of 25 and 15 ml of concentrated HCl was stirred and refluxed for 3 hr. An additional 5 ml of concentrated HCl was added and the mixture was refluxed for an additional 4 hr. The resulting yellow precipitate was removed by filtration and washed thoroughly with H_2O. The precipitate (0.335 g) was dissolved in hot 50% aqueous EtOH and the solution was made slightly basic by the addition of concentrated NH_4OH. Concentration of the solution gave a gel which was removed by filtration and crystallized from $CHCl_3$–MeOH to yield 0.145 g (49%) of **26** as tan crystals. Recrystallization from $CHCl_3$–MeOH afforded 0.055 g of **26** as tan crystals; mp 280–285° dec (with previous sintering). *Anal.* ($C_{21}H_{22}N_4O \cdot \frac{2}{3}H_2O$) C, H, N.

2′-Phenylyohimbano[17,18-*d*]pyrimidine (27). A mixture of 10.2 g of **18**, 6.26 g of benzamidine hydrochloride, 2.0 g of KOH, and 100 ml of EtOH was stirred at room temperature for 20 hr and refluxed for 3.5 hr. The solvent was removed and the residue was triturated with H_2O. Filtration gave 4.44 g of solid which was washed with H_2O, dried, dissolved in $CHCl_3$–EtOH (99.5:0.5), and chromatographed over Al_2O_3 to give 1.48 g of product. Trituration with MeOH gave 0.98 g (8%) of **27** as yellow crystals: mp 304–307° dec; $[\alpha]^{25}D$ −165° (*c* 1.0, pyridine). *Anal.* ($C_{27}H_{26}N_4 \cdot 0.25H_2O$) C, H, N.

Acknowledgment. We wish to thank Mr. L. M. Brancone and his staff for elemental analyses and Mr. W. Fulmor and his staff for spectral determinations.

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Ergot Alkaloids. Ergolines and Related Compounds as Inhibitors of Prolactin Release

John M. Cassady,* George S. Li, Ernest B. Spitzner, Heinz G. Floss,

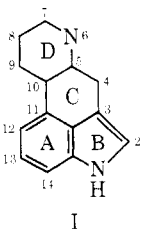
Department of Medicinal Chemistry and Pharmacognosy, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, Indiana 47907

and James A. Clemens

The Lilly Research Laboratories, Indianapolis, Indiana 46206. *Received August 14, 1973*

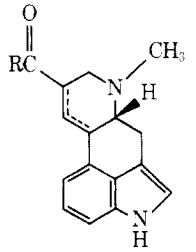
A number of naturally occurring ergot alkaloids, synthetic ergolines, and substituted indoles have been tested for their ability to inhibit the secretion of the hormone prolactin in rats. It has been established that the complete ergoline ring system is necessary for significant activity and that modifications of the D-ring portion of this system have a significant influence on prolactin-inhibiting activity. A number of compounds in the $\Delta^{8,9}$-ergoline series were tested and among these compounds elymoclavine showed very significant activity relative to ergocornine. A number of derivatives of elymoclavine also showed significant activity. In addition, several $\Delta^{9,10}$- and dihydroergolines were tested and although the $\Delta^{9,10}$ compounds were less active in general than the $\Delta^{8,9}$ series, several of the dihydroergolines showed good activity. Total synthesis of a series of ergolines with a cis C,D ring fusion (II series) was achieved from tricyclic ketone **6**. The testing results for these compounds indicate a decrease in prolactin-inhibiting activity.

The ergot alkaloids consist of a series of 3,4-disubstituted derivatives of indole, the majority of which possess the tetracyclic ring structure designated as ergoline (I).

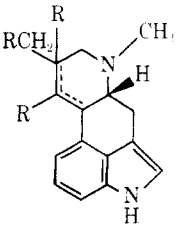


I

These alkaloids occur in various species of *Claviceps* including *Clavicèps purpurea* (Fries) Tulasne.[1,2] In addition, these compounds have been isolated from other closely related fungi[3] and certain species of the Convolvulaceae including *Ipomea, Rivea,* and *Argyreia.*[4] The naturally occurring ergot alkaloids can be conveniently divided into two groups according to their chemical structure,[1] the lysergic acid derivatives (II) and the clavines (III). The clavines are substituted 6,8-dimethylergolines and include a few members, namely the chanoclavines, with a 6,7-seco D ring.



II

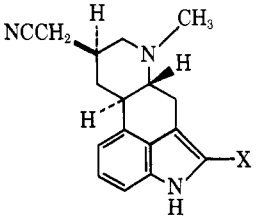


III

The ergot alkaloids have a rich and varied history as therapeutic agents and several are currently used in the treatment of migraine and in the control of postpartum hemorrhage.[5] The lactation inhibitory effect of these compounds has long been recorded in the literature[6] but until recently had received little systematic attention. A series of studies, beginning with a report by Shelesnyak[7] in 1954 on the ability of ergotoxine to inhibit deciduoma formation, has now firmly established that ergolines inhibit lac-

tation, the development of certain hormone-dependent mammary tumors, and nidation *via* an inhibition of prolactin secretion from the anterior pituitary.[5,8] Although the role of prolactin in human breast cancer is still not clear,[9,10] the relationship between breast cancer and prolactin has been strengthened by the observation that a significant percentage of human breast cancers show prolactin dependence.[11]

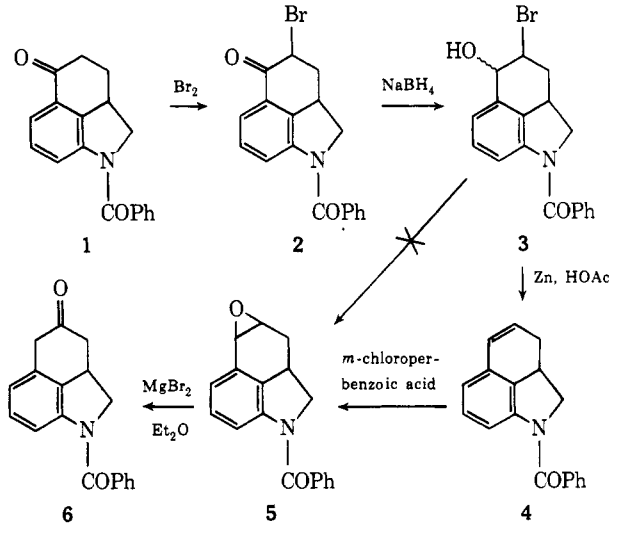
Although it has been observed that the peptide-type ergot alkaloids generally possess more potent pharmacological activity than those of the clavine type, we were interested in developing ergoline structure–prolactin inhibition relationships primarily among the clavines since these compounds exhibit lower toxicity. The utility of this approach has been demonstrated by our testing data and some recent results reporting the potent prolactin inhibition, conception suppression,[12] and antitumor activity[6] of D-6-methyl-8-cyanomethylergoline I (III) and its 2-chloro derivative IV.



III, X = H
IV, X = Cl

Chemistry. In addition to the natural ergolines and related compounds which were obtained for testing, we initiated studies toward the development of general total synthetic routes to the tricyclic and tetracyclic clavines in order to generate a greater variety of structural modifications. Our initial efforts have involved sequences stemming from the tricyclic ketones 1 and 6 (Scheme I) which were reported in conjunction with the first total synthesis of lysergic acid by Kornfeld and coworkers.[13]

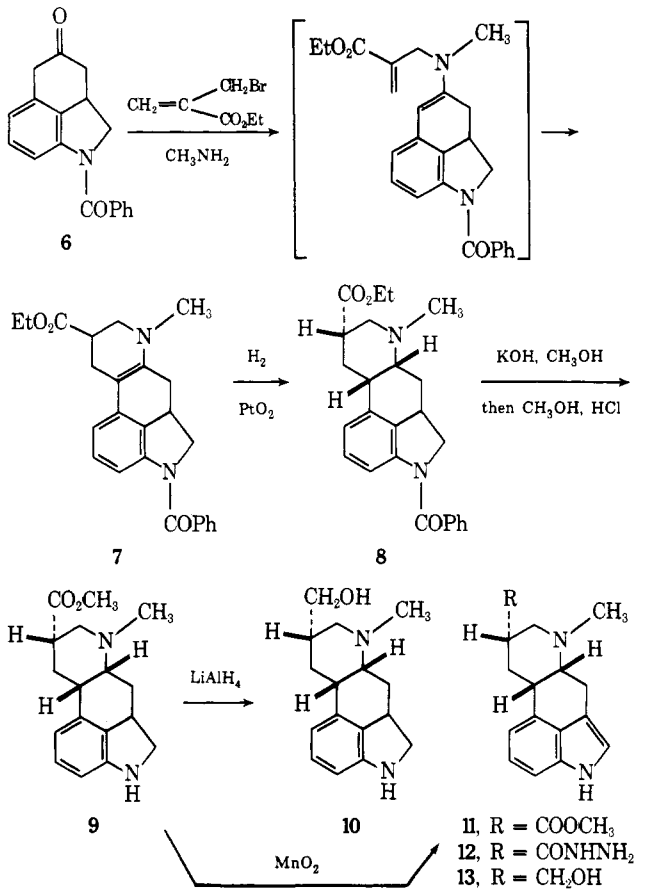
Scheme I



Compound 1 was obtained as a gift from Dr. E. Kornfeld, Eli Lilly and Co., and was converted to the isomeric tricyclic ketone 6 by a five-step sequence developed by Kornfeld, *et al.*,[13] along with an alternate procedure which we have developed (Scheme I). The original objective of our scheme was to decrease the steps involved in the translocation of the ketone function in 1. Unfortunately, bromohydrin 3 gave intractable mixtures when refluxed with methanolic potassium hydroxide and gave back compound 1 on treatment with water under reflux. The failure to form the desired epoxide prompted an alternate procedure in which the bromohydrin was converted to the corresponding alkene by the action of zinc in acetic acid.[14] This latter sequence was equal in steps and more efficient than the literature route.

Our plan was to effect a one-step formation of the ergoline system from ketone 6 by reaction with methylamine and ethyl α-(bromomethyl)acrylate. This annelation process which is outlined in Scheme II presumably proceeds *via* initial attack of methylamine on the bromoacrylic ester to give the β-aminomethylacrylic ester. Reaction with the tricyclic ketone then leads to intermediate enamine formation followed by cyclization to the tetracyclic ergoline ester 7.

Scheme II



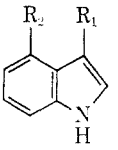
This type of annelation process was developed by Grob and Renk in an early approach to the synthesis of lysergic acid[15] which, however, failed due to naphthalene formation and this approach to lysergic acid was abandoned. They noted in passing that the $\Delta^{5,10}$ tetracyclic ester was readily reduced to the corresponding dihydro compound.

Horii and coworkers have also used this cyclization reaction for the conversion of β-tetralone to a series of lysergic acid analogs (Scheme III). These workers studied in detail the products formed on reduction of the intermediate enamine ester. Catalytic hydrogenation over platinum oxide gave a mixture of the cis-syn ester and the cis-anti ester in a ratio of 9:1. In contrast, reduction with sodium borohydride gave a mixture of the trans-anti and cis-anti esters in a ratio of 7:3.

Horii's structural assignments were based on chemical and spectroscopic evidence and these results established a good model for the subsequent reduction of the tetracyclic enamine ester 7.

Reaction of ketone 6 with the bromoacrylic ester and methylamine gave the expected tetracyclic enamine ester

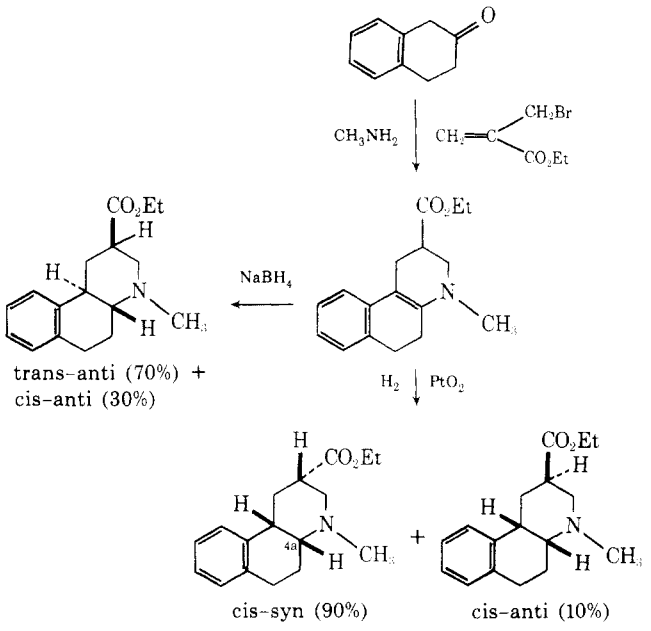
Table I. Substituted Indoles[a]



Compd no.	R_1	R_2	Prolactin control value	Prolactin value after treatment	Inhibition, %	Level of significance[b]	Inhibition (ergocornine), %
14	$CH_2CH(NH_3^+)CH_2CH{=}C(CH_3)_2{}^-OAc$	H	29.5 ± 3.0	20.9 ± 2.5	29	Borderline	79
15	$CH_2C(CO_2CH_2CH_3)_2$ | NHCHO	$CH_2CH{=}C(CH_3)_2$	29.5 ± 3.0	31.7 ± 3.7	0	NS	79
16[c]	$CH_2N(CH_3)_2$	$CH_2CH{=}C(CH_3)_2$	16.1 ± 1.4	14.7 ± 0.9	12	NS	38
17	$CH_2CH(NH_2)COOH$	$CH_2CH{=}C(CH_3)_2$	28.6 ± 2.9	21.4 ± 2.6	25	NS	84
18	$CH_2N(CH_3)_2$	OCH_2Ph	28.8 ± 3.8	29.4 ± 2.7	0	NS	

[a]All compounds were tested at 10 μg per animal unless otherwise specified. Values listed are means ± standard errors. [b]NS = not significant; borderline = almost significant at $p < 0.05$. The level of significance listed was obtained according to Student's t test. [c]Compound **16** was tested at 50 μg per animal.

Scheme III

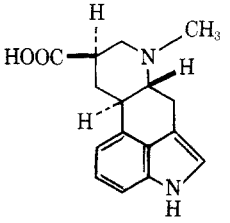


7 in 40–50% yields. The ir, uv, nmr, and mass spectra of this compound and its derivatives were consistent with the structures proposed.

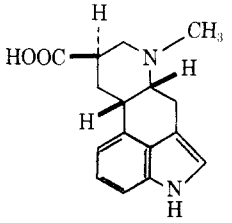
Reduction of enamine ester 7 with hydrogen over platinum oxide gave a reduction product **8**, which was assumed to possess the cis-syn stereochemistry based on Horii's results,[16] along with unreacted starting material. Attempts to obtain complete conversion of the enamine by increasing the reaction time led to an increasing quantity of the corresponding *N*-benzyl compound.

Based on this assumption further conversion of the reduction product was expected to lead into the dihydroisolysergic acid II series. The four possible natural dihydrolysergic acid isomers are shown in Chart I. Attempts to remove the *N*-benzoyl-protecting group by acid hydrolysis failed due to the insolubility of the partially hydrolyzed acid amide; however, treatment of **8** with base followed by reesterification gave the desired indoline ester **9**. Reaction of **9** with $LiAlH_4$ gave 2,3,9,10-tetrahydroisolysergol II (**10**). Entry into the indole series was accomplished by oxidation of **9** with activated manganese dioxide[17] to give racemic methyl dihydroisolysergate II (**11**). This amorphous compound gave a virtually identical ir spectrum tc and cochromatographed on tlc with D-methyl dihydroisolysergate II obtained by esterification of an authentic sample of D-dihydroisolysergic acid II provided by Dr. P. A. Stadler, Sandoz A.G., Basel. Reaction of **11** with hydrazine gave a crystalline hydrazide **12**, mp 225–227° (lit. mp 227–229° for the racemic hydrazide[18]). In addition, reduction of **11** with $LiAlH_4$ gave dihydroisolysergol II (**13**).[18]

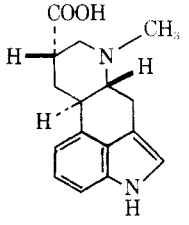
Chart I



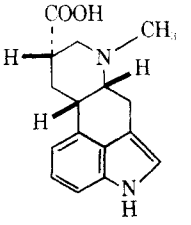
dihydrolysergic acid I



dihydrolysergic acid II



dihydroisolysergic acid I



dihydroisolysergic acid II

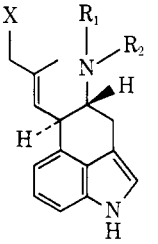
Most of the other compounds tesfed were either samples obtained from various laboratories or materials prepared during our earlier studies in the ergot field.

Among the substituted indoles in Table I, 1-(3-indolyl)-2-amino-5-methyl-4-hexene acetate (**14**) was obtained by a reaction sequence outlined by Weygand and coworkers.[19] Diethyl 4-(γ,γ-dimethylallyl)skatyl formamidomalonate (**15**) and 4-(γ,γ-dimethylallyl)gramine (**16**) were intermediates in the synthesis of 4-(γ,γ-dimethylallyl)tryptophan (**17**) as described by Plieninger and coworkers.[20] A sample of 4-benzyloxygramine (**18**) was obtained by a published route.[21]

The tricyclic clavines (Table II) were obtained by treatment of agroclavine methiodide (**42**) and elymoclavine methiodide (**43**) with silver oxide followed by Emde-Birch reduction to give *N*-methyldeoxychanoclavine I (**19**) and *N*-methylchanoclavine I (**20**), respectively.[22] Demethylation of **20** with diethyl azodicarboxylate as described by Fehr[23] was used to prepare chanoclavine I (**21**).

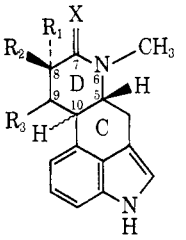
Several of the compounds in the ergoline series (Table

Table II. Tricyclic Clavines



Compd no.	R_1	R_2	X	Prolactin control value	Prolactin value after treatment	Inhibition, %	Level of significance	Inhibition (ergocornine), %
19	CH_3	CH_3	H	28.8 ± 3.8	21.5 ± 2.0	30	NS	
20	CH_3	CH_3	OH	17.0 ± 1.6	12.1 ± 1.7	29	Borderline	73
21	H	CH_3	OH	17.0 ± 1.5	23 ± 3.1	0	NS	70

Table III. Tetracyclic Compounds, Ergoline Series



Compd no.	C,D ring fusion	R_1	R_2	R_3	X	Prolactin control value	Prolactin value after treatment	Inhibition, %	Level of significance	Inhibition (ergocornine), %
11	Cis	COOMe	H	H	H_2	34.2 ± 2.9	25.2 ± 1.86	20	Borderline	65
12	Cis	$CONHNH_2$	H	H	H_2	34.2 ± 2.9	29.9 ± 3.3	12	NS	65
13[a]	Cis	CH_2OH	H	H	H_2	34.2 ± 2.9	27.5 ± 3.6	20	NS	65
22	Trans	H	CON_3	H	H_2	26.0 ± 1.4	24.5 ± 1.8	5.7	NS	77
23	Trans	H	NH_2	H	H_2	26.5 ± 3.6	11.3 ± 2.1	57	$p < 0.01$	
24	Trans	CH_2		H	O	28.8 ± 3.8	24.7 ± 1.7	14	NS	
25	Trans	H	CH_3	H	O	26.5 ± 3.6	16.7 ± 2.3	37	$p < 0.05$	
26	Trans	H	CH_2OH	H	H_2	34.0 ± 6.3	12.4 ± 0.9	63	$p < 0.01$	
		CH_2OH	H	H	H_2					
27	Trans	H	CH_3	OH	H_2	27.7 ± 2.8	24.4 ± 3.1	6.5	NS	
						31.1 ± 5.8	24.5 ± 3.4	21	NS	64

[a]Compound **13** was tested at 100 μg per animal.

III) were obtained by conversions of dihydrolysergic acid I. The dihydrolysergic acid azide hydrochloride (**22**) was obtained by hydrazinolysis of dihydrolysergic acid methyl ester followed by diazotization.[24] Treatment of **22** with dilute HCl gave 6-methyl-8-aminoergoline (**23**).[25] Dihydrolysergic acid lactam (**24**) was prepared by treatment of dihydrolysergic acid with acetic anhydride at 160–170°.[26] Catalytic hydrogenation of **24** gave the dihydrolactam **25**.[26] Dihydroelymoclavine (**26**), consisting of a mixture of dihydrolysergol I and dihydroisolysergol I, was obtained by catalytic hydrogenation of elymoclavine in methanol over Raney nickel at 1400 psi.[27] Fumigaclavine B (**27**) was a gift from Dr. J. F. Spilsbury, the Wellcome Research Laboratories, Beckenham, Kent.

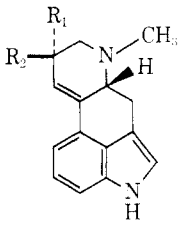
Among the $\Delta^{9,10}$-ergolines (Table IV), lysergic acid α-hydroxyethylamide (**28**) was a gift from Professor D. Groger, Institute for Biochemistry of Plants, Halle. The alkaline double bond isomerization procedure of Schreier[28] was used to prepare lysergine (**29**) and isolysergine (**30**) from agroclavine and isolysergol (**31**) and lysergene (**32**) from elymoclavine. 6-Methyl-8-acetoxymethylene-9-ergoline (**33**) was prepared by treatment of elymoclavine with a mixture of dimethyl sulfoxide and acetic anhydride.[29] The four stereoisomers of lysergylalanine methyl ester (**34–37**) were prepared from lysergic acid and D- or L-alanine methyl ester by the mixed anhydride method using isobutyl chloroformate.[30]

In the $\Delta^{8,9}$ series (Table V) agroclavine (**38**) was obtained as a gift from Dr. H. Kobel, Sandoz A.G., Basel, and elymoclavine (**39**) was isolated from submerged cultures of *Calviceps* strain SD 58[31] as was elymoclavine β-D-fructoside (**40**).[32] Elymoclavine *N*-oxide (**41**) was obtained by treatment of elymoclavine with H_2O_2.[32] The methiodides **42** and **43** of agroclavine and elymoclavine were prepared by reaction of the bases with CH_3I in methanol.[22] Elymoclavine *O*-acetate (**44**) was prepared by acetylation of **39** with acetic anhydride in pyridine.[28] Elymoclavine pyridinium tosylate (**45**) and the corresponding 8-piperidinomethyl-$\Delta^{8,9}$-ergoline (**46**) were prepared from **39** by reaction with tosyl chloride in pyridine to give **45**, followed by catalytic hydrogenation to give the piperidino compound.[28] The elymoclavine **39** derivatives, elymoclavine benzoate **47** and carbamate **48**, were prepared by standard procedures as described in the Experimental Section.

Biological Activity. The compounds listed in Tables I–VI were evaluated for prolactin-inhibiting activity in the rat. The results of these tests are listed in the tables. The test method is described in the Experimental Section. In most runs ergocornine was included as a reference point and these values are also given in the tables.

A number of conclusions can be reached in analysis of the testing data for this series of compounds. It can be seen from the data in Table I that the simple 3,4-disubsti-

Table IV. Tetracyclic Compounds, $\Delta^{9,10}$-Ergoline Series



Compd no.	R_1	R_2	Prolactin control value	Prolactin value after treatment	Inhibition, %	Level of significance	Inhibition (ergocornine), %
28	H	$CONHCH(CH_3)OH$	29.5 ± 3.0	13.8 ± 1.4	53	$p < 0.001$	79
29	H	CH_3	24.4 ± 3.5	18.9 ± 2	14	NS	58
30	CH_3	H	24.4 ± 3.5	21.0 ± 2.2	4	NS	58
31	CH_2OH	H	29.5 ± 3.0	18.4 ± 1.2	37	$p < 0.01$	79
32		$=CH_2$	29.5 ± 3.0	24.8 ± 1.8	16	NS	79
33		$=CHOAc$	24.4 ± 3.5	15.7 ± 1.4	28	$p < 0.02$	58
34[a]	H	$-CNH-C(H)(CH_3)-COOCH_3$	29.5 ± 1.9	28.9 ± 1.7	0	NS	41
35	$-CNH-C(H)(CH_3)-COOCH_3$	H	29.5 ± 1.9	31.0 ± 2.5	0	NS	41
36	H	$-CNH-C(CH_3)(H)-COOCH_3$	23.6 ± 3.1	16.9 ± 2.3	28	NS	69
37[b]	$-CNH-C(CH_3)(H)-COOCH_3$	H	29.5 ± 1.9	24.3 ± 0.9	17	Borderline	41

[a]Compound **34** was tested at 50 μg per animal. [b]Compound **37** was tested at 20 μg per animal.

tuted indoles, even if they have essentially all of the carbon atoms of the ergoline system, are completely inactive. Even the tricyclic clavines in Table II show little activity when compared to their tetracyclic analogs. In this regard it is interesting to compare chanoclavine I (**21**) which is inactive with elymoclavine (**39**) which is almost equipotent with ergocornine in inhibiting prolactin release. From these data it appears that the relatively rigid tetracyclic ergoline system is necessary for significant activity and in addition it is apparent that the clavine-type ergolines can exhibit activity equivalent to the peptide type. In fact, in our series of compounds most of the lysergic acid derivatives in both the I (compounds **22**, **34–37**) and II series (**9**, **11**, **12**) were inactive, although **28** showed good activity.

Examination of the data for compounds in the $\Delta^{8,9}$ series (Table V) indicates that structural modification of the D ring has a great effect on activity. First it is apparent from the lack of activity in compounds **41**, **42**, and **43** that nitrogen atom 6 must be basic and/or uncharged. Substitution at the 8 position is also important and it is apparent that a very large substituent can be accommodated at this position with no decrease in activity. This is evidenced by the fact that elymoclavine (**39**) with an 8-hydroxymethyl group is almost twice as potent as agroclavine with an 8-methyl group. A number of derivatives of elymoclavine (**39**), compounds **40**, **44**, **47**, and **48**, retain considerable activity. The pyridinium tosylate **45** and the 8-piperidinomethyl-$\Delta^{8,9}$-ergoline (**46**) are as potent as elymoclavine, although the 8 substituent in each case is considerably larger in size.

Comparison of $\Delta^{8,9}$-ergolines with their $\Delta^{9,10}$ analogs indicates that the shift of the double bond to the 9,10 position reduces activity. For example, isolysergol (**31**) is less active than elymoclavine (**39**) and agroclavine (**38**) shows good activity while lysergine (**29**) and isolysergine (**30**) are inactive. However, the $\Delta^{8,9}$ double bond is not essential for activity since several of the members of the ergolines with a saturated D ring (Table III) show good activity, *e.g.*, compounds **23** and **26**. Compounds **24**, **25**, and **27** are inactive and this would appear to indicate that substituents at C-7 and C-9 in ring D are not compatible with prolactin-inhibiting activity.

It is clear from Tables III and VI that the stereochemistry of the C,D ring fusion is critical. Compounds in the II series of ergolines (cis ring fusion) are essentially inactive. Comparison of the testing results for compounds **13** and **26** strongly supports this conclusion.

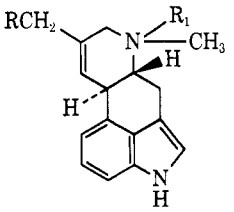
It would also appear that reduction of the 2,3 double bond (indole to indoline) leads to a decrease in activity, for example, the decrease in activity of compound 9 in comparison to **11**.

Analysis of our testing data has therefore defined some of the structure–prolactin-inhibiting activity relationships among the ergolines. Further studies are underway to refine this picture and to evaluate the more promising compounds for their ability to inhibit mammary tumors and/or nidation in animal systems.

Experimental Section

General Procedures. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Uv spectra were recorded on a Perkin-Elmer Coleman 124

Table V. Tetracyclic Clavines, $\Delta^{8,9}$-Ergoline Series



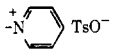
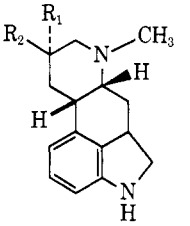
Compd no.	R	R_1	Prolactin control value	Prolactin value after treatment	Inhibition, %	Level of significance	Inhibition (ergocornine), %
38	H		29.8 ± 1.2	16.2 ± 0.5	46	$p < 0.001$	71.5
39	OH		32.54 ± 0.9	9.39 ± 0.3	71.2	$p < 0.001$	75
40	*O*-β-D-fructose		28.6 ± 2.9	16.3 ± 3.2	42	$p < 0.02$	84
41	OH	O (*N*-oxide)	26.0 ± 1.4	21.06 ± 2.4	19	NS	77
42	H	CH_3 (methiodide)	28.6 ± 2.9	22.7 ± 2.2	21	NS	84
43	OH	CH_3 (methiodide)	17.0 ± 1.6	14.1 ± 1.9	17	NS	73
44	$OCOCH_3$		26.0 ± 1.4	11.2 ± 1.7	57	$p < 0.001$	77
45			29.5 ± 1.9	17.8 ± 2.6	40	$p < 0.01$	41
46			29.5 ± 1.9	19.4 ± 0.9	34	$p < 0.001$	41
47	OCOPh		24.4 ± 3.5	13.5 ± 2.2	38	$p < 0.01$	58
48	$OCONH_2$		24.4 ± 3.5	13.5 ± 1.9	38	$p < 0.01$	58

Table VI. Tetracyclic Compounds, 2,3-Dihydroergolines



Compd no.	R_1	R_2	Prolactin control value	Prolactin value after treatment	Inhibition, %	Level of significance	Inhibition (ergocornine), %
9	$COOCH_3$	H	29.5 ± 1.9	27.9 ± 1.6	6	NS	41
10	CH_2OH	H	29.5 ± 1.9	33.6 ± 2.6	0	NS	41

spectrophotometer, ir spectra on a Perkin-Elmer 237B spectrophotometer, and mass spectra were obtained on a Hitachi RMU-6 low-resolution or a CEC 21-110 high-resolution mass spectrometer. Analytical data were obtained from the Microanalysis Laboratory, Department of Chemistry, Purdue University.

Chromatography. The following solvent systems were used with 5 × 20 × 0.025 cm Brinkmann Silplate 52 precoated silica gel plates: AED, Me_2CO-EtOAc-DMF (5:5:1); CMA-1, $CHCl_3$-MeOH (9:1) in NH_3 atmosphere; CMA-2, $CHCl_3$-MeOH (8:2) in NH_3 atmosphere; CMA-3, $CHCl_3$-MeOH-NH_4OH (80:20:2); EA, EtOAc-Me_2CO (1:1); AE, Me_2CO-EtOH (9:1); BE, C_6H_6-EtOAc (8:2).

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*.

In each experiment the 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.

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.[33] 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 the serum was collected and assayed for prolactin as previously described. The results were evaluated statistically using Student's t test.

1-Benzoyl-4-bromo-5-hydroxy-1,2,2a,3,4,5-hexahydrobenz[*c,d*]indole (3). This was prepared by a modification of the method of Kornfeld and coworkers.[13] A suspension of 1-benzoyl-4-bromo-5-keto-1,2,2a,3,4,5-hexahydrobenz[*c,d*]indole, 5 g (0.014 mol) (obtained from Dr. E. Kornfeld, Eli Lilly Co., Indianapolis, Indiana), in 200 ml of anhydrous Et_2O was treated slowly with $NaBH_4$, 2 g, in 50 ml of MeOH. A vigorous reaction occurred and the suspension cleared after stirring at room temperature for 30 min. The mixture was poured into 100 ml of H_2O and extracted with 3 × 200 ml of C_6H_6-Et_2O (1:1). The organic layers were combined and washed with H_2O, dried over Na_2SO_4, filtered, and evaporated to give the bromohydrin, 3.0–3.5 g (60–70%), which melted with decomposition at 80–85° (literature value 87° dec). The ir spectra and tlc (solvent systems CMA-2 and BE) behavior were identical with those of an authentic sample of the bromohydrin.

Attempted Conversion of Bromohydrin 3 into 1-Benzoyl-4,5-epoxy-1,2,2a,3,4,5-hexahydrobenz[*c,d*]indole (5). Bromohydrin **3**, 100 mg (0.278 mmol), was added to a solution of KOH, 100 mg, in 10 ml of MeOH. This mixture was heated under reflux for 3.5 hr. A tlc analysis (CMA-2, BE on silica gel) of the reaction mixture showed it to be multicomponent. None of the components corresponded in retention time to reference epoxide **5**.

Conversion of 1-Benzoyl-4-bromo-5-keto-1,2,2a,3,4,5-hexahydrobenz[*c,d*]indole (2) into 1-Benzoyl-5-keto-1,2,2a,3,4,5-hexahydrobenz[*c,d*]indole (1). A mixture of the bromo ketone **2**, 200 mg (0.56 mmol), and $NaBH_4$, 200 mg, in 10 ml of MeOH was stirred under N_2 at room temperature for 30 min. The reaction mixture was then treated with 1 ml of H_2O and heated under reflux for 1 hr. The mixture was cooled, poured into 40 ml of H_2O, and extracted with 2 × 70 ml of $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried over anhydrous $MgSO_4$, filtered, and evaporated to a syrup. Trituration of this syrup with isopropyl ether gave crude ketone **1**, 130 mg (84%). Recrystallization gave

1, mp 146–147°, which was identical with an authentic reference sample by melting point, ir, and tlc (CMA and BE systems).

1-Benzoyl-1,2,2a,3-tetrahydrobenz[*c,d*]indole (4). A solution of bromohydrin **3**, 3.5 g (0.0097 mol), in 50 ml of HOAc was treated with Zn dust, 10 g, and refluxed for 3 hr. The mixture was cooled, poured into 200 ml of H_2O, neutralized with solid Na_2CO_3, and extracted with 3 × 200 ml of C_6H_6–Et_2O (1:1). The extracts were washed with H_2O, dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum to a syrup. Chromatography of this syrup on a silica gel (MCB, 60–200 mesh) column, 100 g, using C_6H_6 and C_6H_6–EtOAc (95:5) as solvents followed by recrystallization from C_6H_6–petroleum ether gave **4**: 1.6–2.0 g (60–70%); melting point, ir, and tlc values identical with an authentic sample of the alkene.

4-Benzoyl-9-carboethoxy-7-methyl-4,5,5a,6,7,8,9,10-octahydroindolo[4,3-*fg*]quinoline (7). In a dry three-necked flask fitted with an addition funnel and a Dean-Stark trap containing 4A molecular sieve was placed 2–3 ml of dry C_6H_6. The flask was cooled in an ice–salt bath and the C_6H_6 was saturated with 124–155 mg of methylamine (4–5 mmol) and then stirred with cooling for 5–10 min. With vigorous stirring, under N_2, an ice-cold solution of 390 mg (2.04 mmol) of ethyl α-(bromomethyl)acrylate[34] in C_6H_6 was added dropwise and the mixture was stirred with cooling for an additional 15 min.

To this mixture was added a cooled solution of 500 mg (1.80 mmol) of 1-benzoyl-4-keto-1,2,2a,3,4,5-hexahydrobenz[*c,d*]indole in 10 ml of C_6H_6 and the mixture was refluxed with occasional removal of solvent for 24 hr. The reaction mixture was cooled and thoroughly extracted with cold 2 *N* HCl. The combined extract was washed with EtOAc, basified with solid Na_2CO_3, and then extracted with $CHCl_3$. The extract was washed with H_2O, dried, and evaporated *in vacuo*. Trituration of the residual material (often as a foam) with MeOH gave 356 mg (49%) of a pale yellow solid, mp 133–135°. Recrystallization from MeOH gave cream-colored needles: mp 136.5–137.5°; ir ($CHCl_3$) 5.80 (ester) and 6.12 μ (amide and enamine); nmr ($CDCl_3$) δ 1.27 (t, 3 H, J = 7 Hz, CH_2CH_3), 1.87–4.70 (m, 10 H), 2.77 (s, 3 H, NCH_3), 4.17 (q, 2 H, J = 7 Hz, CH_2CH_3), 6.44–7.87 (m, 8 H); uv (MeOH) λ max (ε) 324 nm (12,000), 249 (14,500); λ max (perchlorate) 285 sh (7800), 256 (11,800); mass spectrum m/e (rel intensity) 403 (31), 402 (M^+, 100), 400 (11), 105 (22), 77 (11); mass spectrum (high resolution) calcd for $C_{25}H_{26}N_2O_3$, 402.1944; found, 402.1943. *Anal.* ($C_{25}H_{26}N_2O_3$) C, H, N.

4-Benzoyl-9-carboethoxy-7-methyl-4,5,5a,6,7,8,9,10,10a-decahydroindolo[4,3-*fg*]quinoline (8). A solution of 300 mg (0.747 mmol) of 4-benzoyl-9-carboethoxy-7-methyl-4,5,5a,6,7,8,9,10-octahydroindolo[4,3-*fg*]quinoline in 30 ml of EtOAc was hydrogenated over PtO_2 at 1 atm for 8–10 hr. After filtering through Celite and washing the catalyst with EtOAc, the combined solution was evaporated *in vacuo*.

The residual foam (290–300 mg) was dissolved in C_6H_6 and chromatographed on a column containing activity III, neutral alumina in hexane. Elution with hexane (50 ml) removed nonpolar impurities; elution with 1:1 C_6H_6–hexane (100 ml) led to a mixture of starting enamine, reduced material, and colored impurities (30–50 mg); elution with C_6H_6 and C_6H_6–$CHCl_3$ (5:1 and 1:1) mixtures produced a total of 225–276 mg (75–92%) of the desired product as a foam which showed one spot on tlc (CMA-3 system). Crystallization from Et_2O–petroleum ether gave a white solid: mp 118–120°; ir ($CHCl_3$) 5.82 (ester) and 6.13 μ (amide); nmr ($CDCl_3$) δ 1.00–4.50 (m, 12 H), 1.18 (t, 3 H, J = 7 Hz, CH_2CH_3), 2.48 (s, 3 H, NCH_3), 4.04 (q, 2 H, J = 7 Hz, CH_2CH_3), 6.54–7.84 (m, 8 H); uv (MeOH) λ max (ε) 287 (6100 261 (7800); mass spectrum m/e (rel intensity) 405 (30), 404 (M^+, 100), 105 (56), 77 (23); mass spectrum (high resolution) calcd for $C_{25}H_{28}N_2O_3$, 404.2098; found, 404.2080.

9-Carbomethoxy-7-methyl-4,5,5a,6,6a,7,8,9,10,10a-decahydroindolo[4,3-*fg*]quinoline (Methyl 2,3,9,10-Tetrahydroisolysergate II) (9). To a cooled solution of 525 mg (1.30 mmol) of 4-benzoyl-9-carboethoxy-7-methyl-4,5,5a,6,6a,7,8,9,10,10a-decahydroindolo[4,3-*fg*]quinoline in 10 ml of MeOH was added 10 ml of 20% KOH solution and the mixture was refluxed under N_2 for 24 hr. After cooling the solution was evaporated to dryness under 40° *in vacuo*.

MeOH (20 ml) was cooled in a Dry Ice–Me_2CO bath and saturated with gaseous HCl. The solution was added in one portion to a vigorously stirred suspension of the residual solid mixture of the acid salt and KOH in 20 ml of absolute MeOH, cooled in a Dry Ice–Me_2CO bath. After addition the mixture was stirred with cooling for 15 min and then for 24 hr at room temperature. The solvent was removed under vacuum at room temperature and, after cooling in an ice bath, the residue was basified with a cold saturated Na_2CO_3 solution.

The mixture was thoroughly extracted with EtOAc and the combined extract was washed with a 10% Na_2CO_3 solution and H_2O, then dried, and evaporated to give an orange oil which partly solidified on standing. Trituration with isopropyl ether and filtration gave 197 mg (53%) of an orange solid, mp 152–154°. Recrystallization from isopropyl ether gave clear prisms: mp 158.5–159.5°; ir (Nujol) 2.96 (NH) and 5.81 μ (ester); nmr ($CDCl_3$) δ 1.00–4.07 (m, 12 H), 2.53 (s, 3 H, NCH_3), 3.65 (s, 3 H, CO_2CH_3), 6.30–7.43 (m, 3 H); uv (MeOH) λ max (ε) 285 (1500), 238 (4300); mass spectrum m/e (rel intensity) 287 (22), 286 (M^+, 100), 285 (18), 271 (22), 157 (10), 156 (11), 154 (11), 144 (10), 143 (11), 130 (15); mass spectrum (high resolution) calcd for $C_{17}H_{22}N_2O_2$, 286.1679; found, 286.1681. *Anal.* ($C_{17}H_{22}N_2O_2$) C, H, N.

9-Hydroxymethyl-7-methyl-4,5,5a,6,6a,7,8,9,10,10a-decahydroindolo[4,3-*fg*]quinoline (2,3,9,10-Tetrahydroisolysergol II) (10). To a stirred mixture of $LiAlH_4$, 40 mg, in 3 ml of THF was added slowly 1.5 ml of a solution of 40 mg (0.14 mmol) of methyl 2,3,9,10-tetrahydroisolysergate II in THF. The mixture was refluxed under N_2 for 1 hr, cooled, and treated with a saturated Na_2SO_4 solution. The mixture was next extracted with 3 × 30 ml of $CHCl_3$, washed with H_2O, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to a solid residue. This residue was recrystallized from MeOH to give 28 mg of **10**: mp 232–235°; ir (KBr) 3.01 μ (OH, NH); uv (MeOH) λ max (ε) 284 (5260), 244 (9750); mass spectrum (low resolution) m/e (rel intensity) 259 (1.3), 258 (M^+, 9), 114 (50), 86 (70), 56 (21), 55 (100); mass spectrum (high resolution) calcd for $C_{16}H_{22}N_2O$, 258.1718; found, 258.1713. *Anal.* ($C_{16}H_{22}N_2O$) C, H, N.

9-Carbomethoxy-7-methyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-*fg*]quinoline (Methyl Dihydroisolysergate II) (11). A mixture of 50 mg (0.175 mmol) of 9-carbomethoxy-7-methyl-4,5,5a,6,6a,7,8,9,10,10a-decahydroindolo[4,3-*fg*]quinoline and 200 mg of finely powdered MnO_2 (Attenburrow) in 4 ml of $CHCl_3$ was stirred at room temperature for 20 hr. At that time an analytical thin-layer plate (CMA-3 solvent system) showed the absence of starting material and the presence of a material which gave a blue spot on treatment with van Urk's reagent.

After filtering through Celite and washing the MnO_2 with hot $CHCl_3$, the combined solution was evaporated. The residual oil was chromatographed on activity III, neutral alumina. Elution with hexane removed nonpolar impurities; elution with C_6H_6 led to 10 mg of a clean oil which showed one spot on an analytical thin-layer plate; elution with 9:1 C_6H_6–$CHCl_3$ afforded 32 mg of slightly less pure material (total 42 mg, 85%). This amorphous compound cochromatographed in three systems (CMA-3, EA, and AE) with authentic methyl dihydroisolysergate II: ir (neat) 2.93 (indole NH), 5.80 μ (ester); nmr ($CDCl_3$) δ 1.13–3.83 (m, 9 H), 2.50 (s, 3 H, NCH_3), 3.57 (s, 3 H, CO_2CH_3), 6.34–7.22 (m, 4 H), 8.61 (br s, 1 H, NH); uv (MeOH) λ max (ε) 288 (4300), 277 (4900), 255 (5000), 217 (23,700); mass spectrum (low resolution) m/e (rel intensity) 285 (29), 284 (M^+, 100), 283 (10), 233 (13), 207 (9), 177 (11), 164 (26), 154 (18), 137 (9); mass spectrum (high resolution) calcd for $C_{17}H_{20}N_2O_2$, 284.1523; found, 284.1515.

DL-Dihydroisolysergic Acid II Hydrazide (12). DL-Methyl dihydroisolysergate II (11), 9 mg (0.031 mmol), was heated with anhydrous hydrazine, 200 mg (6.2 mmol), at 120–130° under N_2 for 25 min. The solvent was carefully evaporated *in vacuo;* the residue was washed with 3 × 0.2 ml of water and again dried *in vacuo* to give a homogenous (by tlc, CMA-1) residue which on slow recrystallization from MeOH–Et_2O gave **12**, mp 225–227°.

The reported melting point is 227–229°;[18] ir (neat) 3.0 (NH_2 and NH), 6.0 μ (–$CONHNH_2$); mass spectrum m/e (rel intensity) 285 (20), 284 (M^+, 100), 223 (43), 168 (24), 167 (40), 155 (26), 154 (60), 144 (24), 127 (30).

DL-Dihydroisolysergol II (13). DL-Methyl dihydroisolysergate II (11), 10 mg (0.034 mmol), in 1 ml of THF was slowly added to a stirring mixture of 40 mg of $LiAlH_4$ in 3 ml of THF and the mixture refluxed for 1 hr, cooled, and treated with aqueous Na_2SO_4. This mixture was then extracted with 3 × 30 ml of $CHCl_3$. The $CHCl_3$ layer was washed with dilute $NaHCO_3$ solution and then with H_2O, dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum to a syrup which on crystallization from MeOH gave 4 mg of **13**, mp 229–230°. The reported melting point is 226–229°.[18] An additional 5 mg of crude alcohol was obtained on evaporation of the mother liquor from the recrystallization: mass spectrum (low resolution) m/e (rel intensity) 257 (20), 256 (M^+, 100), 255 (6.4), 197 (14), 167 (20), 154 (33), 144 (37), 137 (14); mass spectrum (high resolution) calcd for $C_{16}H_{20}N_2O$, 256.1574; found, 256.1570.

Elymoclavine 17-Carbamate (48). Sodium cyanate, 130 mg (2.0 mmol), was added slowly to a solution of elymoclavine, 203 mg (0.80 mmol), in trifluoroacetic acid, 2 ml, and 1 ml of CH_2Cl_2. The mixture was stirred at room temperature, under N_2, for 8 hr, then evaporated under vacuum, and taken up into a mixture of H_2O–$CHCl_3$ (3:2). The $CHCl_3$ layer, which contained only elymoclavine, was separated and evaporated to dryness. The residue weighed 70 mg. The water layer was basified with 10% NH_4OH solution and extracted with 3 × 30 ml of $CHCl_3$. The $CHCl_3$ layer was dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness. Chromatography of the residue on a column of silica gel (20 g, activity 2–3, 70–325 mesh, EM Reagent) with Me_2CO–EtOAc–DMF (5:5:1) gave 50 mg of elymoclavine. Further elution gave 50 mg of product (53% based on recovered elymoclavine) after recrystallization of the residue from $CHCl_3$–petroleum ether, mp 107–115°, which was homogeneous on tlc (AED system): ir (KBr) 3.0 (NH, NH_2), 5.9 μ ($CONH_2$); nmr ($CDCl_3$) δ 2.50 (s, NCH_3), 4.6 (s, CH_2O), 8.0 (s, NH); uv (MeOH) λ max (ϵ) 293 (6640), 284 (8300), 222 (29,000); mass spectrum (low resolution) *m/e* (rel intensity) 298 (4), 297 (M^+, 20), 253 (20), 235 (30), 234 (100), 233 (37), 167 (31), 155 (34); mass spectrum (high resolution) calcd for $C_{17}H_{19}N_3O_2$, 297.1477; found, 297.1468. *Anal.* ($C_{17}H_{19}N_3O_2$) C, H, N.

Elymoclavine *O*-Benzoate (47). Elymoclavine, 100 mg (0.4 mmol), was dissolved in 10 ml of dry pyridine and treated with benzoyl chloride, 100 mg (0.8 mmol). The mixture was stirred at 50–60° for 1 hr under N_2.

The resulting mixture was taken up in 150 ml of $CHCl_3$, washed thoroughly with H_2O, dried over anhydrous Na_2SO_4, and evaporated to dryness *in vacuo*. The residue was then chromatographed on a 15-g silica gel column (MCB, 60–200 mesh); elution with C_6H_6–EtOAc (1:1) gave the desired product. Recrystallization from C_6H_6–hexane gave 30 mg of crystalline product (mp 90–92°). Further concentration of mother liquor yielded another 30 mg of product: total yield 60 mg (42%); ir (KBr) 5.85 μ (C=O); nmr ($CDCl_3$) δ 2.6 (s, 3 H, NCH_3), 4.8 (s, 2 H, CH_2OC=O), 6.5–7.8 (m, *ca.* 11 H); uv (MeOH) λ max (ϵ) 293 (11,600), 283 (13,000), 275 (15,600), 228 (90,900), 206 (64,900); mass spectrum (low resolution) 358 (M^+), 237 (53), 236 (100), 167 (21), 154 (42). *Anal.* ($C_{23}H_{22}O_2N_2 \cdot \frac{2}{3}C_6H_6$) C, H, N.

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