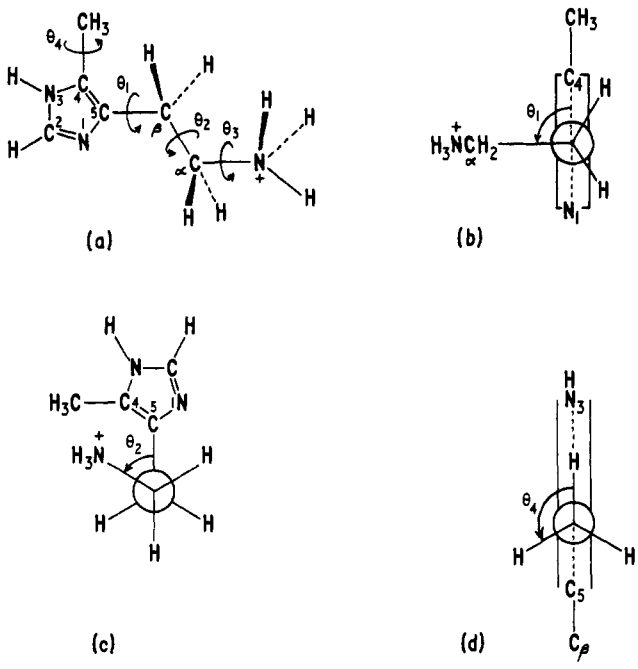

Figure 1. 4-Methylhistamine monocation (N_3–H tautomer) showing (a) atom numbering and torsion angles; (b) torsion angle θ_1 viewed along C_β–C_5 bond, looking from C_β to C_5; (c) torsion angle θ_2 viewed along C_α–C_β bond, looking from C_α to C_β; and (d) torsion angle θ_4 viewed along CH_3–C_4 bond, looking from CH_3 to C_4.

Table I. Energies by EHT of Minimum Energy Conformations for Histamine and 4-Methylhistamine Monocations

Molecule	θ_1, deg	θ_2, deg	Total energy, eV
Histamine	90	60	−799.556
	120	180	−799.599[a]
	120	300	−799.584
	240	60	−799.584
	240	180	−799.599[a]
	270	300	−799.556
4-Methylhistamine	90	60	−903.668
	150	300	−903.678
	180	180	−903.722[a]
	210	60	−903.678
	270	300	−903.668

[a]Indicates global minima.

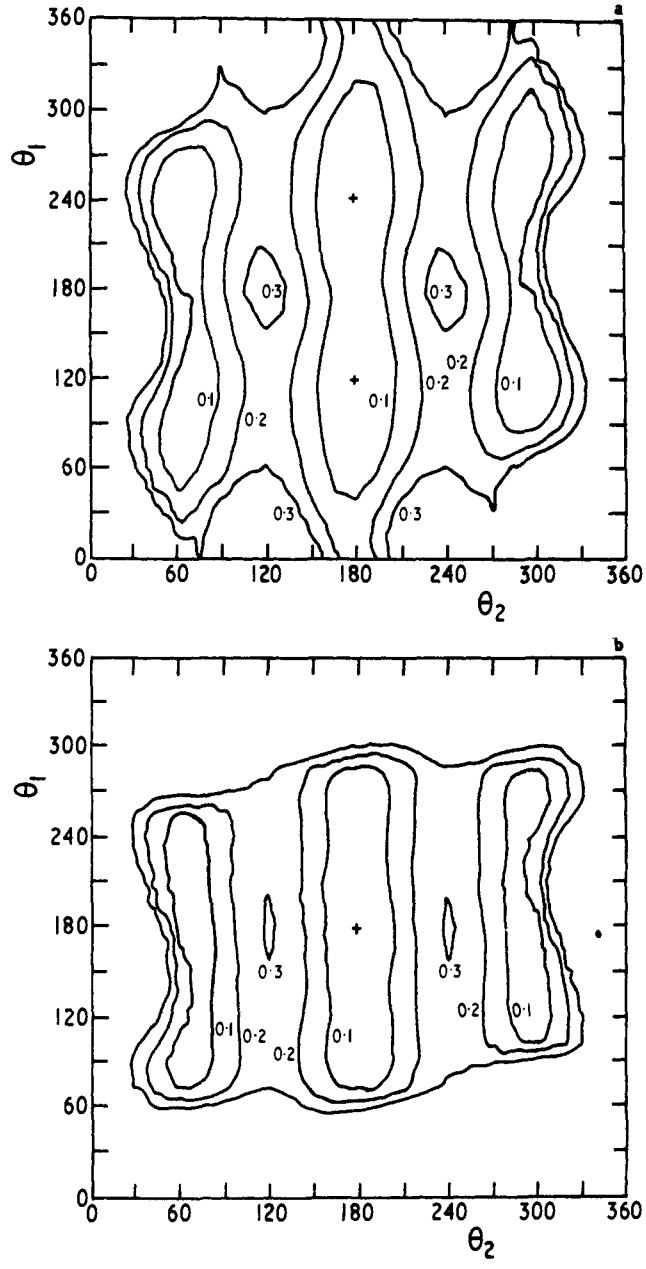

Figure 2. Conformational energy maps of (a) histamine and (b) 4-methylhistamine monocations. The internal energies are indicated by contours spaced by 0.05 eV relative to the global minima (marked by +).

using extended Hückel theory (EHT) taking 15° increments in each angle over the whole geometrical range 0–360°. The results are expressed as a potential energy surface where the variation in the angles is measured along the axes and the variation in energy is indicated by appropriate contours (Figure 2). Stable conformations correspond to minima on these surfaces. The values of the minima found for the two molecules are given in Table I. The justification for using the EHT method is in the measure of agreement previously found,[5,7] between the predictions of conformer population ratios, for histamine and its methyl derivatives, and the values experimentally determined by nuclear magnetic resonance spectroscopy (NMR). This agreement is not obtained when more sophisticated molecular orbital methods such as CNDO or PCILO are employed (see ref 8 for a discussion of this). Furthermore, it must be stressed that in the present paper comparisons are only made between two chemically similar molecules. By using histamine for chemical and pharmacological reference and examining 4-methylhistamine for differences, one can avoid many of the problems associated with assessing the validity of absolute data.

For histamine (Figure 2a) there are three main potential energy troughs corresponding to three stable conformations (one trans and two enantiomerically related gauche forms) each of which has two deep wells. They are defined by the energy contours and enclose the regions of conformational space given by the values of θ_1 and θ_2 corresponding to the boundaries. At the contour 0.1 eV above the global minima (marked by +) the boundaries enclose the ranges θ_1 = 50–275°, θ_2 = 40–90°; θ_1 = 40–320°, θ_2 = 150–210°; and θ_1 = 80–310°, θ_2 = 270–315°. Similarly, 4-methylhistamine (Figure 2b) has three main potential energy troughs corresponding to three stable conformations. By comparison with those of histamine, however, the energy troughs have steeper sides. At the 0.1-eV contour the

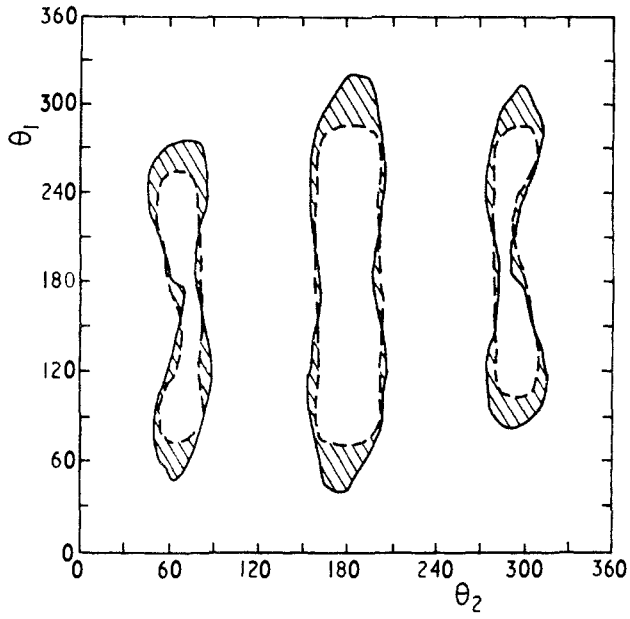

Figure 3. Superimposed 0.1-eV energy contour of histamine (unbroken line) and 4-methylhistamine (dotted line) to reveal the "H_1-essential" conformational regions, indicated by the hatched areas.

boundaries enclose the ranges θ_1 = 70–255°, θ_2 = 45–80°; θ_1 = 70–290°; θ_2 = 155–205°; θ_1 = 105–285°, θ_2 = 280–310°. Thus, for 4-methylhistamine the range of conformations accessible when using the 0.1-eV energy contour as a limit is narrower than it is for histamine. Beyond this range are conformations inaccessible at the level of this choice of limit.

Superimposing the respective 0.1-eV energy contours from the maps of the two molecules shows the regions accessible to histamine but inaccessible to 4-methylhistamine (cf. the hatched areas in Figure 3); those areas within the 0.1-eV energy contour of histamine, which lie outside the corresponding contour for 4-methylhistamine, represent possible "H_1-essential" conformations. At this level, six areas are defined which, through molecular symmetry, correspond to three different conformational regions (see Table II). The selection of 0.1 eV as the critical energy contour is arbitrary, however. Different conformational ranges are available at other energies. A much lower contour, for example, 0.05 eV, would restrict the accessible conformations to smaller ranges of θ (see Table III); conversely, a higher contour (such as 0.2 eV) extends the range.

A better definition can be provided in terms of probabilities, i.e., relative conformational populations. Either the probability of a given conformation or the range of conformations permitted by a given probability may be calculated. The latter is more useful for the present purpose. It is insufficient, however, to obtain the probabilities by simply comparing the internal energies since this presumes that the internal differences are equivalent to free-energy differences; this can only be true if entropy changes are unimportant. Consideration of a surface reveals a danger in using internal energy differences; the relative populations of two valleys in a potential surface depend not only on their depths but also on their curvatures. A broad valley indicates a higher entropy than a narrow valley and so a sufficiently broad valley may have a higher population than a deeper but narrower valley.[1]

Associated with each point (θ_i,θ_j) on the surface is a probability defined as $Z_{ij} = e^{-\epsilon_{ij}/kT}$ where ϵ_{ij} is the energy at the point $\theta_1 = \theta_i$, $\theta_2 = \theta_j$, k is the Boltzmann constant, and T is the absolute temperature, taken as 310 K (37°). The probability function is integrated over the total surface using Simpson's rule to yield Z and normalized by correcting the points using $Z_{ij}^{new} = Z_{ij}^{old}/Z$ so that the function integrates to unity. Thus probability surfaces can be generated, corresponding to the energy surfaces, as in Figure 4 where the axes represent variation in angles (θ_1 and θ_2) and the contours represent probability levels. These surfaces resemble the energy surfaces in contour pattern but give greater weighting to the areas of lower energy. Any region of surface may be specified by an appropriate contour and the potential function can then be integrated within this region; the integral will be a fraction f, lying between the limits of zero and unity which correspond, respectively, to the infinitesimally small region around the global minimum and to the entire surface. The fraction f is the probability that a molecule will be found within the specified region; at the limit f = 1 it is certain to be somewhere on the surface, and at f = 0 it has an infinitesimally small probability of being at the actual global minimum. Since for a large number (N) of molecules it is most probable that $f \times N$ molecules will actually be found in the specified region, f may be used as a measure of the population of the region. Although the values selected for f are arbitrary, the basis for their selection is well defined and the range of values is the same for all molecules. Thus f provides a suitable means of comparing structurally different molecules.

Comparing the regions for f = 0.99 (i.e., the regions accessible to 99% of the molecules at 37°) for histamine and 4-methylhistamine defines the "H_1-essential" conformation at the 99% probability level. This is shown in Figure 5; within the histamine contour (unbroken lines) are the regions accessible to 99% of the histamine molecules; beyond the 4-methylhistamine contour (dotted line) are the regions inaccessible to 99% of the 4-methylhistamine molecules. Between lie six areas (hatched in Figure 5) representing possible "H_1-essential" conformations corresponding to three regions of conformation, viz. one trans and two

Table II. "H_1-Essential" Conformations of Histamine Defined by the 0.1-eV Energy Contours

θ_1, deg	θ_2, deg	Description
255–275	40–90	Gauche
290–320	150–210	Trans
285–310	280–315	Gauche

Table III. Conformational Regions Defined at Different Energy Contours for Histamine and 4-Methylhistamine

Energy contour, eV	Histamine		4-Methylhistamine		Description
	θ_1, deg	θ_2, deg	θ_1, deg	θ_2, deg	
0.05	210–260	50–80	190–240	60–65	Gauche
	75–135	60–80			
	70–290	165–195	80–280	165–195	Trans
	100–150	280–310	120–170	295–300	Gauche
	225–285	280–300			
0.1	50–275	40–90	70–255	45–80	Gauche
	40–320	150–210	70–290	155–205	Trans
	80–310	270–315	105–285	280–310	Gauche
0.2	25–290	35–105	70–260	40–100	Gauche
	0–360	135–225	65–295	140–220	Trans
	70–325	255–325	100–290	260–320	Gauche

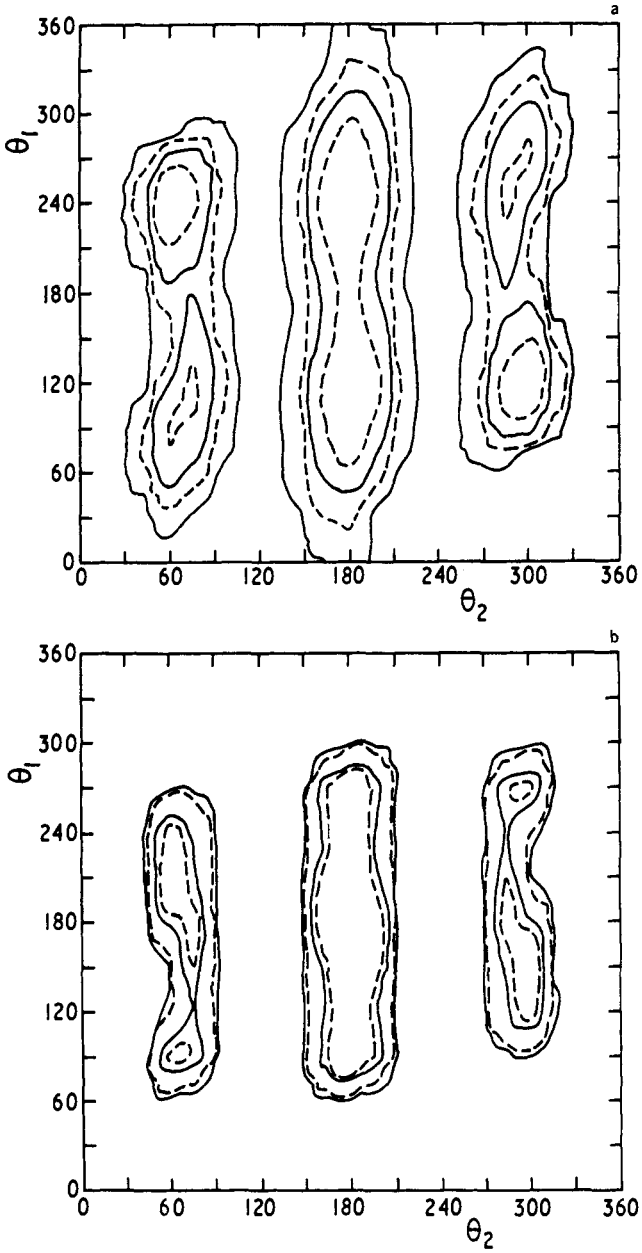

Figure 4. Probability maps of (a) histamine and (b) 4-methylhistamine monocations. The probabilities are indicated by contours at respectively 0.999 (outermost unbroken lines), 0.99 (outermost dotted lines), 0.95 (inner unbroken lines), and 0.70 (inner dotted lines).

gauche. Values of θ with the respective energies for histamine are given in Table IV. None of the conformations corresponds to a stable minimum energy form, although this does not necessarily mean that they are physically improbable. The recently published[9] crystal structure of histamine sulfate shows that histamine dication can assume a nearly coplanar structure ($\theta_1 = 4$ or 9°, $\theta_2 = 180°$) even though the potential energy calculated[5] for this conformation of the lone molecule is approximately 0.1 eV above the minimum.

This procedure identifies three possible "H_1-essential" conformations for histamine and, since they are not stable, implies that they are perhaps involved only in a transient manner while the agonist undergoes a required conformational change. If this is correct, then the question arises as to what other conformations may be involved; one may envisage that a histamine molecule arrives in the neighborhood of the receptor in a more probable form (i.e., near a minimum energy trans or gauche conformation with $\theta_1 \approx$ 120°, $\theta_2 \approx$ 180 or 300°) and that it may either interact directly with the receptor and undergo a change involving the "H_1-essential" conformation or, under a perturbing influence, adopt the "H_1-essential" conformation before forming a drug–receptor complex. Either case requires the ring to rotate partially (from $\theta_1 \approx$ 120° in the minimum energy conformation to $\theta_1 \approx$ 40–60° in the "H_1-essential" conformation) but the former also includes the possibility of there being a functional requirement for the ring to rotate completely through 360°. If this were so, the "H_1-essential" form would truly be transient, and the energy barriers to rotation would be of importance; under these circumstances the trans conformation is much more likely to be active than is the gauche since it has a much lower energy barrier[3] to ring rotation. This was the basis for the previous identification of a trans conformer as the "H_1-essential" form.[4] The present work identifies in addition two gauche conformers for consideration as "H_1-essential" forms provided that the ring is involved in only a partial rotation. Further definition requires comparison with other substituted histamines and this is in progress.

It must be stressed that the above arguments depend on the correct prediction of the energies of nonstable conformations and the energy barriers to rotation. The extended Hückel method is not reliable in this regard and is certainly not suitable for predicting absolute energies. The presumption in the present work is that in comparing two similar molecules the *relative* energies are reasonably well predicted. The same provisos hold for the influence of solvent.

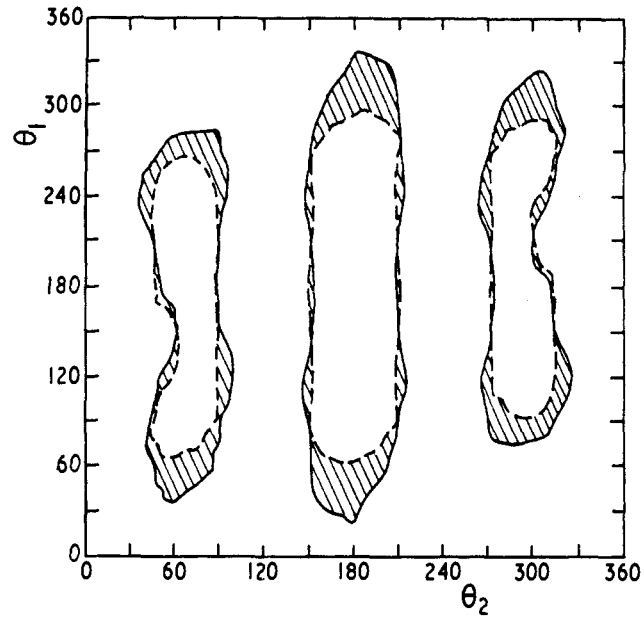

Figure 5. Superimposed 0.99 probability contour of histamine (unbroken line) and 4-methylhistamine (dotted line) to reveal the "H_1-essential" conformational regions, indicated by the hatched areas.

Table IV. "H_1-Essential" Conformations of Histamine Defined by the 0.990 Probability Contours

θ_1, deg	θ_2, deg	Description	ΔE,[a] eV
260–280	30–90	Gauche	0.07–0.20
290–330	150–210	Trans	0.05–0.20
290–320	270–320	Gauche	0.06–0.20

[a] Energy range relative to global minimum for histamine.

Table V. Populations of the Trans Conformer (Mole Fraction, n_t) of Histamine and 4-Methylhistamine Monocations by Different Procedures

Procedure	n_t (histamine)	n_t (4-methylhistamine)	Ref
NMR	0.45	0.45	5
EHT by internal energy difference	0.55	0.75	3
EHT by free-energy difference	0.62	0.67	1, this work

The only test we have is in comparing the predicted trans/gauche conformer ratios with the values found experimentally by NMR.[5] The respective populations of trans conformer monocations at 37°, predicted by EHT, were previously given[3] as 0.55 (histamine) and 0.75 (4-methylhistamine), whereas the value by NMR was the same for either, viz. 0.45 (Table V). Correspondence in the absolute values between EHT prediction and experiment must be regarded as fortuitous especially as the calculations are on isolated molecules, whereas the experiments refer to aqueous solution. What does matter is whether the two methods agree over the differences between molecules; however, as the preceding values show, there is some disagreement since the relative stability of the trans conformer was predicted to be greater for 4-methylhistamine than for histamine (by ~0.5 kcal mol^{-1}) but this was not reflected in the NMR results. The relative populations were predicted, however, on the assumption that the internal potential energy differences between the stable conformations could be equated to the free-energy difference. We have since shown how to refine the predictions, by allowing for the entropy content of the potential energy surface, and that for the histamine monocation this results in a modest *increase* in the predicted trans conformer population[1] (from n_t = 0.55–0.62). Similar refinement for 4-methylhistamine, integrating the surface of Figure 4b around each energy minimum up to a limit of $2kT$, results in a *decrease* in the predicted trans conformer population (from n_t = 0.75–0.67). Thus, taking account of the shape of the energy surface substantially reduces the extent of disagreement between the respective predictions for the two molecules (the relative stabilities now differ by only ~0.1 kcal mol^{-1}), in line with the experimental results. To this extent the EHT predictions are consistent. Further support for the EHT calculations comes from the agreement between calculated barriers to internal rotation derived from EHT and ab initio molecular orbital calculations.[10]

This approach appears likely to have general applicability. In principle, one may compare the conformational properties of a reference material with those of suitable congeners (which need not necessarily be methyl derivatives); differences in conformational accessibility may then be related to biological differences between the molecules. The appearance of a self-consistency within a series would permit one to define conformations "essential" to particular biological activities.

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Tricyclic Quinuclidylidenes as Potential Antihistamine-Bronchodilating Agents

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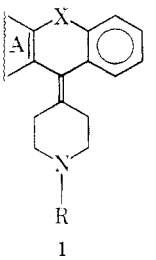
A series of quinuclidylidene derivatives of tricyclic compounds was prepared and examined for their pharmacodynamic effects. In general, the compounds showed primarily an antihistaminic effect.

Previous reports from these[1] and other laboratories[2] have described the pharmacodynamic effects of compounds containing a tricyclic moiety attached via an exocyclic double bond to an N-alkylated piperidine ring as shown in **1**. These compounds have shown potent antihistaminic, antidepressant, and anticholinergic as well as antiserotonin properties in laboratory animals and in man. It was of interest to modify the structure of **1** and replace the N-alkylated piperidine ring by a 3-quinuclidyl system as shown in **2**, especially since several naturally occurring alkaloids and other synthetic quinuclidyl derivatives have shown potent pharmacological activity.[3]

The tertiary carbinols **3** and **4** listed in Table I, required for the dehydration to **2** (Table II), were prepared by the



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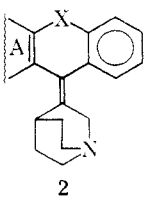

2

X = CH_2CH_2, CH=CH, O, S, etc.

A = phenyl, pyridyl, thienyl, etc.