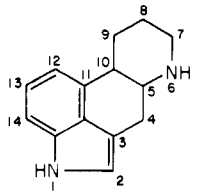
Synthesis and Biological Activity of 8-Arylergolines

Nicholas J. Bach, Edmund C. Kornfeld,*[1] and Douglas E. Dorman

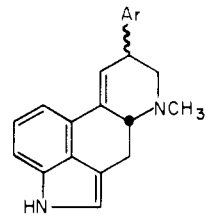
The Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46206. *Received March 2, 1977*

9,10-Didehydro-6-methyl-8β- and 8α-arylergolines **2**, in which the carboxyl group of lysergic acid and isolysergic acid is replaced by various aryl groups, were prepared in two steps by alkylation of aromatic substrates with the tetracyclic allylic alcohol **3**, followed by aromatization with MnO_2. The new ergolines **2** have modest prolactin-inhibiting and rat antimuricidal activities and possess significant α-blocking and antiserotonin properties.

Lysergic acid derivatives, which contain the tetracyclic ergoline[2] nucleus **1**, show a remarkable variety of pharmacological activities[3] depending on the nature and on the configuration of substituents at the 8 position. Ergonovine [1, 6-CH_3-8β-$CONHCH(CH_3)CH_2OH$-Δ^9] has profound uterine-contracting properties, while the well-known lysergic acid diethylamide (LSD) (1, 6-CH_3-8β-$CONEt_2$-Δ^9) is the most potent hallucinogen yet reported. When the side chain at 8 is peptide in nature, as in ergotamine or Hydergine (dihydroergocornine, dihydroergocristine, and dihydroergocryptine methanesulfonates), useful antimigraine and hypotensive activities are observed, respectively. More recently numerous ergolines with either simple or complex side chains at 8 have shown potent dopamine agonist properties and have been useful as prolactin inhibitors and as anti-Parkinsonian drugs.[4] Often when the substituent at 8 is α rather than β in configuration, much diminished biological activity is observed.[3]



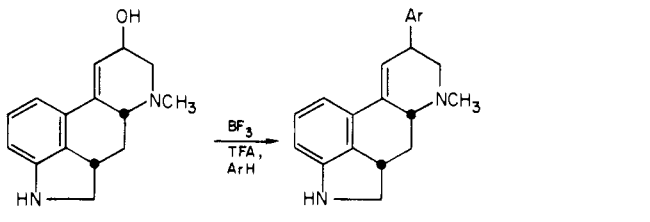
1



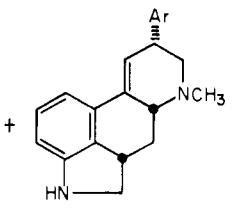
2

With this background we have been interested in the synthesis of ergolines with an *aryl* substituent at 8 as in **2**. Such a structure is intriguing because it combines in a single molecule *two* rigid arylethylamine moieties together with *one* tryptamine component. One might expect, therefore, that such a molecule would interact with at least some biogenic amine receptors.

Chemistry. Since it seemed impractical to synthesize 8-arylergolines (**2**) from natural lysergic acid (**1**, 6-methyl-8β-carboxy-Δ^9), we employed the tetracyclic allylic alcohol **3** (available in nine steps from 3-indolepropionic acid). This compound had been a key intermediate in our total synthesis of lysergic acid.[5] It previously had been shown[5] that **3** readily underwent carbonium ion reactions under acidic conditions (epimerization to the 8α-alcohol as well as the Ritter reaction). With this in mind we found that **3** reacted readily with aromatic substrates in trifluoroacetic acid using boron trifluoride etherate as catalyst to afford mixtures of 8β- and 8α-aryl-9,10-didehydro-2,3-dihydroergolines **4** and **5**. Anisole, methylenedioxybenzene, toluene, benzene, and phenol were alkylated smoothly, and even chlorobenzene gave a small yield of alkylation product. Table I summarizes these experiments.

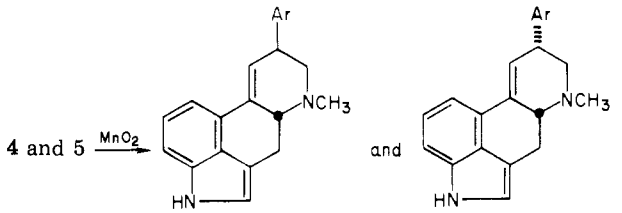


3 **4**



5

Dehydrogenation of the 8-aryl-2,3-dihydroergolines **4** and **5** to the corresponding indoles **6** and **7** was effected using activated MnO_2. See Table II.



6 **7**

The assignment of the α or β configuration of the aryl substituent at 8 was carried out using a rigorous 100- and 220-MHz NMR study of one pair (**25** and **23**) in which the aryl group in **6** and **7** was phenyl. In Table III, the ^1H NMR data for **25** and **23** are compared to that published[6] for the *N,N*-dimethylamides of lysergic acid (DMALA) [1, 6-CH_3-8β-$CON(CH_3)_2$-Δ^9] and isolysergic acid (DMAILA) [1, 6-CH_3-8α-$CON(CH_3)_2$-Δ^9]. It is evident that the spectra of **25** and DMALA are *very* similar, particularly in the measurable coupling constants. On the basis of these similarities we believe that the 8-phenyl in **25** is β and that **25** and DMALA have very similar conformations. By elimination **23** is the 8α-phenyl derivative. The differences in the ^1H NMR spectra of **23** and DMAILA suggest that these two compounds *do not* exist in similar conformations.

Assignment of configurations in other 8α- and 8β-aryl pairs in Tables I and II was made by a study of TLC behavior. 9,10-Didehydro-6-methyl-8β-phenylergoline (**25**) was found to move more slowly on TLC than its 8α-phenyl isomer **23**. The other compounds were assigned by analogy with the phenyl pair.

Pharmacology. In the rat radioimmunoassay for prolactin inhibition,[7] compounds **24**, **26**, and **19** at 1 mg per rat ip showed drops in serum prolactin of 88, 71, and 81%, respectively. Compound **21** was inactive at the same dose level. In this test ergocornine inhibits prolactin significantly (60–90%) at a dose of 10 μg.

In the rat antimuricidal test[8] (which may suggest antidepressant activity), compounds **26**, **21**, and **19** at doses of 5, 10, and 10 mg/kg ip, respectively, were active; while **24** was inactive at 20 mg/kg. In this test *dl*-decarboxylysergic[9] (with no substituent at the 8 position) is active at 0.625 mg/kg.

In isolated smooth muscle testing none of the compounds showed significant oxytocic activity on rat uterus

Table I. Reaction of Allylic Alcohol 3 with Aromatics (ArH)

Compd	Ar in 4 and 5	Formula	Mp, °C, solvent	Yield, %	Analyses
8	α-4-$C_6H_4OCH_3$	$C_{22}H_{24}N_2O$	193-197 dec, MeOH	5	*a*
9	β-4-$C_6H_4OCH_3$	$C_{22}H_{24}N_2O$	195-197 dec, Et_2O	63	C, H, N
10	α-3,4-$C_6H_3O_2CH_2$	$C_{22}H_{22}N_2O_2$	163-165 dec, MeOH	4	*a*
11	β-3,4-$C_6H_3O_2CH_2$	$C_{22}H_{22}N_2O_2$	157-158 dec, EtOAc	46	C, H, N
12	α-4-$C_6H_4CH_3$	$C_{22}H_{24}N_2$	133-135 dec, MeOH	16	C, H, N
13	β-4-$C_6H_4CH_3$	$C_{22}H_{24}N_2$	144-146 dec, Et_2O	30	C, H, N
14	α-C_6H_5	$C_{21}H_{22}N_2$	152-153, MeOH	34	C, H, N
15	β-C_6H_5	$C_{21}H_{22}N_2$	211-213 dec, MeOH-Et_2O	31	*b*
16	4-C_6H_4OH	$C_{21}H_{22}N_2O$	>250, MeOH	59	C, H, N
17	4-C_6H_4Cl	$C_{21}H_{21}ClN_2$	Amorphous	2	C, H, Cl, N

[a] Compound gave the correct molecular ion in the mass spectrum. [b] Compound was converted to the 2,3-didehydro derivative maleic acid salt for analysis.

Table II. MnO_2 Dehydrogenation of 4 and 5 to 6 and 7

Compd	Ar in 6 and 7	Formula	Mp, °C, solvent	Yield, %	Analyses
18	β-4-$C_6H_4OCH_3$	$C_{22}H_{22}N_2O$	235-237, Et_2O	52	C, H, N
19	Maleate salt	$C_{26}H_{26}N_2O_5$	206-208, MeOH-Et_2O	92	C, H, N
20	β-3,4-$C_6H_3O_2CH_2$	$C_{22}H_{20}N_2O_2$	260 dec, MeOH-$CHCl_3$	22	*a*
21	Maleate salt	$C_{26}H_{24}N_2O_6$	Dec >190, Et_2O	90	C, H, N
22	β-4-$C_6H_4CH_3$	$C_{22}H_{22}N_2$	228-230, Et_2O	39	C, H, N
23	α-C_6H_5	$C_{21}H_{20}N_2$	143-144, MeOH	53	*a*
24	Maleate salt	$C_{25}H_{24}N_2O_4$	184-186, MeOH-Et_2O	89	C, H, N
25	β-C_6H_5	$C_{21}H_{20}N_2$	Dec >200	50	*a*
26	Maleate salt	$C_{25}H_{24}N_2O_4$	203-204 dec, MeOH-Et_2O	88	C, H, N

[a] Free base was converted to the following maleate salt for analysis.

Table III. ^1H NMR Data for 8-Substituted Ergolines, δ (*J*)

	2	4α	4β	5	7α	7β	8	9
DMA-LA	6.86 (1.6)	2.68 (14.8, 11.5, 1.6)	3.54 (14.8, 5.5)	3.20 (11.5, 5.5, 3.8, 1)	3.08 (11.3, 5.3, 1)	2.89 (11.3, 10.5)	3.98 (10.5, 5.3, 3.8, small)	6.36 (1, 1, small)
25	6.91 (1.5)	2.76 (14.5, 11, 1.5)	3.57 (14.5, 5.5)	~3.23 (multiplet)	3.16 (11, 5.5, ~1)	2.48 (11, 10.5)	3.97 (multiplet)	6.57 (~2, ~1, ~1)
DMAI-LA	6.79 (1.5)	2.82 (14.1, 11.5, 1.5)	3.25 (14.1, 5.5)	3.42 (11.5, 5.5, 2.5, ~1)	3.18 (12, 7.5, <1)	2.86 (12, 5.2, ~1)	3.78 (7.5, 5.2, 2.5, ~2)	6.30 (~2, ~1, ~1)
23	6.87 (~1)	2.83 (14.5, 11, ~1)	3.45 (14.5, 5)	3.31 (11, 5, 2, 2)	2.92 (multiplet)		3.65 (4.5, 2, ~1.5)	6.50 (4.5, 2)

up to 10 μg/mL. In the rat aorta strip the α-blocking activity of **24** and **19** was about one-tenth that of phentolamine, while that of **26** and **21** was equal to phentolamine (two- to threefold shift in norepinephrine dose response curve to the right at 10 ng/mL). Antiserotonin activity on the rat stomach fundus strip was exhibited by compounds **24**, **26**, **21**, and **19** to the extent of 10, 50, 50, and 100%, respectively, of that of methysergide (fivefold shift of the 5-HT dose–response curve to the right at 1 ng/mL).

Thus, in summary, the 8-arylergolines show only moderate prolactin inhibition and antimuricidal activity, while they possess significant α-blocking and antiserotonin effects.

The introduction of an aryl function at the 8 position (and hence a new arylethylamine moiety) adds yet another parameter to ergoline structure–activity relationships.

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. TLC was carried out on Merck F254 silica gel plates. NMR measurements were made in $CDCl_3$.

General Procedure. Alkylation of Aromatic Substrates with the Allylic Alcohol 3. 9,10-Didehydro-2,3-dihydro-6-methyl-8α-phenylergoline (14) and 9,10-Didehydro-2,3-dihydro-6-methyl-8β-phenylergoline (15). A solution of 1.13 g of **3** in 10 mL of benzene, 25 mL of trifluoroacetic acid, and 2 mL of boron trifluoride etherate was stirred for 0.5 h and then heated under reflux with stirring for 2 h. The reaction mixture was poured onto ice and made basic with ammonium hydroxide. The products were extracted with $CHCl_3$ and were purified by chromatography of Florisil using $CHCl_3$–MeOH mixtures. The 8α-phenyl isomer **14** was eluted first: 0.480 g (34%); mp 152–153 °C from MeOH. The 8β-isomer **15** followed: 0.445 g (31%); mp 211–213 °C dec from MeOH–Et_2O. Alkylations of other substrates were conducted in a similar fashion as summarized in Table I.

General Procedure. MnO_2 Oxidation of 2,3-Dihydroergolines to the Corresponding Ergolines. 9,10-Didehydro-6-methyl-8α-phenylergoline (23). A solution of 1.0 g of **14** in 200 mL of $CHCl_3$ was stirred with 5 g of activated MnO_2[10] for 40 min. The product **23** was purified by chromatography on Florisil using $CHCl_3$–MeOH: 0.53 g (53%); mp 143–144 °C from MeOH. The maleate salt **24** was prepared in MeOH using a 10% excess of maleic acid: mp 184–186 °C from MeOH–Et_2O. Other dehydrogenations summarized in Table II were carried out in a similar way.

Acknowledgment. The authors wish to thank Dr. J. A. Clemens, Mr. E. B. Smalstig, Dr. J. W. Aiken, Mr. J. E. Waddell, Dr. P. Stark, and associates for the biological studies; Mr. G. M. Maciak and associates for the micro-

analyses; and Mr. T. K. Elzey for the NMR measurements.

References and Notes

(1) Dedicated to Professor R. B. Woodward on the occasion of his 60th birthday.
(2) W. A. Jacobs and R. G. Gould, Jr., *J. Biol. Chem.*, **120**, 141 (1937).
(3) A. Hofman, "Die Mutterkorn Alkaloide", F. Enke, Ed., Georg Thieme Verlag, Stuttgart, 1964, pp 176–197.
(4) H. G. Floss, J. M. Cassady, and J. E. Robbers, *J. Pharm. Sci.*, **62**, 699 (1973); J. M. Cassady, G. S. Li, E. B. Spitzner, H. G. Floss, and J. A. Clemens, *J. Med. Chem.*, **17**, 300 (1974); H. G. Floss, *Tetrahedron*, **32**, 882 (1976); L. Lemberger, R. Crabtree, J. A. Clemens, R. W. Dyke, and R. T. Woodburn, *J. Clin. Endocrinol. Metab.*, **39**, 579 (1974); A. N. Lieberman, M. Kupersmith, E. Estey, and M. Goldstein, *Lancet*, **2** (7984), 515 (1976).
(5) E. C. Kornfeld, E. J. Fornefeld, G. B. Kline, M. J. Mann, D. E. Morrison, R. G. Jones, and R. B. Woodward, *J. Am. Chem. Soc.*, **78**, 3087 (1956).
(6) K. Bailey and A. A. Grey, *Can. J. Chem.*, **50**, 3876 (1972).
(7) J. Meites and J. A. Clemens, *Vitam. Horm. (N.Y.)*, **30**, 165–221 (1972).
(8) Z. P. Horovitz, J. P. Piala, J. C. Burke, and R. C. Leaf, *Int. J. Neuropharmacol.*, **5**, 405 (1966).
(9) N. J. Bach, D. A. Hall, and E. C. Kornfeld, *J. Med. Chem.*, **17**, 312 (1974).
(10) J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen, and T. Walker, *J. Chem. Soc.*, 1094 (1952).

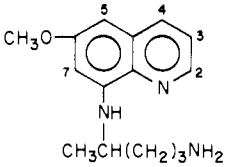
Modifications of Primaquine as Antimalarials. 1. 5-Phenoxy Derivatives of Primaquine

Eugene H. Chen, Andrew J. Saggiomo, Keiichi Tanabe, Basant L. Verma, and Edward A. Nodiff*

Germantown Laboratories, Inc., Affiliated with The Franklin Institute, Philadelphia, Pennsylvania 19144.
Received February 10, 1977

Various 5-phenoxy derivatives of primaquine have been prepared which are more active and less toxic than the parent compound in murine and monkey antimalarial screens. An improved method for the phthalimido alkylation of amines is described.

Primaquine, a derivative of 8-aminoquinoline, is an important radical curative and causal prophylactic anti-

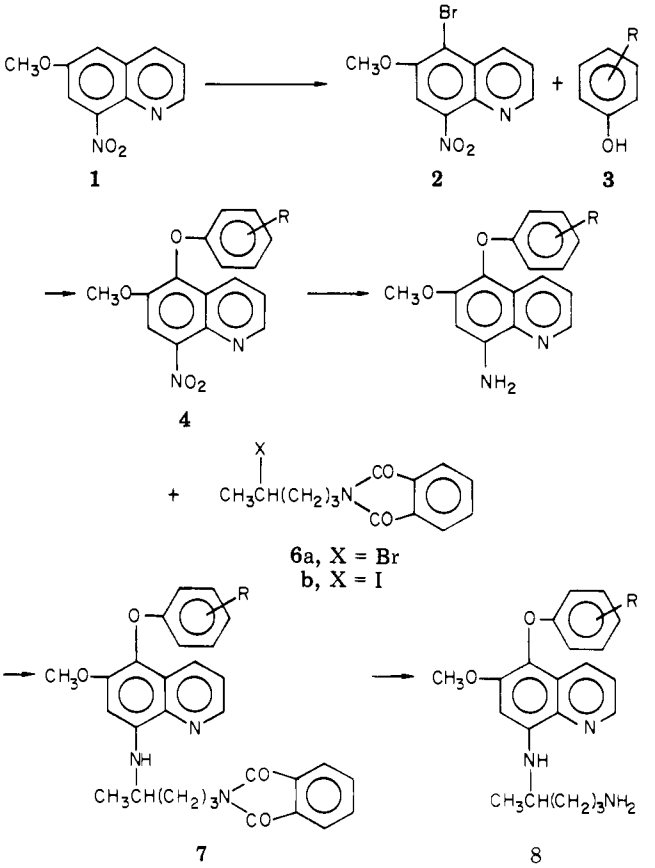


primaquine

malarial agent which suffers from excessive toxicity.[1] We have therefore undertaken a program of molecular modification designed to improve its therapeutic index. Since the highest therapeutic index among the 8-aminoquinolines in the Coatney compilation[2] belonged to a 5-phenoxy derivative, we have initiated our program with the synthesis of a group of 5-phenoxyprimaquines.

Chemistry. The preparative route (Scheme I) was an adaptation of one described by Elderfield et al.[3] and it proceeded, in the main, quite smoothly. However, a persistent, early stumbling block was the resistance of the amino derivatives **5** to phthalimido alkylation with 4-bromo-1-phthalimidopentane (**6a**). The classical phthalimido alkylation methods either failed completely or gave unsatisfactory yields of the penultimate 8-phthalimidoalkylamino intermediates **7**. Thus, the reaction between **5** and **6a**, in refluxing ethanol, as suggested by Elderfield,[3] provided little or none of the desired compounds. Equally unproductive were variations which included a phosphate buffer[3] or sodium iodide[4] or which utilized solvents other than ethanol.[4,5] Direct fusions of **5** and **6a** were also in vain.[3,6] We ultimately devised a method which involved incremental addition of at least 2 equiv each of **6a** and triethylamine and which produced satisfactory yields of **7** in every instance. A further improvement, which in preliminary work has increased yields and reduced reaction times, was the substitution of the iodide **6b** for the bromide **6a**.

Scheme I



Biology. Table I compares primaquine and its 5-phenoxy derivatives (**8a–c**) in the murine blood schizonticidal antimalarial screen. In contrast to primaquine,