Lysergic Acid Analogs: 5-Phenylnicotinamides and Nipecotamides

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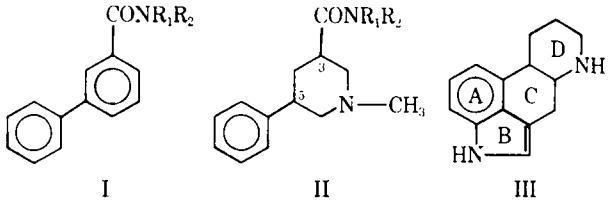
Abstract □ A series of 5-phenylnicotinamides and 1-methyl-5-phenylnipecotamides was synthesized as simplified lysergic acid analogs. Pharmacological evaluation showed that, in general, these compounds are CNS depressants. The nipecotamides, although more toxic, possess MED_{50} values comparable to those found for the analogous 9,10-dihydrolysergamides. The nicotinamides, however, showed greatly reduced activity when compared to the lysergamides.

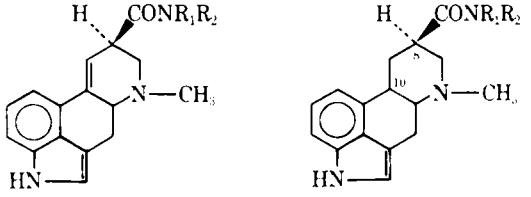
Keyphrases □ Lysergic acid analogs—synthesis and pharmacological screening of 5-phenylnicotinamides and nipecotamides □ 5-Phenylnicotinamides—synthesis, screened for CNS activity □ Nipecotamides—synthesis, screened for CNS activity □ CNS activity—synthesis and screening of 5-phenylnicotinamides and nipecotamides

The potent and diverse pharmacological activity of ergot alkaloids has generated considerable interest in the synthesis of simplified analogs (1). The synthesis and pharmacological evaluation of some 5-phenylnicotinamides (I*a*–I*d*) and 1-methyl-5-phenylnipecotamides (II*a*–II*d*) are reported here. These compounds may be viewed as representing rings A and D of the ergolene system (III). It has been reported that the hallucinogenic activity of *N,N*-diethyllysergamide (LSD, IV*b*), may reside in that portion of the molecule that includes aromatic ring A and the nitrogen atom of ring D (2).

In connection with another study (3), numerous lysergamides (IV) and their 9,10-dihydro derivatives (V) were prepared. It became of interest to compare compounds of type II with the analogous 9,10-dihydrolysergamides (V). The choice of substituents R_1 and R_2 in Compounds I and II was dictated by the pharmacological results obtained previously (3).

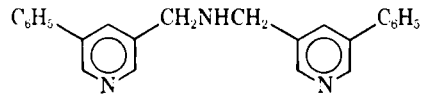


I II III



IV V

a: R_1 = H, R_2 = n-C_4H_9
b: R_1 = C_2H_5, R_2 = C_2H_5
c: R_1 = H, R_2 = cyclo-C_6H_{11}
d: R_1 = H, R_2 = $C(CH_3)_3$



VI

RESULTS AND DISCUSSION

The common starting material for I and II was 5-phenylnicotinic acid, obtained from the hydrolysis of 5-phenylnicotinonitrile. The nitrile was prepared by the hydrogenolysis of 2-chloro-5-phenylnicotinonitrile over palladium-on-charcoal. When the literature procedure (4) was followed using palladium chloride, a substantial quantity of 3,3′-iminobis(methylene-5-phenylpyridine) (VI) was formed as a by-product. The desired product, 5-phenylnicotinonitrile, was obtained in unsatisfactory yield and was difficult to purify.

Compounds I*a*–I*d* (Table I) were obtained in good yield from 5-phenylnicotinic acid by a new, efficient amidation procedure (3), using the appropriate amine and phosphorus oxychloride in a 4–8-min. reaction period. Catalytic reduction of the methobromides of I*a*–I*d* gave the corresponding nipecotamides (II*a*–II*d*) (Table II). The synthesis of lysergamides (IV*a* and IV*b*) and 9,10-dihydrolysergamides (V*a*–V*d*) was described previously (3).

The general pharmacological activity of all compounds listed in Table III was measured in a modified Irwin mouse profile (5, 6), using male albino mice weighing 22 ± 2 g. Administration was made intravenously to two animals per dose at each of four or more dose levels. Following administration of a compound, observations were made on approximately 50 discrete components of behavior and appearance, response to external stimuli and neuromuscular integrity, and performance (6). The LD_{50} and MED_{50} (minimum effective dose) values were calculated using the moving average method of Thompson (7) and Weil (8).

Compounds I*a*–I*d* and II*a*–II*d* commonly caused general central

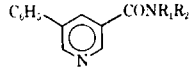


Table I—5-Phenylnicotinamides

Compound	R_1	R_2	Melting Point	Yield[a], %	Recrystallization Solvent	Melting Point of Methobromide (% Yield)
I*a*	H	n-C_4H_9	70–71°	87	Ether–hexane[b]	122–124° (97)
I*b*	C_2H_5	C_2H_5	81–82°[c]	75	Hexane	186–188° (76)
I*c*	H	cyclo-C_6H_{11}	136–137°	68	Hexane	212–215° (89)
I*d*	H	$C(CH_3)_3$	127–129°	49	Hexane[b]	212–213° (91)

[a] Recrystallized product. [b] Crude product was chromatographed on column of neutral aluminum oxide (Activity II, eluent ether) prior to crystallization. [c] M.p. 82° (4).

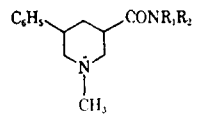


Table II—1-Methyl-5-phenylnipecotamides

Compound	R_1	R_2	Melting Point	Yield[a], %	Recrystallization Solvent
IIa	H	n-C_4H_9	128–130°	42	n-Hexane
IIb	C_2H_5	C_2H_5	180–182°[b]	14	Ether–ethanol
IIc	H	cyclo-C_6H_{11}	154–156°	32	Acetonitrile
IId	H	$C(CH_3)_3$	243–245°[b]	12	Ethyl acetate

[a] Recrystallized product. [b] Hydrochloride.

Table III—Mouse Profile Screen[a]

Compound	MED_{50}, mg./kg. i.v.	LD_{50}, mg./kg. i.v.
Ia	>20	>20
Ib	10.0	56
Ic	18.0	100
Id	5.6	>32
IIa	5.6	18
IIb	1.8	18
IIc	3.2	18.0
IId	10.0	32.0
IVa	0.18	79
IVb	0.056	50
Va	5.6	56
Vb	5.6	56
Vc	18	>32
Vd	1.8	56

[a] Hydrochlorides were administered intravenously in aqueous solution; free bases and maleates required polyethylene glycol 200 or dilute hydrochloric acid for solubilization.

nervous system (CNS) depression and, in particular, a decreased respiratory rate. A comparison of the results obtained for Va–Vd with the simplified analogs IIa–IId showed very similar pharmacological activity on the Irwin screen even though the absolute stereochemistry at chiral centers 3 and 5 of IIa–IId is unknown. The absolute stereochemistry at the analogous positions 8 and 10 of the 9,10-dihydrolysergamides has been established (9). However, IIa–IId were considerably more toxic than Va–Vd by a factor of at least 2–3.

The nicotinamides (Ia–Id), on the other hand, showed greatly reduced activity when compared to the lysergamides, but the presence of the pyridine ring makes for a less valid comparison with lysergamides.

EXPERIMENTAL[1]

5-Phenylnicotinonitrile—A mixture of 20.7 g. of 2-chloro-5-phenylnicotinonitrile (4), 120 ml. of dimethylformamide, 25.5 ml. of triethylamine, and 1.5 g. of 5% palladium-on-charcoal was hydrogenated at room temperature in a Parr apparatus at 3.9 kg./cm.^{2} for 1 hr. The mixture was filtered and the filtrate was concentrated to dryness. The residue was partitioned between dichloromethane and 50 ml. of 2 *N* NaOH. The organic extract was washed twice with 5% HCl and several times with water, dried over magnesium sulfate, and evaporated to dryness *in vacuo*. The residue was recrystallized from *n*-hexane, yielding 12.1 g. (69%) of 5-phenylnicotinonitrile, m.p. 72–74° [lit. (4) m.p. 75–76°].

When the literature procedure (4) was followed using palladium chloride as a catalyst, 3,3′-iminobis(methylene-5-phenylpyridine) (VI) was isolated from the 5% HCl wash of the organic extract described previously. The acidic solution was made basic with 2 *N* NaOH, and the liberated base was extracted into methylene chloride. The dried extract (magnesium sulfate) was evaporated to dryness under vacuum, and the viscous residue was recrystallized from ether and then from acetonitrile, m.p. 98–99°. The NMR ($CDCl_3$) spectrum revealed the presence of 10 aromatic protons at δ 7.47 (multiplet); six pyridine protons at δ 7.85 (multiplet), 8.52 (doublet), and 8.72 (doublet); four methylene protons at δ 3.91 (singlet); and a D_2O-exchangeable proton (NH) at δ 2.25. Mass spectrometric analysis revealed a molecular ion peak at *m/e* 351 (calculated molecular weight 351.4).

Anal.—Calc. for $C_{24}H_{21}N_3$: C, 82.02; H, 6.02; N, 11.96. Found: C, 82.09; H, 6.04; N, 12.00.

5-Phenylnicotinic Acid—A solution of 5.7 g. of 5-phenylnicotinonitrile in 120 ml. of concentrated hydrochloric acid was heated at reflux overnight. The reaction mixture was poured into ice and made basic by the addition of 2 *N* NaOH. The basic solution was then acidified with glacial acetic acid. The fine, white precipitate was filtered, washed repeatedly with water, and air dried. The crude product was recrystallized from about 800 ml. of ethanol, yielding 5.2 g. (82%) of 5-phenylnicotinic acid, m.p. 264–266° [lit. m.p. 260–263° (4) and 267–269° (10)].

5-Phenylnicotinamides (Ia–Id)—A solution of 0.048 mole of the appropriate amine in 20 ml. of chloroform and 1 ml. (0.011 mole) of phosphorus oxychloride were added concurrently to a refluxing slurry of 1.1 g. (0.005 mole) of 5-phenylnicotinic acid in 80 ml. of chloroform. After being kept at reflux for an additional 2 min., the solution was cooled to room temperature, washed with 50 ml. of 1 *M* NH_4OH and with water, dried over magnesium sulfate, and evaporated to dryness *in vacuo*. The residue was then crystallized from the appropriate solvent (Table I). Table I includes melting points and yields, and elemental analysis data are given in Table IV.

1-Methyl-5-phenylnipecotamides (IIa–IId)—The methobromides

Table IV—Elemental Analysis Data for Compounds Ia–Id and IIa–IId

Compound	Empirical Formula	Analysis, % Calc.	Found
Ia	$C_{16}H_{18}N_2O$	C 75.56	75.51
		H 7.13	7.14
		N 11.02	11.04
Ib	$C_{16}H_{18}N_2O$	C 75.56	75.61
		H 7.13	6.96
		N 11.02	11.06
Ic	$C_{18}H_{20}N_2O$	C 77.11	76.83
		H 7.19	7.35
		N 9.99	9.94
Id	$C_{16}H_{18}N_2O$	C 75.56	75.63
		H 7.13	7.2
		N 11.02	11.2
IIa	$C_{17}H_{26}N_2O$	C 74.41	74.21
		H 9.55	9.56
		N 10.21	10.09
IIb	$C_{17}H_{26}N_2O \cdot HCl$	C 65.57	65.59
		H 8.75	8.77
		Cl 11.40	11.60
		N 9.01	8.90
IIc	$C_{19}H_{28}N_2O$	C 75.95	75.84
		H 9.39	9.36
		N 9.33	9.19
IId	$C_{17}H_{26}N_2O \cdot HCl$	C 65.57	65.85
		H 8.75	8.76
		Cl 11.40	11.49
		N 9.01	9.12

[1] Melting points were determined on a Mel-Temp apparatus and are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. The structures of all novel compounds were confirmed by NMR spectroscopy. NMR spectra were obtained on a Varian A-60 instrument.

of Compounds Ia–Id were prepared by bubbling methyl bromide through a solution of the appropriate 5-phenylnicotinamide in ethyl acetate for 3–6 hr. The quaternary salts were not recrystallized prior to use. The methobromides separated very cleanly and in high yields from the reaction medium (Table I). They were filtered, washed thoroughly with cold ethyl acetate, air dried, and converted directly to the corresponding 1-methyl-5-phenylnipecotamide by the general procedure described here.

A solution of 1.5 g. of the methobromide in 75 ml. of ethanol containing 75 mg. of platinum oxide was hydrogenated at room temperature for 3–6 hr. at an initial pressure of 0.7 kg./cm.^{2}. The mixture was filtered and the filtrate was evaporated to dryness. The residue was dissolved in methylene chloride, washed with 2 *N* NaOH and water, dried over magnesium sulfate, and concentrated *in vacuo*. The residue was crystallized from the appropriate solvent or dissolved in ether, treated with anhydrous hydrogen chloride to yield the corresponding hydrochloride, and then recrystallized. The recrystallization solvents, melting points, and yields are listed in Table II, and elemental analysis data are given in Table IV.

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Phase Separation of Cellulose Derivatives: Effects of Polymer Viscosity and Dielectric Constant of Nonsolvent

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Abstract □ In systems containing either cellulose acetate butyrate or ethylcellulose, the intrinsic viscosity of the polymer in the appropriate solvent had no effect on the phase type separated. The latter was dependent on the dielectric constant of the nonsolvent added. Nonsolvents possessing relatively high dielectric constants produced a flocculate phase, while either a coacervate or gel was formed after the addition of nonsolvents of lower dielectric constant.

Keyphrases □ Cellulose derivatives (cellulose acetate butyrate and ethylcellulose)—effects of polymer viscosity and dielectric constant of nonsolvent on phase separation □ Phase separation, cellulose derivatives—effects of polymer viscosity and dielectric constant of nonsolvent □ Nonsolvents—effect on phase separation of cellulose acetate butyrate and ethylcellulose

Starting from a polymer solution in a suitable solvent, the addition of an appropriate concentration of a nonsolvent may produce phase separation. The type of phase separating may be a flocculate, gel, or coacervate (liquid–liquid phase separation). While factors such as pH and electrolytes were reported to govern the phase type in polyelectrolyte systems (1, 2), no studies have been made on nonelectrolytic polymers. Phase separation of cellulose derivatives is of special interest in pharmacy because of its application to microencapsulation of pharmaceuticals (3, 4). The present article reports the effect of various solvent–nonsolvent systems on the type of phase separating in two polymers: ethylcellulose and cellulose acetate butyrate. An attempt was made to study the effect of solvent–nonsolvent systems on the phase type as determined by the viscosity of the polymer (in the appropriate solvent) and the dielectric constant of the nonsolvent added.

EXPERIMENTAL

Materials—The ethylcellulose[1] used had a 48% ethoxyl content. Cellulose acetate butyrate[2], 171-2 grade, had a 17% butyryl content. All solvents and nonsolvents were analytical reagent grade or pure reagents.

Methods—*Determination of Phase Type*—To a solution of the polymer in the appropriate solvent, placed in glass-stoppered centrifuge tubes, the nonsolvent was gradually added until a visual phase change was noted. The stoppered tubes were equilibrated at 25 ± 0.1° for completion of phase separation (4–6 hr.). The separated phase was examined and classified as a flocculate, gel, or coacervate. The latter was found microscopically to exhibit coacervate droplets (10–25 μ in diameter) which rapidly coalesced to a clear oily layer upon standing. The gel phase showed no coacervate droplets and was highly viscous, frequently adhering to the walls of the container.

[1] British Drug Houses Ltd., Poole, England.
[2] Eastman Kodak.