Potential Histamine H_2-Receptor Blockers. 3- and 2-Indole Derivatives as Immobile Analogues of Tautomeric Forms of Cimetidine

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At physiological pH, cimetidine (**1a**) and its analogues burimamide (**1b**) and metiamide (**1c**) exist mainly as an equilibrium mixture of tautomers. A high concentration of tautomer **2** is associated with increased H_2-receptor interaction. 3-Indole derivatives (**5c–f**) and 2-indole derivatives (**6c-f**) were synthesized and tested as immobile analogues of tautomers **2** and **3**, respectively. Weak competitive H_2 antagonism was found in *N'*-cyano-*N*-[2-[(1*H*-indol-3-ylmethyl)thio]ethyl]carbamidothioic acid methyl ester (**5e**) and *N*-[2-[(1*H*-indol-2-ylmethyl)thio]-ethyl]-*N'*-methylthiourea (**6c**).

At physiological pH, the potent H_2-receptor blockers cimetidine (**1a**), thioburimamide (**1b**), and metiamide (**1c**) (Chart I) exist mainly as an equilibrium mixture of tautomers **2** and **3** (80–93%), with little formation of cation **4** (7–20%).[1] Increased concentration of tautomer **2** is associated with high H_2-receptor interaction.[1]

In an attempt to generate immobile forms of tautomers **2** and **3**, the synthesis and biological screening of compounds **5c–f** and **6c–f** were undertaken.

Chemistry. Treatment of quaternary salts **5a**[2] and **6a**[3] with excess 2-aminoethanethiol hydrochloride in the presence of base rendered amines **5b** and **6b**, respectively. These, in turn, were reacted with methyl and phenyl isothiocyanate to give the corresponding thioures **5c,d** and **6c,d**. Reaction of amines **5b** and **6b** with dimethyl cyanocarbonimidodithioate in dimethoxyethane resulted in intermediates **5e** and **6e**, which upon treatment with $MeNH_2$–MeOH rendered compounds **5f** and **6f**.

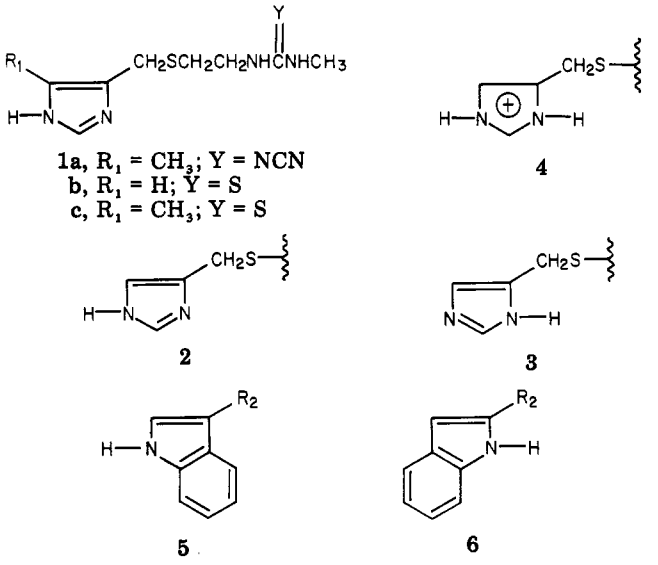
Biological Results and Discussion

The chronotropic response of guinea pig atria to histamine or other H_2 agonists is blocked by the competitive antagonist cimetidine and its analogues.[4]

A chronotropic H_2 antagonism test consists of exposing guinea pig atria to increasing doses of the H_2 agonist, 4-methylhistamine. A parallel shift of the dose–response curve to the right at concentrations of drug which have no effect on the resting heart rate serves as the criterion for competitive H_2 antagonisms.[5–7]

Compounds **5c–f** and **6c–f** were tested for this competitive H_2 antagonism. Activity is expressed as the "potency ratio", defined as the additional amount of agonist needed in the presence of antagonist to obtain the percent EC_{50} maximum response (Table I). As defined, compounds **5e** and **6c** met the criterion for competitive H_2 antagonism, and compounds **5c,d,f** did not shift the dose–response curve and were inactive. Compound **6d** lowered resting rate and was toxic to the tissues. Compound **6e** shifted the curve significantly but not in a parallel manner. The effect was not surmountable by additonal agonist, 4-methylhistamine, a criterion for competitive antagonism.

Chart I



a, R_2 = $CH_2N(CH_3)_3^+I^-$
b, R_2 = $CH_2SCH_2CH_2NH_2$
c, R_2 = $CH_2SCH_2CH_2NHC(=S)NHCH_3$
d, R_2 = $CH_2SCH_2CH_2NHC(=S)NHPh$
e, R_2 = $CH_2SCH_2CH_2NHC(=NCN)SCH_3$
f, R_2 = $CH_2SCH_2CH_2NHC(=NCN)NHCH_3$

Additonal experiments would be required to establish if the compound is a noncompetitive H_2 antagonist. Compound **6f** caused variable base-line effects, increasing resting rate initially, then decreasing the rate.

Compounds **5c–f**, as analogues of tautomer **2**, were expected to show greater activity than **6c–f**. This, however, was not the case. Compound **5e** is weakly active. **6c** is also a weak competitive H_2 antagonist, in contrast to its counterpart **5c** which is inactive.

Recently synthesized histamine H_2 blockers in which the imidazole ring is replaced by thiazole[8] and furan rings[9] clearly demonstrated that imidazole tautomerism per se is not a determining molecular feature for antagonism. This does not, however, preclude the possibility that with imidazole derivatives activity may reside within a particular tautomer.

Experimental Section

Melting points are uncorrected. The NMR spectra were obtained in $CDCl_3$ on a Varian EM 390 spectrometer. Chemical shifts are expressed in parts per million (ppm) on the scale from internal Me_4Si. The IR spectra were measured on a Digilab Model FT 14 spectrometer. The spectroscopic data for all new com-

(1) C. R. Ganellin, in "Histamine Receptors, Proceeding of the A. N. Richards Symposium", Tobias O. Yellin, Ed., Spectrum Publications, Jamaica, New York, 1979, p 377 and references therein.
(2) T. A. Geissman and A. Armen, *J. Am. Chem. Soc.*, **74**, 3916 (1952).
(3) W. Schindler, *Helv. Chim. Acta.*, **40**, 2156 (1957).
(4) R. W. Brimblecombe, W. A. M. Duncan, G. J. Durant, C. R. Ganellin, M. E. Partons, and J. W. Black, *Br. J. Pharmacol.*, **53**, 435 (1975).
(5) R. B. Parker and D. R. Waud, *J. Pharmacol. Exp. Ther.*, **177**, 1 (1971).
(6) D. R. Waud, *Adv. Gen. Cell. Pharmacol.*, **1**, 145 (1975).
(7) T. Levy, *Methods Pharmacol.*, **1**, 77 (1971).
(8) T. O. Yellin, S. H. Buck, D. J. Gilman, D. F. Jones, and T. M. Wordleworth, *Life Sci.*, **25**, 2001 (1979).
(9) D. B. Judd, J. M. Clintherow, B. J. Price, and J. Bradshaw, European Patent 1-699 (1979).

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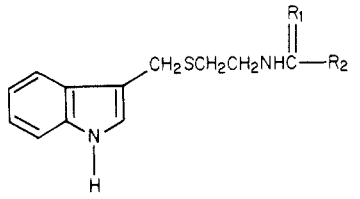
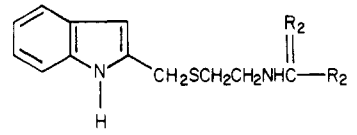
Table I. Antagonism of 4-Methylhistamine Induced Guinea Pig Atria Chronotropic Response (Potency Ratio at 3×10^{-5} M)



5c-f



6c-f

no.	R_1	R_2	potency ratio[a]	competitive antagonism[b]
5c	S	$NHCH_3$	1.06	–[c]
5d	S	NHC_6H_5	1.16	–[c]
5e	NCN	SCH_3	2.56	+
5f	NCN	$NHCH_3$	0.84	–[c]
cimetidine (1d)			36.8	+

no.	R_1	R_2	potency ratio[a]	competitive antagonism[b]
6c	S	$NHCH_3$	3.35	+
6d	S	NHC_6H_5	2.54	–[e]
6e	NCN	SCH_3	6.04	–[d]
6f	NCN	$NHCH_3$	1.76	–[e]
cimetidine (1d)			36	+

[a] Potency ratio = % EC_{50} max of test compound/% EC_{50} max of control. [b] Conditions for significant competitive antagonism (+) = (1) potency ratio > 1.0 ($p < 0.05$), (2) parallel shift in dose-response curve with slopes not significantly different ($p > 0.05$), and (3) no effect on resting heart rate. Failure to meet any of the above conditions leads to inactivity (-). [c] Potency ratio not significantly greater than 1.0 ($p > 0.05$). [d] Nonparallel shift in dose-response curve; slope significantly different ($p < 0.05$). [e] Effect on resting heart rate ($p < 0.05$).

pounds were consistent with the assigned structures. Microanalytical results were within ±0.4% of theory.

2-[(1*H*-Indol-3-ylmethyl)thio]ethanamine (5b). To an ice-cooled solution of 2-aminoethanethiol hydrochloride (9.0 g, 0.08 mol) in H_2O (100 mL) containing sodium hydroxide (6.4 g, 0.16 mol) was added dropwise a solution of gramine methiodide[2] (9.48 g, 0.03 mol) in H_2O (200 mL) with stirring. After 15 min of stirring at room temperature, the reaction mixture was extracted with Et_2O, dried (Na_2SO_4), and concentrated to give **5b** as an oil: yield 2.78 g (62%). This was used without further purification.

***N*-[2-[(1*H*-Indol-3-ylmethyl)thio]ethyl]-*N'*-methylthiourea (5c).** To a solution of **5b** (2.78 g, 0.014 mol) in Et_2O (100 mL) was added dropwise a solution of methyl isothiocyanate (1.5 g, 0.02 mol) in Et_2O (25 mL). A white precipitate resulted. Stirring was continued at room temperature for 30 min. The precipitate was separated by suction filtration and washed with Et_2O to yield 2.22 g (59%) of **5c** as a white solid, mp 98.5–99 °C. Anal. ($C_{13}H_{17}N_3S_2$) C, H, N, S.

***N*-[2-[(1*H*-Indol-3-ylmethyl)thio]ethyl]-*N'*-phenylthiourea (5d).** To a solution of **5b** (2.38 g, 0.012 mol) in Et_2O (50 mL) was added dropwise a solution of phenyl isothiocyanate (1.55 g, 0.012 mol) in Et_2O (25 mL) with stirring. After the solution was stirred at room temperature for 24 h, the resulting precipitate was separated and washed with a little Et_2O to render **5d** as a white solid: yield 3.10 g (78%); mp 154–155 °C. Anal. ($C_{18}H_{19}N_3S_2$) H, N, S; C: calcd, 63.31; found, 62.82.

Methyl *N'*-Cyano-*N*-[2-[(1*H*-indol-3-ylmethyl)thio]ethyl]carbamimidothioate (5e). To a solution of **5b** (2.06 g, 0.01 mol) in EtOH (10 mL) was gradually added a solution of dimethyl cyanocarbonimidodithioate (1.46 g, 0.01 mol) in EtOH (20 mL) with stirring. Stirring was continued for 16 h at room temperature. The reaction mixture was concentrated to give an oil, which upon trituration with Et_2O gave **5e** as a white solid: yield 3.02 g (99%); mp 132–135 °C. An analytical sample was obtained by recrystallization from EtOH, mp 137–138 °C. Anal. ($C_{14}H_{16}N_4S_2$) C, H, N, S.

***N''*-Cyano-*N*-[2-[(1*H*-indol-3-ylmethyl)thio]ethyl]-*N'*-methylguanidine (5f).** To a solution of **5e** (2.19 g, 0.0072 mol) in MeOH (100 mL) was added dropwise an 18.6% solution of $MeNH_2$ in EtOH (24.2 mL, 0.144 mol) with stirring. After 18 h of stirring at room temperature, the reaction mixture was concentrated to give an oily residue. Trituration of the residue with ether gave crude **5f** as white solid, mp 120–125 °C. Recrystallization from CH_2Cl_2 raised the melting point to 130.5–131.5 °C: yield 1.72 g (84%). Anal. ($C_{14}H_{17}N_5S$) H, N, S; C: calcd, 58.51; found, 57.90.

2-[(1*H*-Indol-2-ylmethyl)thio]ethanamine (6b). To a stirred, ice-cooled solution of MeONa (9.72 g, 0.18 mol) in MeOH (50 mL) was added dropwise a solution of 2-aminoethanethiol hydrochloride (10.17 g, 0.09 mol) in MeOH (50 mL). The reaction mixture was allowed to stir at room temperature for 1 h. To this a solution of **6a**[3] (9.49 g, 0.03 mol) in MeOH was added gradually with stirring. After stirring at room temperature for 3 h, the reaction mixture was refluxed for 16 h. White the mixture cooled to room temperature, a white precipitate settled down. This was filtered off, and the filtrate was concentrated to give an oil. The oil was suspended in H_2O (80 mL) and stirred. A white solid precipitate separated. The solid was separated by suction filtration, dissolved in $CHCl_3$, dried ($NaSO_4$), and concentrated to give **6b** as a white solid: yield 6.0 g (97%); mp 119.5–121 °C.

***N*-[2-[(2*H*-indol-2-ylmethyl)thio]ethyl]-*N'*-methylthiourea (6c).** A solution of **6b** (1.03 g, 0.05 mol) and methyl isothiocyanate (0.73 g, 0.01 mol) in dimethoxyethane (60 mL) was stirred at room temperature for 16 h. The solvent was removed and the oily residue was chromatographed on silica using $CHCl_3$ and $CHCl_3$–EtOAc (1:1, v/v) as eluents to give **6c** as a white solid: yield 1.01 g (72%); TLC R_f 0.3 (silica; $CHCl_3$–EtOAc, 1:1, v/v); mp 103–105 °C. Anal. ($C_{13}H_{17}N_3S_2$) C, H, N, S.

***N*-[2-[(1*H*-indol-2-ylmethyl)thio]ethyl]-*N'*-phenylthiourea (6d).** This compound was prepared in similar manner to **6c** from **6b** (1.03 g, 0.003 mol) and phenyl isothiocyanate (1.35 g, 0.01 mol): yield 1.20 g (70%); TLC R_f 0.63 (silica; $CHCl_3$–EtOAc, 1:1, v/v); mp 141–142 °C. Anal. ($C_{18}H_{19}N_3S_2$) C, H, N, S.

Methyl *N'*-Cyano-*N*-[2-[(1*H*-indol-2-ylmethyl)thio]ethyl]carbamimidothioate (6e). This compound was prepared as described for the preparation of **5e** from **6b** (2.06 g, 0.01 mol) and dimethyl cyanocarbonimidodithioate (11.46 g, 0.01 mol) with dimethoxyethane in place of EtOH as the solvent: yield 2.6 g (89%); mp 158–159 °C. Recrystallization from MeOH raised the melting point to 158.5–160 °C. Anal. ($C_{14}H_{16}N_4S_2$) H, N, S; C: calcd, 58.23; found, 54.69.

***N''*-Cyano-*N*-[2-[(1*H*-indol-2-ylmethyl)thio]ethyl]-*N'*-methylguanidine (6f).** This compound was prepared in similar manner as **5f** from **6e** (1.33 g, 0.0044 mol) and 70 mL of 31% $MeNH_2$ in MeOH. A suspension of the crude product in a minimum amount of MeOH was stirred for 10 min and filtered, and the filtrate was discarded. The white solid residue (**6f**) had a melting point of 158–158.5 °C: yield 0.81 g (65%). Anal. ($C_{14}H_{17}N_5S$) H, N, S; C: calcd, 58.51; found, 58.00.

Guinea Pig Atria Chronotropic Response. Male guinea pigs, 350–600 g, were stunned by a blow to the head and killed by exsanguination. The heart was removed and placed in a modified Ringer–Locke buffer (pH 7.4) containing 0.003% atropine sulfate at 37 ± 2 °C and gassed with 95% O_2/5% CO_2. The atria were dissected and suspended at 0.1–0.2 g resting tension in a tissue bath of the same gassed buffer. The bath temperature was maintained at 37 ± 2 °C. Contractions were measured isometrically with a Grass (Model FT0.03C) force-displacement

transducer. Atrial heart rate (beats per minute, bpm) were recorded on a Beckman RM dyanograph recorder with Model 481B preamplifiers and Model 482M8 amplifiers.

Cumulative dose–response curves for the agonist, 4-methylhistamine, induced atrial rates before (curve I) and in the presence of (curve II) test compounds or cimetidine were generated as described below. After three washes of buffer 15 min apart, a control fast record (25 mm/s) was obtained to determine the atrial resting rate, followed by administration of the agonist. Resting rates varied from 180 to 200 bpm. After each agonist response peak, another fast record was obtained before the next dose of agonist. Maximum increases in heart rate were 150–180 bpm.

The agonist was given in cumulative doses of 10^{-7}, 3×10^{-7}, 10^{-6}, 3×10^{-6}, 10^{-5}, 3×10^{-5}, and 10^{-4} M final bath concentrations. The rate of response of 4-methylhistamine peaked within 3 min and remained stable for a number of minutes thereafter. All fast records were taken within 4 min after administration of each dose of agonist.

Upon completion of the cumulative agonist responses, the tissue was washed repeatedly with changes of buffer 10 to 15 min apart until the atrial rate returned to control levels ± 15 bpm. Fifteen minutes after control atrial rates were reached, the test compound (3×10^{-5} M) was added and the process repeated.

A nonlinear fit with a common maximum and slope to quantitative data was performed using program EDXXPH[5,6] (delta response). This analyzes the two curves simultaneously, estimates the potency ratio of the EC_{50} max value with SE, and calculates the parallelism variance ratio. The potency ratio has a 95% confidence region [±SE (t)].

The potency ratio was derived by dividing the agonist EC_{50} max of curve II by the agonist EC_{50} max of curve I. The potency ratio reports how much more agonist was needed in the presence of the test compound to obtain the same heart rate response as with agonist alone.

Modified Ringer–Locke solution was prepared by dissolving 9.0 g of NaCl, 0.42 g of KCl, 1.0 g of $NaHCO_3$, 0.317 g of $CaCl_2 \cdot 2H_2O$, 0.005 g of $MgCl_2 \cdot 6H_2O$, 0.5 g of dextrose, and 0.3 mg of atropine sulfate in 1 L of triple distilled water. The pH was maintained at 7.4 by bubbling 95% O_2/5% CO_2 (Matheson) constantly through the solution and adding acid or base as needed. The finished solution was placed in a reservoir which maintains a constant temperature of 37 °C. The buffer was made fresh each day.

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Antiinflammatory 5,6-Dihydro-11-oxodibenz[*b,e*]azepine-3-acetic Acids[1]

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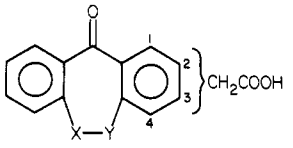
A number of 5,6-dihydro-11-oxodibenz[*b,e*]azepine-3-acetic acids were synthesized. The compounds were up to ~30 times more potent than phenylbutazone as antiinflammatory agents. However, unlike some closely related compounds, for example, the isomeric 2-acetic acids, the compounds were almost devoid of activity in the mouse writhing analgesic assay.

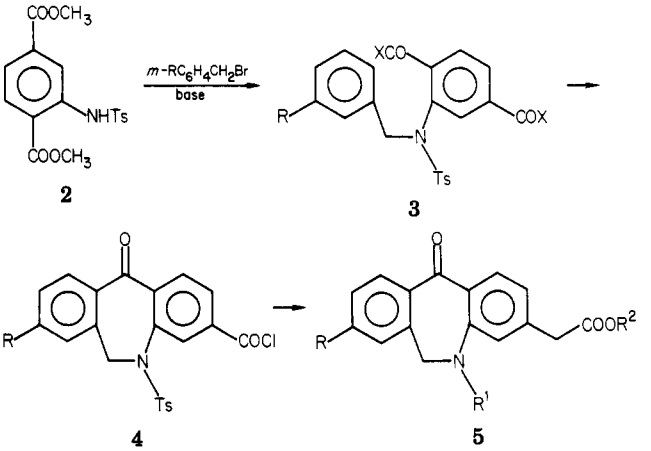
In recent years, substantial antiinflammatory and analgesic activities have been reported for arylacetic and arylpropionic acids, in which the aryl group consisted of a tricyclic moiety with a seven-membered central ring. Thus, the 3-substituted dibenzotropones **1a**,[2] the 2- and



1a, X–Y = CH=CH
b, X–Y = CH_2O
c, X–Y = CH_2S
d, X–Y = CH_2N

3-substituted dibenzoxepins **1b**,[3,4] and the 3-substituted dibenzothiepins **1c**[5] have been subjected to advanced study as potential antiarthritic agents. The syntheses and biological activities of a number of acetic and propionic acids attached to the 2 position of 5,6-dihydro-11-oxodibenz[*b,e*]azepine (**1d**) have also been described.[6] We report here the preparation and bioassays of the isomeric 3-acetic and 3-propionic acids.

Scheme I[a]



[a] Ts = *p*-$CH_3C_6H_4SO_2$.

Chemistry. The compounds were synthesized as shown in Scheme I. Base-catalyzed alkylation of dimethyl 2-(*p*-toluenesulfonamido)terephthalate (**2**) with benzyl bromide or 3-methoxybenzyl bromide gave the products **3** (X = OCH_3), which were converted to the acids by base hydrolysis. Attempted cyclization to the tricycle **4** using polyphosphoric acid was unsuccessful, but the derived acid chlorides (**3**, X = Cl) could be cyclized in the presence of

(1) Contribution No. 565 from the Syntex Institute of Organic Chemistry.
(2) Dunn, J. P.; Green, D. M.; Nelson , P. H.; Rooks, W. H.; Tomolonis, A.; Untch, K. G. *J. Med. Chem.* **1977**, *20*, 1557.
(3) Lassman, H. B.; Kirby, R. E.; Wilker, J. C.; Novick, W. J. *Pharmacologist* **1975**, *17*, 226.
(4) (a) Ueno, K.; Kubo, S.; Tagawa, H.; Yoshioka, T.; Tsukada, W.; Tsubokawa, M.; Kojima, H.; Kasahara, A. *J. Med. Chem.* **1976**, *19*, 941. (b) Tsukuda, W.; Tsubokawa, M.; Masukawa, T.; Kojima, H.; Kasahara, A. *Arzneim.-Forsch.* **1978**, *28*, 128.
(5) Ackrell, J.; Antonio, Y.; Franco, F.; Landeros, R.; Leon, A.; Muchowski, J. M.; Maddox, M. L.; Nelson, P. H.; Rooks, W. H.; Roszkowski, A. P.; Wallach, M. B. *J. Med. Chem.* **1978**, *21*, 1035.

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