variation in the activity of a set of congeners. For example, in a set of neutral congeners having log P_0 of 5.5 and a dependence of activity on log P of 0.6 (slope) in the linear relation between log $1/C$ and log P, the difference in activity of derivatives of log P = 0 and log P = 5 will be 3 log units. Unless this large variation in activity can be separated in structure–activity relationship discussions, it is quite difficult to begin to mechanistically classify different functional groups, especially when one gets beyond simple homologous series. How valuable such scales as that in Table III will ultimately be will not be known until more extensive studies have been made.

Acknowledgment.—We wish to thank Miss Catherine Church (Smith Kline and French research associate), Dr. William Glave, Dr. William Dunn, and Mr. David Soderberg for determining a number of the partition coefficients employed in this work. We thank Dr. Paul Craig of Smith Kline and French for the pK_a of *N*-2-hydroxyethylimidazoline.

Crystal Structure of *dl*-Brompheniramine Maleate [1-(*p*-Bromophenyl)-1-(2-pyridyl)-3-*N*,*N*-dimethylpropylamine maleate]

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Racemic brompheniramine maleate crystallizes in space group $P2_1/c$ with a = 9.863 Å, b = 10.836 Å, c = 21.494 Å, and β = 115.83°. The crystal structure was solved by conventional Patterson and Fourier techniques and refined by least squares to weighted and unweighted R factors of 6.37 and 4.55%, respectively. The propylamine chain is fully extended and adopts an asymmetrical disposition with respect to the 2 aryl moieties. The *p*-bromobenzyl group is partially occluded by the asymmetry and the 2-pyridyl ring is exposed, thus giving the molecule an open side. The maleic acid is in the monoanion form and is H bonded to the NMe_2 group. Molecular parameters are close to expected values with the exception of the location of the second base dissociable proton of the maleate, which is engaged in a very short asymmetric intraion H bond of length 2.415 Å.

The antihistaminic drugs as a class are thought to exert their action by successful competition with histamine for the allergic (H1) receptor site on the walls of smooth muscle tissue.[1] The title compound is a potent histamine antagonist and, because receptor sites are difficult to study directly, it was thought that useful information regarding molecular conformations of antihistaminic drugs could be obtained by defining the structure of this effector molecule.

The structure of histamine has recently been completed by two independent groups[2] and, more recently, one of these groups has published their preliminary results of the first X-ray study of an antihistamine.[3] The present work was begun in an attempt to delineate some of the seemingly relevant structural parameters for antihistaminic action. It is reasonable to suppose that if the antihistamine acts as a competitive inhibitor of histamine then there should be some points of significant structural similarity between them. In particular it seemed important to know if the N–N distance in brompheniramine was comparable to the 4.55-Å distance Kier[4] has postulated for the allergically active conformer of histamine. Another molecular parameter of interest was the dihedral angle between the 2 aromatic rings of brompheniramine since these have been implicated in the binding of this molecule to the H1 site.[5]

Experimental Section

Suitable crystals were easily grown by diffusion of Et_2O into a soln of the complex in EtOH. Preliminary oscillation and Weissenberg photographs of a crystal exhibiting $2/m$ symmetry and max dimensions of 0.20 × 0.18 × 0.20 mm, showed the space group to be $P2_1/c$. The crystal lattice data are summarized in Table I, the unit cell parameters being derived by least-squares

TABLE I

Morphology	$2/m$
Space group	$P2_1/c$
a	9.863 ± 0.01 Å
b	10.836 ± 0.007 Å
c	21.494 ± 0.01 Å
cos β	−0.4356 ± 0.0009
β	115.83 ± 0.05°
V	2067.67 Å^3
ρ_{calcd} 4[$C_{20}H_{23}O_4BrN_2$]/cell	1.42 g/cm^3
ρ_{meas}[$(C_2H_5)_2O$/CH_2Br_2]	1.43 g/cm^3
μ	32.6 cm^{-1}

refinement of these parameters using the 2θ, χ, and ϕ values for 12 reflections during the initial stages of data collection on a Picker FACS 1 diffractometer. A total of 3374 different reciprocal lattice points were examined using Ni-filtered Cu K radiation and the diffractometer in the coupled $\theta/2\theta$ scan mode. The 2θ scan speed was 1°/min over a basic peak width of 1.8°, this width being increased as a function of θ to cope with the dispersion of the Cu Kα doublet.[6] Ten-second, fixed-position, background counts were taken on both sides of every Bragg reflection. A check was kept on the stability of the experimental situation during the 5-day course of the data collection by measuring 3 standard reflections after every 30 data reflections. An examination of the standards as a function of time implied no significant crystal slippage or decomposition and so the data were judged accept-

(1) Barlow, R. B., "Introduction to Chemical Pharmacology," Methuen, London, 2nd ed, 1964, p 369.
(2) M. V. Veidis, G. J. Palenik, R. Schaffrin, and J. Trotter, *J. Chem. Soc. A*, 2659 (1969).
(3) G. R. Clark and G. J. Palenik, *J. Amer. Chem. Soc.*, **92**, 1777 (1970).
(4) L. B. Kier, *J. Med. Chem.*, **11**, 441 (1968).
(5) Ref 1, pp 372–373.
(6) Arndt and Willis, "Single Crystal Diffractometry," Cambridge University Press, New York, N. Y., 1966, pp 173–174.

able. Data reduction included corrections for Lorentz and polarization effects[7] and calcn of observational wts according to the expression $w^{1/2} = 2/F_o[T + (kI)^2 + B]^{1/2}$, where T is the total peak count, I is the net peak count, B is the total background, F_o is the derived structure amplitude, and k is a small constant (0.04 in this case) included to allow for minor instrumental errors.[8] A total of 3164 unique and space-group-permissible reflections, of which 2266 satisfied the observed/unobserved criterion that the net counts should not be less than the smaller of 75 counts or 10% of the total background for that reflection, were obtd. The scattering factors used were derived from the published analytical coefficients of Cromer[9] except for the H curve which was that of Mason and Robertson.[10] The data were corrected for the effects of absorption according to the method of Busing and Levy[11] during the later stages of the structure refinement.

A tabulation of the observed and calcd structure factors for this compnd has been submitted to the Depository of Unpublished Data, National Sciences Library, National Research Council of Canada, Ottawa, Canada. A copy of these data may be obtained free of charge from this source.

Structure Solution and Refinement.—A Patterson map computed with coefficients sharpened to "point atoms at rest"[12] unambiguously showed the positions of the 3 unique Br–Br vectors and from a heavy atom phased Fourier synth suitable locations corresponding to the remainder of the pheniramine moiety could be found. The position of the maleate ion was found on a subsequent electron density difference map. The positional parameters so defined along with individual atom isotropic temp factors were subjected to 3 cycles of unit-weighted, full-matrix, least-squares refinement using the locally modified version of ORFLS.[13] During this process, which reduced the conventional residual R {$R = [\Sigma||F_o| - |F_c||]/\Sigma|F_o|$, where F_o and F_c are the observed and calcd structure factors} from 18.0 to 7.7%, a correction term corresponding to the real part of the anomalous dispersion effect for the Br atom ($\Delta f' = -0.529$) was applied[14] and all atoms of the pyridyl ring were treated as C. A difference map computed at this stage made it possible to distinguish the N from the C atoms of the pyridyl ring and showed sensible positions for the H atoms (the position of the second acidic maleate H was deliberately bypassed here since it was desired to have as few errors in the F_c as possible when this atom was being searched for).

Least-squares refinement was contd with observational wts, making the block diagonal approximation, and with correction for the imaginary part of the anomalous scattering by Br ($\Delta f'' = 1.305$). The H atom parameters were permitted to vary but were constrained to isotropic thermal motion, the remaining atoms being allowed to assume their anisotropic form. A final difference map revealed the remaining H atom of the maleate (see later) and regions of electron density in the range −0.3 to +0.3 e/Å^3 very close to Br. The background level of this map was in the range ±0.1 e/Å^3. That the electron density near the Br was due to the inability of the assumed temp factor model to adequately describe the thermal motion of this atom and not to absorption was shown by the fact that after the data were corrected for absorption[11] and the structure rerefined, no change resulted in either the R factor or the structural parameters and the "ripple" remained. The final weighted and unweighted R factors are 6.37 and 4.55%, respectively. The positional and vibrational parameters are contained in Tables II and III, and the molecular numbering scheme used is given in Figure 1. Figure 2 is a stereo pair of the molecular complex as found in this structural detn. Figure 3 depicts the contents of one unit cell viewed parallel to the crystallog a axis. Table IV gives the molecular parameters involving H atoms whereas those for the non-H atoms are found in Figure 1.

Description and Discussion of the Structure. A. Pheniramine Moiety.—The benzene ring is planar with $\chi^2 = 25.6$ and a maximum distance from this plane of 0.014 Å. The pyridyl ring is also planar ($\chi^2 = 7.0$) with a maximum deviation of 0.010 Å. The equations defining these planes are $-0.4273x + 0.6013y - 0.6751z + 1.1812 = 0$ and $0.3878x - 0.7369y - 0.5538z + 5.3962 = 0$, respectively (in this context the x, y, and z axes are parallel to the crystallographic a, b, and c^* axes, respectively, and the unit vectors are 1 Å in length). The dihedral angle between these planes is 103° 25′ and the bonding angle C(4)–C(7)–C(1′) is 109° 24′. The 3 bond angles at C(7) not quoted in Figure 1 are those with H(7) as one of the ligands. When C(4), C(1′), and C(8) are the second ligand the bond angles are 104° 26′, 106° 31′, and 109° 31′, resp (standard error in each case being 2° 18′). Deviations from ideality here are small but

TABLE II

ATOMIC POSITIONAL PARAMETERS AND HYDROGEN ISOTROPIC U'S OBTAINED FROM THE FINAL LEAST-SQUARES CYCLE

Atom	x/a	y/b	z/c	U_{iso}, Å^2
Br	−0.03052 (8)[a]	−0.15502 (5)	0.04388 (3)	
C(1)	−0.0557 (5)	−0.0621 (4)	0.1129 (2)	
C(2)	0.0355 (5)	0.0389 (4)	0.1413 (2)	
C(3)	0.0200 (6)	0.1031 (4)	0.1936 (2)	
C(4)	−0.0827 (5)	0.0674 (4)	0.2185 (2)	
C(5)	−0.1747 (5)	−0.0334 (4)	0.1884 (2)	
C(6)	−0.1622 (5)	−0.0975 (4)	0.1351 (2)	
C(7)	−0.0869 (5)	0.1333 (4)	0.2801 (2)	
C(1′)	−0.0176 (5)	0.0509 (4)	0.3432 (2)	
C(2′)	0.1382 (5)	0.0533 (4)	0.3835 (3)	
C(3′)	0.2033 (6)	−0.0188 (4)	0.4408 (2)	
C(4′)	0.1114 (6)	−0.0925 (5)	0.4579 (3)	
C(5′)	−0.0412 (6)	−0.0904 (6)	0.4148 (3)	
N(6′)	−0.1098 (4)	−0.0214 (4)	0.3585 (2)	
C(8)	−0.2470 (5)	0.1803 (4)	0.2670 (2)	
C(9)	−0.2972 (5)	0.2833 (4)	0.2148 (2)	
N(1)	−0.4419 (6)	0.3450 (1)	0.2078 (1)	
C_a	−0.4752 (6)	0.4593 (4)	0.1657 (2)	
C_b	−0.5759 (5)	0.2606 (4)	0.1807 (2)	
$C_m(1)$	−0.4748 (5)	0.2559 (4)	0.4929 (2)	
$C_m(2)$	−0.3948 (6)	0.3726 (4)	0.4910 (2)	
$C_m(3)$	−0.3730 (6)	0.4245 (4)	0.4403 (2)	
$C_m(4)$	−0.4173 (5)	0.3819 (4)	0.3682 (2)	
O(1)	−0.4976 (5)	0.2354 (4)	0.5429 (2)	
O(2)	−0.5161 (4)	0.1800 (3)	0.4416 (2)	
O(3)	−0.4758 (4)	0.2764 (3)	0.3496 (2)	
O(4)	−0.3951 (4)	0.4537 (3)	0.3293 (2)	
H(2)	0.113 (5)	0.054 (4)	0.128 (2)	0.08 (1)
H(3)	0.067 (6)	0.171 (5)	0.220 (3)	0.08 (2)
H(5)	−0.243 (4)	−0.058 (4)	0.202 (2)	0.07 (1)
H(6)	−0.209 (4)	−0.161 (4)	0.114 (2)	0.06 (1)
H(7)	−0.012 (5)	0.210 (4)	0.286 (2)	0.07 (1)
H(2′)	0.190 (5)	0.109 (5)	0.372 (2)	0.09 (2)
H(3′)	0.296 (5)	−0.020 (4)	0.471 (2)	0.09 (1)
H(4′)	0.161 (5)	−0.134 (5)	0.502 (3)	0.08 (2)
H(5′)	−0.105 (5)	−0.122 (4)	0.431 (2)	0.11 (1)
H(81)	−0.243 (4)	0.210 (3)	0.311 (2)	0.05 (1)
H(82)	−0.329 (5)	0.109 (4)	0.247 (2)	0.09 (1)
H(91)	−0.210 (4)	0.347 (3)	0.229 (2)	0.06 (1)
H(92)	−0.311 (4)	0.258 (3)	0.173 (2)	0.06 (1)
H_m	−0.438 (6)	0.370 (5)	0.250 (3)	0.10 (2)
$H_a(1)$	−0.496 (5)	0.441 (4)	0.123 (2)	0.11 (1)
$H_a(2)$	−0.579 (5)	0.500 (4)	0.162 (2)	0.07 (1)
$H_a(3)$	−0.389 (5)	0.505 (4)	0.187 (2)	0.08 (1)
$H_b(1)$	−0.648 (5)	0.310 (5)	0.187 (2)	0.09 (2)
$H_b(2)$	−0.557 (5)	0.185 (4)	0.205 (2)	0.06 (1)
$H_b(3)$	−0.603 (5)	0.233 (4)	0.137 (2)	0.08 (1)
$H_m(1)$	−0.485 (5)	0.226 (5)	0.405 (2)	0.10 (1)
$H_m(2)$	−0.354 (5)	0.417 (5)	0.533 (2)	0.09 (1)
$H_m(3)$	−0.317 (5)	0.502 (4)	0.450 (2)	0.05 (1)

[a] The figures in parentheses here are the estimated standard deviations in the last figure quoted, these error estimates were obtained from the diagonal elements of the inverse matrix.

(7) Ref 6, p 277.
(8) S. W. Peterson and H. A. Levy, *Acta Crystallogr.*, **10**, 70 (1957).
(9) D. T. Cromer, *ibid.*, *Sect. A*, **24**, 321 (1968).
(10) R. Mason and G. B. Robertson, "Advances in Structure Research by Diffraction Methods," Vol. 2, R. Brill and R. Mason, Ed., Interscience, New York, N. Y., 1966, p 57.
(11) W. R. Busing and H. A. Levy, *Acta. Crystallogr.*, **10**, 180 (1957).
(12) G. H. Stout and L. H. Jensen, "X-ray Structure Determination," Macmillan, New York, N. Y., 1968, pp 272–274.
(13) W. R. Busing, K. O. Martin, and H. A. Levy, "ORFLS," Report ORNL-TM-305, Oak Ridge, Tenn., 1962.
(14) D. T. Cromer, *Acta Crystallogr.*, **18**, 17 (1965).

TABLE III

ANISOTROPIC THERMAL PARAMETERS FOR THE NON-HYDROGEN ATOMS[a]

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
Br	0.1231 (5)[b]	0.0722 (4)	0.0686 (4)	−0.0055 (3)	0.0491 (3)	0.0193 (4)
C(1)	0.069 (3)	0.046 (2)	0.053 (2)	0.010 (2)	0.029 (2)	0.020 (2)
C(2)	0.072 (4)	0.060 (3)	0.070 (3)	−0.003 (3)	0.045 (3)	−0.007 (3)
C(3)	0.073 (3)	0.051 (3)	0.068 (3)	−0.005 (2)	0.037 (3)	−0.009 (3)
C(4)	0.043 (3)	0.040 (2)	0.049 (2)	0.002 (2)	0.019 (2)	0.002 (2)
C(5)	0.046 (3)	0.049 (3)	0.062 (3)	0.002 (2)	0.026 (2)	0.001 (2)
C(6)	0.056 (3)	0.039 (2)	0.059 (3)	−0.004 (2)	0.016 (2)	−0.001 (2)
C(7)	0.051 (3)	0.042 (2)	0.055 (2)	−0.002 (2)	0.023 (2)	−0.002 (2)
C(1′)	0.048 (3)	0.041 (2)	0.044 (2)	−0.003 (2)	0.014 (2)	0.001 (2)
C(2′)	0.050 (3)	0.050 (3)	0.080 (3)	0.005 (2)	0.029 (3)	0.001 (2)
C(3′)	0.050 (3)	0.067 (3)	0.079 (3)	0.010 (3)	0.011 (3)	0.009 (2)
C(4′)	0.073 (4)	0.082 (4)	0.056 (3)	0.022 (3)	0.007 (3)	0.011 (3)
C(5′)	0.068 (4)	0.101 (5)	0.078 (4)	0.036 (4)	0.022 (3)	−0.014 (3)
N(6′)	0.052 (3)	0.078 (3)	0.058 (2)	0.023 (2)	0.010 (2)	−0.008 (2)
C(8)	0.061 (3)	0.043 (2)	0.052 (2)	0.007 (2)	0.030 (2)	0.013 (2)
C(9)	0.056 (3)	0.047 (2)	0.051 (2)	0.002 (2)	0.027 (2)	0.008 (2)
C_a	0.094 (4)	0.047 (3)	0.068 (3)	0.014 (2)	0.042 (3)	0.019 (3)
C_b	0.062 (3)	0.056 (3)	0.064 (3)	−0.002 (2)	0.028 (3)	0.006 (2)
N(1)	0.060 (2)	0.038 (2)	0.043 (2)	0.006 (2)	0.026 (2)	0.012 (2)
O(1)	0.126 (3)	0.105 (3)	0.065 (2)	0.013 (2)	0.056 (2)	−0.016 (3)
O(2)	0.078 (2)	0.054 (2)	0.059 (2)	−0.001 (1)	0.027 (2)	−0.016 (2)
O(3)	0.109 (3)	0.054 (2)	0.052 (2)	−0.015 (1)	0.043 (2)	−0.018 (2)
O(4)	0.106 (3)	0.057 (2)	0.061 (2)	0.033 (2)	0.051 (2)	−0.002 (2)
$C_m(1)$	0.050 (3)	0.063 (3)	0.052 (2)	0.009 (2)	0.020 (2)	0.006 (2)
$C_m(2)$	0.074 (3)	0.063 (3)	0.050 (3)	−0.011 (2)	0.029 (3)	−0.010 (3)
$C_m(3)$	0.083 (4)	0.052 (3)	0.055 (3)	−0.018 (2)	0.036 (3)	−0.021 (3)
$C_m(4)$	0.064 (3)	0.049 (3)	0.054 (3)	0.001 (2)	0.033 (2)	0.007 (2)

[a] Anisotropic thermal motion is described by the expression $\exp[-2\pi(U_{11}h^2a^{*2} + U_{22}k^2b^{*2} + U_{33}l^2c^{*2} + 2U_{23}klb^*c^* + 2U_{13}hla^*c^* + 2U_{12}hka^*b^*)]$. [b] Figures in parentheses here are comparable to those of Table II.

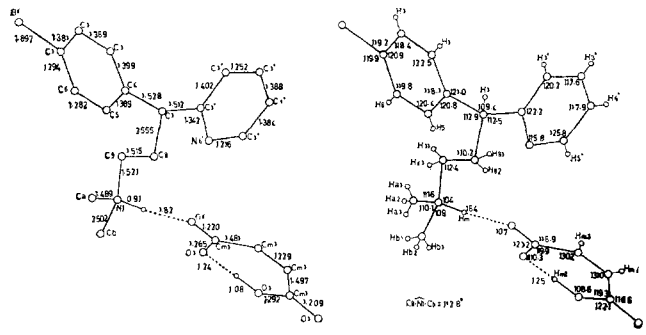

Figure 1.—The atomic numbering scheme and some bond distances and angles. If X is a C, N, or O atom then standard deviations in Br–X, X–X and X–H distances average 0.005, 0.006, and 0.06 Å, respectively. Bond angles of the types Br–X–X, X–X–X, H–X–X, and X–H–X have average standard errors of 0.4, 0.4, 3.0, and 2.0°, respectively. Molecular parameters not shown here are contained in Table IV.

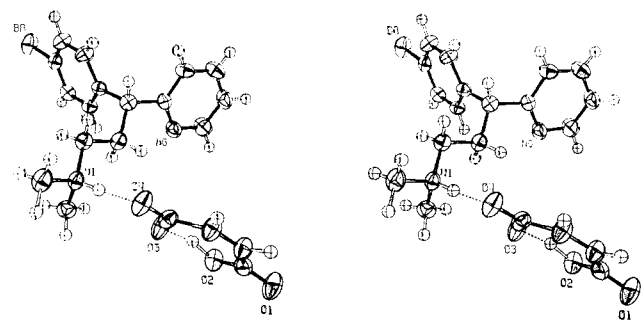

Figure 2.—A computer drawn (C. K. Johnson, "ORTEP", Report ORNL-3794, Oak Ridge National Laboratory, Oak Ridge, Tenn., 1965) stereo pair of the complex. Nonhydrogen atom thermal ellipsoids are scaled to include 35% probability. Hydrogen atoms were assigned artificial isotropic temperature factors of 2.0 Å^2.

may be attributed to a slight bend in the bisector of the angles C(4)–C(7)–C(1′) and C(8)–C(7)–H(7).

Because of the greater basicity of the dimethylpropylamino group over the pyridyl function is it not surprising that the maleate ion is H bonded to this former structural unit. The N(1)–O(4) distance is 2.718 Å and the bond angles at H_m and O(4) are 163° 54′ and 107° 12′, respectively. Further discussion of the maleate ion is deferred to a later section.

The trans disposition of the non-H substituents of the C_α–C_β bond in histamine [corresponding to C(8)–C(9) in this structure] has been correlated with the binding of this molecule to the H1 receptor site[4] and this arrangement has been found in the only other known crystal structure of a histamine antagonist,[3] as well as in that of histamine itself.[2] The torsion angle about the C(8)–C(9) bond in the present compound is 171° 39′ and the molecular arrangement when viewed along this bond direction is shown in Figure 4. Whether or not this trans conformation is a necessary characteristic of a histamine antagonist remains an open question but the above two citations, when taken in conjunction with the present work, suggest that it may be so.

The distance between the 2 more basic N atoms of histamine is at a maximum for the fully extended conformer. This distance has been predicted by Kier[4] for the physiologically active monocation as 4.55 Å and calcd as 4.60 Å from the published data for the doubly protonated form of histamine.[2] The correlation of the inter-N distance with physiologic activity is obviously too great a simplification since the stereospecificity of the receptor–antagonist interaction[15] implies at least 3 "points of attachment." The distance of 5.267 Å between N(1) and N(6′) in bromopheniramine is obviously at variance with those quoted for histamine. Despite the fact that conformational mobility arguments may be invoked which permit these 2 com-

(15) R. T. Brittain, P. F. D'Arcy, and J. H. Hunt, *Nature (London)*, **183**, 734 (1959).

TABLE IV

DISTANCES AND ANGLES INVOLVING HYDROGEN ATOMS

Bond	Distance, Å
C(2)–H(2)	0.96 (4)[a]
C(3)–H(3)	1.00 (6)
C(5)–H(5)	0.95 (5)
C(6)–H(6)	0.87 (4)
C(7)–H(7)	1.11 (5)
C(2′)–H(2′)	0.97 (6)
C(3′)–H(3′)	0.89 (5)
C(4′)–H(4′)	0.96 (5)
C(5′)–H(5′)	0.76 (5)
C(8)–H(81)	0.98 (4)
C(8)–H(82)	1.01 (5)
C(9)–H(91)	0.97 (4)
C(9)–H(92)	0.91 (4)
C_a–H_a(1)	0.93 (6)
C_a–H_a(2)	1.14 (5)
C_a–H_a(3)	1.01 (5)
C_b–H_b(1)	1.03 (6)
C_b–H_b(2)	0.91 (4)
C_b–H_b(3)	0.94 (4)
C_m(2)–H_m(2)	1.00 (5)
C_m(3)–H_m(3)	0.96 (4)

Bond	Angles, deg
p-Bromophenyl System	
C(1)–C(2)–H(2)	120 (3)
C(3)–C(2)–H(2)	122 (3)
C(2)–C(3)–H(3)	117 (3)
C(4)–C(3)–H(3)	121 (3)
C(4)–C(5)–H(5)	125 (3)
C(6)–C(5)–H(5)	115 (3)
C(1)–C(6)–H(6)	120 (3)
C(5)–C(6)–H(6)	120 (3)
Pyridyl System	
C(1′)–C(2′)–H(2′)	122 (3)
C(3′)–C(2′)–H(2′)	117 (3)
C(4′)–C(3′)–H(3′)	121 (3)
C(3′)–C(4′)–H(4′)	125 (3)
C(5′)–C(4′)–H(4′)	117 (3)
C(4′)–C(5′)–H(5′)	124 (5)
N(6′)–C(5′)–H(5′)	109 (5)
C(2′)–C(3′)–H(3′)	121 (3)
Aliphatic Portion	
C(4)–C(7)–H(7)	104 (3)
C(1′)–C(7)–H(7)	107 (2)
C(8)–C(7)–H(7)	110 (2)
C(7)–C(8)–H(81)	105 (2)
C(7)–C(8)–H(82)	107 (3)
C(9)–C(8)–H(81)	111 (2)
C(9)–C(8)–H(82)	110 (3)
H(81)–C(8)–H(82)	113 (4)
C(8)–C(9)–H(91)	112 (2)
C(8)–C(9)–H(92)	114 (3)
N(1)–C(9)–H(91)	108 (2)
N(1)–C(9)–H(92)	106 (3)
H(91)–C(9)–H(92)	104 (4)
N(1)–C_a–H_a(1)	110 (4)
N(1)–C_a–H_a(2)	111 (3)
N(1)–C_a–H_a(3)	106 (3)
H_a(1)–C_a–H_a(2)	109 (4)
H_a(1)–C_a–H_a(3)	97 (5)
H_a(2)–C_a–H_a(3)	123 (4)
N(1)–C_b–H_b(1)	109 (3)
N(1)–C_b–H_b(2)	112 (3)
N(1)–C_b–H_b(3)	113 (3)
H_b(1)–C_b–H_b(2)	110 (4)
H_b(1)–C_b–H_b(3)	108 (4)
H_b(2)–C_b–H_b(3)	105 (4)
C(9)–N(1)–H_m	104 (4)
C_a–N(1)–H_m	108 (4)
C_b–N(1)–H_m	109 (4)
Maleate Ion	
C_m(1)–O(2)–H_m(1)	109 (3)
C_m(4)–O(3)–H_m(1)	110 (2)
C_m(4)–O(4)–H_m	107 (2)
C_m(1)–C_m(2)–H_m(2)	106 (3)
C_m(3)–C_m(2)–H_m(2)	122 (3)
C_m(2)–C_m(3)–H_m(3)	120 (2)
C_m(4)–C_m(3)–H_m(3)	110 (2)

[a] The estimated standard deviations in the last digit quoted are enclosed in parentheses. The method of Ahmed and Pippy, "Scan of Interatomic Distances and Angles," Program NRC12, Division of Biochemistry, National Research Council of Canada, Ottawa, Canada, 1967, for independent atoms was employed.

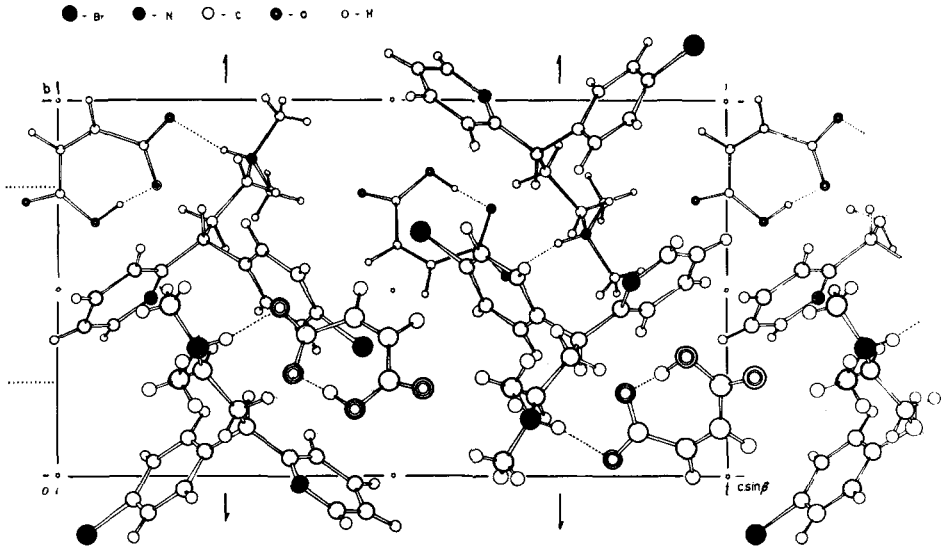

Figure 3.—A packing diagram of several molecules. The conformation is most clearly shown by the molecule in the bottom left corner.

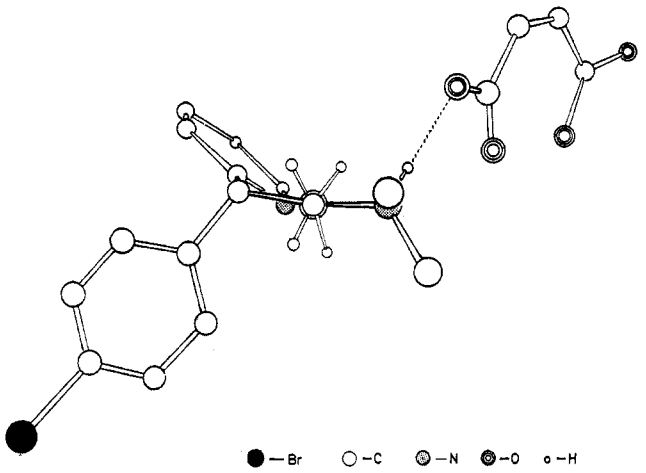

Figure 4.—A view of the molecular complex along the C(8)–C(9) bond.

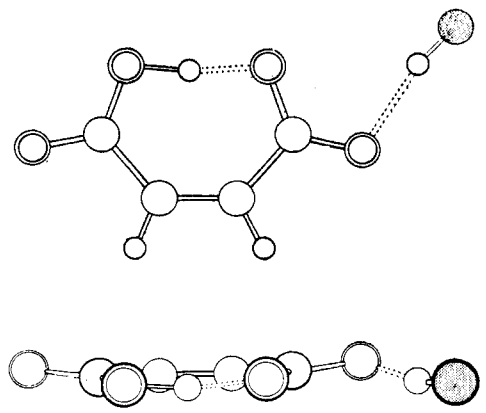

Figure 5.—The views of the maleate ion and the N atom to which it is H bonded. Atomic coding here is consistent with that of Figures 3 and 4.

pounds to bind similarly to the H1 site it is almost certain that they do not, since the outcome of the site-effector molecule interaction is quite different in the two cases.

The various diagrams of this paper show that the *N,N*-dimethylpropylamino structural feature is fully extended and adopts an asymmetric conformation with respect to the two aryl groups.

The asymmetrical disposition of the alkylamine chain may be described by three parameters; the distance of the saturated N from the centroid of the pyridyl ring of 6.212 Å, the angle between this ring and the basal plane of the "N pyramid" [defined by the atoms C(9), C_a, C_b] of 34° 57′, and the angle between the C(7)–N(1) vector and the normal to the plane of the pyridyl ring of 59°; corresponding figures for the benzene ring are 5.568 Å, 71° 20′, and 105°. It may be thought that close Van der Waals contacts could be responsible for the molecular dissymmetry, but neither an extensive search through lists of computed interatomic distances nor a close examination of a space-filling Corey–Pauling–Koltun molecular model has revealed any such interaction. The conclusion then is that the solid-state conformation is probably that predominating in solution and that it reflects some intrinsic property of the species.

If this viewpoint is accepted, the open-sided nature of this conformation becomes more meaningful and it can be correlated very nicely with the suggestions of Barlow[5] regarding the binding of the pheniramines and of triprodiline to the receptor site. The conformation of this latter compound is not known with any reliability and we have begun a crystallographic study of it in order to gain more information about histamine antagonists. The preliminary crystallographic data on triprolidine·HCl are as follows: space group is $P2_1/c$, a = 14.91 Å, b = 9.65 Å, c = 13.22°, β = 90.3°, ρ_{meas} = 1.20 g/cm³, ρ_{calcd} for 4 formula units of $C_{19}H_{23}ON_2Cl$/cell = 1.18 g/cm³.

B. Maleate Ion.—The relative ease with which the first base-dissociable proton of maleic acid is removed (pK_{a1} = 1.83) and the much greater than usual difficulty experienced (pK_{a2} = 6.07)[16] in titrating the second acidic function implies that neither of these 2 CO_2H groups is "normal" in its properties. Cardwell, *et al.*,[17] used this information in conjunction with evidence from ir spectroscopy to suggest that the second proton is bound between the 2 CO_2H groups. A previous paper by Shahat[18] on the structure of maleic acid had already determined that the 2 CO_2H were not equiv with respect to C–O bonding pattern and these data, when applied to the internal H bond suggestion, lead to the conclusion that this H is bonded more closely to one oxygen atom than it is to the other.

Two crystal structures of the maleate ion have been published. The first, of potassium hydrogen maleate, hereinafter called KHMal, done by Darlow and Cochran,[19] has a crystallographic mirror plane perpendicular to the ethylenic linkage which causes the intraion H-bonded H to be visualized at the midpoint of this linkage, if it is to be seen at all. Because of this fact these workers were unable to state whether this H was truly symmetrically bound or whether it was statistically disordered about the midpoint, although their evidence points towards the former situation. Ellison and Levy[20] have investigated potassium hydrogen chloromaleate, KHClMal, using neutron diffraction. The presence of the Cl atom destroys any molecular symmetry of the type found above, thus removing any bias in the method. This neutron diffraction work showed that the H atom was symmetrically bonded between the two oxygen atoms. Molecular orbital studies of Murthy, *et al.*,[21] for the hydrogen maleate ion, in which the O(2)–O(3) distance was constrained to be 2.40 Å, have resulted in a symmetric potential well for the H nucleus.

The present compound is a complex between brompheniramine and maleic acid but, as may have been predicted from their basic and acidic nature, complex formation results in a complete transfer of one proton, leaving the residual hydrogen maleate ion. In light of the accrued information on this species it was then expected to find the H midway between O(2) and O(3) (In this section the m subscripts for the C and H atoms of the maleate ion are dropped since no confusion need arise and this will facilitate comparisons to be made).

A difference Fourier map computed with all atoms except the H in question [H(1)] contributing to the calcd structure factors revealed a peak of 0.3 e/Å³ (all other hydrogens were found to occur at about this electron density) approximately 1.0 Å from O(2), 1.3 Å from O(3), and slightly displaced from the line joining these atoms. This atom was refined in the manner outlined above and its positional parameters are given in other parts of this paper.

Because of the fact that this finding was unexpected and also because in this H resides only 0.4% of the scattering matter, the evidence for the truth of this assertion is summarized below in three points.

(i) The final location, as determined by least squares, is coincident with the region of significantly positive electron density found in the difference map.

(ii) The H(1)–O(2) bond length is 1.08 Å with an associated estimated standard deviation of 0.05 Å. The distance from O(2) to the midpoint of the line joining O(2) and O(3) is 1.207 Å. The 2.7σ difference between these two distances is significant at better than the 99% confidence level.[22]

(iii) The C–O bond distances indicate that C(1)–O(2) (1.292 Å) corresponds to a single bond, that C(1)–O(1) (1.209 Å) corresponds to a double bond and that the C(4)–O(3) (1.265 Å) and C(4)–O(4) (1.230 Å) bonds are of intermediate order.[23] If it is accepted that the H is indeed between the two oxygens then these distances are compelling evidence for a covalent (*i.e.*, 1.0 Å) bond

(16) "Handbook of Chemistry and Physics," R. C. Weast, Ed., 49th ed, Chemical Rubber Co., Cleveland, Ohio, 1969, p 90.

(17) H. M. E. Cardwell, J. D. Dunitz, and L. E. Orgel, *J. Chem. Soc.*, 3740 (1953).

(18) M. Shahat, *Acta. Crystallogr.*, **5**, 763 (1952).

(19) S. F. Darlow and W. Cochran, *ibid.*, **14**, 1250 (1961).

(20) R. D. Ellison and H. A. Levy, *ibid.*, **19**, 260 (1969).

(21) A. S. N. Murthy, S. N. Bhat, and C. N. R. Rao, *J. Chem. Soc. A*, 1251 (1970).

(22) D. W. J. Cruickshank and A. P. Robertson, *Acta Crystallogr.*, **6**, 698 (1953).

(23) J. D. Dunitz and P. Strickler, in "Structural Chemistry and Molecular Biology," A. Rich and N. Davidson, Ed., N. H. Freeman, San Francisco, Calif., 1968.

between O(2) and H(1) and a H bond type linkage (albeit a strong one) between O(3) and H(1).

The very strong interactions of this arrangement are partially relieved in 2 ways. As in the KHMal, KHClMal, and maleic acid structures the internal angles of the ring system are strained considerably. The two angles O(2)–C(1)–C(2) and O(3)–C(4)–C(3) are not significantly different from each other and average 119° 36′ ± 42′. Similarly the angles C(1)–C(2)–C(3) and C(2)–C(3)–C(4) are insignificantly different and average 130° 24′ ± 24′. These angles are however significantly different from their unstrained counterparts of 121° 18′ and 121° 30′, respectively.[24] A situation closely paralleling this has been found in the 3 structures mentioned above.

The second manner in which the strain is relieved is by rotation of the CO_2H groups around their C–C bonds. The atoms of the C spine here are all within 0.007 Å of the plane with equation $-0.815x + 0.4940y - 0.3027z - 6.0592 = 0$. ($\chi^2 = 3.6$). The O(1), O(2), O(3), and O(4) atoms on the other hand are 0.163(5), −0.156(4), −0.133(4), and 0.126(4) Å from this plane. These figures imply that the torsion angle about C(1)–C(2) for CO_2H 1 is 8° 23′ and that about C(3)–C(4) for CO_2H 2 is 6° 46′ the directions of twist being such as to put O(2) and O(3) on the same side of the plane of the carbons. A view of the ion showing this conformation is included in Figure 5.

A similar situation was found in KHClMal but not in KHMal or maleic acid. At present there seems little reason for O(2) and O(3) being on the same side of the C spine but is is intended to investigate the structures of disodium maleate and maleic acid in the hope of shedding some light on this question, or at least partially delineate its occurrence.

(24) S. F. Darlow, *Acta Crystallogr.*, **14**, 1257 (1961).

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Steroidal Androgen Biosynthesis Inhibitors

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A screening procedure using a rat testicular microsomal preparation with [21-^{14}C]17α-hydroxyprogesterone as substrate was used to search for inhibitors of 17,20-lyase. A series of 17β-acylaminoandrost-4-en-3-ones and derivatives has been prepared and their syntheses have been described; they are shown to be androgen synthesis inhibitors *in vitro* and *in vivo*. These steroidal androgen synthesis inhibitors are demonstrated to be more specific in their action than the nonsteroidal inhibitors previously known. A mechanism for the action of these compounds is postulated.

Selective control of androgen biosynthesis is of potential interest in the treatment of benign prostatic hypertrophy, hirsutism, acne, and androgen-dependent tumors. Nonsteroidal synthesis inhibitors are known[1] which display varying degrees of selectivity in respect to enzymes involved in the adrenal and testicular synthesis of steroids including androgens.[2]

The major pathways[2,3] which have been established for testicular androgen biosynthesis involve hydroxylation of progesterone and pregnenolone to the 17α-hydroxyl derivatives and cleavage by 17,20-lyase(s) to yield androst-4-ene-3,17-dione and 3β-hydroxyandrost-5-en-17-one, respectively. Testosterone arises by reduction of the former at C-17 and in the latter by the combined action of 3(or 17)β-hydroxy steroid: NAD(P) oxidoreductase, 1.1.1.51, and 3-keto steroid Δ^5,Δ^4-isomerase, 5.3.3.1. The possibility of direct formation of testosterone from progesterone has also been suggested but not conclusively established.[4] Of several possibilities we chose to search for inhibitors of the 17,20-lyase step in androgen synthesis because of its key role in the conversion of C-21 to C-17 steroids and in the hope that the enzyme might show considerable structural specificity with respect to inhibitors. Nonsteroidal inhibitors were not excluded from consideration but steroidal inhibitors were judged to have the best chance to show a selective action.

Assay Method.—An *in vitro* screening procedure was used which involved measurement of [^{14}C]acetate formed in the side-chain cleavage of [21-^{14}C]17α-hydroxyprogesterone[5] by a rat testicular microsomal preparation. (See footnote *a*, Table I for the protocol used.)

Chemistry.—The first significant observation was that testosterone acetate but not testosterone was a potent inhibitor of the 17,20-lyase, and prompted a

(1) R. Neher and F. W. Kahnt, *Experientia*, **21**, 310 (1965).

(2) For an excellent review of this general subject see R. Gaunt, B. G. Steinetz, and J. J. Chart, *Clin. Pharmacol. Ther.*, **9**, 657 (1968).

(3) J. H. Richards and J. B. Hendrickson, "The Biosynthesis of Steroids, Terpenes and Acetogenins," W. A. Benjamin, Inc., New York, N. Y., 1964, pp 351–357.

(4) (a) R. I. Dorfman, E. Forchielli, and M. Gut, *Recent Progr. Horm. Res.*, **19**, 14 (1963); (b) R. I. Dorfman and F. Ungar, "Metabolism of Steroid Hormones," Academic Press, New York, N. Y., 1965, p 1127; (c) M. A. Drosdowky, E. Forchielli, and R. I. Dorfman, *J. Eur. Steroides*, **2**, 515 (1967).

(5) Kindly supplied to us by Dr. Robert E. Erickson, formerly of these laboratories.