Conversion of Ergolines to Hexahydro- and Octahydrobenzo[f]quinolines (Depyrroloergolines)

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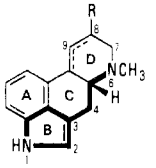
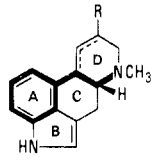
A general method has been developed for removal of the pyrrole ring from the ergolines. Oxidation of various ergolines at the 2,3 double bond gave formamido ketones **10**, which afforded the amino ketones **11**. These were deaminated to give the ketones **12**, from which the carbonyl group was removed by reduction. The resulting depyrroloergolines (**9**) have, in contrast to the ergolines, little or no dopamine agonist activity in two tests.

The ergot alkaloids and derivatives thereof exhibit a remarkable variety of pharmacological activities.[1] Among these are vasoconstrictor, oxytocic, α-blocking, serotonin antagonist, and hallucinogenic properties. Recently, the dopamine agonist activity of the class has been discovered and thoroughly studied.[2,3] As a result, several new ergoline drugs, among them bromocriptine,[4] lergotrile,[5] and pergolide[6] (**7**), have been shown to be effective in dopamine-related disorders (galactorrhea–amenorrhea, parkinsonism, etc.).

In a previous paper,[7] we proposed that the structural moiety in the ergolines (**1a**,**b**) which was responsible for dopamine agonism was the rigid pyrroleethylamine portion, as shown in **1a**, rather than the phenethylamine, as shown in **1b**, as suggested by others.[8] Nichols[9] had independently made the same proposal.

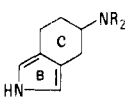


1a



1b

In support of this suggestion, we synthesized, the rigid pyrroleethylamine partial structures **2** and **3** and found



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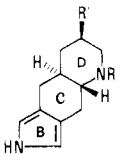

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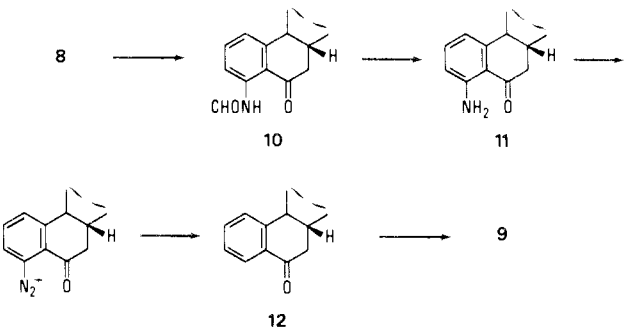
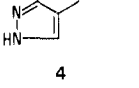
Scheme I



them to have significant dopaminergic activity. Of added interest was the observation that the isosteric *pyrazoleethylamines* **4** and **5** were at least as active as the pyrroles



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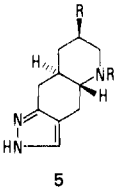

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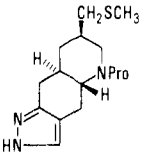
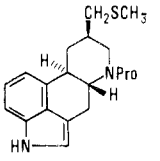
2 and **3**. Of particular note was the analogue **6** that was comparable in potency to the highly active ergoline drug pergolide[6] (**7**).



6



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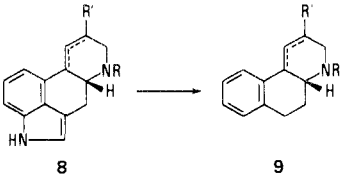
While this line of evidence supported strongly the pyrroleethylamine hypothesis cited above, we are now able to buttress further the argument as follows. If one were able to degrade active ergoline dopamine agonist **8** to the depyrrolo derivative **9** and if **9** were *inactive* compared to



8 **9**

8, the importance of the pyrroleethylamine moiety would be evident. Simple hexahydro- and octahydrobenzo[*f*]-quinolines of the type **9** have been prepared previously by total synthesis[10] but have apparently not been tested for

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(2) J. A. Clemens, C. J. Shaar, E. B. Smalstig, N. J. Bach, and E. C. Kornfeld, *Endocrinology*, **94**, 1171 (1974).
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(4) B. Hökfelt and S. J. Nillius, *Acta Endocrinol. (Copenhagen), Suppl.*, **216**, 1–230 (1978).
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(8) P. F. Teychenne, E. A. Jones, K. G. Ishak, and D. B. Calne, *Gastroenterology*, **76**, 575 (1979); N. Camerman, L. Y. Y. Chan, and A. Camerman, *Mol. Pharmacol.*, **16**, 729 (1979).
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Table I. Dopaminergic Activity of Ergolines and Depyrroloergolines

		prolactin inhibn:[a] serum prolactin, ng/mL				rat turning[b]		
no.	compd, salt	dose, μg/kg ip	control, X ± SEM	treatment, X ± SEM	% inhibn	signif level	dose, mg/kg ip	% of rats exhibiting turning	av[c] turns per first 15 min
13	ergonovine, maleate	50	18.3 ± 2.8	11.7 ± 0.6	36	$p < 0.05$	1	0	0
14	depyrrolo-ergonovine	50	22.9 ± 2.1	28.4 ± 3.9	24 (increase)	$p < 0.2$ (NS)[d]	1	0	0
15	agroclavine	50	31.5 ± 3.5	11.7 ± 1.4	63	$p < 0.001$	1	100	95
16	depyrrolo-agroclavine, oxalate	50	38.8 ± 2.6	35.2 ± 3.4	9	$p < 0.5$ (NS)	1	0	0
7	pergolide, mesylate	50	30.4 ± 3.4	1.6 ± 0.4	95	$p < 0.001$	1	100	102
19	depyrrolo-pergolide, oxalate	50	17.9 ± 2.5	11.6 ± 3.0	35	$p < 0.2$ (NS)	1	67	48

[a] Values are means plus or minus standard error for 10 rats. [b] Values are based on four to six rats per group. [c] After rats began turning. [d] NS = not statistically different from control.

dopaminergic activity. Catechol derivatives of **9**, however, have been synthesized by Cannon and co-workers[11] and have been shown to be active in various dopamine agonist tests, depending upon the substitution pattern of the catechol.

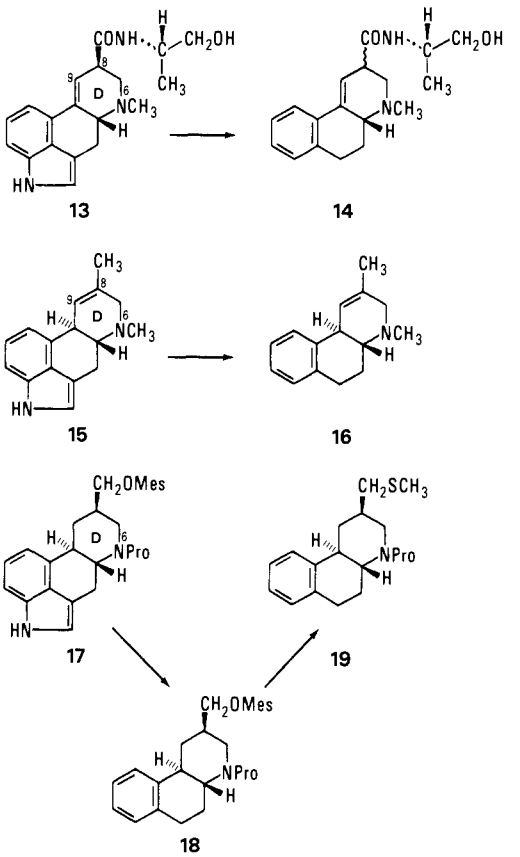
We report in this paper a general method for converting ergolines (**8**) to the corresponding depyrrolo compounds **9** and the relative *inactivity* of the latter in two dopaminergic tests.

Chemistry. The route developed for the conversion **8** to **9** is shown in Scheme I. The ergoline **8** was oxidized with periodate to yield the formamido ketone **10**,[12] which on hydrolysis afforded the amino ketone **11**.[12] **11** was deaminated via diazotization[12] and H_3PO_2 reduction to give the ketone **12**. Reductive removal of the ketone function in **12** was effected by treatment with Et_3SiH[13] and BF_3 in CF_3COOH to yield **9**. To test the generality of the sequence, the following conversions were carried out.

Ergonovine (**13**), the oxytocic ergoline, with a Δ^9 double bond afforded **14** (side chain configuration unassigned), while agroclavine (**15**) with a Δ^8 double bond gave **16** (Scheme II). Finally, in the ring D saturated series the mesylate ester **17**[14] led to **18**. Subsequent reaction of **18** with CH_3SNa gave depyrrolopergolide (**19**). This route to **19** was adopted because periodate oxidation of pergolide (**7**) takes place first at the sulfur atom to yield the corresponding sulfoxide[14] rather than at the 2,3 double bond. The method outlined in Scheme I, therefore, works with a variety of side chains at position 8, with various substituents on the 6-nitrogen and with or without unsaturation in ring D.

Pharmacology. The dopaminergic activity of the new depyrroloergolines was evaluated using two standard methods, and the results are listed with those of the related ergolines in Table I. In the first method, the effect on

Scheme II



the serum prolactin levels by the drugs in reserpinized male rats was measured according to the method of Clemens et al.[2,15] Secondly, the contralateral rotational behavior of unilateral 6-hydroxydopamine nigrostriatal-lesioned rats was determined using the method of Ungerstedt and Arbuthnot.[16] It is evident from Table I that removal of the pyrrole ring from dopaminergic ergolines resulted in the *loss* of dopamine agonist activity. Ergonovine (**13**), however, was not a good test case, since it was a poor dopamine

(11) J. G. Cannon, C. Suarez-Gutierrez, T. Lee, J. P. Long, B. Costall, D. H. Fortune, and R. J. Naylor, *J. Med. Chem.*, **22**, 341 (1979). J. G. Cannon, T. Lee, H. D. Goldman, J. P. Long, J. R. Flynn, T. Verimer, B. Costall, and R. J. Naylor, *ibid.*, **23**, 1 (1980).
(12) N. J. Bach, E. C. Kornfeld, J. A. Clemens, E. B. Smalstig, and R. C. A. Frederickson, *J. Med. Chem.*, **23**, 492 (1980).
(13) C. T. West, S. J. Donnelly, D. A. Kooistra, and M. P. Doyle, *J. Org. Chem.*, **38**, 2675 (1973).
(14) E. C. Kornfeld and N. J. Bach, U.S. Patent 4 166 182 (Aug 28, 1979).
(15) A. M. Crider, J. M. Robinson, H. G. Floss, J. M. Cassady, and J. A. Clemens, *J. Med. Chem.*, **20**, 1473 (1977).
(16) J. Ungerstedt and G. W. Arbuthnot, *Brain Res.*, **24**, 485 (1970).

agonist at the dose levels employed. Agroclavine (**15**), on the other hand, a very potent dopaminergic drug, showed complete loss of activity when the pyrrole ring was removed. Finally, depyrrolopergolide (**19**) when compared with the highly active agent pergolide (**7**) exhibited a dramatic, although not total, loss of activity. These observations, therefore, provide additional support for the idea that the pyrroleethylamine moiety of the ergolines is highly important for dopaminergic activity.

Experimental Section

Elemental analyses are indicated only by symbols of the elements and are within 0.4% of the theoretical values. All new compounds were monitored by measurement of IR, UV, and NMR spectra. Mass spectra were determined also for most structures and were consistent with other spectral measurements. Melting points were determined on a Mel-Temp apparatus and are corrected. All reactions were followed by TLC carried out on Merck F254 silica gel plates. In the multistep sequences, when intermediates were noncrystalline, each was homogeneous by TLC and was characterized by appropriate physical measurements (IR, NMR, MS, etc.) before use in the following reaction.

(4a*R*)-7-(Formylamino)-2,3,4,4a,5,6-hexahydro-*N*-[2-hydroxy-1(*S*)-methylethyl]-4-methyl-6-oxobenzo[*f*]quinoline-2-carboxamide. A suspension of 2.0 g (4.5 mmol) of ergonovine, maleate salt, in 50 mL of H_2O was mixed with a solution of 1.9 g (9.0 mmol) of $NaIO_4$ in 200 mL of H_2O. After the mixture was stirred for 2 h, it was diluted with aqueous $NaHCO_3$ and extracted several times with $CHCl_3$–*i*-PrOH. The extracts were washed with brine, dried (Na_2SO_4), and evaporated. The crude product was purified by chromatography on 30 g of Florisil using $CHCl_3$/2–10% MeOH in the elution: yield 0.47 g (29%); mp >190 °C dec; $[\alpha]^{25}_D$ −70.4° (*c* 10, $CHCl_3$). Anal. ($C_{19}H_{23}N_3O_4$) C, H, N.

(4a*R*)-2,3,4,4a,5,6-Hexahydro-*N*-[2-hydroxy-1(*S*)-methylethyl]-4-methyl-6-oxobenzo[*f*]quinoline-2-carboxamide. Ergonovine, maleate salt, 4.0 g (9 mmol), was oxidized as above with $NaIO_4$. The crude formamido ketone product was dissolved in 150 mL of MeOH and 100 mL of 10% NaOH. The mixture was stirred for 1 h, diluted with H_2O, and extracted with $CHCl_3$. The extract was washed with brine, dried (Na_2SO_4), and evaporated. The product was purified by chromatography on 35 g of Florisil using $CHCl_3$/2–4% MeOH as eluant. The yield of amorphous amino ketone was 0.46 g (1.4 mmol) (15.5% from ergonovine). It was dissolved in 20 mL of 6 N HCl. The solution was cooled in ice, and to it was added dropwise a solution of 100 mg (1.5 mmol) of $NaNO_2$ in 5 mL of H_2O. Stirring in ice was continued for 10 min, and the mixture was then added rapidly and dropwise to 25 mL of 50% H_3PO_2. The resulting mixture was stirred in ice for 2.25 h, poured on ice, made basic with 10% NaOH, and extracted with $CHCl_3$–*i*-PrOH. The extracts were washed with brine, dried (Na_2SO_4), and evaporated. The ketone was purified by chromatography on 30 g of Florisil using $CHCl_3$/0–2% MeOH in the elution: yield 115 mg (26%); mp <100 °C from MeOH. Anal. ($C_{18}H_{22}N_2O_3$) C, H, N.

(4a*R*)-2,3,4,4a,5,6-Hexahydro-*N*-[2-hydroxy-1(*S*)-methylethyl]-4-methylbenzo[*f*]quinoline-2-carboxamide (14). The crude ketone prepared as above, 0.49 g (1.56 mmol), was dissolved in 40 mL of trifluoroacetic acid. Triethylsilane, 10 mL, and BF_3 etherate, 2 mL, were added, and the mixture was stirred for 30 min. It was then poured onto ice, made basic with NH_4OH, and extracted with $CHCl_3$. The extracts were washed with brine, dried (Na_2SO_4), and evaporated. The product was purified by chromatography on 30 g of Florisil using $CHCl_3$/1–2% MeOH as eluant: yield 0.31 g. Attempts to prepare crystalline salts were fruitless, so the base was crystallized from ether: yield 85 mg (18%); mp 175–176 °C; $[\alpha]^{25}_D$ +347.8° (*c* 10.2, $CHCl_3$). Anal. ($C_{18}H_{24}N_2O_2$) C, H, N.

[4a*R*-(4aβ,10bα)]-7-Amino-3,4a,5,10b-tetrahydro-2,4-dimethylbenzo[*f*]quinolin-6(4*H*)-one. A solution of 5.8 g (24 mmol) of agroclavine and 2 mL of CH_3SO_3H (30 mmol) in 200 mL of MeOH was added to a solution of 10.7 g (50 mmol) of $NaIO_4$ in 400 mL of H_2O. The mixture was stirred for 3.5 h, diluted with aqueous $NaHCO_3$, and extracted with $CHCl_3$. The extracts were washed with brine, dried (Na_2SO_4), and evaporated. Attempts to purify the product, which appeared to be a mixture of formamido and amino ketones, were fruitless. The crude product, therefore, was dissolved in a mixture of 125 mL of MeOH and 100 mL of 5 N NaOH. Hydrolysis to the amino ketone was complete in 2.25 h. The mixture was diluted with H_2O and extracted with $CHCl_3$, and the extracts were washed with brine, dried (Na_2SO_2), and evaporated. The crude amino ketone was purified by chromatography on 100 g of Florisil using $CHCl_3$/2–3% MeOH as eluant: yield 2.55 g (43%). A portion was recrystallized twice from ether–hexane, mp 136–138 °C. Anal. ($C_{15}H_{18}N_2O$) C, H, N.

[4a*R*-(4aβ,10bα)]-3,4,4a,5,6,10b-Hexahydro-2,4-dimethylbenzo[*f*]quinoline (16) Oxalic Acid Salt. The crude amino ketone above, 2.3 g (9 mmol), was deaminated as in the first series above using $NaNO_2$ and H_3PO_2. Purification of the resulting ketone was effected by chromatography: yield 1.08 g (50%). Attempts to form crystalline salts were unsuccessful. The crude product, therefore, was reduced as above with CF_3COOH–Et_3SiH–BF_3 etherate. The oxalic acid salt of the product was prepared and recrystallized from EtOH–ether: yield 0.84 g (58%); mp 173–175 °C; $[\alpha]^{25}_D$ +39.52° (*c* 10, MeOH). Anal. ($C_{17}H_{21}NO_4$) C, H, N.

[4a*R*-(4aβ,10bα)]-1,2,4,4a,5,10b-Hexahydro-2β-[[(methylsulfonyl)oxy]methyl]-4-propylbenzo[*f*]quinolin-6(2*H*)-one. The mesylate ester 17,[14] 4.1 g (11.3 mmol), was oxidized as above with CH_3SO_3H–$NaIO_4$. The noncrystalline formamide ketone product was hydrolyzed with NaOH as previously described: yield of amorphous amino ketone 2.6 g (63%). Deamination was conducted as above: yield of ketone 1.65 g (66%); mp 145–146 °C from MeOH. Anal. ($C_{18}H_{25}NO_4S$) C, H, N, S.

[4a*R*-(4aβ,10bα)]-1,2,3,4,4a,5,6,10b-Octahydro-2β-[(methylthio)methyl]-4-propylbenzo[*f*]quinoline (19) Oxalic Acid Salt. To a solution of 1.2 g (3.4 mmol) of the above ketone in 50 mL of CF_3COOH was added dropwise, with stirring, 5 mL (33 mmol) of Et_3SiH followed by 4 mL (32 mmol) of BF_3 etherate. Stirring was continued for 45 min, after which the mixture was poured onto ice, made basic with NH_4OH, and extracted with EtOAc. The extracts were washed with H_2O and with brine, dried (Na_2SO_4), and evaporated. The product was purified by chromatography on 35 g of Florisil using $CHCl_3$/0–3% MeOH in the elution: yield 0.85 g (2.5 mmol). The oxalic acid salt was prepared in EtOH, but it, like the base, was amorphous. To a solution of 1.2 g (25 mmol) of MeSH in 50 mL of DMF, cooled in ice, was added in portions 1.2 g of NaH (50% in mineral oil, 25 mmol). The cooling bath was removed, and to the solution was added a solution of the above amorphous oxalic acid salt in 15 mL of DMF. The mixture was stirred at 25 °C under N_2 for 2.25 h. Water was added, and the product was extracted with EtOAc. The extracts were washed (brine), dried (Na_2SO_4), and evaporated. The product was purified by chromatography on 30 g of Florisil using $CHCl_3$/0–3% MeOH in the elution: yield 0.59 g. The oxalic acid salt was prepared and was recrystallized from MeOH–ether: yield 0.575 g (44% overall from the crystalline ketone mesylate ester); mp 156–157 °C; $[\alpha]^{25}_D$ +44.08° (*c* 9, MeOH). Anal. ($C_{20}H_{29}NO_4S$) C, H, N, S.

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