United States Patent
Kornfeld et al.

8-THIOMETHYLERGOLINES

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Field of Search .......................... 260/285.5

References Cited

UNITED STATES PATENTS


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ABSTRACT

8-Thiomethylergolines, prolactin inhibitors.

6 Claims, No Drawings
have a surprising variety of pharmaceutical activities. For example, lysergic and isolysergic acid are 8-
carboxy-6-methyl-\(\Delta^2\)-ergolines (9, 10-
didehydroergolines). The amides of lysergic acid, many of which have valuable and unique pharmacologic
properties, include the naturally occurring oxytocic alkaloids — ergocornine, ergokryptine, ergonovine, er-
gocristine, ergosine, ergotamine etc. — and synthetic oxytocics such as methergine as well as the synthetic
hallucinogen — lysergic acid diethylamide or LSD. The amides of 6-methyl-8-carboxyergoline, known gener-
cally as dihydroergot alkaloids, are oxytocic agents of lower potency and also lower toxicity than the ergot
alkaloids themselves. Ergotamine, a \(\Delta^2\)-ergoline, has been used in the treatment of migraine and recently,
both ergocornine and 2-bromo-\(\alpha\)-ergokryptine have been shown to be inhibitors of prolactin and of dime-
thylenzanthracene (DMBA)-induced tumors in rats, according to Nagasawa and Meites, Proc. Soc. Exptl.
3,752,888 and 3,752,814).

D-6-methyl-8-cyanomethyl ergoline was first prepared by Semonsky and co-workers, Coll. Czech. Chem.
Commun., 33, 577 (1968), and its use in preventing pregnancy in rats was published by the same group in
Nature, 221, 666 (1969). (See also U.S. Pat. No. 3,732,231). The compound was thought to interfere with
the secretion of hypophyseal leuteotropic hormone and the hypophysial gonadotropins. It was also sug-
gested that the compound inhibited the secretion of prolactin. (See Seda et al., Reprod. Fert., 24, 263
(1971) and Mante and Finn, id. 441)). Semonsky and co-workers, Coll. Czech. Chem. Comm., 36, 220
(1971), described the preparation of D-6-methyl-8-
erylonylacetic acid, a compound which is stated to have anti-fertility and anti-lactating effects on rats. The
effect of these compounds in neoplastic disease is unknown. Ergolines with a thiomethyl substituent or a de-
rivatizing thereof have not previously been prepared.

SUMMARY OF THE INVENTION

This invention provides 8-thiomethyl ergolines of the formula:

\[
\begin{align*}
  & \text{wherein} \\
  & R \text{ is } H, \text{CN}, \\
  & \begin{array}{l}
  O \\
  \| \\
  C - \text{alk.}
  \end{array} \\
  & \text{phenyl, or alk;} \\
  & R' \text{ is } H, \text{Cl}, \text{or } \text{Br;} \\
  & \text{alk is } C_1-C_3 \text{ alkyl; and} \\
  & R'' \text{ and } R''' \text{ when taken singly are } H; \text{ and, when} \\
  & \text{taken together with the carbon atoms to which they} \\
  & \text{are attached, form a double bond.}
\end{align*}
\]

The term alk in the above formula comprehending as it does \(C_1-C_3\) alkyl groups, includes the following radicals: methyl, ethyl, n-propyl and isopropyl. In the above formula, when \(R''\) and \(R'''\) are hydrogen, the compounds are generally denominated as D-6-alkyl-
8-thiomethyl (or mercaptemethyl) ergolines. When \(R''\) and \(R'''\) are taken together with the carbon atoms to
which they are attached to form a double bond, the res-
ulting compounds are known generically as D-6-alkyl-
8-thiomethyl or mercaptemethyl-9,10-
didehydroergolines. Compounds illustrative of the
scope of the above formula include the following:

D-2-chloro-6-methyl-8-propionythiomethyl ergoline
D-2-chloro-6-methyl-8-butyrylthiomethyl-9,10-
didehydroergoline
D-2-chloro-6-ethyl-8-thiomethyl-9,10-
didehydroergoline
D-2-chloro-6-methyl-8-ethylmercaptemethyl-9,10-
didehydroergoline
D-2-chloro-6-methyl-8-ethylmercaptemethyl-9,10-
didehydroergoline
D-2-chloro-6-methyl-8-propionylmercaptemethylergoline
D-2-chloro-6-methyl-8-propionylmercaptemethylergoline and the like.

The compounds of this invention in which \(R\) is other
than \(H\) are prepared by reacting via nucleophilic dis-
placement an ester of a D-6-alkyl-8-
hydroxymethyl ergoline or of a 9,10-didehydroergoline,
optionally substituted at C-2 with chlorine or bromine,
with salts of thiocyanic acid, thiophenol, a thiosalicylic
acid (alk-COSH) or an alkylthiol (alk-SH). Esters use-
ful as starting materials in the above synthetic pro-
cedure include the mesyl (methanesulfonyl), the p-
toluensulfonfyl (p-tosyl) and the like esters formed
with the hydroxy group of 8-hydroxymethyl-6-
mercaptemethyl ergoline. 8-hydroxymethyl-6-mercap-
9,10-
didehydroergoline or of a 2-halo derivative of either of
the above compounds. These mesyloxy and p-toslyloxy
derivatives are either known compounds or can be pre-
pared from the corresponding hydroxy derivatives by
processes available in the art. In carrying out reactions
with thiophenol or with an alkyl thiol, the sodium salt
of the mercaptan group is usually formed, using sodium
methylate or sodium hydride. Also, an alkali metal thi-
ocyantate is used. The nucleophilic displacement reac-
tion is carried out in an inert solvent such as dimethyl
formamide (DMF), dimethylsulfoxide (DMSO) or the
like. Ordinarily, the reaction is carried out at room
In each experiment the rats were killed by decapitation, and 150 μl aliquots of serum were assayed for prolactin. Each male rat received an intraperitoneal injection of 2.0 mg of reserpine in aqueous suspension 18 hours before administration of the ergoline derivative. The purpose of the reserpine was to keep prolactin levels uniformly elevated. The derivatives were dissolved in 10% ethanol at a concentration of 10 μg/ml and were injected intraperitoneally at a standard dose of 50 μg/kg. Each compound was administered to a group of 10 rats, and a control group of 10 intact males received an equivalent amount of 10 percent ethanol. 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 to calculate the level of significance, “p.”

The difference between the prolactin level of the treated rats and prolactin level of the control rats, divided by the prolactin level of the control rats gives the percent inhibition of prolactin secretion attributable to the compounds of this invention. The table which follows gives prolactin inhibition percentages for a series of compounds coming within the scope of Formula I above. In the table, column 1 gives the name of the compound; column 2, the dose level of the compound in the prolactin inhibition test; column 3, the percent prolactin inhibition; and column 4, the level of significance.

The invention is further illustrated by Examples 1–6 which follow.

### Table

<table>
<thead>
<tr>
<th>Name of Compound</th>
<th>Dose (μg)</th>
<th>% Prolactin Inhibition</th>
<th>&quot;p&quot; Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-6-methyl-8-phenylethaceto-methyl-9,10-dieethyl-ergoline</td>
<td>10</td>
<td>50</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>D-6-methyl-8-phenylethaceto-methyl-9,10-dieethyl-ergoline</td>
<td>10</td>
<td>52</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>D-6-methyl-8-acetylthiomethyl-ergoline</td>
<td>10</td>
<td>40</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>D-6-methyl-8-thioxacyanethyl-ergoline</td>
<td>10</td>
<td>66</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>D-6-methyl-8-thioxacyanethyl-ergoline</td>
<td>10</td>
<td>49</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>D-6-methyl-8-acetylthiomethyl-9,10-dieethyl-ergoline</td>
<td>10</td>
<td>41</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

### EXAMPLE 1

**Preparation of D-6-Methyl-8-Thioxacyanethyl-ergoline**

A reaction mixture was prepared from 2 g. of D-6-methyl-8- p-toluene sulfonylamidemethyl-ergoline, 2 g. of sodium thioacetate and 100 ml. of dimethylsulfoxide (DMSO). The mixture was heated in the range 100°–110°C, for 4.5 hours. The reaction mixture was then cooled and poured over an ice water mixture. 6-Methyl-8-thioacyanethyl-ergoline was insoluble in water and precipitated. The solid was collected by filtration and melted at about 181°–3°C, with decomposition after recrystallization from an ether-hexane solvent mixture.

**Analysis:** Calc: C, 68.65; H, 6.44; N, 14.13; S, 10.78; Found: C, 68.31; H, 6.66; N, 13.99; S, 10.48.
EXAMPLE 2
Preparation of D-6-methyl-8-phenylmercaptomethylglycine

A suspension of 10 g. of D-6-methyl-8-hydroxymercapto-4-lactic acid in 300 ml. of pyridine was prepared. To this suspension was added slowly a solution containing 0.6 ml. of methanesulfonyl chloride and 200 ml. of pyridine. The resulting mixture was stirred at room temperature under a nitrogen atmosphere for about one-half hour and then poured into 2.5 liters of saturated aqueous sodium bicarbonate. The alkaline aqueous layer was diluted to 6 liters with water, and the diluted layer allowed to stand at room temperature. D-6-methyl-8-mesoxylxymercapto-4-lactic acid formed in the above reaction slowly crystallized. The solution was chilled to about 0°C in order to cause more of the compound to precipitate. The solution was then filtered, and the filter cake recrystallized from ethanol. A further quantity of D-6-methyl-8-mesoxylxymercapto-4-lactic acid was obtained by extracting the filtrate with ethyl acetate, separating the ethyl acetate layer and removing the ethyl acetate from the ethyl acetate solution by evaporation in vacuo. Recrystallization of the D-6-methyl-8-mesoxylxymercapto-4-lactic acid prepared as above from ethanol yielded material melting at about 192°C with decomposition.

Analysis: Calc.: C, 61.05; H, 6.63; N, 8.38; S, 9.59; Found: C, 60.85; H, 6.46; N, 8.45; S, 9.30.

A solution of 2.5 ml. of thiophenol in 25 ml. of DMSO was prepared. 0.1 g. of sodium methyate were added. Next a solution of 700 mg. of D-6-methyl-8-mesoxylxymercapto-4-lactic acid in 50 ml. of DMSO was added in drop-wise fashion to the sodium thiophenolate solution. Two hours after the addition had been completed, the reaction mixture was stirred at room temperature under a nitrogen atmosphere for about 2 hours, and was then poured into a saturated aqueous tartaric acid solution. The acetic layer was extracted with chloroform. The chloroform extract was separated and discarded. The acid layer was then made basic with the excess of 14N ammonium hydroxide and the resulting alkaline layer was extracted with chloroform from the ethyl acetate layer. The chloroform extract was separated and dried. Evaporation of the chloroform left a residue which was dissolved in ethyl acetate. The ethyl acetate solution was thoroughly washed with water followed by a wash with saturated aqueous sodium chloride solution. The ethyl acetate layer was dried. Removal of the ethyl acetate by evaporation in vacuo yielded a residue comprising D-6-methyl-8-phenylmercaptomethylglycine which was recrystallized from ethanol and melted at 194-2°C with decomposition. The compound was then dissolved in chloroform and chromatographed over florisoril (25 g.).

The chromatogram was developed with a chloroform-methanol (19:1) solvent mixture. Fractions containing D-6-methyl-8-phenylmercaptomethylglycine as determined by thin layer chromatography were combined. Evaporation of the solvent from the combined fractions and recrystallization of the residue from ether hexane solvent mixture yielded D-6-methyl-8-phenylmercaptomethylglycine: MP = 195-6°C with decomposition.

Analysis: Calc.: C, 75.82; H, 6.95; N, 8.04; S, 9.20; Found: C, 75.85; H, 6.69; N, 7.97; S, 9.19.

Following the above procedure D-6-methyl-8-mesoxylxymercapto-4-lactic acid was reacted with thiophenol to yield D-6-methyl-8-phenylmercaptomethyl-9,10-didehydroergoline which melted at about 200-2°C with decomposition after recrystallization from methanol.

Analysis: Calc.: C, 76.26; H, 6.40; N, 8.08; S, 9.25; Found: C, 76.02; H, 6.42; N, 7.99; S, 9.02.

The corresponding maleate salt was prepared by dissolving the compound in tetrahydrofuran and adding an equivalent amount of maleic acid also in tetrahydrofuran. The maleate salt melted at 198°C after recrystallization from methanol.

Analysis: Calc.: C, 67.51; H, 5.67; N, 6.06; S, 6.93; Found: C, 67.29; H, 5.69; N, 5.79; S, 6.71.

EXAMPLE 3
Preparation of D-6-methyl-8-phenylmercaptomethylglycine.

Ten milliliters of dimethyl formamide (DMF) were cooled to about 0°C. 1 ml. of methanol was added followed by 1.0 g. of sodium hydroxide as a 50% suspension in mineral oil in portions. The resulting mixture was stirred for about 1 hour and then allowed to warm to room temperature. Then, following the procedure of Example 2, a solution of 0.1 g. of D-6-methyl-8-mesoxylxymercapto-4-lactic acid in 50 ml. of DMF was added in dropwise fashion to the sodium salt of methanol. The resulting product was isolated and purified by the procedure of Example 2 to yield D-6-methyl-8-phenylmercaptomethylglycine melting at about 153-5°C. Recrystallization of the compound thus obtained (omitting the chromatographic purification step of Example 2) from an ether-hexane solvent mixture yielded D-6-methyl-8-phenylmercaptomethylglycine.

Analysis: Calc.: C, 71.28; H, 7.74; N, 9.78; S, 11.19; Found: C, 71.08; H, 7.59; N, 9.83; S, 10.99.

Following the above procedure D-6-methyl-8-phenylmercaptomethyl-9,10-didehydroergoline was prepared from the corresponding 8-mesoxylxymercapto-4-lactic acid by reaction with methylmercapto. The compound melted at 181-3°C with decomposition after recrystallization from ether-octane solvent mixture.

Analysis: Calc.: C, 71.79; H, 7.09; N, 9.85; S, 11.27; Found: C, 72.01; H, 6.84; N, 9.62; S, 11.27.

The corresponding maleate salt was prepared by dissolving the compound in ether and adding an equivalent amount of maleic acid also in ether. Maleate salt melted at 159-60°C with decomposition.

Analysis: Calc.: C, 68.28; H, 6.07; N, 6.99; S, 8.01; Found: C, 69.92; H, 6.13; N, 6.78; S, 7.86.

EXAMPLE 4
Preparation of D-6-methyl-8-acetylmethylmercaptomethylglycine

Following the procedure of Example 2, thiocacetic acid (as the sodium salt) was reacted with D-6-methyl-8-mesoxylxymercapto-4-lactic acid in DMF solution to yield D-6-methyl-8-acetylmethylmercaptomethylglycine which was isolated and purified by the procedure of that example. Chromatography of the crude product over florisoril using chloroform containing 2 percent ethanol as eluent yielded purified D-6-methyl-8-acetylmethylmercaptomethylglycine MP = 153-5°C with decomposition.

Analysis: Calc.: C, 68.75; H, 7.05; N, 8.91; S, 10.20; Found: C, 68.70; H, 7.22; N, 8.62; S, 10.47.
Following the above procedure, D-6-methyl-8-
ethylmercaptomethyl-9,10-didehydroergoline was
prepared from the corresponding 8-meslyloxymethyl
compound. The purified compound thus prepared
was melted in the range 165°-170°C. After decompostion
Recrystallization from an ether-hexane solvent mixture.
Analysis: Calc.: C, 66.20; H, 6.45; N, 8.97; S, 10.26;
Found: C, 69.48; H, 6.71; N, 9.02; S, 10.56.

The corresponding maleate salt was prepared by dis-
olving the base in ether and adding an equivalent
amount of maleic acid in ether. The maleate salt melted
at 178°-180°C. with decomposition.

Analysis: Calc.: C, 61.67; H, 5.65; N, 6.54; S, 7.48;
Found: C, 61.95; H, 5.50; N, 6.84; S, 7.63.

D-2-chloro-6-methyl-8-
ethylmercaptomethylergoline was also prepared by
the above procedure. Recrystallization of the residue
remaining after combining fractions from chromato-
ography shown to contain D-2-chloro-6-methyl-8-
eethylmercaptomethylergoline by thin layer chromato-
ography, using a solvent mixture of ether and hexane
or recrystallization yielded purified material melting at
40°-50°C.

Analysis: Calc.: C, 61.97; H, 6.07; N, 8.03; S, 9.19;
Found: C, 61.75; H, 5.78; N, 7.73; S, 9.41; S, 10.32.

EXAMPLE 5
Preparation of D-6-methyl-8-mercaptopentylmethylergoline

A reaction mixture containing 1.0 g. of D-6-methyl-
ethylmercaptomethylergoline (from Example 4),
0.0 ml. of ethanand 100 ml. of 4N aqueous hydro-
chloric acid was refluxed under a nitrogen atmosphere
for five and one-half hours. The reaction mixture
was cooled and made basic with an excess of 14N ammo-
nium hydroxide. The aqueous alkaline layer was ex-
tracted with chloroform, and the chloroform yielded a
residue comprising D-6-methyl-8-
mercaptopentylmethylergoline formed in the above reaction.
The residue was chromatographed over 75 g. of florosil
using chloroform containing 5 percent ethanol as the
luant. D-6-methyl-8-mercaptopentylmethylergoline was
identified in chromatographic fractions by thin layer hromatography as a more polar, and therefore more
moving material than starting material. Fractions
containing D-6-methyl-8-
mercaptopentylmethylergoline were combined and recryst-
allized from ethanol. The compound thus purified melted at
255°-260°C. with decomposition.

Analysis: Calc.: C, 70.55; H, 7.40; N, 10.28; S, 11.77;
Found: C, 70.31; H, 7.65; N, 10.04; S, 12.00.

The above procedure was repeated except that meth-
limercaptan was used in place of thionene acid for re-
crystallization with D-2-chloro-6-methyl-8-
eslyoxymethylmethylergoline to form D-2-chloro-6-methyl-
ethylmercaptomethylergoline. Chromatography
yielded the residue obtained by combining chromatographic fractions shown to contain the desired material using an ether-hexane mixture for recrys-
tallization yielded purified D-2-chloro-6-methyl-8-
ethylmercaptomethylergoline melting at 194°-195°C.

Analysis: Calc.: C, 63.63; H, 6.60; N, 8.73; S, 9.99;
Found: C, 63.42; H, 6.55; N, 8.47; S, 10.12; S, 11.35.

EXAMPLE 6
Preparation of D-6-methyl-8-thiocyanomethyl-9,10-
didehydroergoline

A reaction mixture containing 2.16 g. of D-6-methyl-
8-meslyoxymethyl-9,10-didehydroergoline (prepared
from the corresponding 8-hydroxymethyl derivative by
the procedure of Example 2), and 2 g. of sodium thi-
cyanate in 100 ml. of DMSO was heated at a tempera-
ture in the range 50°-70°C, under a nitrogen atmo-
sphere for about one hour, and then for an additional
hour in the range 70°-100°C. The reaction mixture was
cooled, diluted with water, and the aqueous layer ex-
tracted with ethyl acetate. The ethyl acetate layer was
separated and filtered to remove an insoluble purple
decomposition product. The ethyl acetate layer was
washed with water and with saturated aqueous sodium
chloride, and was then dried. The solvent was removed
therefrom by evaporation in vacuo. The resulting resi-
due was chromatographed over 50 g. of florosil using an
eluant composed of chloroform containing 15 percent
ethanol. Fractions shown to contain D-6-methyl-8-
thiocyanomethyl-9,10-didehydroergoline (formed in
the above reaction) by thin layer chromatography were
combined, the solvent removed therefrom, and the
resulting residue rechromatographed over florosil using
chloroform as an eluant. Again, fractions shown to con-
tain D-6-methyl-8-thiocyanomethyl-9,10-
didehydroergoline by thin layer chromatography were
combined and the solvent removed therefrom by evap-
oration. Recrystallization of the resulting residue from
an ether-hexane solvent mixture yielded purified D-6-
mercapto-8-thiocyanomethyl-9,10-didehydroergoline
melting at about 190°-195°C. with decomposition.

Analysis: Calc.: C, 69.12; H, 5.80; N, 14.22; S, 10.85;
Found: C, 69.03; H, 5.85; N, 14.40; S, 11.32.

Being prolactin inhibitors, the compounds of this in-
vention are also potentially useful for suppressing the
growth of breast adenocarcinomas in female mammals.
For example, D-6-methyl-8-thiocyanomethylmethylergoline has demonstrated an ability to suppress the growth of
adenocarcinomas induced by administration of dime-
thylbenzanthraecene in female rats at a dose level of 1.2
mg/kg. The compound is administered to the female rat
suspended in corn oil, although it would also be practi-
cable to administer the compound in the form of a
pharmaceutical-acceptable acid addition salt in aque-
sous solution.

We claim:

1. A compound of the formula:

![Chemical structure](image)

wherein

R is H, CN.
phenyl, or alk;
R' is H, Cl, or Br;
alk is C₁–C₃ alkyl; and
R'' and R''' when taken singly are H; and, when
taken together with the carbon atoms to which they
are attached, form a double bond or a non-toxic,
pharmaceutically-acceptable acid addition salt
thereof.

2. A compound according to claim 1, said compound
being D-6-methyl-8-phenylmercaptomethyl-9,10-
didehydroergoline.

3. A compound according to claim 1, said compound
being D-6-methyl-8-methylmercaptomethyl-9,10-
didehydroergoline.

4. A compound according to claim 1, said compound
being D-6-methyl-8-thiomercaptomethylergoline.

5. A compound according to claim 1, said compound
being D-6-methyl-8-thiocyanomethylergoline.

6. A compound according to claim 1, said compound
being D-6-methyl-8-acetylimercaptomethylergoline.

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