Table IV—Effect of Pyridine Concentration on Color Stability[a]

Pyridine, M	$10^5 k_{obs}$, sec^{-1}
0.41	9.8
2.06	0.92
4.12	1.7
8.24	0.45

[a] Formaldehyde, 4.47×10^{-4} M; Ia, 8.22×10^{-4} M; sodium periodate, 3.12×10^{-2} M; 25°.

critical in that sodium periodate must be in at least a twofold excess for maximal color development (Table V). Therefore, a relatively high concentration of sodium periodate should be used when a wide concentration range of aldehyde is to be studied.

A calibration curve for the determination of formaldehyde gave excellent results. The slope of the line was 1156 liters $mole^{-1}$ cm^{-1} (1-cm cell used) with an intercept of 0.008 when calculated by linear regression analysis. The sample correlation coefficient was 0.999 with a standard error of the estimate of 0.009 ($S_{y \cdot x}$). Formaldehyde concentrations down to 4×10^{-5} M can be determined using a 1-cm cell and a spectrophotometer[4] (no scale expansion). It is quite conceivable that lower concentrations could be determined if enough sample were available to allow for the use of longer path length cells. Above concentrations of 10^{-3} M, deviation from Beer's law was observed.

Although other aliphatic aldehydes reacted more slowly than formaldehyde, each gave a similar color yield. It is not unexpected that acetone and benzaldehyde did not react since much higher concentrations of these compounds must be present to give a positive spot test using a variation of this reaction (2). Furthermore, on the basis of spot test data, no interference from a variety of carboxylic acid derivatives is expected (2).

[4] Cary 15.

Table V—Effect of Ratio of Sodium Periodate to Formaldehyde on Color Formation

Sodium Periodate: Formaldehyde[a]	A_{515}[b]
0.70	0
1.40	0.133
1.75	0.362
2.10	0.563
3.49	0.553
6.99	0.563
13.67	0.572

[a] Molar concentrations. [b] Absorbance measured 25 min after the addition of sodium periodate and pyridine.

This method represents a rapid and sensitive means for the determination of formaldehyde in aqueous solutions. Total analysis time for a single determination is 30 min, with as many as 30 samples being analyzed per hour.

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ACKNOWLEDGMENTS AND ADDRESSES

Received September 26, 1974, from the *College of Pharmacy, University of Kentucky, Lexington, KY 40506*

Accepted for publication November 29, 1974.

Presented at the 17th national meeting of the APhA Academy of Pharmaceutical Sciences, New Orleans, November 1974.

Supported in part by American Cancer Society Institutional Grant IN-106.

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Nidation Inhibition by Simple Ergoline Derivatives

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Abstract □ The ability of four ergoline-type compounds (elymoclavine, its *O*-benzoate and *O*-carbamate, and *N*-methyl-6,7-seco-elymoclavine) to inhibit nidation in rats was determined and found to parallel their prolactin-inhibiting activity.

Keyphrases □ Nidation—inhibition by four ergoline-type compounds, rats, relationship to prolactin-inhibiting ability □ Ergoline-related compounds—inhibition of nidation, relationship to prolactin-inhibiting ability □ Elymoclavine and related compounds—inhibition of nidation, rats

Research interest in the pharmacology of ergot alkaloids is currently focusing on two areas: their antihypertensive activity and their effect on hormone release from the anterior pituitary gland. The latter effect, primarily due to a direct inhibition of the synthesis and release of prolactin, manifests itself in the inhibition of some prolactin-dependent processes, *e.g.*, lactation in various animals and in humans, development of certain types of mammary tumors, and implantation of the fertilized egg (nidation) in rats and mice (1). While nidation inhibition in rats is generally thought to be predominantly or exclusively the result of prolactin inhibition, Flückiger and Wagner (2) obtained results that led them to conclude that 2-bromo-α-ergokryptine, a modified peptide ergot alkaloid which is undergoing clinical evaluation, has a specific nidation-inhibiting effect.

Since it has been shown (1, 3–5) that the peptide portion of these alkaloids is not required for activity, it was of interest to compare the ability of some simple ergolenes to inhibit prolactin release and nidation. For this comparison, four compounds were se-

Table I—Nidation Inhibition of Some Simple Ergolene Derivatives in Rats

	Series 1			Series 2				Series 3		
	Control	Elymoclavine Carbamate (1 mg)	*N*-Methylsecoelymoclavine (1 mg)	Control	D-6-Methyl-8-ergoline-1-yl-acetamide Tartrate (1 mg)	Elymoclavine Benzoate (1 mg)	Elymoclavine (1 mg)	Control	Elymoclavine Carbamate (0.1 mg)	Summarized Controls
Number of pregnant animals/total number of animals in group	6/8	0/7[a]	4/7[b]	7/7	0/6[a]	0/7[a]	0/7[a]	2/3	3/6[b]	15/18
Average number of fetuses per pregnant animal	9.7	—	10.5	9.2	—	—	—	8.5	8.7	9.3
Well-developed fetuses per pregnant animal	9.3	—	9.0	8.4	—	—	—	8.5	8.3	8.8
Resorbed fetuses per pregnant animal	0.3	—	1.5[b]	0.7	—	—	—	0.0	0.3	0.5
Percentage of resorbed fetuses/total number of fetuses	3.4/58	—	14.3/42[b]	7.8/64	—	—	—	0/17	3.8/26	5.0/139
Mean weight developed fetuses, g ± *SEM*	2.95 ± 0.05	—	3.55 ± 0.05[a]	—	—	—	—	—	—	—
Weight of pregnant animals at beginning of experiment, g ± *SEM*	179 ± 4	—	190 ± 9[b]	—	—	—	—	—	—	—

[a] Significantly different from the parallel and summarized controls ($p = 0.05$). [b] Difference from controls not statistically significant.

lected which had been assayed for prolactin inhibition in rats (5). Three of these compounds (elymoclavine, its benzoate, and its carbamate) were active (95, 66, and 66% of inhibition shown by ergocornine as reference); the fourth (*N*-methyl-6,7-secoelymoclavine), although structurally closely related, had only borderline activity (40% of reference).

EXPERIMENTAL

Nidation inhibition by these compounds was determined using virgin female rats of the Wistar strain weighing 170–230 g at the beginning of the experiment. They were caged with fertile males and their vaginal smears were examined each morning. The day of finding spermatozoa in the vagina was considered Day 1 of the experiment, and from this day on the animal was caged separately from males.

The compounds to be tested were dissolved in 0.2% aqueous tartaric acid solution at concentrations of 1 or 0.1 mg/ml (except in the case of elymoclavine benzoate which required addition of 10% ethanol for solution). They were administered, *via* stomach tube, to groups of six or seven animals once a day on Days 6 and 7. Each animal received 1 ml of solution/day, *i.e.*, 1 or 0.1 mg of drug, corresponding to approximately 5 or 0.5 mg/kg. The time of administration and the doses were chosen on the basis of previous experience (4). Control animals received 1 ml of 0.2% tartaric acid solution.

On Day 20, the animals were killed and the uterus was examined. The number of well-developed fetuses and of resorbed fetuses was determined, and the well-developed fetuses were weighed in some experiments (Table I).

RESULTS AND DISCUSSION

The experiments clearly show that elymoclavine, elymoclavine benzoate, and elymoclavine carbamate completely suppress the nidation of embryos and thus pregnancy in rats when given orally in doses of 5 mg/kg on the 5th and 6th days after copulation. When given at the lower dose of 0.5 mg/kg, elymoclavine carbamate did not significantly reduce the number of animals found pregnant. D-6-Methyl-8-ergoline-1-yl-acetamide tartrate, a known potent lactation and nidation inhibitor, was effective at both the higher (Table I) and the lower dose (6). *N*-Methylsecoelymoclavine, when given in the dose of 5 mg/kg in the same way as the other drugs, had no significant effect on nidation but caused an interesting, unexplained 20% increase in weight of the fetuses.

It follows from the results of these experiments that, in the simple ergolene series, the nidation-inhibitory activity parallels prolactin-inhibiting ability at least qualitatively.

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ACKNOWLEDGMENTS AND ADDRESSES

Received August 16, 1974, from the *Pharmaceutical and Biochemical Research Institute, 17, Kouřimská, Praha 3-Vinohrady, Czechoslovakia, and the ‡Department of Medicinal Chemistry and Pharmacognosy, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, IN 47907

Accepted for publication November 29, 1974.

Supported in part by the National Institutes of Health Grants AM 11662, CA 13278, and GM 42382.

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