Preparation and Biological Evaluation of 2-Azaergolines

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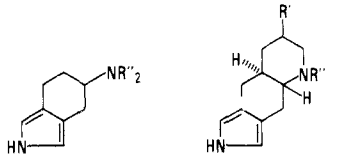
A general method for converting ergolines, **6**, to the corresponding 2-azaergolines, **7**, has been developed. The series **7** has surprisingly few of the pharmacological properties seen with the parent ergolines.

In our previous paper,[1] we reported the preparation and biological evaulation of bicyclic and tricyclic ergoline partial structures **1** and **2** and of several pyrazole analogues



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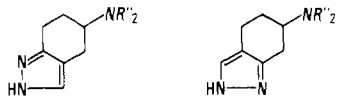
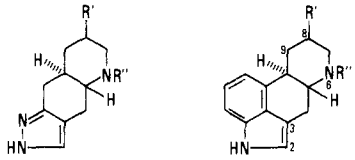


3 **4**

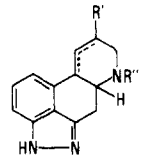
thereof (**3–5**). These new structures, especially the linear tricyclic tertiary amines **2** and **5**, exhibited much of the dopaminergic activity of the parent ergolines, **6**. We



5 **6**

concluded, therefore, that the benzene ring of the ergolines was *not* essential for such activity and that the rigid pyrroleethylamine moiety in **6** was the structural feature important for dopamine agonist activity.

Since the pyrazoles **3–5** were at least as active as the related pyrroles, **1** and **2**, it was of considerable interest to develop methods for the synthesis of tetracyclic pyrazole isosteres (**7**) of the ergolines (**6**). We assumed, based on



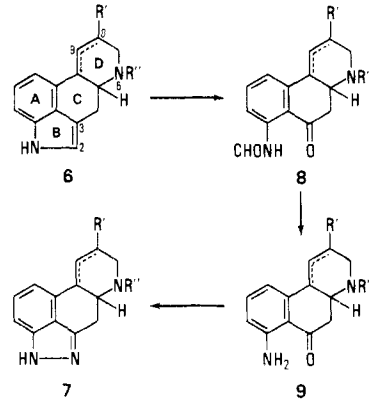
7

the activity of **3–5**, that **7** would retain the dopaminergic activity of **6** and would also show improved stability compared with **6**.

We report in this paper (a) a general method for converting ergolines (**6**) to 2-azaergolines (**7**) and (b) the surprisingly poor biological activity of the latter.

Chemistry. Our route to the 2-azaergolines is given in Scheme I. Oxidative cleavage of the 2,3-indole double bond was effected using periodate to yield the formamido ketones **8**.

Scheme I



6 **8** **7** **9**

It was gratifying to note that this oxidation could be carried out either with a saturated ring D or in the presence of a Δ^8 or Δ^9 double bond.

A previously reported cleavage of the 2,3 bond was by ozonization.[2] Hydrolysis of the formamido function in **8** led to the amino ketones **9**.[2] Diazotization of **9** and reduction of the resulting diazonium salts with sulfur dioxide afforded directly the 2-azaergolines **7**. The method was compatible with a variety of substituents at the ergoline 8 position (not R′ = CH_2SCH_3) and with the usual lower alkyl functions on the 6-nitrogen. Elymoclavine (**6**; Δ^8, R′ = CH_2OH, R″ = CH_3) was converted to 2-azaelymoclavine (**7**; Δ^8, R′ = CH_2OH, R″ = CH_3), and the periodate oxidation worked well also on ergonovine [**6**; Δ^9, R′ = $CONHCH(CH_3)CH_2OH$, R″ = CH_3]. The properties of the new compounds are summarized in Table I.

Pharmacology. Not surprisingly, perhaps, the intermediate formamido ketones **8** and amino ketones **9** showed little of pharmacological interest. Compounds **8d** and **9a**, for instance, were devoid of dopamine agonist activity in the prolactin inhibition test[3] at our usual screening dose of 50 μg/kg ip. Quite unexpectedly, however, the 2-azaergolines (**7**) which were evaluated were also devoid of in vivo dopaminergic activity. Compounds **7a,c,e**, for instance, neither inhibited prolactin[3] nor caused turning in the unilateral 6-hydroxydopamine nigrostriatal lesioned rat test.[4]

The 2-azaergolines were relatively nontoxic (LD_{50} > 400 mg/kg) as compared to the ergolines. In order to assess the series for some of the other activities seen with the ergolines, **7a** was tested in various isolated smooth muscle systems as follows: (1) *oxytocic* (isolated rat uterus); (2) *α-adrenergic antagonism* (isolated rat aorta), agonist = norepinephrine; (3) *α-adrenergic antagonism* (isolated guinea pig ileum field stimulated twitch), agonist = clonidine; (4) *anticholinergic* (isolated guinea pig ileum),

(1) N. J. Bach, E. C. Kornfeld, N. D. Jones, M. O. Chaney, D. E. Dorman, J. W. Paschal, J. A. Clemens, and E. B. Smalstig, *J. Med. Chem.*, **23**, preceding paper in this issue (1980).

(2) M. Bellati, G. Casnati, G. Palla, and A. Minghetti, *Tetrahedron*, **33**, 1821 (1977).

(3) A. M. Crider, J. M. Robinson, H. G. Floss, J. M. Cassady, and J. A. Clemens, *J. Med. Chem.*, **20**, 1473 (1977).

(4) U. Ungerstedt, *Acta Physiol. Scand., Suppl.*, **no. 367**, 69 (1971).

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Table I. Properties of 2-Azaergolines and Intermediates

no.	R′	R″	Δ	base formula	salt	solvent	mp, °C	yield, %	anal.
8a	CH_2OMes	Me		$C_{17}H_{22}N_2O_5S$		Et_2O	145-146	32	C, H, N, S
8b	$COOCH_3$	Me	9	$C_{17}H_{18}N_2O_4$		MeOH	*a*	9	*e*
8c	CH_2OH	Me	8	$C_{16}H_{18}N_2O_3$		Et_2O-MeOH	142-144[a]	50	C, H, N
8d	CH_2OCH_3	Pr		$C_{19}H_{26}N_2O_3$	maleate	MeOH-Et_2O	172-173	51	C, H, N
8e	$CONHCH(CH_3)CH_2OH$	Me	9	$C_{19}H_{23}N_3O_4$		MeOH	>190[a]	29	C, H, N
9a	CH_2OCH_3	Me		$C_{16}H_{22}N_2O_2$		Et_2O	140-141	57[b]	C, H, N
9b	CH_2OMes	Me		$C_{16}H_{22}N_2O_4S$		Et_2O	139-140	87	C, H, N, S
7a	CH_2OCH_3	Me		$C_{16}H_{21}N_3O$	CH_3SO_3H	MeOH-Et_2O	226-230	63[c]	C, H, N, S
7b	CH_2OMes	Me		$C_{16}H_{21}N_3O_3S$		MeOH	183-185[a]	92	C, H, N, S
7c	CH_2SCH_3	Me		$C_{16}H_{21}N_3S$	CH_3SO_3H	MeOH	~290[a]	67[c]	C, H, N, S
7d	CH_2OH	Me	8	$C_{15}H_{17}N_3O$	HCl	EtOH	280[a]	37[d]	C, H, N, Cl
7e	CH_2OCH_3	Pr		$C_{18}H_{25}N_3O$	CH_3SO_3H	MeOH-Et_2O	257-259[a]	87	C, H, N, S

[a] Decomposition. [b] From 8a. [c] From 7b. [d] From 8c. [e] MS.

Table II

	total jumps	mean jumps per mouse ± SE	% inhibn of jumping
saline	9821	818 ± 153	
7c (3 mg/kg)	5113	426 ± 117	47.9
saline	12099	1008 ± 232	
7c (10 mg/kg)	6096	508 ± 191	49.6

agonist = acetylcholine; (5) *antiserotonin* (isolated rat stomach strip), agonist = serotonin. Concentrations up to 10 μg/mL of compound **7a** showed no muscle response or blocking effect on *any* of these preparations.

From these results, compound **7a** does not possess oxytocic, α-adrenergic antagonism, anticholinergic, or antiserotonin activity on isolated smooth muscle.

Broad screening of compound **7c** in whole animal tests showed only weak muscle-relaxant properties[5] and moderate hypotensive activity.[6] Of more interest, however, was the evaluation of the series for potential neuroleptic activity.

Treatment of mice with a combination of *d*-amphetamine and L-Dopa produces a syndrome characterized by explosive stereotyped jumping. This response is blocked specifically by neuroleptic agents, and, therefore, this test can be used as a screen for neuroleptic[7] activity. Compound **7c** was tested in this manner and found to inhibit the jumping, indicative of possible neuroleptic activity. It was tested at 3 and 10 mg/kg sc using 12 treated and 12 control mice at each dose. The experimental protocol was as follows:

(1) control mice

d-amphetamine (3 mg/kg, ip) $\xrightarrow{15\text{ min}}$
saline (sc) + L-Dopa (300 mg/kg, ip) $\xrightarrow{10\text{ min}}$
test (count jumps for 30 min)

(2) treated mice

d-amphetamine (3 mg/kg, ip) $\xrightarrow{15\text{ min}}$
drug (3 or 10 mg/kg sc) +
L-Dopa (300 mg/kg, ip) $\xrightarrow{10\text{ min}}$
test (count jumps for 30 min)

The results are shown in Table II.

A known neuroleptic, haloperidol, in this same test gave a 77% inhibition of jumping at 0.3 mg/kg and an 82% inhibition at 1 mg/kg.

Thus, the 2-azaergolines (**7**) show none of the classical activities of the ergolines (**6**). Why this is so is not immediately obvious, in view of the dopaminergic activity[1] of the pyrazoles **3–5**. One difference between the azaergolines and **3–5** is basicity. The azaergolines are indazoles and are, therefore, *weaker* bases than **3–5**. They form *mono* salts, while **3–5** form *di* salts. Whether this difference has bearing on the biological properties is unknown. Factors such as metabolism and distribution to the target organs could also influence activity. Further work with the 2-azaergolines is in progress.

Experimental Section

Elemental analyses are indicated only by symbols of the elements and are within 0.4% of the theoretical values. All new compounds were monitored by measurement of IR, UV, and NMR spectra. Mass spectra were determined also for most structures and were consistent with other spectral measurements. Melting points were determined on a Mel-Temp apparatus and are corrected. All reactions were followed by TLC carried out on Merck F254 silica gel plates. The following are illustrative procedures.

[4a*R*-(2β,4aβ,10bα)]-*N*-[1,2,3,4,4a,5,6,10b-Octahydro-4-methyl-2-[[(methylsulfonyl)oxy]methyl]-6-oxobenzo[*f*]-quinolin-7-yl]formamide (8a). A solution of 1.0 g (3 mmol) of 8β-[(mesyloxy)methyl]-6-methylergoline[8] and 0.2 mL (3.1 mmol) of CH_3SO_3H in 50 mL of MeOH was added to a solution of 1.3 g (6 mmol) of $NaIO_4$ in 100 mL of H_2O. The mixture was stirred at 25 °C for 2.75 h and diluted with excess aqueous $NaHCO_3$, and the product was extracted with $CHCl_3$. The extract was washed with brine and dried, and the solvent was distilled. The crude product was purified by chromatography twice on Florisil (35 g) using $CHCl_3$/1–5% MeOH as eluant: yield 360 mg (32%); mp 145–146 °C. Anal. ($C_{17}H_{22}N_2O_5S$) C, H, N, S.

[4a*R*-(2β,4aβ,10bα)]-7-Amino-1,3,4,4a,5,10b-hexahydro-4-methyl-2-[[(methylsulfonyl)oxy]methyl]benzo[*f*]quinolin-6(2*H*)-one (9b). A mixture of **8a** (815 mg) in 50 mL of MeOH and 50 mL of 10% NaOH was stirred at 25 °C for 1.75 h. It was diluted with H_2O, and the product was extracted with $CHCl_3$. The extracts were washed with brine, dried, and concentrated: yield 650 mg (87%); mp 139–140 °C from Et_2O. Anal. ($C_{16}H_{22}N_2O_4S$) C, H, N, S.

8β-[(Mesyloxy)methyl]-6-methyl-2-azaergoline (7b). The amino ketone **9b**, 3.55 g (10.5 mmol), was dissolved in 75 mL of 6 N HCl, and the solution was cooled in ice. A solution of 760 mg (11 mmol) of $NaNO_2$ in 25 mL of H_2O was added dropwise with continued cooling, and stirring was maintained for 15 min. The resulting solution was then added in portions to 200 mL of H_2O presaturated with SO_2 at 0–5 °C. Sulfur dioxide was bubbled in during the addition and for an additional 20 min. The mixture was allowed to stand at 25 °C for 16 h. It was then poured onto ice and made basic with 10% NaOH. The product was extracted with $CHCl_3$–*i*-PrOH. The extract was washed with brine, dried, and concentrated: yield 3.25 g (92%); mp 183–185 °C from

(5) S. Irwin, *Psychopharmacologia*, 13, 222–257 (1968).
(6) A. Nagaoka, K. Kikuchi, and Y. Aramaki, *Jpn. J. Pharmacol.*, 19, 401–408 (1969).
(7) H. Lal, *Neuropharmacology*, 15, 669 (1976).
(8) E. C. Kornfeld and N. J. Bach, U.S. Patent 3 901 894 (Aug 26, 1975).

MeOH. Anal. ($C_{16}H_{21}N_3O_3S$) C, H, N, S.

6-Methyl-8β-[(methylthio)methyl]-2-azaergoline Methanesulfonic Acid Salt (7c) from 7b. A solution of 7.5 g (0.15 mol) CH_3SH in 250 mL of DMF was cooled in ice. NaH, 7.2 g (0.15 mol; 50% in mineral oil), was added in portions with stirring. To the resulting mixture was then added a solution of 4.2 g (12 mmol) of **7b** in 75 mL of DMF. The cooling bath was removed, and the mixture was stirred at 25 °C for 2 h. Water was added, and the product was extracted with EtOAc. The extract was washed with H_2O and brine, dried, and concentrated. The crude product, 3.16 g (90%), was purified by chromatography on Florisil using $CHCl_3$ with 1–5% MeOH as eluant: yield 2.55 g; mp 223–226 °C. The pure base was suspended in 60 mL of boiling MeOH. To the suspension was added a solution of 0.6 mL of CH_3SO_3H in 5 mL of MeOH. The hot solution was filtered and cooled: yield 3.07 g (67%); mp 290 °C dec. Anal. ($C_{17}H_{25}N_3O_3S$) C, H, N, S.

[4aR-(2β,4aβ,10bα)]-7-Amino-1,3,4,4a,5,10b-hexahydro-2-(methoxymethyl)-4-methylbenzo[f]quinolin-6-(2H)-one (9a) from 8a. A solution of 730 mg (1.93 mmol) of **8a** in 60 mL of MeOH and 60 mL of 10% NaOH was heated under reflux under N_2 for 1 h. It was diluted with H_2O, and the product was extracted with $CHCl_3$–*i*-PrOH. The extract was washed with brine, dried, and concentrated. The crude product was purified by chromatography on 30 g of Florisil using $CHCl_3$–2% MeOH as eluant: yield 340 mg (51%); mp 140–141 °C from Et_2O. Anal. ($C_{16}H_{22}N_2O_2$) C, H, N. These conditions brought about both hydrolysis of the formyl group and displacement of the mesylate ester. When the reaction was conducted at 25 °C (1.75 h), only the amide was hydrolyzed to give **9b** in 87% yield.

8β-(Methoxymethyl)-6-methyl-2-azaergoline Methanesulfonic Acid Salt (7a) from 7b. A solution of 2.4 mmol of **7b** in 100 mL of MeOH and 5 mL of 40% trimethylbenzylammonium methoxide in MeOH was heated under reflux for 48.5 h. The solution was then cooled and diluted with H_2O, and the product was extracted with $CHCl_3$. The extract was washed with brine, dried (Na_2SO_4), and concentated. The crude product was purified by chromatography on 300 g of Florisil using $CHCl_3$–2% MeOH as eluant: yield 550 mg; mp 195–196 °C. The mesylate salt was prepared in MeOH–Et_2O: yield 670 mg (63%); mp 226–230 °C. Anal. ($C_{17}H_{25}N_3O_4S$) C, H, N, S.

[4aR-(2β,4aβ,10bα)]-N-[1,2,3,4,4a,5,6,10b-Octahydro-2-(methoxymethyl)-6-oxo-4-propylbenzo[f]quinolin-7-yl]-formamide Maleate Salt (8d). A solution of 1.9 g (5 mmol) of 8β-(methoxymethyl)-6-propylergoline methanesulfonic acid salt[9] in 50 mL of H_2O and 50 mL of MeOH was added to a solution of 2.14 g (10 mmol) of $NaIO_4$ in 200 mL of H_2O. The resulting mixture was stirred for 2.25 h. Excess aqueous $NaHCO_3$ was then added, and the product was extracted with $CHCl_3$. The extract was washed with brine and dried (Na_2SO_4), and the solvent was distilled. The product was purified by chromatography on 35 g of Florisil using $CHCl_3$/1–2% MeOH as eluant. The maleate salt was prepared in MeOH–Et_2O: yield 1.1 g (51%); mp 172–173 °C. Anal. ($C_{23}H_{30}N_2O_7$) C, H, N.

Isolated Smooth Muscle Testing of 7a. All tissues were removed from animals after killing them by a blow on the head. Tissues were placed in physiological salt solution (Krebs, pH 7.4) at room temperature and then dissected free of fat and connective tissue. Whole tissues, or strips prepared from them, were suspended in 10-mL organ baths containing Krebs solution maintained at 37.5 °C and aerated with a 5% carbon dioxide–95% oxygen mixture. The tissues were attached to Grass FT-03 isometric transducers connected to a Grass Model 7 polygraph recorder and allowed to equilibrate for 1–2 h before drug addition. Compound **7a** was dissolved in H_2O and added to the 10-mL tissue bath in a volume of 0.1 mL.

Acknowledgment. The authors thank G. M. Maciak and associates for the microanalyses. We are indebted also to Dr. D. T. Wong, F. B. Bymaster, Dr. R. R. Ruffolo, J. E. Waddell, and R. W. Kattau for pharmacological studies.

(9) E. C. Kornfeld and N. J. Bach, U.S. Patent 4 166 182 (Aug 28, 1979).

Tricyclics with Analgesic and Antidepressant Activity. 1. [[(Alkylamino)ethyl]thio]dibenz[b,f]oxepins and 10,11-Dihydro Derivatives

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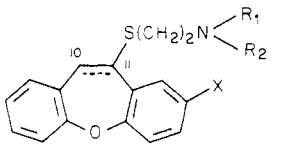
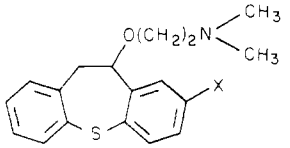
Received October 9, 1979

A series of [[(alkylamino)ethyl]thio]dibenz[b,f]oxepins (I) and their 10,11-dihydro derivatives (II) was synthesized and subjected to broad analgesic/CNS screening. Several analogues of both types, carrying small N-substituents and frequently a nuclear fluorine function, have been found to possess potent analgesic activity in the phenylquinone writhing assay (PQW) and the tail-flick test in mice. Many of these compounds also exhibited significant activity in antagonizing tetrabenazine-induced ptosis, as exemplified by **10b**, **16b**, and **18b**. Results from the mouse jumping test indicated low physical dependence potential for these compounds, and further evidence for a nonnarcotic profile was provided by the absence of significant naloxone interactions with the tail-flick response. Compound **10b** did not produce tolerance in mice following chronic administration in the PQW screen.

A previous publication[3] from this laboratory has described the synthesis and pharmacology of a series of spiro[dibenz[b,f]oxepinpiperidine] derivatives, some of which displayed potent oral analgesic activity by inhibiting phenylquinone-induced writhing in mice. As part of a continued program aimed at discovering tricyclic analgesics with a nonclassic profile, or pain-relieving agents of multiple clinical utility, we have synthesized a series of [[(alkylamino)ethyl]thio]dibenz[b,f]oxepins (I) and their



I, 10,11-dehydro
II, 10,11-dihydro



III, X = H
IV, X = Cl

10,11-dihydro derivatives (II) for broad analgesic/CNS

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(3) H. H. Ong, J. A. Profitt, T. C. Spaulding, and J. C. Wilker, *J. Med. Chem.*, **22**, 834 (1979).

0022-2623/80/1823-0494$01.00/0