# Isomeric Tropane Analogues of Histamine $H_2$-Receptor Antagonists



Jerome R. Bagley and Thomas N. Riley*

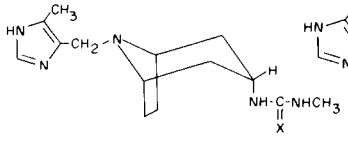
Department of Medicinal Chemistry, School of Pharmacy, University of Mississippi, University MS 38655

Received September 28, 1981

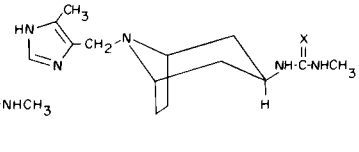
In an attempt to investigate stereochemical requirements of antagonists of the histamine $H_2$-receptor, tropane analogues of cimetidine and metiamide have been synthesized possessing axial and equatorial *N*-methylthiourea and *N*-methyl-*N*-cyanoguanidine moieties at the 3-position of the tropane system. The tropane analogues of this study have been fully characterized with regard to configuration at C-3 and to conformation of the piperidine ring of the tropane nucleus.

*J. Heterocyclic Chem.*, **19**, 485 (1982).

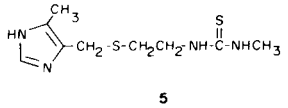
In our continuing study of stereochemical factors affecting the pharmacological actions of medicinal agents, we have undertaken a study of the stereochemical requirements of the histamine $H_2$-receptor with regard to interactions with antagonist molecules. This study involved the synthesis and stereochemical characterization of certain tropane analogues (**1-4**) of metiamide (**5**) and cimetidine (**6**). The tropane analogues of **5** and **6** were designed to incorporate the essential structural features for antagonists acting at histamine $H_2$-receptors including the 4(5)-methylimidazole ring system and a polar, neutral *N*-methylthiourea function (**1** and **3**) or a *N*-methyl-*N*-cyanoguanidine moiety (**2** and **4**) with appropriate intramolecular separation between these two important structural features (1). The tropane nitrogen atom may be considered isosteric with the chain sulfur atom of **5** and **6**. The role of the chain sulfur atom in the $H_2$-receptor antagonistic properties of metiamide and cimetidine has been proposed to involve stabilization of a pharmacophoric tautomer of the imidazole moiety as a result of the electron-withdrawing properties of the sulfur atom (2).



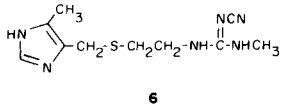
**1**, X = S
**2**, X = NCN



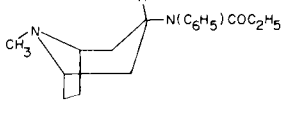
**3**, X = S
**4**, X = NCN



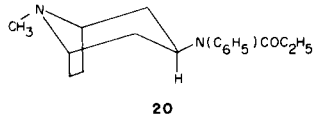
**5**



**6**

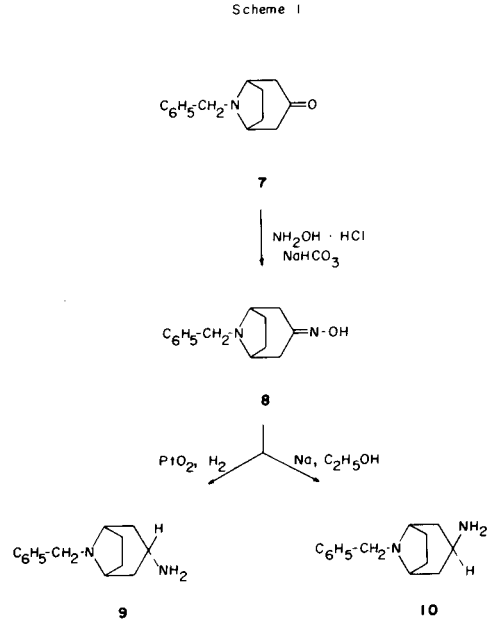


**19**



**20**

Scheme I



**7**

**8**

**9**

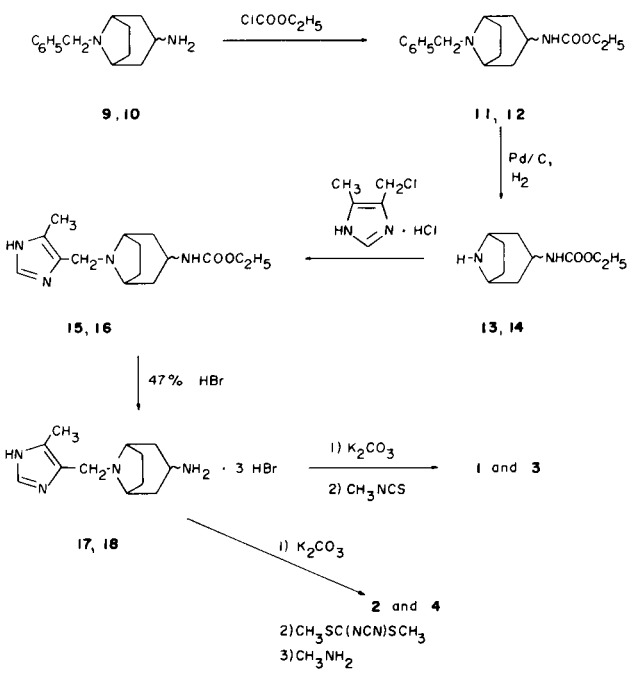
**10**

In the tropane analogues the tropane ring nitrogen atom should effectively accomplish this same objective particularly in view of the likelihood that this atom will be protonated at physiological *p*H ($pK_b$ ~4-5 based on atropine) thereby enhancing the electron-withdrawing properties of this function. This structural feature should further stabilize the imidazole ring system of **1-4** in the desired pharmacophoric tautomer.

The target compounds of this study were also designed to provide evidence regarding the steric requirements for effective antagonism of the histamine $H_2$-receptors. The tropane analogues provide for a conformationally defined orientation of the side chains of **5** and **6** as well as a defined orientation of the *N*-methylthiourea and *N*-methyl-*N*-cyanoguanidine functions which is achieved by axial (**1** and **2**) and equatorial (**3** and **4**) orientation at C-3.

The desired stereochemistry of the proposed analogues of metiamide (**1** and **3**) and cimetidine (**2** and **4**) was achieved by selective transformations performed early in the synthesis of these compounds (Scheme I). 8-Benzylnortropinone (**7**), obtained from 2,5-dimethoxytetrahydrofuran, 1,3-acetonedicarboxylic acid and benzylamine by the procedure of Archer (3) was converted to its oxime

Scheme II




derivative (**8**) using hydroxylamine hydrochloride and sodium bicarbonate. The oxime was reduced using platinum oxide-hydrogen and using sodium in ethanol to give isomeric primary amines which were tentatively assigned the axial **9** and equatorial **10** orientations on the basis of reports of stereoselective reductions of tropinone (4) and tropananil (5). The configurations of the 3-amino groups of **9** and **10** were confirmed by examination of the pmr spectra of these isomers. The $H_3$-resonance of **9** ($\delta$ 3.29) in deuteriochloroform was obscured by a broad signal for $H_{1,5}$ centered at $\delta$ 3.18, however, protonation of the amine function of **9** (as the dioxalate salt) resulted in a shift of the $H_3$ resonance in deuterium oxide so that a triplet at $\delta$ 3.87 (J = 7 Hz) could be observed. This is a common resonance pattern for $H_{3\beta}$ in which the piperidine ring of the tropane nucleus exists in a slightly flattened chair conformation (5,6). Flattening of the ring system in **9** is apparently related to repulsive interaction between the axial C-3 amine function and the C-6,7 bridge. The resonance for $H_{3\alpha}$ in the pmr spectrum of **10** appeared as a triplet of triplets (J = 7, 11 Hz) centered at $\delta$ 2.92 which is characteristic for 3$\beta$-substituted tropanes in which the piperidine ring assumes a relatively undistorted chair conformation (6). Further evidence for the assigned configurations of **9** and **10** is the significant differences in base widths of the $H_3$ signals. Coupling of the pseudoequatorial $H_{3\beta}$ of **9** results in a small base width for this signal (~20 Hz) whereas the corresponding value for axial $H_{3\alpha}$ of **10** is far broader (~40 Hz) arising from axial-axial (J = 11 Hz) and axial-equatorial (J = 7 Hz) coupling of this proton. The upfield position of the axial $H_{3\alpha}$ signal in the pmr spectrum of **10** relative to the chemical shift for the pseudoequatorial $H_{3\alpha}$ signal of **9** provides additional support for the assignment of configuration at C-3 for these isomers.

The remaining synthetic transformations involved in conversion of the primary amines **9** and **10** (Scheme II) would not be expected to alter configuration at C-3 thereby facilitating assignment of stereochemistry at C-3 in the target compounds **1-4**. Treatment of **9** and **10** with ethyl chloroformate provided the carbamates, **11** and **12**, which were converted to the nortropane derivatives using 10% palladium-on-carbon in the presence of hydrogen. The nortropane isomers (**13** and **14**) were alkylated with 5-methyl-4-imidazolylmethyl chloride hydrochloride which was prepared according to the procedure of Durant *et al.*, (7) *via* lithium aluminum hydride reduction of ethyl 5-methyl-4-imidazolecarboxylate followed by chlorination using concentrated hydrochloric acid. Hydrolysis of **15** and **16** with 48% hydrobromic acid provided good yields of the iosmeric amine hydrobromides, **17** and **18**. Treatment of the isomeric amine free bases with methyl isothiocyanate gave the isomeric tropane analogues of metiamide (**1** and **3**). Synthesis of the cimetidine analogues, **2** and **4**, involved treatment of **17** and **18** with dimethylcyanodithioimidocarbonate to provide the isomeric isothioureas which were in turn treated with aqueous methylamine to give the desired products. Attempts to convert the *N*-methylthiourea isomers (**1** and **3**) directly to the *N*-methyl-*N*-cyanoguanidine isomers (**2** and **4**) using lead cyanamide (8) proved unsuccessful.

It was of interest to determine the conformational preference of the piperidine ring of the target tropane analogues of this study in view of our previous experiences with conformational heterogeneity of tropane isomers of the 4-(propananilido)piperidine analgesics (5). Our earlier studies indicated that tropane derivatives possessing a 3$\alpha$-propananilido function **19** preferred a piperidine ring boat conformation presumably because of repulsive interactions between the bulky propananilido moiety with the C-6,7 bimethylene bridge whereas 3$\beta$-propananilidotropanes (**20**) exhibited a normal chair conformation for the piperidine ring. The pmr studies of the conformational preferences for **1-4** in methanol-$d_4$ and DMSO-$d_6$ (with added deuterium oxide) suggest a normal chair conformation for the equatorial isomers (**3** and **4**) and a slightly flattened chair conformation for the axial isomers (**1** and **2**) as evidenced by broader base widths, 40-44 Hz, for the axial $H_{3\alpha}$ signals **3** and **4** as compared to base widths of 19-22 Hz for the pseudoequatorial $H_{3\beta}$ signals in **1** and **2**. Analyses of the resonance patterns for the $H_3$ signals of these isomers was not possible because of poor signal resolution seen in solvents used in this study. The piperidine ring conformational homogeneity found in the

tropane isomers of this study is apparently related to the ability of the 3α-*N*-methylthiourea and 3α-*N*-methyl-*N*-cyanoguanidine moieties of **1** and **2** to adopt an orientation that minimizes repulsive interactions with the C-6,7 bimethylene bridge.

The target compounds of this study are currently being evaluated for their antagonistic properites at histamine $H_2$-receptors.

## EXPERIMENTAL

All melting points are uncorrected and were determined with a Mel-Temp apparatus. Infrared spectra were determined with a Beckman IR-33 spectrophotometer. The nmr spectra were taken on a Jeolco C-60HL spectrometer using TMS as internal standard. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. Hydrochloride salts were prepared by dissolving free amine base in diethyl ether, chilling and then adding ethereal hydrogen chloride. Hydrogenoxalate salts were prepared by adding a hot ethanolic solution of the free amine base to a boiling solution of 2-molar-equivalents of oxalic acid. The resulting solutions were cooled and crystalline salts obtained by filtration.

8-Benzyl-1α*H*,5α*H*-notropan-3-one Oxime (**8**).

A 200 ml, aqueous solution of hydroxylamine hydrochloride (32.2 g, 0.464 mole) was added in one portion to a solution of 8-benzylnortropinone (3) (50.0 g, 0.232 mole) in 200 ml of 95% ethanol. Sodium bicarbonate (39.0 g, 0.464 mole) was added in portions to the solution and the resultant mixture was heated on a steam bath for 30 minutes then stirred at room temperature for an additional 18 hours. The white precipitate was collected by filtration, washed with water (3 × 200 ml portions) and dried *in vacuo* to give 48.6 g (91%) of **8**, mp 122-123°; ir (potassium bromide): 1656 $cm^{-1}$ (C=N); nmr (deuteriochloroform): δ 3.35-3.65 (m, $H_{1_\alpha}$ and $H_{5_\alpha}$, 2H), 3.82 (s, $CH_2C_6H_5$, 2H), 7.35-7.82 (m, $C_6H_5$, 5H). The oxime prepared in this manner was used without further purification for conversion to **9** and **10**.

*Anal.* Calcd. for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.17. Found: C, 73.29; H, 7.92; N, 12.04.

8-Benzyl-3α-amino-1α*H*,5α*H*-nortropane (**9**).

A solution of 8-benzylnortropin-3-oxime (**8**) (15.0 g, 0.65 mole) in 100 ml of ethanol and 25 ml of acetic acid was treated with 1.0 g of platinum oxide and hydrogenated at 3.15 $kg/m^2$ for 48 hours. The reaction mixture was filtered through Celite and the filtrate converted *in vacuo*. The residual oil was taken up on 100 ml of 10% hydrochloric acid and the acidic solution was washed with ether. The free amine was liberated with 12 *N* sodium hydroxide and the alkaline solution extracted with ether (3 × 50 ml portions). The combined ethereal extracts were washed with water (3 × 25 ml portions) and dried (sodium sulfate). Evaporation of solvent yielded a clear oil which was distilled to provide 6.5 g (46%) of **9**, 100-109° (0.05 mm); nmr (deuteriochloroform): δ 1.15 (s, $-NH_2$, 2H), 2.96-3.46 (m, $H_{1_\alpha}$, $H_{5_\alpha}$, $H_{3\beta}$, 3H), 3.57 (s, $CH_2C_6H_5$, 2H), 7.22-7.60 (m, $C_6H_5$, 5H). The dioxalate salt of **9** was prepared, mp 202-203°.

*Anal.* Calcd. for $C_{14}H_{20}N_2 \cdot 2C_2H_2O_4$: C, 54.54; H, 6.10; N, 7.07. Found: C, 54.26; H, 6.67; N, 7.02.

8-Benzyl-3β-amino-1α*H*,5α*H*-nortropane (**10**).

Small pieces of sodium (37 g, 1.61 g-atoms) were added to a solution of **8** in 200 ml of ethanol at such a rate as to maintain a brisk reflux. An additional 100 ml of ethanol was added to the reaction during the addition of sodium in order to ensure dissolution of the sodium ethoxide. When all of the sodium had dissolved, the reaction was refluxed for 16 hours, cooled and 500 ml water added. The solution was concentrated *in vacuo* and the resultant aqueous fraction was chilled and carefully acidified with concentrated hydrochloric acid. The acidic solution was washed with ether and made basic with 12 *N* sodium hydroxide. The free amine was extracted into ether (3 × 200 ml portions) and the combined extracts washed with water and then dried over sodium sulfate. Removal of the solvent *in vacuo* yielded a colorless oil which was distilled to give 15.5 g (66%) of **10**, bp 100-114° (0.8 mm); nmr (deuteriochloroform): δ 1.05 (s, $-NH_2$, 2H), 2.92 (nonet, J = 7, 11 Hz, $H_{3_\alpha}$, 1H), 3.05-3.30 (m, $H_{1_\alpha}$ and $H_{5_\alpha}$, 2H), 3.55 (s, $CH_2C_6H_5$, 2H), 7.07-7.50 (m, $C_6H_5$, 5H). The dioxalate salt of **10** was prepared, mp 136-140° (ethanol-water).

*Anal.* Calcd. for $C_{14}H_{20}N_2 \cdot 2C_2H_4O_2 \cdot 0.5\ H_2O$: C, 53.33; H, 6.22; N, 6.91. Found: C, 53.25; H, 6.35; N, 6.81.

8-Benzyl-3α- and 3β-(*N*-carbethoxy)amino-1α*H*,5α*H*-nortropane (**11** and **12**).

A solution of ethyl chloroformate (6.6 g, 0.061 mole) in 25 ml of acetonitrile was added dropwise to an ice-chilled suspension of **9** or **10** (12.0 g, 0.055 mole) and anhydrous sodium carbonate (30.0 g, 0.283 mole) in 100 ml of acetonitrile. The stirred reaction mixture was refluxed for 16 hours and filtered. It was found necessary to filter the hot reaction mixture in the preparation of **12** to avoid precipitation of product during the filtration process. Filtrate containing crude **11** and **12** were concentrated *in vacuo* to leave oily residues which were dissolved in 10% hydrochloric acid. The acid solution was washed wi.h ether and alkalinized with 12 *N* sodium hydroxide. Alkaline suspensions of **11** and **12** were extracted with chloroform (3 × 100 ml portions) and the combined chloroformic extracts washed with 3 × 50 ml portions of water and dried (sodium sulfate). Evaporation of solvent from **11** provided a brown oil which was distilled to give 13.1 g (81%) of **11**, bp 163-171° (0.2 mm); ir (liquid film): 1720 $cm^{-1}$ (C=O): nmr (deuteriochloroform): δ 1.25 (t, J = 7 Hz, $COOCH_2CH_3$, 3H), 3.05-3.33 (m, $H_{1_\alpha}$, $H_{5_\alpha}$, 2H), 3.55 (s, $CH_2C_6H_5$, 2H), 4.15 (q, $COOCH_2CH_3$, 2H), 7.17-7.55 (m, $C_6H_5$, 5H). The hydrochloride salt of **11** (mp 202-205°, acetonitrile-ether) was prepared in the usual manner. Evaporation of solvent from **12** yielded 11.9 g (75%) of **12** as colorless flakes from hexane-petroleum ether, mp 101-102°; ir (potassium bromide): 1688 $cm^{-1}$ (C=O); nmr (deuteriochloroform): δ 1.21 (t, J = 7 Hz, $COOCH_2CH_3$, 3H), 3.05-3.35 (m, $H_{1_\alpha}$, $H_{5_\alpha}$, 2H), 3.52 (s, $CH_2C_6H_5$, 2H), 4.08 (q, $COOCH_2CH_3$, 2H), 7.10-7.42 (m, $C_6H_5$, 5H).

*Anal.* (**11**) Calcd. for $C_{17}H_{24}N_2O_2 \cdot HCl$: C, 62.85; H, 7.76; N, 8.63. Found: C, 62.56; H, 7.89; N, 8.65. (**12**) Calcd. for $C_{17}H_{24}N_2O_2$: C, 70.80; H, 8.39; N, 9.72. Found: C, 70.95; H, 8.50; N, 9.72.

3α- and 3β- (*N*-Carbethoxy)amino-1α*H*,5α*H*-nortropane (**13** and **14**).

Solutions of **11** and **12** (2.2 g, 0.023 mole and 12.5 g, 0.043 mole, respectively) in 50 ml ethanol, 1 ml acetic acid, 10% palladium-on-carbon (0.2 g) and 100 ml ethanol, 5 ml acetic acid, 10% palladium-on-carbon (1.2 g), respectively, were hydrogenated (2.45 kg/m) at room temperature for 24 hours. The solutions were filtered with the aid of Celite and concentrated *in vacuo*. The residual oils were dissolved in 10% HCl hydrochloric acid, the acidic solution washed with 3 portions of ether then alkalinized with 12 *N* sodium hydroxide and extracted with 3 portions of chloroform which was dried over sodium sulfate. Concentration of the chloroformic solution of **13** provided a colorless oil following distillation, bp 113-115° (0.05 mm); ir (liquid film): 1710 $cm^{-1}$ (C=O); nmr (deuteriochloroform): δ 1.22 (t, J = 7 Hz, $COOCH_2CH_3$, 3H), 3.42-3.72 (m, $H_{1_\alpha}$, $H_{5_\alpha}$, 2H), 4.16 (q, $COOCH_2CH_3$, 2H). The picrate salt of **13** was prepared by adding a hot solution of **13** in 95% ethanol to a boiling saturated solution of picric acid in hot 95% ethanol and then chilling, mp 199-200.5°. Concentration of the chloroformic solution of **14** provided 6.6 g (77%) following distillation, bp 102-106° (0.05 mm); ir (liquid film): 1710 $cm^{-1}$ (C=O); nmr (deuteriochloroform): δ 1.22 (t, J = 7 Hz, $COOCH_2CH_3$, 3H), 3.47-3.67 (m, $H_{1_\alpha}$, $H_{5_\alpha}$, 2H), 4.10 (q, $COOCH_2CH_3$, 2H). The oxalate salt of **13** was prepared in the usual manner, mp 171-171.5° (ethanol).

*Anal.* (**13**) Calcd. for $C_{10}H_{28}N_2O_2 \cdot C_6H_3N_3O_7$: C, 44.96; H, 4.95; N, 16.39. Found: C, 45.08; H, 5.12; N, 16.90. (**14**) Calcd. for $C_{10}H_{28}N_2O_2 \cdot C_2H_2O_4$: C, 49.99; H, 6.99; N, 9.72. Found: C, 50.02; H, 7.30; N, 9.64.

(5-Methylimidazol-4-yl)methylchloride Hydrochloride.

A paste made up of ethyl 4-methyl-5-imidazolecarboxylate (37.5 g, 0.243 mole) and a 25 ml of dry THF was added in portions to a stirring

suspension of lithium aluminum hydride (12.0 g, 0.316 mole) in 1.0 ℓ of dry tetrahydrofuran under a flow of nitrogen. After refluxing for 4 hours, the suspension was cooled in an ice-water bath and the excess hydride destroyed with successive additions of 12 ml water, 12 ml of 15% sodium hydroxide and 45 ml of water. The white suspension was brought to room temperature and filtered. The filtered salts were digested in 500 ml of hot tetrahydrofuran and refiltered. The combined organic filtrates were concentrated *in vacuo* and the residual orange oil was dissolved in a minimum amount of ethanol and 500 ml of hot ethyl acetate/ether (3:2) was added. The solution was chilled yielding 15.0 g (55%) of (5-methylimidazol-4-yl)methanol as white prisms, mp 138° [lit (9) 138°]. A solution of 15.0 g of (5-methylimidazol-4-yl)methanol in 50 ml of concentrated hydrochloric acid was heated on a steam bath for 30 minutes then cooled and concentrated *in vacuo* leaving a yellow solid that crystallized from a minimum amount of ethanol to which a small volume of dry ether was added to provide 8.5 g (67%) of (5-methylimidazol-4-yl)methyl chloride hydrochloride as a white powder, mp 236-237 [lit (9) 222°].

8-(5-Methylimidazol-4-yl)methyl-3α- and 3β-(*N*-carbethoxy)amino-1α*H*,5α*H*-nortropane (**15** and **16**).

A solution of (5-methylimidazol-4-yl)methyl chloride hydrochloride (4.8 g, 0.029 mole) in 40 ml of methanol was added dropwise to a suspension of **15** (5.2 g, 0.026 mole) or **16** (7.6 g, 0.038 mole) in 100 ml of ethanol containing 5 equivalents of anhydrous sodium carbonate. The reaction mixtures were refluxed (with stirring) for 2 hours, cooled, filtered and concentrated to yield a brown foam. This residue was partitioned between 50 ml of water and 100 ml chloroform/methanol (5:1). The organic extract was dried (sodium sulfate) and concentrated *in vacuo* to a brown solid which was recrystallized from acetonitrile to provide **15** and **16** as white solids in yields of 3.3 g (43%) and 7.2 g (65%), respectively. Characterization of **15** provided, mp 168-169°; ir (potassium bromide) 1685 $cm^{-1}$ (C=O); nmr (tetradeuteriomethanol): δ 1.26 (t, J = 7 Hz, $COOCH_2CH_3$, 3H), 2.22 (s, Im-$CH_3$, 3H), 4.12 (q, J = 7 Hz, $COOCH_2CH_3$, 2H), 7.51 (s, $H_3$ of Im). Characterization of **16** provided, mp 184.5-185°; ir (potassium bromide): 1682 $cm^{-1}$ (C=O); nmr (hexadeuteriodimethylsulfoxide): δ 1.16 (t, J = 7 Hz, $COOCH_2CH_3$, 3H), 2.11 (s, Im-$CH_3$, 3H), 3.33 (s, Im-$CH_2$-, 2H), 3.91 (q, J = 7 Hz, $COOCH_2CH_3$, 2H), 7.18 (s, $H_3$ of Im, 1H).

*Anal.* Calcd. for $C_{15}H_{24}N_4O_2$: C, 61.62; H, 8.27; N, 19.16. Found: (**15**) C, 61.54; H, 8.55; N, 19.10 and (**16**) C, 61.50; H, 8.49; N, 19.05.

8-(5-Methylimidazol-4-yl)methyl-3α- and 3β-amino-1α*H*,5α*H*-nortropane Trihydrobromide (**17** and **18**).

Solutions of **15** (3.2 g, 0.011 mole) and **16** (6.9 g, 0.024 mole) in 30 and 50 ml of 48% hydrobromic acid (purified by distillation from stannous chloride), respectively, were refluxed for 30 minutes. The reaction solutions were then concentrated *in vacuo* to dryness and the residual orange oils were dissolved in hot 2-propanol. The 2-propanol solutions were stirred overnight and the resultant precipitates collected by filtration to provide 4.5 g (88%) of **17** trihydrobromide and 9.8 g (90%) of **18** trihydrobromide as cream-colored powders. Compound **17** trihydrobromide gave, mp >300° dec; nmr (deuterium oxide): δ 2.50 (s, Im-$CH_3$, 3H), 3.87 (t, J = 6 Hz, $H_{3\beta}$, 1H), 4.10-4.37 (m, $H_{1\alpha}$ and $H_{5\alpha}$, 2H), 4.50 (s, Im-$CH_2$- 2H), 8.80 (s, $H_3$ of Im, 1H). Compound **18** trihydrobromide was characterized as follows: mp >300° dec; nmr (deuterium oxide): δ 2.52 (s, Im-$CH_3$, 3H), 3.95 (nonet, J = 7 and 11 Hz, $H_{3\alpha}$, 1H), 4.25-4.45 (m, $H_{1\alpha}$ and $H_{5\alpha}$, 2H), 4.53 (s, Im-$CH_2$-, 2H), 8.83 (s, $H_3$ of Im, 1H).

*Anal.* (**17**) Calcd. for $C_{12}H_{20}N_4 \cdot 3$ HBr: C, 31.12; H, 5.01; N, 12.10. Found: C, 31.05; H, 5.22; N, 12.01. (**18**) Calcd. for $C_{12}H_{20}N_4 \cdot 3$ HBr · 2 $H_2O$: C, 28.88; H, 5.45; N, 11.23. Found: C, 28.79; H, 5.73; N, 11.42.

*N*-Methyl-*N'*-[8-(5-methylimidazol-4-yl)methyl-1α*H*,5α*H*-nortropan-3β- and 3β-yl]thiourea (**1** and **3**).

Solutions of **17** (2.1 g, 4.5 mmoles) and **18** (9.9 g, 22.0 mmoles) in water were made basic (potassium carbonate, 10.9 mmoles and 55 mmoles, respectively) and the solutions concentrated *in vacuo* to dryness. Following crystallization from 2-propanol, the free bases of **17** and **18** were dissolved in 10 and 75 ml of ethanol, respectively and treated with ethanolic solutions of methylisothiocyanate (0.386 g, 5.0 mmoles and 1.70 g, 23.0 mmoles, respectively). The solutions were gently refluxed for 30 minutes and cooled. A crude sample of **1** was obtained by *in vacuo* concentration of the ethanolic reaction solution to a white foam followed by digestion in hot acetonitrile. Filtration of the hot acetonitrile suspension gave **1** (0.865 g, 65%) as a white powder, mp 189-191°; ir (potassium bromide): 1552 $cm^{-1}$ (C=S); nmr (hexadeuteriodimethylsulfoxide): δ 2.14 (s, Im-$CH_3$, 3H), 2.88 (d, J = 4 Hz, $NHCH_3$, 3H), 3.00-3.33 (m, $H_{1\alpha}$ and $H_{5\alpha}$, 2H), 3.47 (s, Im-$CH_2$-, 2H), 4.08-4.43 (m, $H_{3\beta}$, 1H), 7.41 (s, $H_3$ of Im, 1H). Compound **3** was obtained by filtration of the ethanolic reaction mixture to provide 4.2 g (68%) of a white powder, mp 155-158°; ir (potassium bromide): 1555 $cm^{-1}$ (C=S); nmr (hexadeuteriodimethylsulfoxide): δ 2.16 (s, Im-$CH_3$, 3H), 2.84 (d, J = 4 Hz, $NHCH_3$, 3H), 3.45 (s, Im-$CH_2$-, 2H), 3.98-4.66 (m, $H_{3\alpha}$, 1H), 4.12-4.35 (m, $H_{1\alpha}$ and $H_{5\alpha}$, 2H), 7.43 (s, H of Im, 1H).

*Anal.* (**1**) Calcd. for $C_{14}H_{23}N_5S \cdot H_2O$: C, 53.99; H, 8.09; N, 22.49; S, 10.30. Found: C, 54.13; H, 7.70; N, 22.49; S, 9.84. (**3**) Calcd. for $C_{14}H_{23}N_5S$: C, 57.30; H, 7.90; N, 23.87; S, 10.97. Found: C, 56.93; H, 7.83; N, 23.55; S, 10.64.

*N''*-Cyano-*N*-methyl-*N'*-[8-(5-methylimidazol-4-yl)methyl-1α*H*,5α*H*-nortropan-3α- and 3β-yl]guanidine (**2** and **4**).

The free bases of **17** and **18** were formed as described in the preparation of **1** and **3**. Solutions of the free base of **17** (1.0 g, 4.5 mmole) and **18** (1.0 g, 4.5 mmoles) in 10 ml of ethanol were treated with dimethylcyanodithioimidocarbonate (0.731 g, 5.0 mmoles) in 15 ml of ethanol. The reaction was allowed to stir overnight at room temperature at which time a 40% aqueous solution of methylamine (10 ml) was added. The colorless solutions were stirred an additional 24 hours, concentrated *in vacuo* and collected by filtration from hot acetonitrile to provide 0.322 g (23%) of **2** and 0.316 g (23%) of **4** as white powders. Characterization of **2** involved, mp 195-197°; ir (potassium bromide): 2180 (N-C≡N), 1605 and 1580 $cm^{-1}$ (>C=N-); nmr (hexadeuteriodimethylsulfoxide): δ 2.15 (s, Im-$CH_3$, 3H), 2.77 (d, J = 4 Hz, $NHCH_3$, 3H), 3.04-3.30 (m, $H_{1\alpha}$ and $H_{5\alpha}$, 2H), 3.36 (s, Im-$CH_2$-, 2H), 3.57-3.94 (m, $H_{3\beta}$, 1H), 7.43 (s, $H_3$ of Im, 1H). Characterization of **4** involved, mp 202-203°; ir (potassium bromide): 2165 (N-C≡N), 1590 $cm^{-1}$ (>C=N-); nmr (hexadeuteriodimethylsulfoxide): δ 2.18 (s, Im-$CH_3$, 3H), 2.72 (d, J = 4 Hz, $NHCH_3$, 3H), 3.08-3.36 (m, $H_{1\alpha}$, $H_{5\alpha}$, 2H), 3.48 (s, Im-$CH_2$-, 2H), 3.65-4.25 (m, $H_{3\alpha}$, 1H), 7.41 (s, $H_3$ of Im, 1H).

*Anal.* (**2**) Calcd. for $C_{15}H_{23}N_7 \cdot 0.25$ $CH_3CN \cdot 0.5$ $H_2O$: C, 58.10; H, 7.71; N, 31.70. Found: C, 58.13; H, 7.77; N, 31.76. (**4**) Calcd. for $C_{15}H_{23}N_7$: C, 59.77; H, 7.69; N, 32.54. Found: C, 59.57; H, 7.56; N, 32.31.

Acknowledgments.

The authors wish to acknowledge financial support of this research as provided by a National Research Service Award (number T32 GM 07099) from the National Institute of General Medical Sciences of the National Institutes of Health and by the Research Institute of Pharmaceutical Sciences, School of Pharmacy, University of Mississippi.

## REFERENCES AND NOTES

(1) R. Ganellin, *J. Med. Chem.*, **24**, 913 (1981).

(2) G. J. Durant, J. C. Emmett and C. R. Ganellin, "Cimetidine. Proceedings of the Second International Symposium on Histamine $H_2$-Receptor Antagonists", W. L. Burland and M. A. Simkins, eds., Excerpta Medica, Amsterdam-Oxford, 1977, p 1.

(3) S. Archer, U. S. Patent 2,845,427 (1958); *Chem. Abstr.*, **53**, 432e (1959).

(4) A. Nickon and L. F. Fieser, *J. Am. Chem. Soc.*, **74**, 5566 (1952).

(5) J. R. Bagley and T. N. Riley, *J. Heterocyclic Chem.*, **14**, 599 (1977).

(6) A. F. Casy, "PMR Spectroscopy in Medicinal and Biological Chemistry", Academic Press, New York, NY, 1971, Chapter 7.

(7) G. J. Durant, J. C. Emmett, C. R. Ganellin, A. M. Roe, R. A. Slater, *J. Med. Chem.*, **19**, 923 (1976).

(8) G. J. Durant, J. C. Emmett, C. R. Ganellin, P. D. Miles, M. E. Parsons, H. D. Prain, G. R. White, *ibid.*, **20**, 901 (1977).

(9) A. J. Ewins, *J. Chem. Soc.*, **99**, 2052 (1911).

(10) J. R. Timmons, L. S. Wittenbrook, *J. Org. Chem.*, **32**, 1566 (1967).