Ergot Alkaloids. Synthesis of 6-Methyl-8-ergolenes as Inhibitors of Prolactin Release

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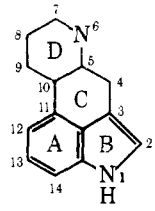
A general synthetic route from elymoclavine (**4a**) to a variety of C-17 substituted 8-ergolenes has been established. [The C-17 position is the carbon attached to C-8 of the ergoline (1) skeleton as indicated in structure **2**.] This route involves displacement reactions on the allylic chloride (**4h**) prepared from **4a** by reaction with thionyl chloride. Conversion of the naturally occurring tricyclic clavines, chanoclavine I (**5a**) and isochanoclavine I (**5b**), to the tetracyclic clavine, agroclavine (**4i**), has been achieved. The new compounds prepared were tested for prolactin-inhibiting ability and were found to possess activity. One of the compounds prepared, 6-methyl-8-ergolenylacetamide (**4k**), was very potent, comparing favorably in activity to the best prolactin inhibitors reported to date.

A number of the natural ergot alkaloids and related synthetics in the ergoline (1) series are of great value as drugs for the treatment of a variety of disorders.[1] Recently considerable interest has developed in the potential use of compounds of this type in the therapy of prolactin-dependent conditions based on the discovery that compounds of this class are effective inhibitors of release of the pituitary hormone prolactin.[2-6]



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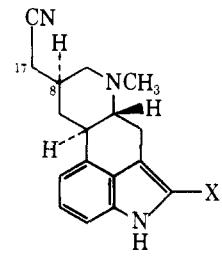
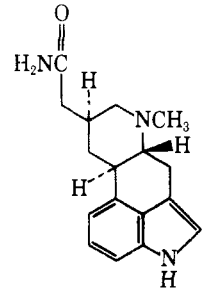
Previous efforts[2-5] to establish the relationship between ergoline structure and prolactin-inhibitory activity allow a number of conclusions. First, the entire tetracyclic ergoline system (1) with a trans CD ring fusion is necessary for significant activity. Substituents can be accommodated at the 2, 6, and 8 positions but not at 7 and 9. In general, reduction of the 2,3 double bond seems to diminish activity. A compound with a double bond at the 8,9 position is generally more active than the 9,10 isomer, however this unsaturation is not essential to activity since a number of ergolines, compounds with a saturated D ring, are potent prolactin inhibitors. Our emphasis has been to establish these relationships among the clavine alkaloids which are in general less pharmacologically potent than the peptide-type alkaloids. Currently three semisynthetic ergoline derivatives in the clavine series are undergoing clinical evaluation as prolactin inhibitors here and in Europe. Two of the compounds, VUFB 6605 (**2a**, X = H) and VUFB 6683 (Deprenon, 3) were developed by Semonsky and coworkers in Prague.[6-8] Compound **2b** (Lilly compound 83636, lergotrile mesylate) was developed at Eli Lilly and Co. and is currently undergoing clinical trials as a prolactin inhibitor.[5]

We have established the naturally occurring 8-ergolene, elymoclavine (**4a**), and several C-17 derivatives such as **4b** and **4c** to be potent prolactin inhibitors.[3] Based on this observation we were interested in developing general synthetic routes from the tricyclic clavines such as chanoclavine I (**5a**) to elymoclavine and from elymoclavine to a variety of C-17 analogs. In addition, it should be possible to ultimately convert the 8-ergolenes synthesized into the corresponding dihydro compounds which would establish alternate

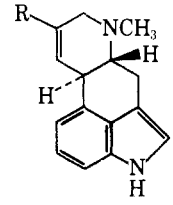


2a, X = H; VUFB 6605
b, X = Cl; lergotrile



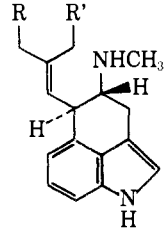
3. VUFB 6683

routes to compounds such as **2a**,**b** and **3** utilizing elymoclavine rather than lysergic acid as a starting material for these potentially important drugs.



4a, R = CH_2OH
b, R = CH_2N^+(pyridinium)TsO^-
c, R = CH_2-c-NC_5H_{10}
d, R = COOH
e, R = COCl
f, R = $CON(CH_2CH_3)_2$
g, R = $CH_2N(CH_2CH_3)_2$
4h, R = CH_2Cl
i, R = CH_3
j, R = CH_2CN
k, R = CH_2CONH_2
l, R = CH_2-c-NC_4H_8
m, R = CH_2NHPh
n, R = $CH_2N(Ac)Ph$

Very few C-17 substituted 8-ergolenes are reported in the literature and in these cases the routes to the compounds are specific. For example elymoclavine pyridinium tosylate (**4b**) and the corresponding 8-piperidinomethyl-8-



5a, R = OH; R′ = H
b, R = H; R′ = OH

ergolene (**4c**) were prepared from elymoclavine (**4a**) by reaction with tosyl chloride in pyridine to give **4b** followed by catalytic hydrogenation to give the piperidino compound **4c** in 37% yield.[9] 6-Methyl-8-diethylaminomethyl-8-ergolene (**4g**) was prepared by a multistep synthesis from $\Delta^{8,9}$-lysergic acid (**4d**) via the acid chloride **4e** and the amide **4f** in 21% overall yield.[10]

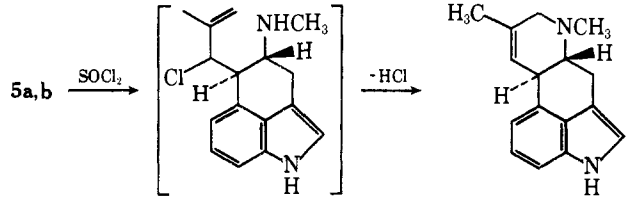
Chemistry. Elymoclavine (**4a**) is available from submerged cultures of *Claviceps* strain SD-58 which can be readily adapted to large-scale production.[11] Reaction of **4a** with thionyl chloride in dioxane gave a product which was shown to be 6-methyl-8-chloromethyl-8-ergolene (**4h**) by examination of its NMR, ir, and high-resolution mass spectra and by $LiAlH_4$ reduction to agroclavine (**4i**), a known naturally occurring clavine alkaloid. This allylic chloride is reasonably stable and ideally reactive to a variety of nucleophiles thereby opening a general route to a variety of C-17 substituted 8-ergolenes by simple displacement reactions.

Reaction of **4h** with sodium cyanide in DMSO gave the corresponding nitrile **4j** in good yield. The nitrile was converted to the corresponding amide **4k** by reaction with mixtures of H_2O_2 and NaOH in aqueous ethanol. These compounds are the 8,9-dehydro analogs of the potent prolactin inhibitors VUFB 6605 (**2a**) and VUFB 6683 (**3**) developed by the Prague group.

Although our main focus is on the potential prolactin-inhibiting ability of these compounds, it should be noted that this approach can be used to synthesize a variety of 17-deoxy-$\Delta^{8,9}$ analogs of known drugs. For example, reaction of the chloride with diethylamine gives **4g**, the 17-deoxy-$\Delta^{8,9}$ analog of LSD which had been prepared previously by a multistep conversion from $\Delta^{8,9}$-lysergic acid.

By reaction of the allylic chloride with the appropriate amine, the C-17 substituted pyrrolidino- (**4l**), anilino- (**4m**), acetanilino- (**4n**), and piperidino-6-methyl-8-ergolenes (**4c**)[9] were prepared.

In connection with our efforts to develop synthetic routes from substituted indoles to the tetracyclic ergolines we have discovered an efficient process to convert naturally occurring tricyclic clavines such as chanoclavine I (**5a**) and isochanoclavine I[12] (**5b**) into agroclavine (**4i**). Under conditions very similar to those used to convert elymoclavine into the allylic chloride, reaction of either **5a** or **5b** with thionyl chloride in dioxane gave agroclavine in 50–60% yield. The fact that both isomers gave agroclavine may be explained by a process involving a common intermediate such as **6**.

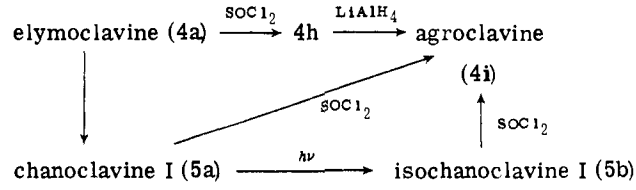


6 **4i** (agroclavine)

This type process operates in other cases, i.e., on treatment of γ-methylallyl alcohol with thionyl chloride one observes exclusive conversion to α-methylallyl chloride whereas α-methylallyl alcohol gives γ-methylallyl chloride. In both of these cases the SNi′ process predominates to virtual exclusion of the SNi reaction.[12]

By virtue of the chemical conversions just described we have established an additional chemical interrelationship among several of the naturally occurring clavine alkaloids (Scheme I). Elymoclavine had previously been converted into chanoclavine I which had in turn been converted to isochanoclavine I.[13]

Scheme I



Biological Activity. The compounds prepared were evaluated for prolactin-inhibiting activity in the rat and these results are listed in Table I. The testing method is described in the Experimental Section. In all cases ergocornine was included as a reference compound and these values are listed in Table I. On the basis of our previous work[3] it was established that the 8-ergolenes as a group exhibited significant prolactin-inhibiting activity. Further, it appeared that substitution on the D ring especially at the 8 position was essential to significant activity. This activity extended to substituents of considerable size.[3] On the basis of our previous data and the data in Table I it also appears that the polarity of the substituents (i.e., R = CH_2OH > R = CH_2OAc > R = CH_3 > R = CH_2Cl) parallels enhanced prolactin-inhibiting ability. A number of the compounds contained in this series give essentially complete inhibition of prolactin at 10 μg/animal comparing favorably to the best drugs reported to date. Compound **4k**, the $\Delta^{8,9}$ analog of Deprenon, is especially potent. The corresponding cyano compound **4j**, however, is apparently less potent than lergotrile and so activity may not correlate directly to the nature of the substituent at C-8 and the degree and position of D-ring unsaturation.

Further evaluation of the potential of these 8-ergolenes as prolactin-inhibiting drugs is underway and involves a determination of their relative toxicities and ability to inhibit prolactin-dependent rat mammary tumors.

Experimental Section

General Procedures. Uv spectra were recorded on a Perkin-Elmer Coleman 124 spectrophotometer and are reported in wavelength (nm) followed by molar extinction coefficient (ϵ). Ir spectra were recorded from KBr pellets with a Beckman IR-33 spectrophotometer. Mass spectra (MS) were obtained on a Hitachi RMU-6 low-resolution or a CEC 21-110 high-resolution mass spectrometer; *m/e* values are reported with relative intensity. NMR spectra (60 or 100 MHz) were recorded in $CDCl_3$ unless otherwise specified with either a Varian Associates A-60 or JEOL PFT-100 spectrometer. Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane (1%) as an internal standard. Analytical data were obtained from the Microanalysis Laboratory, Department of Chemistry, Purdue University.

Determination of Prolactin-Inhibiting Ability. Adult male rats of the Sprague–Dawley strain (Harland Industries, Cumberland, Ind.) weighing about 200 g were used. All rats were housed in an air-conditioned room with controlled lighting (lights on 6 a.m. to 8 p.m.) and fed Purina lab chow and water ad libitum.

Every male rat received an intraperitoneal injection of 2.0 mg of reserpine in aqueous suspension 18 hr before administration of the ergot derivatives. The purpose of the reserpine was to keep prolactin levels uniformly elevated.[3] All compounds to be tested were dissolved in 10% EtOH at a concentration of 10 μg/ml. The derivatives were injected intraperitoneally at a standard dose of 50 μg/kg. Each compound was administered to a group of ten rats, and a control group of ten intact males received an equivalent amount of 10% EtOH. One hour after treatment all rats were killed by decapitation, and 150-μl aliquots of serum were assayed for prolactin by radioimmunoassay using the NIAMD kit. Results were expressed as nanograms of NIAMD-prolactin-PR-1 per milliliter of serum. The results were evaluated statistically using Student's t test.

6-Methyl-8-chloromethyl-8-ergolene (4h). A solution containing 500 mg of elymoclavine (**4a**) in 300 ml of dioxane was

Table I. Tetracyclic Clavines, 8-Ergolenes[a]

Compd no.	R	Prolactin control value	Prolactin value after treatment	Inhibn, %	Level of significance[b]	Inhibn of ergocornine,[c] %
4a	$-CH_2OH$	32.5 ± 0.9	9.39 ± 0.3	71	$p < 0.001$	75
4g	$-CH_2N(CH_2CH_3)_2$	31.1 ± 5.8	14.8 ± 1.8	52	$p < 0.02$	64
4h	$-CH_2Cl$	21.4 ± 1.3	17.7 ± 0.8	17	$p < 0.05$	43
4j	$-CH_2C{\equiv}N$	39.2 ± 5.9	20.1 ± 1.6	49	$p < 0.01$	58
4k	$-CH_2CONH_2$	34.6 ± 2.3	5.7 ± 0.5	83	$p < 0.001$	82
4l	$-CH_2$-c-NC_4H_8	25.6 ± 1.3	14.6 ± 1.5	43	$p < 0.001$	71
4m	$-CH_2NHPh$	29.0 ± 3.4	16.5 ± 1.4	43	$p < 0.001$	67
4n	$-CH_2N(Ac)Ph$	29.0 ± 3.4	11.8 ± 1.0	59	$p < 0.001$	67

[a] All compounds were tested at 10 μg per animal. Values listed are means ± standard errors. [b] The level of significance was obtained according to Student's t test. [c] Included as a reference compound in all assays.

placed in a 500-ml round-bottom flask fitted with a dropping funnel. The solution was maintained under a N_2 atmosphere. A solution of 2.0 g of thionyl chloride in 50 ml of dioxane was added slowly with stirring at 25°. After the addition had been completed, the stirring was continued for 45 min at 60°. The mixture was then cooled and concentrated under vacuum to ca. 50 ml. The residue was dissolved in 200 ml of water and the aqueous solution was taken to pH 8 by addition of solid $NaHCO_3$. The solution was then extracted several times with equal volumes of chloroform; the chloroform extracts were combined, filtered through Celite, and dried over Na_2SO_4. Evaporation of the chloroform gave a syrup which was immediately chromatographed on a silica gel column using chloroform followed by 1% methanol in chloroform as the eluting solvent. Fractions shown to contain a compound different from the starting material (higher R_f) by thin-layer chromatography were combined. Evaporation of the solvent gave a clear syrup which on trituration with mixtures of isopropyl ether, chloroform, and hexane with cooling gave 330 mg (60%) of yellow crystalline 4h: mp 193° dec; ir, absence of hydroxyl absorption; NMR (DMSO-d_6) δ 4.45 (s, 2 H, CH_2Cl), 6.6 (s, 1 H, $HC{=}CCH_2Cl$); uv (MeOH) 295 (11,300), 285 (3100), 219 (56,400); MS 274 (22), 273 (27), 272 (M^+, 80), 271 (64), 237 (100); MS (high resolution) calcd for $C_{16}H_{17}N_2Cl$, 272.108; found, 272.108. Anal. ($C_{16}H_{17}N_2Cl$) C, H, N.

6-Methyl-8-cyanomethyl-8-ergolene (4j). A solution containing 100 mg (2.0 mmol) of sodium cyanide and 100 mg (0.367 mmol) of 6-methyl-8-chloromethyl-8-ergolene in 10 ml of dry dimethyl sulfoxide (DMSO) was placed in a 25-ml round-bottom flask under a N_2 atmosphere. The reaction mixture was stirred at room temperature for 1.5 hr and was then mixed with 100 ml of water and extracted with several equal quantities of EtOAc. The organic layer was then washed with water, dried over Na_2SO_4, and evaporated to a syrup. The syrup was dissolved in acetone and filtered through a short column of alumina. The filtrate was concentrated and the resulting syrup was recrystallized from an EtOAc–cyclohexane solvent mixture giving 74 mg (75%) of crystalline 6-methyl-8-cyanomethyl-8-ergolene, mp 176–180°. An analytical sample was obtained by preparative layer chromatography on 2.0-mm silica gel plates using mixtures of EtOAc–acetone (75:25). The rechromatographed compound was then recrystallized from EtOAc–cyclohexane giving **4j**: mp 186–187° dec; ir 4.5 μ (C≡N); uv (MeOH) 293 (8245), 284 (9170), 223 (27,900); NMR (100 MHz) δ 2.58 (NCH_3, s, 3 H), 2.6–3.6 (m, 7 H), 3.84 (C-10 CH, br s, 1 H), 6.60 (vinyl, s, 1 H), 6.8–7.3 (arom, m, 4 H), and 7.95 (indole NH, s, 1 H); MS (low resolution) *m/e* 263 (M^+, 100), 262 (70), 107 (80); MS (high resolution) calcd for $C_{17}H_{17}N_3$, 263.142; found, 263.142. Anal. ($C_{17}H_{17}N_3$) C, H, N.

6-Methyl-8-ergolenylacetamide (4k). 8-Cyanomethyl-6-methyl-8-ergolene (124 mg, 0.47 mmol) was dissolved in 6 ml of absolute EtOH, chilled in an ice bath, and treated with 0.2 ml of 30% H_2O_2 and 0.5 ml of a 3 *N* NaOH solution. The mixture was warmed to 50° and stirred for 1 hr under N_2. It was then digested with H_2O (50 ml), neutralized with dilute HCl solution, readjusted to slight alkalinity with solid $NaHCO_3$, and extracted extensively with EtOAc. The EtOAc extracts were dried over Na_2SO_4.

Preparative layer chromatography (Brinkmann, alumina, 1.0 mm, $CHCl_3$–MeOH, 9:1) and recrystallization from $CHCl_3$–MeOH–hexane gave 55 mg (42%) of **4k**: mp 236–238° dec; ir (KBr) 3.0 (NH_2) and 6.1 μ ($CONH_2$); uv (MeOH) 295 (5060), 283 (5620), 223 (22,400); MS (low resolution) *m/e* 281 (M^+, 0.5), 280 (2), 168 (33), 159 (15), 115 (17), 86 (20), 60 (60), 45 (100); MS (high resolution) calcd for $C_{17}H_{18}N_3O$ (M − 1), 280.145; found, 280.145. Anal. ($C_{17}H_{19}N_3O$) C, H, N.

6-Methyl-8-pyrrolidinomethyl-8-ergolene (4l). 8-Chloromethyl-6-methyl-8-ergolene (100 mg, 0.367 mmol) was dissolved in 10 ml of dry DMSO and treated with 100 mg (1.41 mmol) of freshly distilled pyrrolidine. The mixture was stirred at room temperature for 1 hr under N_2 and then was taken up in 200 ml of $CHCl_3$ thoroughly washed with H_2O, dried over Na_2SO_4, concentrated in vacuo, and column chromatographed on alumina (Brinkmann, activity II–III, 20 g) eluting with $CHCl_3$ and $CHCl_3$–EtOAc (1:1) to give 60 mg (50%) of **4l**. Recrystallization from EtOAc–hexane gave crystalline **4l**: mp 148–149°; ir (KBr) 3.25, 3.4, 13.6, and 14.9 μ; NMR δ 1.7 (m, 4 H, $-CH_2CH_2-$), 2.4 (m, 7 H, NCH_3 and α-pyrrolidine H's), 3.1 (s, 2 H, $-CH_2N-$), 6.4 (s, 1 H, $-CH{=}C-$); uv (MeOH) 293 (7000), 283 (8100), 225 (28,620), 205 (35,000); MS (low resolution) *m/e* 307 (M^+, 3), 237 (63), 236 (100), 235 (70), 221 (30), 108 (40), 154 (50); MS (high resolution) calcd for $C_{20}H_{25}N_3$, 307.205; found, 307.207. Anal. ($C_{20}H_{25}N_3$) C, H, N.

6-Methyl-8-diethylaminomethyl-8-ergolene (4g). 8-Chloromethyl-6-methyl-8-ergolene (100 mg, 0.366 mmol) was dissolved in 10 ml of DMSO in a N_2 atmosphere. Diethylamine (0.60 ml, 424 mg, 5.72 mmol) was introduced via syringe. The N_2 flow was then stopped and the sealed mixture allowed to stir at room temperature for 3 hr. The reaction mixture was poured into 100 ml of water and 5 ml of saturated $NaHCO_3$ solution. The chloroform extractions (3 × 100 ml) were dried over Na_2SO_4, concentrated, and chromatographed on an alumina plate (Brinkmann, 10 × 20 cm × 1 mm, F-254) with ethyl acetate–hexane. The desired band was powdered and extracted with ethyl acetate to afford after evacuation of solvent 78 mg (69%) of colorless oil. Recrystallization from benzene–petroleum ether provided pale yellow crystals, mp 94–95° (lit.[10] mp 92–94°). The mass, ir, NMR, and uv spectra of this compound are in agreement with the assigned structure.

6-Methyl-8-piperidinomethyl-8-ergolene (4c). 6-Methyl-8-chloromethyl-8-ergolene (49.0 mg, 0.18 mmol) was dissolved in 35 ml of acetonitrile by stirring under N_2 for 15 min. Piperidine (0.20 ml, 0.172 g, 2.02 mmol) was introduced via syringe and the mixture was stirred at room temperature for 15 hr. After most of the solvent was removed in vacuo, the mixture was diluted with 75 ml of water and 5 ml of saturated $NaHCO_3$ solution and extracted with chloroform (3 × 75 ml). The chloroform extract was dried over Na_2SO_4, concentrated to an oil, and chromatographed on an alumina plate (Brinkmann, 10 × 20 cm × 1 mm, F-254) with ethyl acetate. The desired band was powdered and extracted with ethyl acetate. The resulting solution was evaporated to give 46.7 mg (82%) of crude **4c**. Recrystallization from EtOAc–hexane in the cold afforded 39.7 mg (69%) of yellow needles, mp 168–170° dec (lit.[9] mp 169–170°).

6,8-Dimethyl-8-ergolene (4i, Agroclavine) from Isochanoclavine I (5b) and Thionyl Chloride. Isochanoclavine I (1 mg, 0.004 mmol) was mixed with thionyl chloride (13.3 mg, 0.112 mmol) and stirred in a sealed vial for 1 hr. TLC analysis of the reaction mixture [$CHCl_3$–MeOH (8:2) or C_6H_6–EtOAc (8:2)] showed the disappearance of starting material and the appearance of a new product which had the same R_f value as agroclavine.

6,8-Dimethyl-8-ergolene (4i, Agroclavine) from Chanoclavine I (5a) and Thionyl Chloride. Chanoclavine I (10 mg, 0.039 mmol) was dissolved in dioxane (10 ml), treated with thionyl chloride (20 mg, 0.168 mmol) in dioxane (2 ml), and stirred at room temperature for 0.5 hr under N_2 atmosphere. It was then neutralized with dilute $NaHCO_3$ solution and extracted with $CHCl_3$ (3 × 50 ml). The $CHCl_3$ was washed with H_2O, dried over Na_2SO_4, and evaporated to a syrup. The syrup was chromatographed on a 20 × 20 cm × 2.0 mm Brinkmann silplate, developing with $CHCl_3$–MeOH (8:2) to give 5 mg (54%) of **4i**. The ir and TLC [$CHCl_3$–MeOH (8:2), Me_2CO–EtOAc–DMF (5:5:1)] were identical with that of authentic agroclavine.

6,8-Dimethyl-8-ergolene (4i, Agroclavine) from 8-Chloromethyl-6-methyl-8-ergolene (4h). 8-Chloromethyl-6-methyl-8-ergolene (50 mg, 0.183 mmol) was added to a stirred slurry of $LiAlH_4$ (200 mg, 5.27 mmol) in THF (20 ml) and refluxed for 1.5 hr under N_2. The mixture was then combined with H_2O and $CHCl_3$ (150 ml), washed with H_2O, dried over Na_2SO_4, and chromatographed on a silica gel column (10 g). Elution with $CHCl_3$–MeOH (95:5) gave after trituration with hexane 17 mg (39%) of **4i**. The ir and TLC (see previous experiment) were identical with an authentic sample of agroclavine.

6-Methyl-8-anilinomethyl-8-ergolene (4m). 8-Chloromethyl-6-methyl-8-ergolene (**4h**, 100.0 mg, 0.368 mmol) was dissolved in 15 ml of DMSO under N_2. Aniline (0.6 ml, 0.62 g, 6.6 mmol) was added via syringe and allowed to react for 65 hr. The mixture was poured into 100 ml of water with 5 ml of saturated $NaHCO_3$ solution and extracted with 3 × 100 ml of EtOAc. The organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residual oil was chromatographed on silica gel using gradient elution from CH_2Cl_2 to 10% MeOH in CH_2Cl_2 to easily remove unreacted aniline from alkaloid products. Fractions containing the desired product were rechromatographed on a silica gel plate (10 × 20 cm × 2 mm) eluting with 9:1 CH_2Cl_2–MeOH to afford, after extraction with same solvent system, 107 mg (89%) of a solid foam, **4m**: ir (KBr) 2.93 (NH), 6.25, 6.67, 9.75, and 13.50 μ; MS (low resolution) *m/e* 329 (4), 328 (6), 237 (58), 236 (100), 235 (36), 167 (29), 154 (29), and 93 (28); NMR δ 2.4–4.0 (m, 12 H), 2.54 (NCH_3, s, 3 H), 6.35–7.4 (m, ~9 H); MS (high resolution) calcd for $C_{22}H_{22}N_3$ (M − 1), 328.181; found, 328.183. This sensitive compound was acetylated for further characterization.

6-Methyl-8-acetanilinomethyl-8-ergolene (4n). 8-Anilinomethyl-6-methyl-8-ergolene (**4m**, 100 mg, 0.304 mmol) was stirred in 3 ml of MeOH and 5 ml of acetic anhydride for 5 hr. After dilution with water and basification with Na_2CO_3 the mixture was extracted with 4 × 50 ml of CH_2Cl_2. The extract was dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed on an alumina plate (10 × 20 cm × 1.5 mm) eluting with EtOAc–PhH to afford on extraction with EtOAc 69 mg (61%) of **4n**. Two recrystallizations from THF–petroleum ether gave an analytical sample: mp 185–186° dec; ir (KBr) 6.02 (C=O), 7.81 (CO), 13.51, and 14.50 μ; uv (MeOH) 222 (26,000), 274 (5310), 282 (5570), and 292 (4710); NMR (100 MHz) δ 1.88 ($NCOCH_3$, s, 3 H), 2.51 (NCH_3, s, 3 H), 2.4–3.8 (m, 6 H), 4.14 (–NCH_2–, d, J = 14, 1 H), and 8.13 (indole NH, s, 1 H); MS (low resolution) *m/e* 371 (M^+, 19), 237 (100), 167 (19), and 154 (21); MS (high resolution) calcd for $C_{24}H_{25}N_3O$, 371.200; found, 371.200. Anal. ($C_{24}H_{25}N_3O$) C, H, N.

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4-Trifluoromethylimidazoles and 5-(4-Pyridyl)-1,2,4-triazoles, New Classes of Xanthine Oxidase Inhibitors

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The syntheses of a number of 2-substituted 4-trifluoromethylimidazoles and 3-substituted 5-(4-pyridyl)-1,2,4-triazoles are described. The trifluoromethylimidazoles were prepared from 3,3-dibromo-1,1,1-trifluoroacetone after hydrolysis with aqueous sodium acetate solution and condensation with an aldehyde in the presence of ammonia. Basic hydrolysis of the trifluoromethyl group was found to provide a facile method for the synthesis of imidazole-4-carboxylic acids. In the imidazole series a 2-aryl substituent and a free imino group were required for xanthine oxidase inhibitory activity. The triazoles were obtained through the reaction of an aroylhydrazine and an imino ether followed by thermal ring closure of the intermediate acylamidrazone. As in the imidazole series, a free imino group is an absolute requirement for in vitro activity. Additional structure–activity relationships of these compounds are presented.

Various purine analogs have been shown by many investigators to inhibit the enzyme xanthine oxidase. Among these, allopurinol, 4-hydroxypyrazolo[3,4-*d*]pyrimidine, a potent xanthine oxidase inhibitor,[1,2] has found use therapeutically in the treatment of hyperuricemia associated with gout.[3,4] However, the reported conversion of such purine analogs into nucleotides[5–13] with resulting antimetabolite activity led to a search for specific xanthine oxidase in-