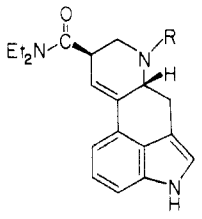
Synthesis and LSD-like Discriminative Stimulus Properties in a Series of *N*(6)-Alkyl Norlysergic Acid *N*,*N*-Diethylamide Derivatives

Andrew J. Hoffman and David E. Nichols*

Department of Medicinal Chemistry and Pharmacognosy, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, Indiana 47907. *Received November 5, 1984*

A convenient method for the synthesis of *N*(6)-alkyl norlysergic acid *N*,*N*-diethylamide derivatives was developed. A series of these compounds was synthesized and tested for substitution in the two-lever drug discrimination assay, in rats trained to discriminate injections of *d*-LSD tartrate (185.5 nmol/kg, ip) from saline. A dose–response curve for each of the compounds in the series was generated. Structure–activity relationships were developed, based on comparison of the estimated ED_{50} values from these curves. Of the compounds that substituted for LSD, the *N*(6)-ethyl and -allyl were approximately 2–3 times more potent than LSD itself. The *N*(6)-propyl was equipotent to LSD, while the isopropyl derivative was half as active. The *n*-butyl compound was 1 order of magnitude less potent than LSD, suggesting a similarity to the SAR of certain serotonin and dopamine agonists. By contrast, no generalization occurred to norlysergic acid *N*,*N*-diethylamide and the *N*(6)-2-phenethyl derivative.

Among the various classes of hallucinogenic drugs, the *d*-lysergic acid amides remain the most potent. Of the various structural modifications that have been carried out, few have yielded compounds that retain to any significant degree the remarkable potency of the diethylamide[1] LSD (1).



1 R = CH_3 (LSD)
2 CH_2CH_3
3 $CH_2CH_2CH_3$
4 $CH(CH_3)_2$
5 $CH_2CH_2CH_2CH_3$
6 $CH_2CH{=}CH_2$
7 $CH_2CH_2C_6H_5$

One area in the structure–activity relationships of lysergic acid amides that has not been systematically explored, however, is the effect of alkyl substitution at the basic nitrogen, N(6).

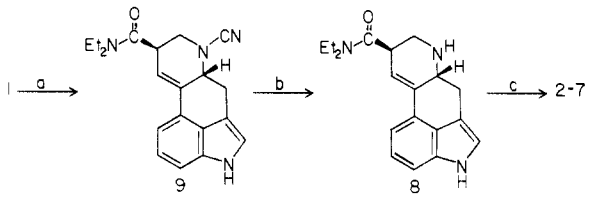
Niwaguchi et al.[2,3] have reported the preparation of several *N*(6)-alkyl norlysergic acid *N*,*N*-diethylamide derivatives, and Hashimoto et al.[4,5] have performed pharmacological assays that demonstrated the oxytocic activity of these compounds and also their ability to elicit hyperthermia in the rabbit. However, no data were reported that would give an indication of their relative hallucinogenic potential.

It was envisioned that selected *N*(6)-alkyl norlysergic acid *N*,*N*-diethylamide derivatives might exhibit very interesting pharmacological properties. It is known, for example, that LSD and various other ergolines have significant dopamine agonist potency.[6,7] This dopaminergic activity is often enhanced when the basic amino function is substituted with an *n*-propyl group. This is true not only in ergolines but also in aporphines[8] and in structurally simpler aminotetralin and phenethylamine-type compounds.[9,10]

Although similar structure–activity relationships have not been elucidated for serotonin agonists, Arvidsson et al.[11] have recently reported that 2-amino-8-hydroxy-1,2,3,4-tetrahydronaphthalene has optimum serotonin agonist activity when the amino is substituted with di-*n*-propyl groups.

For all of these reasons, it appeared that an examination of the effects of modification of the *N*(6)-alkyl group of LSD would be rewarding. Therefore, in this paper we

Scheme I



a. BrCN, CCl_4, REFLUX b. Zn, HOAc, H_2O, REFLUX
c. RX, K_2CO_3, DMF, 25°C

Table I. Characterization of Compounds 2–7[a]

compd	time,[b] h	% yield[c]	mp,[d] °C	mass calcd	mass measd
2[h]	4.0	91	108–110[e]	337.21541	337.21540
3	9.0	72	87–88[f]	351.23106	351.23109
4	144.0	62	106–108	351.23106	351.23065
5	72.0	55	83–86	365.24671	365.24667
6[i]	0.5	88	88–90[g]	349.21541	349.21563
7	120.0	85	103–105	413.24671	413.24667

[a] Refer to the Experimental Section for a description of how purity for compounds 2–7 was determined. [b] All alkyl halides were iodides except in the preparation of 6 and 7 where alkyl bromides were used. [c] Isolated by Chromatotron. [d] Crystallized from benzene–hexanes. [e] Lit.[2] mp 74–75 °C. [f] Lit.[2] mp 73–75 °C. [g] Lit.[2] mp 129–131 °C. [h] $[\alpha]_D$ = +40.5 (*c* 0.46, EtOH). [i] $[\alpha]_D$ = +41.8 (*c* 0.44, EtOH).

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Table II. Drug Discrimination Testing Results

compd	dose,[a] nM/kg 5.75	11.5	23.0	46.5	93.0	185.5	371.0	742.0	ED_{50}, μM/kg (95% c.i.)	potency ratio (95% c.i.)
1		0/8	2/8	4/8	6/8	8/8			0.046 (0.029–0.072)	1.00
2	2/8	3/8	3/8	5/8	8/8				0.020 (0.010–0.041)	1.63 (2.63–1.00)
3		2/8	2/8	4/8	6/8	8/8			0.037 (0.019–0.071)	1.00 (1.62–0.62)
4			1/8	2/8	3/8	5/8	8/8		0.100 (0.052–0.186)	0.41 (0.66–0.25)
5				0/8	1/8	1/8	3/8	7/8	0.357 (0.209–0.610)	0.13 (0.21–0.08)
6	3/8	4/8	4/8	6/8	8/8				0.013 (0.006–0.027)	2.01 (3.27–1.24)
7	*b,c*									
8	*b,d*									

[a] Data expressed as number scored LSD correct/number tested. [b] Complete generalization did not occur at the highest doses used. [c] 25% LSD appropriate responding at 0.742 μM/kg, the highest dose tested. [d] 50% LSD appropriate responding at 3.710 μM/kg, the highest dose tested.

report the details of the synthesis of a series of *N*(6)-alkyl norlysergic acid *N,N*-diethylamide derivatives **2–7** and an examination of their discriminative stimulus properties in rats that have been trained to discriminate saline treatment from ip injection of LSD tartrate (185.5 nmol/kg) using the two-lever drug discrimination paradigm.[12]

Chemistry. The synthesis of free bases **2–7** used for pharmacological evaluation was accomplished in three steps from LSD, as outlined in Scheme I. Von Braun degradation of LSD (**1**) with cyanogen bromide led to the formation of the *N*(6)-cyano compound **9**. This was accomplished with refluxing carbon tetrachloride as the solvent. Surprisingly, use of methylene chloride at room temperature, as reported for methyl 9,10-dihydrolysergate by Fehr et al.,[13] led only to decomposition of the starting material. This cyanamide was subjected to reduction with zinc and acetic acid[13] to yield **8**. The secondary amine was treated with various alkyl halides in DMF–K_2CO_3, to form the *N*(6)-alkylated products **2–7** (Table I), obtained as a mixture of diastereomers. The separation of the isomers was easily accomplished by centrifugal preparative layer chromatography, CPLC (Chromatotron, Harrison Research).

We were not able to prepare norlysergic acid *N,N*-diethylamide following the method of Niwaguchi et al.[2,3] The failure occurred in attempts to remove the *N*(6)-cyano group. Although base hydrolysis afforded an *N*(6)-carbamoyl derivative, as reported, this resisted repeated attempts at conversion to norlysergic acid *N,N*-diethylamide using dilute nitrous acid and a variety of reaction conditions. Attempts to remove the *N*(6)-cyano group using dilute HCl hydrolysis[2] resulted only in intractable mixtures. An attempted N(6)-demethylation of LSD following the method of Crider,[14] using trichloroethyl chloroformate, was similarly unsuccessful.

Results and Discussion

The results of substitution tests in the two-lever drug discrimination assay are presented in Table II. The ED_{50} values represent the dose at which 50% of the rats tested selected the LSD-appropriate lever. Potency ratios included in the table were obtained using a 3 point × 3 point parallel-line bioassay for quantal data and reflect the potency of the test compound relative to LSD. Potency ratios were calculated only when the two lines did not differ significantly from parallelism.

Several interesting results emerge from the data. First, the LSD-like stimulus properties of the molecule drop sharply when the *N*-alkyl exceeds an *n*-propyl in length. Lower activity for the *N*-isopropyl **4** also indicates that bulky N-substituents are not well tolerated. Most intriguing is the fact that compounds **2**, **3**, and **6** all retained activity comparable to, or slightly greater than, LSD itself. This can be contrasted with other types of modifications on the structure of LSD where activity is invariably decreased as a result of the change.[15] Indeed, the *N*-allyl compound **6** appears to be significantly more potent than LSD in this assay. This finding parallels the reports by Hashimoto et al.,[4,5] where it was found that the allyl compound was more potent than LSD, both in eliciting contraction of the rat uterus and in producing hyperthermia in rabbits. Although it is not possible to predict whether this compound is also more potent as an hallucinogen in man, the high potency seen in three different bioassay systems suggests that it is.

Experimental Section

Melting points were taken on a Mel-Temp apparatus and are uncorrected. ^1H NMR spectra were recorded on a Nicolet NTCFT 470-MHz spectrometer (Purdue University Biomedical Magnetic Resonance Laboratory). Chemical shifts are reported in δ values (parts per million) relative to the proton resonance of chloroform at 7.25 ppm (Table III). Multiplicities are expressed as follows: s = sharp singlet, b = broad singlet, d = doublet, t = triplet, q = quartet, p = pentet, x = hextet (6), h = heptet (7), m = multiplet, and w = doublet of doublets. Exact mass measurements were obtained on a Kratos MS-50s mass spectrometer at a calibrated resolution of 15 000. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter. All reactions were carried out in the dark or in weak indirect lighting since all of the compounds were particularly sensitive to UV light.

9,10-Didehydro-*N,N*-diethyl-6-cyanoergoline-8β-carboxamide (9). Pure lysergic acid *N,N*-diethylamide free base was prepared from lysergic acid monohydrate by the method of Johnson et al.[16] and was obtained in 66% yield after purification by column chromatography over alumina (Brockman) and elution with 3:1 benzene–chloroform. Following a modification of the procedure of Niwaguchi,[2] 323 mg (1 mM) of **1** was dissolved in 10 mL of chloroform. This was diluted with 70 mL of reagent carbon tetrachloride and was added, over 1 h, to a refluxing solution of 440 mg (4.15 mM) of BrCN in 30 mL of CCl_4. The reaction was stirred under a nitrogen atmosphere with external heat provided by an oil bath held at 110 °C. After the addition was complete, reflux was continued for 6 h. The mixture was allowed to cool and was washed once with 30 mL of 1% aqueous tartaric acid. Following concentration of the organic solution by rotary vacuum evaporation, the residue was partitioned between dichloromethane (2 × 35 mL) and 50 mL of 1% tartaric acid solution. The organic layer was dried in the dark over anhydrous

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Table III. ^{1}H NMR Chemical Shifts (ppm)

	compd								
gp (mult[a])	1	2	3	4	5	6	7	8	9
N_1H (b)	7.92	7.93	7.90	8.20	7.96	7.92	7.90	8.00	8.08
Ar (d)	7.21	7.20	7.19	7.17	7.19	7.20	7.19	7.20	7.18
Ar (d)	7.20	7.19	7.18	7.16	7.17	7.19	7.17	7.19	7.09
Ar (t)	7.15	7.14	7.14	7.12	7.14	7.14	7.15	7.14	7.07
H2 (t)	6.90	6.89	6.89	6.87	6.88	6.89	6.90	6.89	6.89
H9 (s)	6.34	6.33	6.33	6.34	6.32	6.34	6.34	6.35	6.22
H8 (m)	3.87	3.82	3.78	3.72	3.78	3.79	3.85	3.79	3.85
4 (w)	3.55	3.53	3.52	3.53	3.52	3.53	3.54	3.49	3.48
2 CH_2	multiplets in range 3.50–3.30								
5 (m)	3.22	3.50	3.40	3.68	3.45	3.48	3.61	3.54	4.16
7 (w)	3.05	3.13	3.14	3.12	3.14	3.20	3.20	3.02	3.67
7 (t)	2.89	2.88	2.87	2.75	2.88	2.84	3.04	2.76	3.60
4 (t)	2.67	2.66	2.62	2.62	2.63	2.68	2.69	2.67	2.96
CH_3 (t)	1.24	1.24	1.23	1.22	1.23	1.23	1.25	1.26	1.23
CH_3 (t)	1.17	1.18	1.16	1.18	1.16	1.17	1.19	1.17	1.12
	N(6)-Alkyl Substituent								
CH	2.58 s	3.07 x	2.89 t	3.57 h	2.94 m	3.70 w	3.15 m	1.96 b (N_6H)	
		2.83 x	2.66 t		2.64 m	3.17 m	2.84 m		
CH		1.14 t	1.61 m	1.25 d	1.56 m	5.99 m	2.98 m		
				0.96 d			2.93 m		
CH			0.93 t		1.37 m	5.28 d			
						5.22 d	7.3–7.2 m (Ar)		
CH					0.96 t				

[a] See the Experimental Section for multiplicity abbreviations.

sodium sulfate. Filtration and solvent removal afforded a purple residue that was passed over 5 g of neutral alumina and eluted with 9:1 chloroform–methanol. This crude material was then purified by centrifugal chromatography (chromatotron) using a 2-mm plate of neutral alumina (Merck 1092) and elution with dichloromethane. An ammonia atmosphere was maintained by bubbling nitrogen gas through concentrated ammonium hydroxide and continuously purging the chromatotron chamber. The use of silica gel for this purification gave a blue product and a lower overall recovery. The product band eluted from the plate was concentrated under vacuum in the dark and was recrystallized from ethyl acetate or 2-propanol: yield 237 mg (71%); mp 190–191 °C (*i*-PrOH) (lit.[2] mp 187–188 °C).

9,10-Didehydro-*N*,*N*-diethylergoline-8β-carboxamide (8). Following a modification of the procedure of Fehr et al.,[13] a mixture of 334 mg (1 mM) of **9**, 3.0 mL of glacial acetic acid, 0.6 mL of water, and 0.60 g of powdered zinc was stirred together under a nitrogen atmosphere for 4 h, with external heating provided by an oil bath held at 130 °C. The reaction flask was then placed in an ice bath, and 3 mL of water and a sufficient quantity of concentrated ammonium hydroxide were added to make the contents strongly alkaline. The basic suspension was extracted with 5 × 10 mL of dichloromethane. The combined organic extract was then dried (Na_2SO_4), filtered, reduced by rotary evaporation, and dried under high vacuum to yield 295 mg of a tan solid that was one major spot by TLC (silica; 8:2 chloroform–methanol). Purification by centrifugal chromatography over alumina, elution with 9:1 chloroform–methanol under ammonia vapor, and concentration of the eluate band gave a solid that was recrystallized from ethyl acetate–hexanes to yield 190 mg (61%) of tan crystals, mp 196–198 °C (dec) (lit.[2] mp 185–186 °C).

9,10-Didehydro-*N*,*N*-diethyl-6-alkylergoline-8β-carboxamides. General Method. A mixture of 66 mg of **8** (0.21 mmol), 48 mg of anhydrous potassium carbonate (0.35 mmol), and alkyl iodide or bromide (0.24 mmol) in 2 mL of freshly distilled DMF in a small amber vial was stirred under N_2 at room temperature. The reaction was monitored by TLC (silica; 9:1 $CHCl_3$–MeOH) at 1-h intervals to determine reaction completion. When the starting material **8** had been consumed, the solvent was stripped from the reaction under high vacuum. The resulting residue was extracted with chloroform (5 × 5 mL), dried (Na_2SO_4), and reduced by rotary evaporation to yield the product, usually as a white solid. Centrifugal chromatography over a 1-mm alumina plate and elution with methylene chloride under ammonia atmosphere led to the separation of two blue, highly fluorescent fast-moving bands. The first band eluted from the plate was the major component and was concentrated, dissolved in a minimum of hot benzene, filtered, and cooled. Hexane was added when necessary to induce crystallization. Crystalline yields of 15–20 mg were obtained for the desired compounds **2–7**. These were chromatographically pure, as determined by TLC analysis in the following systems: 9:1 $CHCl_3$–MeOH with 50 drops of NH_4OH per 500 mL, on silica, and $CHCl_3$ with 50 drops of NH_4OH per 500 mL, on neutral alumina. Spots were visualized with long-wave UV and Keller's spray reagent. The crystalline materials had sharp melting points and showed no spurious absorptions by 470-MHz ^{1}H NMR analysis.

Pharmacology. Animals. Male, Sprague–Dawley rats, weighing approximately 200 g at the beginning of the study, were obtained from Murphy Breeding Labs Inc., Plainfield, IN. For the first week, all rats were group housed (eight per cage) with food and water available ad lib. Following the initial acclimatization period, the rats were housed individually in a temperature-controlled room (25 °C) with a 0600-2000 lights on–2000-0600 lights off schedule.

Immediately following scheduled discrimination sessions, the animals were returned to their home cages and allowed to feed freely on rat chow (Lab Blox) for 30 min. This schedule has been reported[17] to maintain the rat at about 80% of free-feeding weight. On Sundays, no sessions were run and the animals were allowed to feed at their regularly scheduled time. Water was available continuously, except during the training and testing periods. The sample of animals participating in any given experiment was selected from the pool of trained rats available during the 5-month period taken to conduct this study.

Apparatus. Five identical standard operant chambers (Coulbourn Instruments) equipped with two response levers separated by a food pellet delivery system were employed. Food pellets (Bioserve, 45 mg dustless) were used as reinforcement. Chambers contained a white house light and masking white noise and were enclosed in ventilated sound-attenuated cubicles. The operant chambers were controlled by solid-state logic interfaced through a Coulbourn Instruments Dynaport to an IBM-PC located in an adjacent control room. Data acquisition and control were handled by the IBM-PC using software developed in this laboratory.

Drug Administration. The training dose of *d*-LSD tartrate (NIDA) (185.5 nmol/kg, 0.08 mg/kg) or appropriate test drug

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doses were administered in solution in a volume of 1.0 mL/kg of body weight. All test compounds, as the free bases, were first dissolved in a small amount of 95% ethanol and were then diluted to the desired concentrations with an isotonic solution of 1% ascorbate in 0.72% sodium chloride solution. All injections were administered intraperitoneally 30 min before the start of discrimination sessions.

Discrimination Training. To avoid positional preference, half of the animals were trained to press LSD-L and SAL-R, while the other half were trained vice versa. Rats were trained on an FR32 schedule with 15-min maintenance sessions. Responding rates were found to be 1450 ± 600 per 15-min session among different animals. No significant difference in responding rate was seen between the training dose of LSD and saline ($p > 0.05$, grouped Student's t-test). The complete training procedure has been published in a previous article.[18]

Stimulus Generalization. Those rats that had successfully acquired 85% correct responding on the appropriate lever during the 6-week training period were included in the stimulus generalization testing procedure. Testing sessions were run on Wednesdays and Saturdays only. Training sessions were held the rest of the week with Sundays off. On test days, the animal was placed in the operant chamber 30 min after injection. Test sessions lasted until the rat emitted 32 responses on either lever or until 5 min had passed, whichever came first. If the rat did not emit 32 responses on either lever within 5 min, he was scored as disrupted and was not included in the calculations. No reinforcement was given during test sessions. In order to receive a test drug, the animals were required to satisfy the 85% correct lever response criterion on each of the two preceding training sessions. Also following the procedure of Colpaert et al.,[19] test data were discarded and the test condition later retested if the test session was followed by failure to meet the 85% criterion in either of the two subsequent training sessions. This procedure was employed to increase the reliability of the individual test data. It has been reported[19] that incorrect lever selections in trained rats typically occur in bursts of one to three sessions. This correction procedure assists in avoiding the contamination of test data that may occur during such bursts. If the animal was not included in the testing procedure on a given day, the session was used for training.

Several preliminary experiments to determine appropriate dosages for new compounds were carried out; these data were discarded. Dosages for each of the test compounds were based on these initial experiments. The drug treatments in this study, including LSD and the vehicle for the ergoline solutions (control), were randomized over the entire experimental period.

Data Analysis. Animals were scored as drug positive if they selected the LSD-appropriate lever (i.e., if they emitted 32 responses on the drug lever before emitting 40 total responses). If generalization occurred (greater than 80% drug appropriate responding), these quantal data were analyzed by the method of Litchfield and Wilcoxon[20] to determine an ED_{50}. Parallelism was tested, and potency ratios were determined from a 3 point × 3 point parallel line bioassay for quantal data.[21]

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Registry No. 1, 50-37-3; 2, 65527-62-0; 3, 65527-63-1; 4, 96930-86-8; 5, 96930-87-9; 6, 65527-61-9; 7, 96930-88-0; 8, 35779-43-2; 9, 35779-41-0.

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Synthesis and Antiallergic Activities of 1,3-Oxazolo[4,5-*h*]quinolines

John H. Musser,*[1] Howard Jones,[†] Stanley Sciortino,[†] Kevin Bailey,[†] Stephen M. Coutts,[‡] Atul Khandwala,[‡] Paula Sonnino-Goldman,[§] Mitchell Leibowitz,[§] Peter Wolf,[§] and Edward S. Neiss*

Departments of Medicinal Chemistry, Biochemical Research, and Pharmacology, Revlon Health Care Group, Research and Development Division, Tuckahoe, New York 10707. *Received October 18, 1984*

A series of new 1,3-oxazolo[4,5-*h*]quinolines has been prepared. These compounds were tested as inhibitors of antigen-induced release of histamine (AIR) in vitro from rat peritoneal mast cells (RMC) and as inhibitors of IgE-mediated passive cutaneous anaphylaxis in the rat (PCA). After several modifications of the original lead, the most potent compound of the series was determined to be 5-chloro-1,3-oxazolo[4,5-*h*]quinoline-2-carboxylic acid methyl ester (**4a**). It has an IC_{50} of 0.3 μM in the RMC assay and an ED_{50} (intraperitoneal) of 0.1 mg/kg in the PCA test, which is 10 times and 60 times more potent than disodium cromoglycate (DSCG), respectively. Of greater importance, it is orally active (ED_{50} = 0.5 mg/kg) as an inhibitor of the PCA test.

Since the introduction of disodium cromoglycate (DSCG) for the treatment of asthma and allergy disease,[2] a large number of chemical series have been reported as antiallergic agents.[3] As part of a program to develop new antiallergic agents,[4] we synthesized some 1,3-oxazolo[4,5-*h*]quinolines.

Our interest in the 1,3-oxazolo[4,5-*h*]quinoline ring system evolved from a chemical lead discovered in our selective screening program. The known 8-quinolinyl 2-methoxycarbanilate (**1**)[5] was found active as an inhibitor (IC_{50} = 2.0 μM) of anaphylactically induced histamine

[†] Department of Medicinal Chemistry.
[‡] Department of Biochemical Research.
[§] Department of Pharmacology.

(1) Current address: Wyeth Laboratories, P.O. Box 8299, Philadelphia, PA 19101.
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