covered). Anal. ($C_8H_9FO_2$) C, H, F.

(±)-1-(2,5-Dimethoxy-4-iodophenyl)-2-aminopropane Hydrochloride [(±)-8]. Compound (8a) was hydrolyzed in the manner described by Coutts and Malicky[10] to give the title compound in 71% yield, mp 196 °C (lit.[10] mp 198-200 °C) after two recrystallizations from $EtOH-Et_2O$.

(±)-N-Acetyl-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (8a). To a stirred mixture of 4.42 g (0.02 mol) of silver trifluoroacetate[24] and (±)-*N*-acetyl-1-(2,5-dimethoxyphenyl)-2-aminopropane[2] (4.74 g, 0.02 mol) in $CHCl_3$ (5 mL) was added dropwise, over a 2-h period, a solution of I_2 (5.08 g, 0.02 mol) in $CHCl_3$ (65 mL). After the mixture was stirred for 18 h, the precipitated AgI was removed by filtration. The filtrate was washed with aqueous $NaHSO_3$ and H_2O and dried over anhydrous $MgSO_4$. Evaporation of the $CHCl_3$ yielded 5.5 g of a brown residue, which was recrystallized from boiling $EtOH-H_2O$ to give 2.21 g of the title compound, mp 162-163 °C (lit.[10] mp 165-166 °C).

(R)-(-)-1-(2,5-Dimethoxy-4-iodophenyl)-2-aminopropane Hydrochloride [(-)-8]. By the same procedures for (±)-8, 13 g (0.056 mol) of (*R*)-(-)-1-(2,5-dimethoxyphenyl)-2-aminopropane hydrochloride[25] [$[\alpha]^{25}_D$ -18.7° (H_2O)] was converted to 10.7 g (81%) of the *N*-acetyl derivative, mp 106-107 °C; iodination with 11.5 g (0.045 mol) of I_2 and 10 g (0.045 mol) of silver trifluoroacetate in 150 mL of $CHCl_3$ gave 4.7 g (31%) of (*R*)-(+)-*N*-acetyl-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane: mp 184-185 °C; $[\alpha]^{23}_D$ +9.6° (MeOH). Hydrolysis with NaOH,[10] followed by acidification, afforded 2.93 g (74%) of the title compound: mp 218-219 °C; $[\alpha]^{23}_D$ -12.0° (H_2O). Anal. ($C_{11}H_{17}ClINO_2$) N.

(R)-(-)-1-(2,5-Dimethoxy-4-nitrophenyl)-2-aminopropane Hydrochloride [(-)-9]. To an aqueous solution of 10 g (0.043 mol) of (*R*)-(-)-1-(2,5-dimethoxyphenyl)-2-aminopropane hydrochloride[25] was added an excess of 5 N NaOH. The liberated free base was taken up in $C_6H_6-Et_2O$, dried (anhydrous $MgSO)_4$, and filtered. Removal of the solvents in vacuo yielded a colorless oil, which was dissolved in 40 mL of HOAc. This solution was added dropwise during 0.5 h to 43 mL of 50% HNO_3 (*d* 1.13), and the mixture was stirred and kept at 0-5 °C. The resulting clear solution was poured over ice, made alkaline with 50% NaOH, and extracted with $C_6H_6-Et_2O$. Evaporation of the solvent gave a residue, which was dissolved in dilute HCl, and this solution was evaporated in vacuo to a nearly colorless solid residue. Recrystallization from $EtOH-Et_2O$ gave 10.5 g (88%) of product: mp 231-232 °C dec; $[\alpha]^{23}_D$ -12.5° (H_2O). Anal. ($C_{11}H_{17}ClN_2O_4$) C, H, Cl, N. We prepared the racemic (±)-9 by direct nitration of (±)-1, using the above method, mp (HCl salt) 207-209 °C (lit.[10] mp 203-204 °C).

Compounds (±)-1, (±)-2, (±)-4, (±)-5, and 7 were gifts from the NIDA, while (±)-3 was available from a previous study.

Affinity Assay. Male Sprague-Dawley rats (200-250 g) were used in this study. The fundus preparation employed was essentially that of Vane,[26] with the previously described modifications.[8,11] Cumulative dose-response curves were obtained, after a 1-h equilibration period, for serotonin oxalate (7-10 increasing concentrations) both in the absence and in the presence of increasing concentrations of test compound. At least four to five dose-response curves were obtained for each pA_2 determination and at least triplicate pA_2 values were obtained (Table I). Certain compounds, notably (±)-4, (-)-8 and (-)-9, produced an agonistic response at the highest concentrations tested; when this occurred, the crest of this response was used as the new base line. The interaction of test compound with 5-HT receptors was assumed to be competitive when Schild plot slopes were between -0.8 and -1.2.

Behavioral Assay. The drug discrimination training procedure for these animals has been reported previously.[15] Specfically, 30 male Sprague-Dawley rats were trained to discriminate racemic DOM (1.0 mg/kg) from saline in a two-lever operant task. In this procedure, the administration of saline or DOM, 15 min prior to a variable-interval, 15-s (VI-15 s) schedule of reinforcement, served as the discriminative cue for the correct (reinforced) lever. Occasional periods (2.5 min) of nonreinforcement were used to assess the degree of stimulus control exerted over behavior by saline and DOM and to evaluate the 4-substituted derivatives of 2,5-DMA. For those compounds where generalization (transfer, substitution) occurred, ED_{50} values were determined from the dose-response data by the method of Litchfield and Wilcoxin.[27] (For a discussion of the use of the ED_{50} value as it relates to classification of drugs on the basis of their discriminative stimulus characteristics in rats, see Barry.[28]) These ED_{50} values are the calculated doses at which the rats perform 50% appropriate drug-lever responding.

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Potential Histamine H_2-Receptor Antagonists.[1] 4. Benzylhistamines

John C. Emmett,* Graham J. Durant, C. Robin Ganellin, Anthony M. Roe, and John L. Turner

Smith Kline & French Research Ltd., The Frythe, Welwyn, Hertfordshire, England AL6 9AR. *Received December 28, 1981*

As part of our studies aimed at designing histamine H_2-receptor antagonists, the effect on histaminergic activity of introducing benzyl substituents at various positions in the histamine molecule is described. New synthetic methods are reported for the novel 4-benzyl-, β-benzyl- and 4,N^τ-dibenylhistamines and the reported 2-benzylhistamine. The novel N^τ-benzylhistamine was synthesized by the versatile route reported by us for the synthesis of N^τ-methylhistamine. These benzylhistamines, together with the reported N^α- and N^π-benzylhistamines, were tested for agonist and antagonist activity at both H_1 and H_2 receptors. The results obtained indicate that introduction of a benzyl group into the histamine molecule causes a marked reduction in H_1- or H_2-agonist activity, and none of the compounds showed consistent antagonist activity. Evidently, the sterically demanding benzyl substituent is not easily accommodated in the agonist binding mode and is unable to locate a lipophilic receptor region for potential hydrophobic binding.

The discovery of the selective antagonist burimamide has permitted the characterization of histamine H_2 receptors and furnished a class of drugs with a completely novel pharmacological action.[2] Chemical modification of

(1) Paper 3: G. J. Durant, J. C. Emmett, C. R. Ganellin, A. M. Roe, and R. A. Slater, *J. Med. Chem.*, **19**, 923 (1976).
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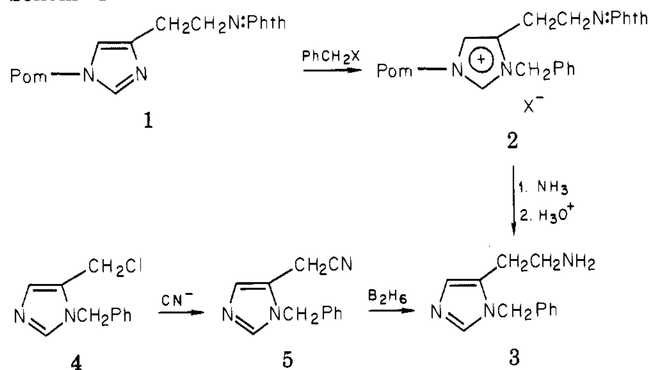
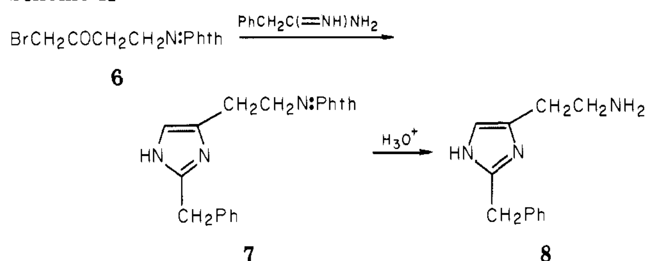
Scheme I[a]



[a] N:Phth = phthalimido; Pom = pivaloyloxymethyl.

Scheme II[a]



[a] N:Phth = phthalimido.

burimamide led to the orally active antagonist metiamide[3] and then to cimetidine,[4] which is now established as a clinically useful drug for the treatment of peptic ulcer and associated gastrointestinal disorders.[5]

In our work in this field, several lines of investigation were chosen in attempts to design H_2-receptor antagonists. Some of these approaches have been outlined previously.[6] Our starting point was the natural agonist molecule histamine, which was modified to alter its chemical properties while always retaining some definite aspect of histamine structure to assist in receptor recognition.

In one approach, nonpolar lipophilic substituents were introduced at various positions on the histamine molecule with the purpose of increasing drug–receptor association through potential hydrophobic or van der Waals interaction with possible nonpolar regions of the receptor.[7] By analogy with active-site-directed enzyme inhibitors designed from substrates, in which both the position and nature of additional lipophilic substituents can be critical,[8] we attempted to identify the sites in the histamine molecule where substituents can be accommodated without loss of receptor binding by testing a series of methylhistamines.[1]

The results obtained enabled us to identify the 4- and N^α-positions for introduction of a wider range of lipophilic substituents into the histamine molecule. In addition to the incorporation of a variety of lipophilic substituents at these positions, we also chose to compare the effect of substituting the lipophilic benzyl group at each position in the molecule with the corresponding effect of a methyl group. This was partly prompted by reports that N^α-benzylhistamine and 1-benzyl-4-(β-aminoethyl)pyrazole inhibited histamine-induced gastric secretion in the dog.[9] It was also felt that any loss of agonist activity resulting from methyl substitution could be caused in some instances by a reduction in efficacy, rather than a loss of receptor binding; therefore, it seemed advisable to test the effect of another (preferably more lipophilic) substituent at each position.

In this paper, we describe the synthesis and pharmacological activity of six of the seven monobenzylhistamines and one dibenzylhistamine.

Synthesis. N^α-Benzylhistamine (**27**)[10] and 2-benzylhistamine (**8**)[11] had been reported, but inadequately characterized, at the start of this work. The remaining benzylhistamines were novel, and this necessitated the development of several new routes, which have been referred to previously.[1,12] Since the completion of these studies and their patent disclosure,[13] an alternative synthesis of 2-benzylhistamine has been reported by an independent group.[14]

N^π-Benzylhistamine (**3**) was readily synthesized from the N^τ,N^α-protected histamine (**1**) as reported[12] (Scheme I). Compound **3** was also prepared in very low yield by chain extension of the chloro compound (**4**),[15] a route previously established[15] for the synthesis of N^π-methylhistamine.

2-Benzylhistamine (**8**) has been claimed as a product of the reaction of 1,2,4-tribenzamidobutene and benzoyl chloride.[11] More recently, Dziuron and Schunack[14] have prepared this compound from 2-benzyl-4(5)-(hydroxymethyl)imidazole using the standard chain extension via the corresponding 4(5)-chloromethyl and 4(5)-cyanomethyl intermediates. We synthesized **8** by the cyclization method previously described[1] for 2-methylhistamine (Scheme II). Reaction of the bromo ketone (**6**) with 2-phenylacetamidine gave a moderate yield of the phthaloyl-protected histamine (**7**), which was then hydrolyzed to **8**.

N^τ-Benzylhistamine (**12a**), previously unreported, was synthesized in high yield via the selective alkylation of the cyclic urea (**10a**) (Scheme III), followed by acid hydrolysis of the quaternary salt (**11a**), a method reported previously[1] for the synthesis of N^τ-methylhistamine. An investigation of the stability of the quaternary salt (**11a**) showed that it was readily ring opened by nucleophiles. Treatment with hot MeOH gave the carbamate (**14**), and boiling water furnished a mixture of **12a** and the urea (**13**), which is

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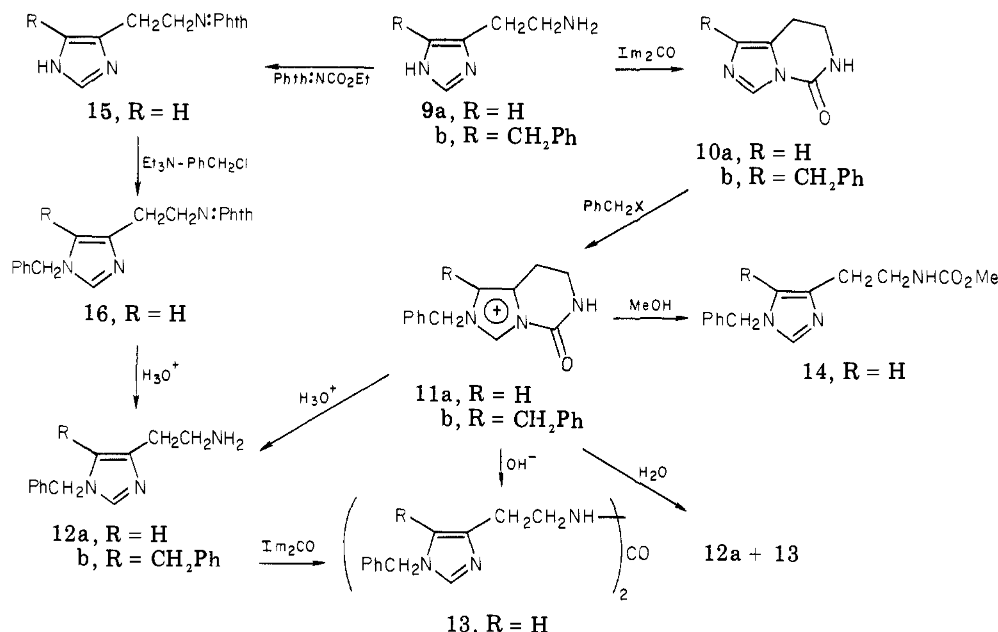
Scheme III[a]



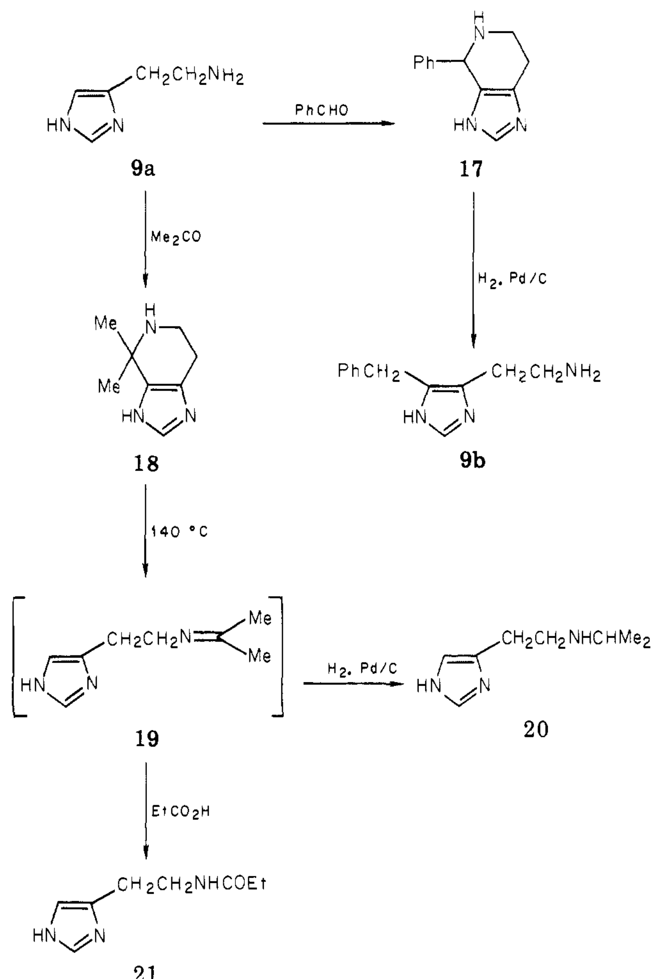
presumably formed by reaction of unprotonated amine (**12a**) with **11a**. Addition of acid in this hydrolysis favored exclusive formation of **12a**, while addition of base (Na_2CO_3) gave the urea (**13**) as the sole product. Compound **13** was also obtained from the reaction of **12a** with carbonyldiimidazole. This route to N^{τ}-alkylhistamines, employing the acid hydrolysis of a cyclic urea quaternary salt, is now firmly established as the route of choice for these compounds. Since the first reports[1,13] of the use of this method, it has recently been extended to the synthesis of N^{τ}-methyl- and N^{τ}-ethylhistidine.[16]

Compound **12a** was also prepared by selective N^{τ}-benzylation of N^{α}-phthaloylhistamine (**15**)[12] to give **16**, followed by acidic removal of the phthaloyl protecting group (Scheme III). Preferential alkylation at the N^{τ} atom of **15** was also utilized[12] in the preparation of **1**, an important intermediate for the synthesis of the isomeric N^{π}-benzylhistamine (**3**) (Scheme I).

4-Benzylhistamine (**9b**) was synthesized by a convenient novel method involving reductive ring opening of the spinaceamine (**17**)[17] (Scheme IV). At present, this method seems likely to be limited to the synthesis of 4-(arylmethyl)histamines from arylspinaceamines in which the aryl group assists in weakening the carbon–nitrogen bond. Thus, it was found that the hydrogenolysis of the dimethylspinaceamine (**18**)[18] did not occur at room temperature and under more vigorous conditions (130–135 °C) gave N^{α}-isopropylhistamine (**20**). This unexpected ring-cleavage product is probably formed by an initial thermal ring opening to give the Schiff base (**19**), which is then reduced to **20**. In support of this mechanism, it was subsequently found that thermolysis of **18** in boiling propionic acid (140 °C), gave N^{α}-propionylhistamine (**21**). The structures of **20** and **21** were established unequivocally by independent synthesis.

4,N^{τ}-Dibenzylhistamine (**12b**), previously unreported, was synthesized from **9b** via **10b** by analogy with N^{τ}-benzylhistamine (**12a**) (Scheme III). The versatility of this

Scheme IV



cyclic urea route to N^{τ}-alkylhistamines is clearly demonstrated in this example, since alkylation at the N^{τ} position is not affected by the presence of a bulky ortho substituent, and **12b** was obtained in high yield. β-Benzylhistamine (**25**), previously unreported, was synthesized by the novel method shown in Scheme V. The benzylidene derivative (**23**), readily obtained from the condensation of benzaldehyde and 4(5)-(cyanomethyl)imidazole (**22**),[19] was se-

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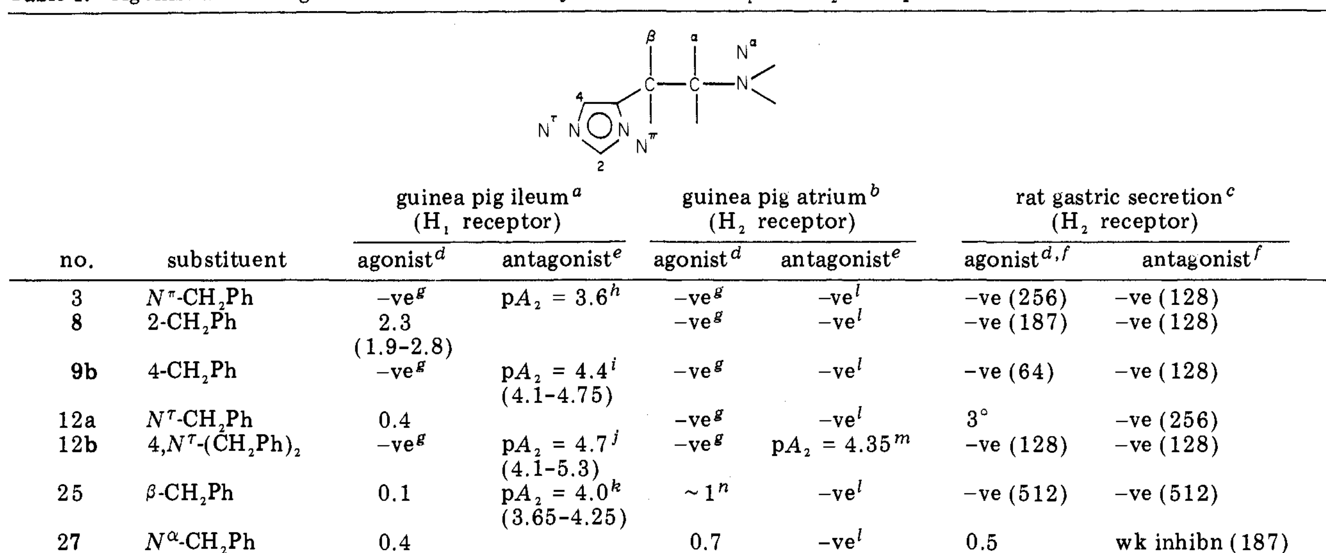
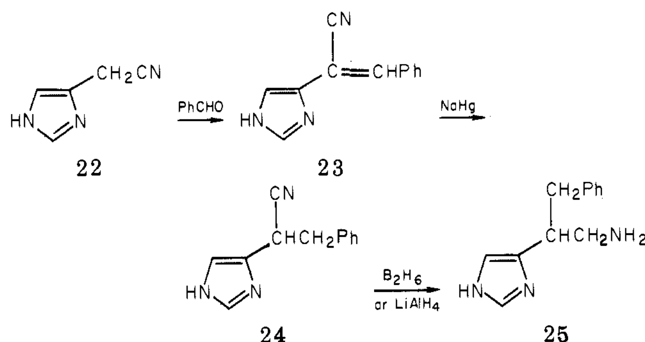
Table I. Agonist and Antagonist Activities of Benzylhistamines at H_1 and H_2 Receptors



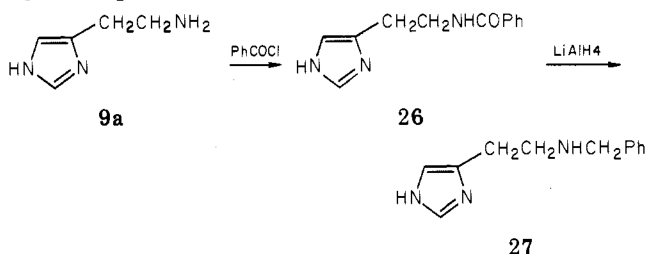
no.	substituent	guinea pig ileum[a] (H_1 receptor) agonist[d]	guinea pig ileum[a] (H_1 receptor) antagonist[e]	guinea pig atrium[b] (H_2 receptor) agonist[d]	guinea pig atrium[b] (H_2 receptor) antagonist[e]	rat gastric secretion[c] (H_2 receptor) agonist[d,f]	rat gastric secretion[c] (H_2 receptor) antagonist[f]
3	N^{π}-CH_2Ph	–ve[g]	pA_2 = 3.6[h]	–ve[g]	–ve[l]	–ve (256)	–ve (128)
8	2-CH_2Ph	2.3 (1.9–2.8)		–ve[g]	–ve[l]	–ve (187)	–ve (128)
9b	4-CH_2Ph	–ve[g]	pA_2 = 4.4[i] (4.1–4.75)	–ve[g]	–ve[l]	–ve (64)	–ve (128)
12a	N^{τ}-CH_2Ph	0.4		–ve[g]	–ve[l]	3[o]	–ve (256)
12b	4,N^{τ}-$(CH_2Ph)_2$	–ve[g]	pA_2 = 4.7[j] (4.1–5.3)	–ve[g]	pA_2 = 4.35[m]	–ve (128)	–ve (128)
25	β-CH_2Ph	0.1	pA_2 = 4.0[k] (3.65–4.25)	~1[n]	–ve[l]	–ve (512)	–ve (512)
27	N^{α}-CH_2Ph	0.4		0.7	–ve[l]	0.5	wk inhibn (187)

[a] In vitro in the presence of atropine (0.5 μM).[2,22] [b] Spontaneously beating right atrium.[2,22] [c] In vivo, lumen-perfused stomach of the atropinized (1 mg/kg^{-1}) anesthetized rat.[2,22] [d] Agonist activity relative to histamine (= 100). [e] Expressed as $pA_2 = -\log K_B$, where the dissociation constant (K_B) was calculated from $K_B = B/x - 1$.[2,22] pA_2 for cimetidine = 6.1 (6.03–6.17), slope = 0.82. [f] Figures in parentheses represent maximum dose (μM/kg) tested. [g] Less than 0.1% of histamine (781 μM/L). [h] Slope = 1.1, no limits. [i] Slope = 1.1. [j] Slope = 0.7. [k] Slope = 1.3. [l] pA_2 < 3.3 (486 μM/L). [m] Slope = 1.0, no limits. [n] Achieved 20% maximum response. [o] See text; completely blocked by standard dose (6 μM/kg) of cimetidine.

Scheme V



Scheme VI



lectively reduced with sodium amalgam to give the α-benzylnitrile (**24**). Reduction of **24** with either $LiAlH_4$ or diborane gave moderate yields of **25**, isolated as the dimaleate.

N^{α}-Benzylhistamine (**27**) was synthesized by $LiAlH_4$ reduction of N^{α}-benzoylhistamine (**26**),[20] which was in turn obtained by controlled benzoylation of histamine (Scheme VI). It has been synthesized previously[10] by reductive condensation of histamine with benzaldehyde, a method which is liable to form spinaceamines[17] as byproducts.

Pharmacological Results and Discussion

The benzylhistamines, as their salts, were assayed for histamine H_2-receptor agonist and antagonist activity in vivo in the lumen-perfused anesthetized rat preparation[2,21] and in vitro on the guinea pig right atrium.[2,22] The compounds were also tested for H_1-receptor agonist and antagonist activity on the isolated guinea pig ileum.[2,21]

Agonist Activity. It is apparent from the results obtained (Table I) that introduction of a benzyl group into the histamine molecule causes either marked reduction or complete abolition of histamine H_1- and H_2-agonist activity. Test results from the ileum assay showed that 2-benzylhistamine (**8**) is the most active agonist at the H_1 receptor with an activity of approximately 2.3% of that of histamine. Hepp, Dziuron, and Schunack[23] have reported the H_1-agonist activity of this compound as 0.8% of histamine, a revision of their earlier[24] estimate of 2.5%. The other compounds (**12a**, **25**, and **27** in Table I), which were shown to possess weak H_1-agonist activity, were at least 200 times less active than histamine. When evaluated as H_2-receptor agonists, no compound in Table I showed agonist activity in both assays as high as 1% of histamine.

However, N^{τ}-benzylhistamine (**12a**) did stimulate gastric acid secretion. The effect was slow in onset and was sustained for several hours; the total acid output was about 8% of that produced by an equimolar dose of histamine (n = 13), but the potency relative to histamine was only 3% when peak responses were compared. The compound did not achieve maximal acid output in doses up to 64 μM kg^{-1}, but it should not be regarded as a partial agonist, since when tested at doses of up to 256 μM kg^{-1} against near maximal histamine-induced acid output it did not inhibit the histamine response. The stimulant effect produced by N^{τ}-benzylhistamine is blocked by a standard dose (6 μM kg^{-1}) of cimetidine. However, since N^{τ}-

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(20) O. Gerngross, *Z. Physiol. Chem.*, **108**, 50 (1919).
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benzylhistamine was inactive in the atrial assay (at 100–400 μM), it is unlikely that this compound acts directly on H_2 receptors. A possible explanation for the secretory activity would be partial metabolic debenzylation to histamine. It is also possible that the compound acts to release histamine locally or stimulate secretion by some other mechanism, but none of these possibilities has been verified experimentally.

β-Benzylhistamine (**25**) showed weak submaximal histamine-like activity in the atrial assay, but this is unlikely to be due to the action of the compound at H_2 receptors, since it lacked agonist activity in the gastric secretion assay and failed to block the effects of histamine in either H_2 assay; i.e., it is not a true partial agonist. N^{α}-Benzylhistamine (**27**) gave a weak histamine-like response in all three assays, but HPLC analysis showed that **27** contained an impurity peak corresponding to contamination by histamine at 0.6% molar, a level which would fully account for the agonist activity. The best estimate for the activity of **27**, therefore, must be <1% of histamine, a result that contrasts with the relatively high activity (10%) reported by Ash and Schild,[25] suggesting that the sample tested by these authors was likely to be grossly contaminated. In earlier work[26] an activity of 0.5% on the guinea pig ileum has been reported for this compound.

Antagonist Activity. None of the compounds showed consistent inhibition of histamine in both H_2-receptor mediated assays. N^{α}-Benzylhistamine (**27**) showed weak inhibitory activity at a high dose in the gastric secretion assay but was inactive in the in vitro H_2-receptor assay. 4,N^{τ}-Dibenzylhistamine (**12b**) was the only compound to show dose-related competitive inhibitory activity in the guinea pig atrial assay, although when tested alone it exerted a marked negative chronotropic effect at concentrations of 54 μM and above. It was, however, only weakly active in the rat gastric acid secretion assay. Four of the compounds in Table I were weak competitive antagonists of histamine when tested for H_1-receptor antagonism in vitro on the guinea pig ileum.

Discussion

The previous study of methylhistamines[1] has shown that 4-methyl- and N^{α}-methylhistamines are sufficiently active as agonists at H_2 receptors to suggest that substituents may be accommodated at the 4- and N^{α}-positions of the histamine molecule without incurring a loss in receptor affinity. Other methylhistamines were much less active, but the possibility remained that their reduced activity (relative to histamine) was due to a loss of efficacy rather than loss of affinity. The present results indicate that benzyl substituents are not readily accommodated. Benzyl groups are electronically almost neutral (σ_m estimated[27] to be −0.01) and they should, therefore, have little effect on the pK_a or tautomeric characteristics of the imidazole ring, properties which have assumed importance for H_2-receptor agonists.[21] It is conceivable that the lipophilic character of benzyl might contribute to limit access to the H_2 receptor, but this seems unlikely in view of the discovery of the new more lipophilic H_2-receptor antagonist, oxmetidine.[28] The most plausible conclusion is that the benzyl substituent is sterically too bulky to permit the molecule to interact with the receptor in a fashion analogous to that of histamine. That none of the monobenzylhistamines showed consistent antagonist activity also suggests that the benzyl group is unable to locate a lipophilic region adjacent to the receptor active site for potential hydrophobic binding. It is, however, still possible that such regions exist. The in vitro activity of 4,N^{τ}-dibenzylhistamine is intriguing and may offer a clue, but it is necessary to probe for such regions by using differently shaped nonpolar substituents, e.g., aralkyl or higher alkyl groups.

Experimental Section

Melting points were determined on an "Electrothermal" electrically heated apparatus with a thermometer corrected for stem exposure. NMR spectra were recorded on a Varian A-60 instrument (Me_4Si), UV spectra were recorded on a Beckman DK2 instrument, and IR spectra were recorded on a Pye-Unicam SP 100 spectrophotometer. HPLC analyses were performed on a Perkin-Elmer LC 75 instrument linked to a Waters pump. Microanalyses for elements indicated are within 0.4% of theoretical values. Solvents were dried over molecular sieves.

Biological Test Procedures. The general assay procedures have been described previously.[2,22]

Guinea Pig Ileum (Histamine H_1 Activity). Compounds were tested in this in vitro preparation in the presence of atropine (0.5 μM). Agonist activity was assayed up to a concentration of 781 μM (0.1% histamine), and relative activities were assessed from cumulative dose–response curves. A 2 + 2 parallel assay was performed with one compound (**8**). Antagonist activity was determined against histamine (0.1–109 μM) stimulated contraction, and cumulative dose–response curves were plotted for active compounds at three dose levels (nine observations).

Guinea Pig Right Atrium (Histamine H_2 Activity). Compounds were tested in this in vitro preparation in the presence of propranolol (0.5 μM). Agonist activity was assayed up to a concentration of 781 μM (0.1% histamine), and relative activities were assessed from cumulative dose–response curves. Antagonists were tested against histamine (0.2–781 μM) up to a dose of 486 μM. One compound (**12b**) was active, and this was tested at three dose levels (five observations).

Rat Gastric Secretion (Histamine H_2 Activity). We tested compounds in vivo by intravenous administration, using the lumen-perfused stomach of the atropinized (1 mg kg^{-1}) urethane-anesthetized rat. Agonists were tested by matching single doses with those of histamine (0.5–1 μM kg^{-1}) and antagonists as single doses during a near maximal acid secretory response produced by intravenous infusion of histamine (0.25 μM kg^{-1} min^{-1}).

***N^{τ}*-Benzylhistamine (3).** This compound was preferably synthesized via the N^{τ},N^{α}-bisprotected histamine (1), as reported.[12] It was also prepared from 1-benzyl-5-(chloromethyl)imidazole (4),[15] described as follows: A solution of the hydrochloride of 4 (20 g, 0.087 mol) in absolute EtOH (400 mL) was added dropwise to a solution of KCN (52.5 g, 0.187 mol) in H_2O (70 mL) while the temperature was maintained between −3 and 1 °C. The mixture was then stirred for 1 h, left at 0 °C overnight, and filtered, and CO_2 was passed through the filtrate until no further precipitation occurred. After filtration, the solvent was removed in vacuo (40 °C), the residue was extracted with $CHCl_3$, and the extracts were dried (K_2CO_3). The oily residue obtained after removal of the solvent was extracted with ether to give crude **5** (4.2 g, 25%), mp 71–73 °C. Chromatography on neutral alumina, eluting with benzene, gave the pure product: mp 76–77 °C (from di-*n*-butyl ether); ^1H NMR ($CDCl_3$) δ 3.48 (d, CH_2CN), 5.20 (s, CH_2), 7.4 (m, Ph, Im 2 H and Im 4 H), Anal. ($C_{12}H_{11}N_3$) C, H, N.

A solution of **5** (0.96 g, 0.005 mol) in dry THF (30 mL) was added over 5 min to a solution of diborane (0.02 mol) in THF (135 mL), and the mixture was heated with stirring for 7 h at 60–65 °C and then stirred for 14 h at 20 °C. Wet THF and 11 N HCl (50 mL) were added, the mixture was evaporated, and the residue was boiled with 5 N HCl (100 mL) for 1 h. After evaporation again, the residue was extracted with water (7 mL), the solution was filtered, and the filtrate was basified with K_2CO_3. Extraction with $CHCl_3$ several times, concentration of the extracts, and treatment of the base (0.16 g) with *i*-PrOH–HCl, followed by the

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addition of Et_2O, gave **3** (0.15 g, 11%) as the dihydrochloride, mp 215–216.5 °C. Recrystallization gave an analytically pure sample, mp 218–219.5 °C, and was indistinguishable from the sample prepared from the protected histamine derivative (1). Anal. ($C_{12}H_{17}Cl_2N_3$) C, H, N, Cl.

Attempted reduction of **5** with $LiAlH_4$ in a mixture of Et_2O–C_6H_6 gave a small amount (2%) of **3** after purification of the multicomponent reaction product by ion exchange chromatography, treatment with oxalic acid, and conversion of the crude oxalate to the dihydrochloride. Attempted reduction with $LiAlH_4$ in THF gave an intractable tarry product.

2-Benzylhistamine (8). A solution of NaOEt, from Na (2.6 g) in dry EtOH (60 mL), was added to a solution of phenylacetamidine hydrochloride (20.4 g, 0.12 mol) in EtOH (60 mL). The stirred mixture was heated to reflux, and a solution of 1-bromo-4-phthalimidobutan-2-one[1] (11.8 g, 0.04 mol) in EtOH (350 mL) was added over 3 h. The mixture was heated for an additional 2 h, cooled, and filtered, and the filtrate was evaporated to dryness. The residual oil was dissolved in 2-propanol and acidified with 2-propanolic HCl, and ethyl acetate was added to give the crude product (**7**; 7.3 g, 50%), mp 231–234 °C. Further recrystallization (EtOH) gave a sample: mp 240–242 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.96 (t, CH_2Im), 3.86 (t, CH_2N), 4.28 (s, CH_2Ph), 7.31 (s, Ph), 7.34 (s, Im 4 H), 7.82 (s, Phth). The microanalysis suggested that 8% of this compound was present as the monohydrobromide (C, H, N, Br, Cl).

A solution of **7** (7 g) in 5 N HCl (200 mL) was heated under reflux overnight, cooled to 0 °C, and filtered. Evaporation of the filtrate and recrystallization from EtOH–Et_2O gave the crude product (3.5 g, 67%), mp 238–240 °C. A further recrystallization (EtOH) gave the pure product (**8**; 2.5 g, 48%): mp 253–256 °C (lit.[14,15] mp 236 and 245 °C); ^{1}H NMR (D_2O) δ 3.36 (m, CH_2CH_2), 4.44 (s, CH_2), 7.51 (m, Ph), 7.4 (t, Im 4 H). Anal. ($C_{12}H_{17}Cl_2N_3$) C, H, N.

***N*$^\tau$-Benzylhistamine (12a). Route A.** A stirred solution of 5-oxo-5,6,7,8-tetrahydroimidazo[1,5-*c*]pyrimidine[1] (157 g, 1.15 mol) and benzyl chloride (630 mL) in dry DMF (1.8 L) was heated at 100 °C overnight. After the solution was cooled, the product was filtered off and washed with ether to give the chloride of **11a** (250 %, 82%): mp 235–236 °C dec; ^{1}H NMR (D_2O) δ 3.15 (m, CH_2Im), 3.71 (m, CH_2N), 5.56 (s, CH_2Ph), 7.50 (d, 1-H), 7.59 (s, Ph), 9.46 (d, 3-H). Anal. ($C_{13}H_{14}ClN_3O$), C, H, N, Cl. The bromide of **11a** (mp 224–225 °C) was obtained in 99% yield in the absence of DMF. Anal. ($C_{13}H_{14}BrN_3O$) C, H, N, Br.

A solution of **11a** (250 g) in 5 N HCl (3 L) was heated under reflux overnight. Evaporation to dryness and recrystallization of the residue from ethanol (twice) gave the dihydrochloride of **12a** (190 g, 73%): mp 182–184 °C; ^{1}H NMR (D_2O) δ 3.30 (m, CH_2CH_2), 5.46 (s, CH_2N), 7.50 (m, Ph + Im 4 N), 8.83 (s, Im 2 H). Anal. ($C_{12}H_{17}Cl_2N_3$) C, H, N, Cl. This salt also crystallized in another form, mp 209–211 °C with 2–3% deficiency of HCl.

Route B. *N*$^\alpha$-Phthaloylhistamine[12] (23 g, 0.095 mol) was dissolved in DMF (115 mL) containing Et_3N (10.6 g, 1.04 mol). The mixture was warmed to 50 °C, and benzyl chloride (13.4 g, 1.04 mol) was added dropwise with stirring. After addition, the mixture was heated on a steam bath for 2.5 h and concentrated, and the residue was agitated with H_2O and extracted with $CHCl_3$. Concentration, acidification with *i*-PrOH–HCl, and recrystallization of the crude solid (*n*-BuOH) gave the hydrochloride of **16** (10 g, 31%), mp 241–243 °C. Further recrystallization (*n*-BuOH) gave a sample: mp 242–243 °C; ^{1}H NMR (D_2O) δ 3.19 (t, CH_2Im), 4.01 (t, CH_2N), 5.40 (s, CH_2Ph), 7.22 (d, Im 4 H), 7.37 (m, Ph), 7.70 (m, Phth), 8.99 (d, Im 2 H). Anal. ($C_{20}H_{18}ClN_3O_2$) C, H, N.

Hydrolysis of **16** (1.55 g) by the method described for **8** gave the dihydrochloride of **12a** (0.95 g, 74%).

***N*,*N*′-Bis[2-(1-benzylimidazol-4-yl)ethyl]urea (13).** *N*$^\tau$-Benzylhistamine dihydrochloride (0.83 g, 0.003 mol) was basified with NaOEt (0.006 mol) in ethanol to yield the amine base after filtration and evaporation to dryness. A mixture of this base and carbonyldiimidazole (0.24 g, 0.0014 mol) was heated at 100 °C for 1 h and cooled, and water was added to give **13** (0.44 g, 65%) as the hemihydrate, mp 113–117 °C. Recrystallization from chloroform/cyclohexane gave a sample: mp 116–118 °C; ^{1}H NMR ($CDCl_3$) δ 2.69 (t, CH_2Im), 3.42 (t, CH_2N), 5.04 (s, CH_2Ph), 6.71 (d, Im 4 H), 7.30 (m, Ph), 7.48 (d, Im 2 H). Anal. ($C_{25}H_{28}N_6O\cdot0.5H_2O$) C, H, N. Compound **13** gave a dipicrate, mp 157–159 °C (Me_2CO–Et_2O). Anal. ($C_{37}H_{34}N_{12}O_{15}$) C, H, N.

Compound **13** was also prepared (91%) by heating **11a** (2.2 g) in 1 N NaOH (30 mL) at reflux temperature for 45 min. Cooling and filtration gave the product.

Hydrolysis of **11a** (1 g) in boiling water for 16 h gave **13** (0.42 g, 60%), after cooling and filtration, and a small amount of the hydrochloride of **12a** (0.25 g, 28%), after evaporation of the filtrate and treatment of the residue with EtOH–HCl.

***N*$^\tau$-Benzyl-*N*$^\alpha$-carbomethoxyhistamine (14).** A solution of the bromide of **11a** (0.44 g) in MeOH (50 mL) was heated under reflux for 4 h. Concentration and addition of picric acid and then H_2O gave the picrate of **14** (0.66 g, 95%), mp 179–180 °C, identical with the product obtained from the reaction of **12a** with methyl chloroformate: ^{1}H NMR (Me_2SO-d_6) 2.78 (t, CH_2Im), 3.22 (t, CH_2N), 3.50 (s, CH_3), 5.44 (s, CH_2Ph), 7.2 (br, NH), 7.41 (s, Ph), 7.55 (d, Im 4 H), 8.66 (s, picrate), 9.11 (d, Im 2 H). Anal. ($C_{20}H_{20}N_6O_9$) C, H, N.

4-Benzylhistamine (9b). A solution of 4-phenyl-4,5,6,7-tetrahydroimidazo[4,5-*c*]pyridine[17] (30 g, 0.15 mol) in glacial acetic acid (600 mL) was hydrogenated over Pd/C (10%, 10 g) at 100 atm and room temperature for 26 h. After removal of the catalyst and evaporation to dryness, the residue was dissolved in nitromethane, and the solution was acidified with hydrogen bromide gas. Addition of ether precipitated the crude product, which was recrystallized from 2-ethoxyethanol–nitromethane to give **9b** (43 g, 79%), mp 146–148 °C, as the dihydrobromide: ^{1}H NMR (D_2O) δ 3.25 (s, CH_2CH_2), 4.2 (s, CH_2), ~7.4 (m, Ph), 8.7 (s, Im 2 H).

Hydrogenolysis of 18. A solution of the dimethylspinaceamine (**18**;[18] 1.56 g) in glacial acetic acid (80 mL) was hydrogenated over Pd/C (10%, 1 g) at 130–135 °C (128 atm) for 14 h. After removal of the catalyst and evaporation to dryness, the residue was dissolved in EtOH–HCl, the cloudy solution was filtered, and a solution of picric acid in EtOH was added. Addition of water gave a crude picrate (2.17 g), which was recrystallized from H_2O–EtOH to give the dipicrate of **20** (1.84 g, 31%), mp 199–201 °C (lit.[29] mp 175 °C). Anal. ($C_{20}H_{21}N_9O_{14}$) C, H, N. Treatment of this dipicrate with hydrochloric acid (5 N) and washing with toluene gave the dihydrochloride, mp 196–198 °C (lit.[30] mp 197.5–199 °C), identical with a sample obtained by reaction of isopropylamine with 4(5)-(2-chloroethyl)imidazole:[29] ^{1}H NMR (D_2O) δ 1.38 (d, CH_3), 3.35 (m, CH_2CH_2), 3.55 (m, CH), 7.46 (s, Im 4 H), 8.73 (d, Im 2 H). Anal. ($C_8H_{17}Cl_2N_3$) C, H, N, Cl.

Attempted hydrogenolysis of **18** under the conditions described for the preparation of **9b** gave back **18** unchanged.

Thermolysis of 18. A solution of **18** in propionic acid was heated under reflux (141 °C) overnight. After the solution was cooled and evaporated to dryness, a solution of picric acid in 2-propanol was added to give the picrate of **21** (0.33 g), mp 193–195 °C, identical with a sample prepared from the reaction of histamine with propionic anhydride: ^{1}H NMR (Me_2SO-d_6) δ 0.97 (t, CH_3), 2.07 (q, CH_2CO), 2.8 (t, $ImCH_2$), 3.37 (q, CH_2NH), 7.43 (s, Im 4 H), 8.65 (s, C_6H_2), 9.1 (d, Im 2 H). Anal. ($C_{14}H_{16}N_6O_8$) C, H, N.

4,*N*$^\tau$-Dibenzylhistamine (12b). A solution of 4-benzylhistamine base (10.5 g, 0.055 mol) and carbonyldiimidazole (13.8 g, 0.083 mol) in DMF (200 mL) was heated to 100 °C over 1 h and then at this temperature for a further 30 min. Evaporation and treatment with water gave **10b** (10.3 g, 91%), mp 175–177 °C. Recrystallization from *i*-PrOH–cyclohexane gave a sample: mp 178–180 °C; ^{1}H NMR ($CDCl_3$) δ 2.70 (t, CH_2), 3.44 (m, CH_2N), 3.91 (s, CH_2Ph), 6.7 (br, NH), 7.28 (s, Ph), 8.19 (s, 3-H). Anal. ($C_{13}H_{13}N_3O$) C, H, N.

Reaction of **10b** (1 g) with benzyl bromide (10 mL) at 90 °C overnight, cooling and washing with Et_2O gave **11b** (1.7 g, 98%): mp 219–221 °C; ^{1}H NMR (D_2O) δ 2.95 (t, CH_2Im), 3.70 (t, CH_2N), 4.11 (s, CH_2Ph), 5.39 (s, NCH_2Ph), 7.40 (m, 2 Ph), 9.33 (s, 3-H). Anal. ($C_{20}H_{20}BrN_3O$) C, H, N, Br.

The dihydrochloride of **12b** was obtained (82%) from **11b** by acid hydrolysis (see **12a**, route A) and recrystallization of the crude

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product (94%, mp 221–223 °C) from i-PrOH/Et_2O: ^1H NMR (D_2O) δ 3.25 (m, CH_2CH_2), 4.18 (s, CH_2Ph), 5.25 (s, CH_2N), 7.20 (m, 2 Ph), 8.80 (s, Im 2 H). Anal. ($C_{19}H_{23}Cl_2N_3$) C, H, N, Cl.

4(5)-(1-Cyano-2-phenylethyl)imidazole (24). NaOH (5 N, 10 mL) was added to a solution of 4(5)-(cyanomethyl)imidazole[19] (10 g, 0.093 mol) and benzaldehyde (15 g, 0.14 mol) in MeOH (100 mL). After standing at room temperature for 24 h, the reaction mixture was poured into an equal volume of water to give **23** (14 g, 77%), mp 189–190 °C. Recrystallization from EtOH gave a sample: mp 190–191 °C; IR ν_{CN} 2222 cm^{-1}; UV λ_{max} 324 nm (ϵ 2×10^4). Anal. ($C_{12}H_9N_3$) C, H, N.

Powdered sodium amalgam (5%, 240 g) was added in portions over 15–20 min at room temperature to a vigorously stirred solution of **23** (6.7 g, 0.034 mol) in a mixture of MeOH (360 mL) and H_2O (120 mL) through which CO_2 was passed. After addition, CO_2 was passed through the stirred mixture for a further 2.5 h, the solution was decanted and filtered, and the residue was washed with MeOH. Evaporation and addition of H_2O gave **24** (5 g, 76%), mp 105–107 °C. Recrystallization from EtOH/H_2O gave a sample: mp 108.5–110 °C; IR ν_{CN} 2237 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.25 (br, CH_2), 4.2 (br, CH), 7.25 (m, Ph) (imidazole protons not observed due to the presence of paramagnetic impurities). Anal. ($C_{12}H_{11}N_3$) C, H, N.

β-Benzylhistamine (25). Method A. A solution of **24** (1 g 0.005 mol) in dry THF (60 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (0.77 g) in THF (20 mL), and the mixture was heated under reflux for 2 h. Addition of H_2O, followed by filtration and evaporation, gave an oily base, which was converted to the dimaleate on addition of a solution of maleic acid in MeOH. Addition of ether gave an oily solid, which was recrystallized from i-PrOH–Et_2O to give the dimaleate of **25** (0.76 g, 35%): mp 146–148 °C; ^1H NMR (D_2O) δ 3.15 (m, CH_2Ph), 3.55 (m, CH_2N + CH), 6.38 (s, maleate), 7.30 (m, Ph + Im 4 H), 8.71 (d, Im 2 H). Anal. ($C_{20}H_{23}N_3O_8$) C, H, N.

Method B. A solution of $BF_3 \cdot Et_2O$ (5.7 g) in dry diglyme (20 mL) was added dropwise over 30 min to an ice-cooled mixture of $NaBH_4$ (1.3 g, 0.03 mol) and a solution of **24** (1 g, 0.005 mol) in diglyme (20 mL). The mixture was stirred for 3 h and left to stand overnight, and the diglyme was removed at 40 °C (0.5 mm). The residue (in MeOH) was acidified with 11 N HCl and then basified with aqueous KOH, and the mixture was heated under reflux for 30 min. The mixture was acidified (11 N HCl) and evaporated, the residue was extracted, and the aqueous solution was extracted with $CHCl_3$. Evaporation and addition of maleic acid gave the dimaleate of **25** (0.6 g, 27%), mp 145–147 °C.

N^α-Benzylhistamine (27). Reduction of N^α-benzoylhistamine[20] (2 g, 0.0093 mol) with $LiAlH_4$ (0.35 g, 0.0093 mol) in dry THF, followed by treatment with EtOH–HCl and recrystallization from EtOH–Et_2O, gave the dihydrochloride of **27** (1.7 g, 67%), mp 225–227 °C (lit.[10] mp 220–222 °C). HPLC analysis of **27** on a Partisil SCX column, with 0.125 M $(NH_4)H_2PO_4$ as the mobile phase, showed a small impurity (0.6% M) with a retention time corresponding to that of histamine.

Acknowledgment. We are grateful to Dr. M. E. Parsons and R. C. Blakemore for providing the pharmacological data, to Dr. E. S. Pepper for NMR data, to D. Darkin for HPLC data, and to M. J. Graham for microanalyses. We also thank J. R. Barber, J. Keeley, J. M. Padbury, G. Perry, and M. J. Poulter for their experimental contributions.

Alkylation of the Prosthetic Heme in Cytochrome P-450 during Oxidative Metabolism of the Sedative–Hypnotic Ethchlorvynol

Paul R. Ortiz de Montellano,* Hal S. Beilan, and James M. Mathews

Departments of Pharmaceutical Chemistry and Pharmacology, University of California, San Francisco, California 94143.
Received January 25, 1982

The clinically used sedative–hypnotic ethchlorvynol destroys hepatic microsomal cytochrome P-450 enzymes in a process catalyzed by the same hemoproteins. Abnormal porphyrins accumulate in the livers of phenobarbital-pretreated rats after administration of ethchlorvynol. The abnormal porphyrin fraction has been isolated and shown to consist of the four possible regioisomers of N-(5-chloro-3-ethyl-3-hydroxy-2-oxo-4-pentenyl)protoporphyrin IX. Cytochrome P-450 inactivation thus appears to result from alkylation of the prosthetic heme by the oxidatively activated acetylenic function in ethchlorvynol. The autocatalytic destruction of the hemoprotein is likely to alter the metabolism and elimination of ethchlorvynol and coadministered drugs and may be the cause of the porphyrinogenic properties of ethchlorvynol.

Ethchlorvynol (1-chloro-3-ethyl-1-penten-4-yn-3-ol), introduced in 1955, is still in use as a sedative–hypnotic, although its utility has been diminished by evidence that it is a habituating agent with a lower safety margin than the short-acting barbiturates.[1] Its continued use and abuse, however, remain sufficiently widespread for ethchlorvynol to be implicated in a significant number of drug overdose incidents.[2] Surprisingly little is known, considering the 25 years it has been in clinical use, concerning the metabolism of ethchlorvynol or its interactions with hepatic enzymes. Although little unchanged drug is excreted,[3] only a minor fraction of the administered drug is accounted for by the known metabolites. The only metabolites that have been clearly identified are an unusual C-glucuronide of ethchlorvynol[4] and 1-chloro-3-ethynyl-1-pentene-3,4-diol,[5] the derivative in which the ethyl group has been hydroxylated. The disappearance of ethchlorvynol from plasma is first order at therapeutic doses[3] but appears to be zero order in overdose situations,[6] a change which suggests that elevated serum concentrations of the drug saturate the processes responsible for its removal. The pertinent observation has also been made that heme biosynthesis is stimulated in vitro[7] and in vivo[8] by ethchlorvynol, an interaction that may explain its deleterious effect in patients with acute porphyrias.

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