Inhibition of Prolactin by Ergoline Congeners

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Two derivatives of phenethylamine and one of aminotetralin have been synthesized and their effects on the spontaneous release of prolactin from rat pituitaries *in vitro* have been investigated. Two of the compounds were found to inhibit prolactin release.

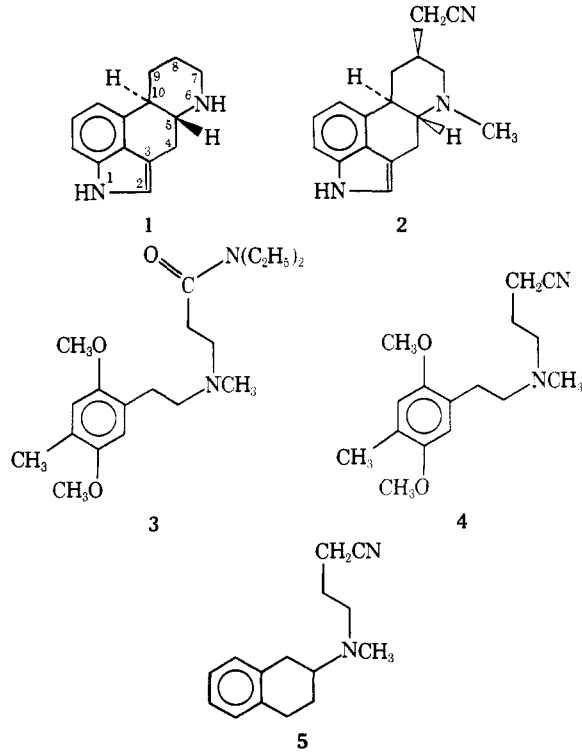
A number of derivatives of ergoline 1 are capable of blocking pituitary prolactin secretion. It has been shown that ergocornine,[1-3] ergotamine,[4] ergonovine,[5] 2-bromo-α-ergokryptine,[6,7] and lysergic acid diethylamide (LSD)[8] all have inhibitory effects on prolactin secretion. A direct result of the prolactin release inhibiting effect of these compounds is their ability to block ova implantation.[9] Shelesnyak[10] has reported that a number of ergot compounds can interrupt pregnacy in the rat by preventing the development of decidual tissue. Ergosine, ergovaline,[11] and argoclavine[12-14] are also effective in interrupting early pregnancy. In recent years synthetic derivatives of ergoline have been shown to be active in blocking implantation. The ability of D-6-methyl-8-cyanomethylergoline[15] (2) and of several amides of D-6-methylergoline-8-acetic acid[16] to prevent pregnancy has been reported.

In an effort to elucidate the nature of the pharmacophore possessing implantation blocking ability two derivatives of phenethylamine, 3 and 4, and one of aminotetralin 5 have been prepared. With the aromatic ring and the tertiary nitrogen of 3, 4, and 5 superimposed on the aromatic ring and N-6 of the ergoline structure 1, the similarities become apparent. The *N,N*-diethylamide function in 3 correlates with the *N,N*-diethylamide of LSD, and the cyanomethyl functions in 4 and 5 correlate with the cyanomethyl in structure 2.

It has been suggested that the mechanism of action of 2 in prevention implantation is one of general hypothalamic stimulation causing the release of the prolactin-inhibiting factor (PIF).[17,18] Wuttke, *et al.*,[3] have reported an increase in PIF activity by the action of ergot drugs on the hypothalamus. However, it has also been shown that the ergot drugs can act directly on the pituitary to inhibit prolactin release.[1,2,4]

The effects of 3, 4, and 5 on the spontaneous release of prolactin from the pituitary *in vitro* have been investigated. It is hoped that these results may have predictive value concerning the potential implantation blocking ability of these compounds.

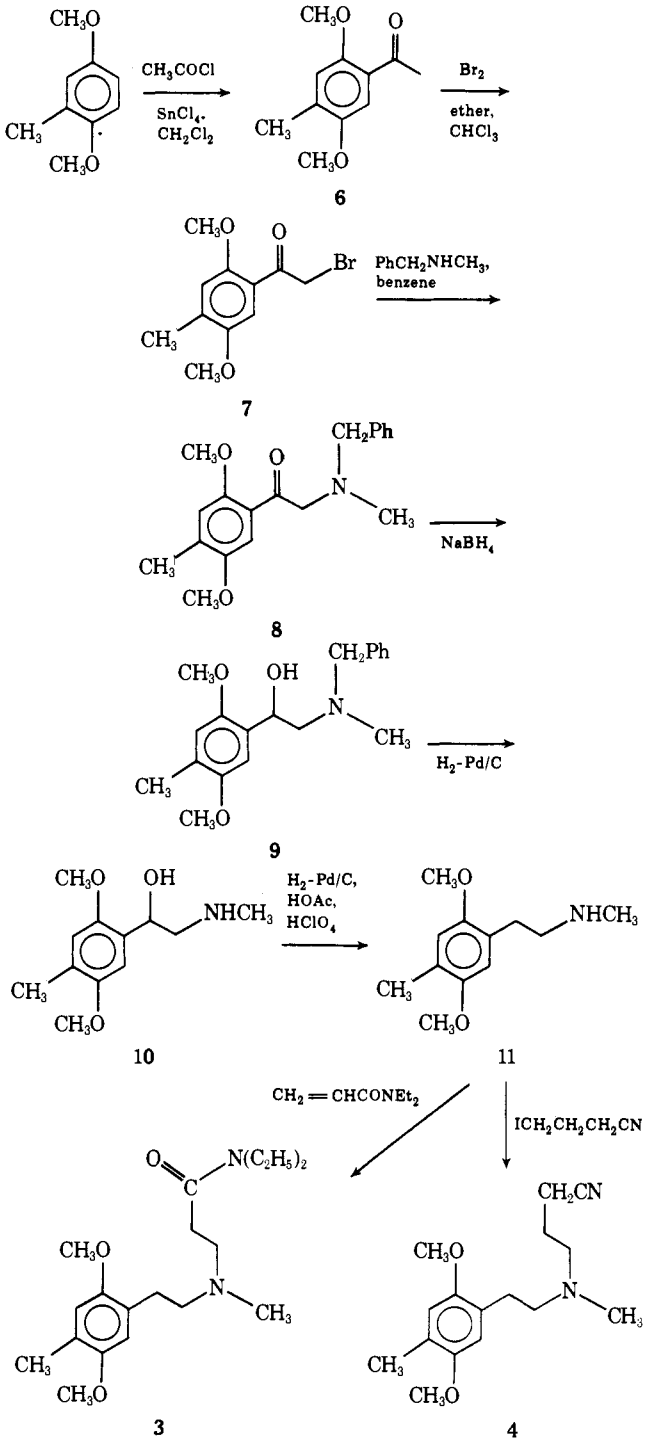
The influence of ergot alkaloids on pituitary prolactin has recently been reviewed by Floss, *et al.*[20] Meites and Clemens[21] have compared the structural relationships of ergot derivatives with their ability to inhibit prolactin secretion. They found that the complex peptide similar to the ergocornine side chain could not inhibit prolactin release. A large group at position 8 of the ergolin structure is not necessary for prolactin inhibiting activity. However, the nature of the substituent at this position is critical since variation of functional group greatly influences potency. The presence of unsaturation at the 9,10 position of the ergoline structure has an inconsistent effect upon pregnancy inhibition. Both 2 and D-6-methyl-8-cyanomethylergolene have been shown to block implantation in rats.[15,22] However, saturation of the 9,10 double bond of ergokryptine results in reduced potency.[10] Conversely, Semonsky and coworkers[16] found the amide of D-6-methylergolene-8-acetic acid to have no effect in preventing implantation in rats, whereas the 9,10 saturated derivative, D-6-methylergoline-8-acetamide, was active.



In the past, several approaches to synthetic congeners of lysergic acid derivatives have been based on the presence of a phenethylamine moiety in the lysergic acid structure. Baltzly and coworkers[23,24] found oxytocic activity in a number of substituted phenethylamines based on ergonovine. The presence of the phenethylamine moiety in both the psychotomimetic amphetamines and LSD has been recognized.[25-29] It has been observed that within a series of ring-substituted amphetamines, hallucinogenic activity generally increases as the energy of the highest occupied molecular orbital increases.[30,31] By placing appropriate substituents on the aromatic ring, one can approach the electronic activation found in the lysergic acid molecule.[31] Baltzly's[23,24] phenethylamine analogs of ergonovine were active when methoxy ring substituents were present but were inactive when the ring was unsubstituted. The similarities between the ergoline structure and the lysergic acid structure are obvious. Therefore, in order to better approximate the electronic character expected of the ergoline nucleus, the 2,5-dimethoxy-4-methyl ring substitution has been chosen for compounds 3 and 4.[30]

Lysergic acid derivatives have also been considered as structural congeners of 2-aminotetralin. Based on work with an extensive series of 2-aminotetralins, Marini-Bettolo and coworkers[32] suggested that this moiety is the fac-

Scheme I



tor responsible for the sympatholytic activity of certain lysergic acid alkaloids. The presence of the aminotetralin structure in lysergic acid has also been considered in the preparation of aminotetralins related to psychotomimetics.[29,33,34] This approach to the ergoline structure is manifest in **5**.

Chemistry. The preparation of **3** and **4** followed the sequence outlined in Scheme I. The preparation of **5** followed Scheme II. Both synthetic pathways involve α-bromination of a ketone, displacement of the bromine by benzylmethylamine, followed by reduction of the amino ketone, and substitution on the secondary amine nitrogen. *N*-Methyl-2-(2′,5′-dimethoxy-4′-methylphenyl)ethylamine (**11**) has previously been prepared by Ho, *et al.*,[35] *via* reduction of the nitrostyrene. The route described here gives a better yield overall.

Consistent values for the elemental composition of the fumarate salt of **3** could not be obtained. However, the mass spectrum with *m/e* 336, infrared, and nuclear magnetic resonance spectra are consistent with the proposed structure.

Experimental Section

All boiling points are uncorrected. Melting points were determined in open glass capillaries using a Thomas-Hoover Uni-Melt apparatus and are uncorrected. Elemental analyses were performed by Midwest Microlab Ltd., Indianapolis, Ind., and by the Division of Medicinal Chemistry, University of Iowa. Where analyses are indicated by symbols of the elements, the analytical results obtained were within ±0.4% of the theoretical values. Infrared spectra were recorded on a Beckman IR-10 spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian Associates T-60 spectrometer using tetramethylsilane as an internal standard. Mass spectral data were obtained on a Finnigan Model 1015 mass spectrometer.

2,5-Dimethoxy-4-methylacetophenone (6). To a cooled solution of 60.8 g (0.4 mol) of 2,5-dimethoxytoluene and 31.4 g (0.4 mol) of acetyl chloride in 400 ml of CH_2Cl_2 was added dropwise 104 g (0.44 mol) of anhydrous $SnCl_4$, maintaining the temperature between 0 and 10°. After addition was complete the solution was allowed to warm to 25° and to stir 0.5 hr and then was heated to reflux for 2 hr. The mixture was stirred overnight at 25° and then poured over 100 g of ice. The organic layer was washed once with 6 *N* HCl and twice with H_2O, dried (Na_2SO_4), and evaporated. The residue was recrystallized from MeOH–H_2O: yield 69 g (89%); mp 74–76° (lit.[36] 74°).

2,5-Dimethoxy-4-methyl-α-bromoacetophenone (7). Using a modification of Wild's procedure,[37] 112 g (0.58 mol) of **6** was dissolved in 750 ml of $CHCl_3$ and 500 ml of Et_2O and the mixture cooled below 6°. Bromine, 93 g (0.58 mol), was added dropwise with stirring. After the addition was complete the mixture was allowed to warm to 25° and to stir for 3 hr. The reaction was poured into 600 ml of 10% HCl. The organic layer was washed with H_2O, $NaHCO_3$ (5%), and again with H_2O until the washings were neutral. After drying ($CaSO_4$), concentration of the organic phase yielded crystalline product. The material was recrystallized from $CHCl_3$–hexane: yield 135.0 g (86%); mp 115–117° (lit.[38] mp 116–117.5°). *Anal.* ($C_{11}H_{13}BrO_3$) C, H.

α-Benzylmethylamino-2,5-dimethoxy-4-methylacetophenone Hydrochloride (8). A solution of 18 g (0.066 mol) of **7** and 16 g (0.132 mol) of benzylmethylamine in 200 ml of benzene was heated to reflux for 24 hr. After cooling to 5° the solution was filtered and acidified with HCl gas. The solvent was evaporated and the product was recrystallized from 2-propanol–ether: yield 17.3 g (75%); mp 198.5–200°. *Anal.* ($C_{19}H_{24}NO_3Cl$) C, H, N.

***N*-Benzyl-*N*-methyl-2-hydroxy-2-(2′,5′-dimethoxy-4′-methylphenyl)ethylamine Hydrochloride (9).** A solution of 82.5 g (0.264 mol) of **8** as the free base and 5.3 g (0.132 mol) of $NaBH_4$ in 500 ml of 95% EtOH was stirred overnight at 25°. The EtOH was removed *in vacuo;* the residue was taken up in H_2O and extracted with ether. The ether was dried ($MgSO_4$), and the product was precipitated with HCl gas and recrystallized from 2-propanol: yield 87 g (84%); mp 183–184°. *Anal.* ($C_{19}H_{26}NO_3Cl$) C, H, N.

***N*-Methyl-2-hydroxy-2-(2′,5′-dimethoxy-4′-methylphen-**

Scheme II

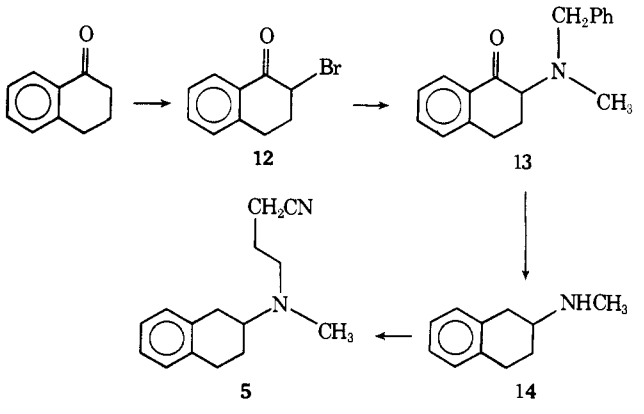


Table I. Effect of Ergocornine and Ergoline Congeners on Prolactin Secretion *in Vitro* by Anterior Pituitaries of Estrogen-Treated Female Rats

Group	Concn, *M*	Control prolactin secretion, %	
		μg of Pr per AP/2[b,d]	cpm of Pr per AP/2[c,d]
Ergocornine methanesulfonate[a]	10^{-4}	38.0 ± 3.9**	7.3 ± 0.9**
	10^{-5}	37.1 ± 3.7**	6.5 ± 0.8**
	10^{-6}	38.3 ± 3.1**	7.8 ± 0.7**
	10^{-7}	37.2 ± 4.5**	10.8 ± 1.4**
Compound **3**[a]	10^{-3}	55.9 ± 4.2**	30.8 ± 4.2**
	10^{-4}	74.7 ± 8.6*	63.1 ± 6.5*
	10^{-5}	101.8 ± 11.8	98.2 ± 14.7
Compound **4**[a]	10^{-3}	82.1 ± 4.6	84.0 ± 9.4
	10^{-4}	82.7 ± 7.1	60.7 ± 13.7
	10^{-5}	105.4 ± 11.5	101.8 ± 8.7
Compound **5**[a]	10^{-3}	55.3 ± 3.0**	42.8 ± 3.8**
	10^{-4}	83.8 ± 5.3	82.8 ± 8.1
	10^{-5}	101.3 ± 8.3	100.3 ± 5.6

[a]Three flasks in each group each containing explants equivalent to one pituitary half. Explants were incubated for 1 hr in 0.3 ml of Earle's saline containing ^{3}H-L-Leu (10 μCi/ml; sp act. = 64 Ci/mmoi) and then in 0.6 ml of medium 199 or in medium 199 containing test substances for 4 hr at 37° with 5% CO_2 in O_2. The amount of Pr secreted and the radioactivity in the secreted Pr were determined for the 4-hr experimental incubation. [b]Control explants incubated in 199 released 53.2 ± 3.4 μg of Pr per AP/2 equivalent to NIAMD RPL-RP-1 during the 4-hr incubation interval. Values represent the mean ± S.E.M.% of the control. [c]cpm in Pr band from acrylamide gels of incubation medium. Controls = 30,462 ± 1823 cpm of Pr per AP/2. Values represent the mean ± S.E.M.% of the control. [d]*, $p < 0.05$. **, $p < 0.005$. AP = anterior pituitary; Pr = prolactin.

yl)ethylamine **Hydrochloride (10).** To a slurry of 2 g of 10% Pd/C in a few milliliters of H_2O was added 78.8 g (0.224 mol) of **9** and 500 ml of absolute EtOH. The mixture was hydrogenated at 50 psig for 4 hr at which time the reaction was complete. The mixture was filtered, the solvent evaporated, and the residue recrystallized from 2-propanol: yield 53.6 g (92%); mp 165–166°. *Anal.* ($C_{12}H_{20}NO_3Cl$) C, H, N.

***N*-Methyl-2-(2′,5′-dimethoxy-4′-methylphenyl)ethylamine (11).** A mixture of 50 g (0.19 mol) of **10**, 2 g of 10% Pd/C, and 1 ml of 70% $HClO_4$ in 400 ml of glacial HOAc was hydrogenated for 60 psig for 9 hr. The mixture was filtered, KOAc added to precipitate perchlorate anion and filtered again, and the solvent removed *in vacuo*. The residue was taken up in H_2O and made basic (NaOH), and extracts were dried ($MgSO_4$) and evaporated. The residue was distilled: yield 36.3 g (91%); bp 112–114° (0.1 mm) [lit.[35] bp 96–99° (0.075 mm)]; mp (hydrochloride) 150–151.5° [lit.[35] mp (hydrochloride) 150–151°].

4-Iodobutyronitrile. The reaction of 4-chlorobutyronitrile with NaI in acetone gave 4-iodobutyronitrile in 81% yield: bp 55–60° (0.1 mm) [lit.[39] bp 109–111° (15 mm)].

***N*-Methyl-*N*-(3-cyanopropyl)-2-(2′,5′-dimethoxy-4′-methylphenyl)ethylamine Hydrobromide (4).** A solution of 15 g (0.072 mol) of **11** and 7 g (0.036 mol) of 4-iodobutyronitrile in 150 ml of benzene was heated to reflux for 24 hr. After cooling to 4°, the solution was filtered, washed with H_2O, dried (Na_2SO_4), and evaporated. The residue was dissolved in dry ether and treated with a fresh solution of HBr in Et_2O. The ether was evaporated and the salt recrystallized from acetone–ether: yield 5.2 g (40%); mp 96–97.5°. *Anal.* ($C_{16}H_{25}N_2O_2Br$) C, H, N.

***N*-Methyl-*N*-(3-(*N*,*N*-diethylamido)propyl)-2-(2′,5′-dimethoxy-4′-methylphenyl)ethylamine Fumarate (3).** Following the procedure of Norris and Blicke[40] 2 g (0.016 mol) of *N*,*N*-diethylacrylamide was added to a solution of 1 g (0.005 mol) of **11** in 25 ml of benzene. The mixture was heated to reflux for 20 hr on a steam bath. After cooling, the solvent was removed. The residue was dissolved in ether and a solution of 0.58 g (0.005 mol) of fumaric acid in methanol was added. After long standing in the cold, the oily salt crystallized. The crystals were collected and recrystallized from acetone–ether: recrystallized yield 0.8 g (38%); mp 69–71°; ir (neat) 1630 cm^{-1} (C=O, amide) as the free base; mass spectrum *m/e* 336 (M^+). *Anal.* Calcd for $C_{23}H_{26}N_2O_7$: C, 61.04; H, 8.02; N, 6.19. Found: C, 56.84; H, 8.13; N, 5.17.

2-Bromo-1-tetralone (12). To an ice-cooled solution of 142 g (0.92 mol) of 1-tetralone in 1 l. of $CHCl_3$ and 1 l. of Et_2O was added dropwise 149 g (0.93 mol) of bromine. After stirring for 3 hr, the mixture was washed with H_2O, dilute $NaHSO_3$, dilute $NaHCO_3$, and again with H_2O. The solution was dried ($MgSO_4$) and evaporated. The product crystallized from Et_2O–hexane: yield 159 g (76%); mp 40–41° (lit.[41] mp 38–39°).

***N*-Methyl-*N*-benzyl-2-amino-1-tetralone Hydrochloride (13).** To an ice-cooled solution of 52.4 g (0.233 mol) of **12** in 400 ml of dry benzene under constraint nitrogen purge was added 56.5 g (0.466 mol) of methylbenzylamine. When addition was complete the mixture was heated to reflux for 18 hr. The reaction was cooled to 25°; 200 ml of dry Et_2O was added and cooled to 4°. Nitrogen flow was stopped; the reaction mixture was filtered and then extracted twice with 200 ml of 3 *N* HCl. The acid extracts were washed once with Et_2O and then evaporated *in vacuo*. The residue was crystallized from 2-propanol: yield 46.2 g (66%): mp 196–197°. *Anal.* ($C_{18}H_{20}NOCl$) C, H, N.

***N*-Methyl-2-aminotetralin (14).** Following the procedure of Sprenger, *et al.*,[42] 17 g (0.0565 mol) of **13** with 3 g of 10% Pd/C in 300 ml of glacial HOAc was hydrogenated at 60 psig and 40°. After 18 hr 10 ml of $HClO_4$ (70%) in 10 ml of HOAc was added and hydrogenation continued at 40 psig and 50° for an additional 18 hr. The mixture was filtered, KOAc added to precipitate perchlorate anion and filtered again, and the solvent removed *in vacuo*. The residue was taken up in H_2O which was washed once with ether and then made basic (NaOH) and extracted with Et_2O. The ether extracts were dried ($MgSO_4$) and evaporated. The residue was distilled: yield 6.8 g (75%); bp 82–84° (0.3 mm) [lit.[43] bp 85° (0.5 mm)]; hydrochloride mp 184–186° (lit.[44] mp 185–186°).

***N*-Methyl-*N*-(3-cyanopropyl)-2-aminotetralin Hydrobromide (5).** A solution of 12.4 g (0.077 mol) of **14** and 7.45 g (0.038 mol) of 4-iodobutyronitrile in 100 ml of benzene was heated to reflux for 24 hr. After cooling Et_2O was added and *N*-methyl-2-aminotetralin hydroiodide was filtered off. The filtrate was washed once with H_2O, dried (Na_2SO_4), and evaporated. The residue was dissolved in dry Et_2O and treated with a fresh solution of HBr in Et_2O. The salt was recrystallized from 2-propanol–ether: yield 8.0 g (67%); mp 165–168°. *Anal.* ($C_{15}H_{21}N_2Br$) C, H, N.

Pharmacological Evaluation. Mature female Sprague–Dawley rats were given seven daily subcutaneous injections of 10 μg of 17β-estradiol (Sigma) to reduce the variation in the prolactin content of their anterior pituitaries (AP). The animals were killed by decapitation and the AP separated from the posterior lobes and cut into eight explant size pieces. Four explants in each flask were incubated for 1 hr in 0.3 ml of Earle's saline containing 10 μCi/ml of ^{3}H-L-Leu (sp act. = 64 Ci/mmol, New England Nuclear), rinsed in medium 199 (Cultur STAT, medium 199 Earle's base without serum, Baltimore Biological Laboratories), and then incubated with 0.6 ml of 199 or 199 with test compounds for an additional 4 hr. Prolactin levels in the medium and radioactivity in the secreted prolactin were determined for the 4-hr incubation interval. Details on the preparation of explants and the incubation procedures have been described previously.[45]

Ergocornine methanesulfonate (EC) was obtained through the courtesy of Sandoz Pharmaceuticals, Hanover, N. J. Aqueous stock solutions of EC were mixed such that 50 μl of the stock solution added to 4.95 ml of medium 199 yields medium containing 10^{-4}, 10^{-5}, 10^{-6}, and 10^{-7} *M* EC. Similar aqueous stock solutions of the test compounds **3**, **4**, and **5** were added to medium 199 in 50-μl volumes to yield medium containing 10^{-3}, 10^{-4}, and 10^{-5}

M of each of these compounds. Medium without addition of EC or test compounds served as the control.

Prolactin levels in duplicate 250-μl samples of incubation medium from each flask were determined by acrylamide gel disk electrophoresis and densitometry.[46] NIAMD RPL-RP-1 rat prolactin with a reported biological potency of 11 IU/mg (mouse deciduoma assay) was used as the densitometric standard. After densitometric analysis, the prolactin band was cut from each gel for radioactivity evaluation. The gel slices were placed in filter paper cones (Whatman No. 42 ashless) and dessicated overnight. The cones were combusted in a Packard tritium oxidizer (Model 300) and the condensates were mixed with 14.0 ml of modified Packard formula II high water compatibility scintillation mixture containing: naphthalene, 100 g; PPO, 5 g; dimethyl-POPOP, 0.3 g; dioxane, 730 ml; toluene, 135 ml; and absolute methanol, 55 ml. Condensates from prolactin bands of acrylamide gels of medium from AP explants incubated without ^{3}H-L-Leu served as background radioactivity controls. Samples were counted on a Beckman DPM^{100} liquid scintillation counter. Quenching of radioactivity detection was comparable for all samples as shown by uniformity of external standard ratios. Counting efficiency was about 25%. A paired "*t*" test was used to evaluate the significance of the percentage comparisons. The *t* values were computed as follows: $t = (100\% - \bar{x}\%\text{ of control}) \div \text{S.E.M.}\ \bar{x}\%\text{ of control}$.

Results and Discussion

The effects of various concentrations of **3**, **4**, **5**, and ergocornine on the prolactin secretion *in vitro* by anterior pituitaries of estrogen-treated female rats are summarized in Table I. Compound **3** was found to inhibit secretion at the two highest concentrations while **4** was relatively inactive at all concentrations employed and **5** was effective only at 10^{-3} *M*. It is interesting that increasing the concentration of ergocornine from 10^{-7} to 10^{-4} *M* did not bring about an increase in prolactin secretion inhibition. Apparently concentrations lower than 10^{-7} *M* must be employed in order for ergocornine to show an expected dose–response curve.

In order to show that the inhibitory effects of **3** and **5** were not the result of a nonspecific cytotoxicity, a second experiment of similar design to the first was carried out. Compounds **3** and **5** were reevaluated at 10^{-3} *M* concentrations in a 5-hr incubation using pituitaries from normal adult female rats. Prolactin and growth hormone levels in the medium at the end of the 4-hr experimental incubation were determined. In addition, representative explants from each group were evaluated histologically. The results of the second study were similar to those of the first. Compounds **3** and **5** at 10^{-3} *M* significantly inhibited the spontaneous release of prolactin by incubated anterior pituitaries of female rats by about 80 and 40%, respectively. Neither compound influenced growth hormone release nor did they promote cytotoxic effects that could be observed by routine light microscopic histologic examination. In addition, bromide ion was found inactive as a blocker of prolactin release.

Regarding the possibility of cytotoxicity as an explanation for inhibition of spontaneous prolactin secretion by rat pituitaries *in vitro*, it is worth noting that explant death using short term incubations such as these produces just the opposite result of that which was observed here. Large amounts of prolactin and growth hormone are detectable in the medium when explants are purposely "killed" during incubation.† A similar outpouring of luteinizing hormone by rat pituitaries *in vitro* following the addition of toxic doses of metabolic inhibitors to incubation medium has also been reported.[47] The lack of any evidence of cytotoxicity upon histological examination of the explants and the fact the growth hormone release was unaffected by compounds **3** and **5** further rule out the possibility of cytotoxicity.

†J. A. Parsons, unpublished observations.

The possible actions of these agents on prolactin secretion *in vivo* and their ability to block prolactin dependent physiological processes remain to be determined. However, the *in vitro* data, which must be viewed as preliminary, indicate that the phenethylamine and aminotetralin approaches to the ergoline structure have produced compounds which do show some degree of prolactin-inhibiting activity. Although neither **3** nor **5** approach the potency of ergocornine, further evaluation of the compounds is in order to verify these observations and study their mode of action. Such studies along with other aspects of the SAR of nonindolic ergoline congeners are being pursued.

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Descarboxylysergic Acid (9,10-Didehydro-6-methylergoline)

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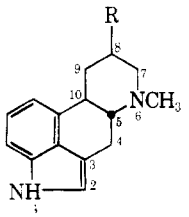
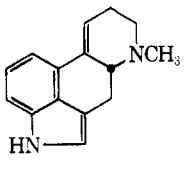
dl-Descarboxylysergic acid (**2**) has been synthesized by two routes from 9,10-didehydro-2,3-dihydro-8β-hydroxy-6-methylergoline (**3**). Since **2** shows many of the pharmacological activities of other ergot derivatives, a side chain at the 8 position in an ergoline is *not* essential for biological activity. The unique rigid arylethylamine moiety in this class is probably the key structural feature.

The structures of most of the known ergot alkaloids and their derivatives are based on the tetracyclic ergoline ring system **1** and differ mainly in the character of the side chains (R) at the 8 position. The pharmacology of the various members varies remarkably with the composition of the side chain.[1] Lysergic acid (**1**, R = COOH, $\Delta^{9,10}$), for instance, has very unexceptional biological activity, while its diethylamide (LSD) (**1**, R ± $CONEt_2$, $\Delta^{9,10}$) is one of the most potent CNS agents known. Ergonovine [**1**, R = $CONHCH(CH_3)CH_2OH$, $\Delta^{9,10}$] has profound oxytoxic activity, while other derivatives are serotonin antagonists, vasodilators, hypotensives, prolactin inhibitors,[2,3] etc. With these observations in mind it was of interest to prepare and evaluate the compound in which the side chain at position 8 was absent, *i.e.*, **2** (descarboxylysergic acid). We describe here two synthetic routes to this compound (*dl* form) and record some of its pharmacological properties.



1

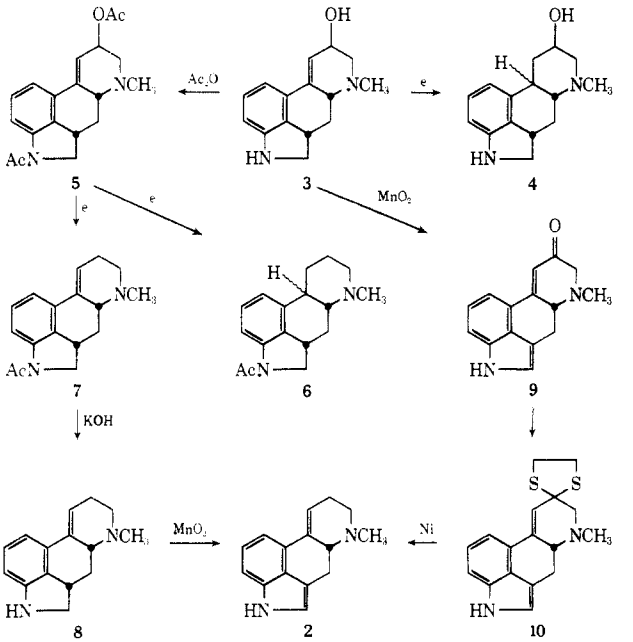


2

Chemistry (Scheme I). An obvious starting material for the synthesis of **2** was the tetracyclic unsaturated alcohol **3**, which was used in our total synthesis of lysergic acid.[4] It is available in nine steps from 3-indolepropionic acid. Initial attempts to cleave the allylic hydroxyl in **3** by electrolytic reduction led only to saturation of the 9,10 double bond to yield the dihydro derivative **4**. Similar reductions on the diacetyl derivative **5** were more fruitful. Electrolytic reduction of **5** at a potential of −2.70 V led to both allylic cleavage and saturation of the 9,10 double bond to afford **6**. At a potential of −2.30 V, however, the product was the desired 9,10-didehydro-2,3-dihydroergoline (**7**). Hydrolysis of the acetyl amide function in **7** led to the indoline **8**, which was transformed on oxidation with MnO_2 to *dl*-descarboxylysergic acid (**2**).

An alternative route to **2** was developed by subjecting

Scheme I



the tetracyclic allylic alcohol **3** to MnO_2. Oxidation of both alcohol and dihydroindole functions took place, and the α,β-unsaturated ketone **9** which resulted was converted to the corresponding dithioethylene ketal **10**. This derivative on desulfurization with Raney nickel led in poor yield to *dl*-descarboxylysergic acid (**2**). In its present state of development, the electrochemical route to **2** is the preferred one.

Pharmacology. In the mouse behavior screen normal male mice were given graded ip injections (0.1 up to 300 mg/kg) of descarboxylysergic acid maleic acid salt to determine the pattern of behavioral effects produced by the drug. The LD_{50} was about 50–100 mg/kg, and the profile of activities observed was remarkably similar to that shown by LSD. However, previous studies have shown that such observations are not reliably predictive of hallucinogenic activity in man.

In isolated smooth muscle studies **2** maleate salt was