(14) W. Borsche and W. Jacobs, *Ber.*, **47**, 354 (1914).

(15) M. J. Jorgenson, *Org. React.*, **18**, 1 (1970).

(16) D. W. Boykin, A. R. Patel, R. E. Lutz, and A. Burger, *J. Med. Chem.*, **10**, 459 (1967).

(17) D. W. Boykin, A. R. Patel, and R. E. Lutz, *ibid.*, **11**, 273 (1968).

(18) C. J. Ohnmacht, F. Davis and R. E. Lutz, *ibid.*, **14**, 17 (1971).

(19) C. J. Ohnmacht, A. R. Patel, and R. E. Lutz, *ibid.*, **14**, 926 (1971).

(20) G. Illuminati and H. Gilman, *J. Amer. Chem. Soc.*, **71**, 3349 (1949).

(21) A. Burger and S. N. Sawhney, *J. Med. Chem.*, **11**, 270 (1968).

(22) T. S. Osdene, P. B. Russell, and L. Rane, *ibid.*, **10**, 431 (1967).

(23) W. E. Rothe and D. P. Jacobus, *ibid.*, **11**, 366 (1968).

(24) C. K. Banks, *J. Amer. Chem. Soc.*, **66**, 1127 (1944).

(25) E. Breitner, E. Roginski, and P. N. Rylander, *J. Chem. Soc.*, 2918 (1959).

(26) J. Hamer, W. J. Link, A. Jurjevich, and T. L. Vigo, *Recl. Trav. Chim. Pays-Bas*, **81**, 1058 (1962).

(27) S. Fatutta and F. Furlan, *Ric. Sci. Parte 2, Sez. B*, **4**, 485 (1964) [*Chem. Abstr.*, **61**, 14673f (1964)].

(28) H. Wojahn, *Arch. Pharm. (Weinheim)*, **274**, 83 (1938).

Emetic Activity of Reduced Lysergamides

Fatima N. Johnson,* Istvan E. Ary,

Arthur D. Little, Inc., Cambridge, Massachusetts 02140

David G. Teiger,

Sterling-Winthrop Research Institute, Rensselaer, New York 12144

and Ronald J. Kassel

Chemical Research Division, Chemical Laboratory, Edgewood Arsenal, Maryland 21010. Received October 10, 1972

A new efficient method for the direct amidation of *d*-lysergic acid was used to prepare a variety of lysergamides. A pharmacological evaluation of these compounds, their di- and tetrahydro derivatives, and derivatives bearing substituents in the indole portion of the molecule showed that, in general, only 9,10-dihydrolysergamides of primary amines possess activity comparable to the potent emetic activity of the components of dihydroergotoxine.

As part of a study of compounds possessing high CNS activity and a high therapeutic index, we were attracted by derivatives of lysergic acid,[1] in particular, by the reported emetic activity of dihydroergotoxine.[2],† We have investigated the emetic properties of a wide variety of lysergamides (1), their di- (2 and 3) and tetrahydro (7 and 8) derivatives, and derivatives bearing substituents in the indole portion of the molecule in an effort to relate emetic activity to the structure of the lysergamide. The present study showed that, in general, only 9,10-dihydrolysergamides of primary amines possess activity comparable to the potent emetic activity of the components of dihydroergotoxine.

Chemistry. *d*-Lysergic acid amides have been previously synthesized by way of the azide,[3] the acid chloride,[4] and the mixed anhydrides with trifluoroacetic acid[5] or sulfuric acid.[6] We wish to report a more convenient new method which effects the direct conversion of *d*-lysergic acid to the amide using the appropriate amine and $POCl_3$ in a 4–8-min reaction period. The desired normal amide (8β), free from the iso epimer (8α), was obtained in good yield (reported yields are not optimum) by isolation of the corresponding maleate salt from the crude reaction mixture. All steps were carried out with considerable experimental ease. Table I lists the amides that were prepared by the new method employing either one of two modifications A and B (see Experimental Section). Modification B appears to be more general and effective for the preparation of amides from bulkier amines. For example, the *tert*-butylamide **1b** was not obtained when method A was employed but was isolated in 41% yield when method B was used.

The scope of the reaction was further explored by attempting the amidation of 9,10-dihydrolysergic acid. Using method B this acid was cleanly converted in 70% yield to the *N*-cyclohexylamide **2c**. However, conversion to the *N*-ethyl- and *N*,*N*-di-*n*-butylamides was unsuccessful.

Attempts to prepare 1-*d*-lysergoyl-4-phenylpiperazine (**1**, $R_1,R_2 = (CH_2CH_2)_2NC_6H_5$) were unsuccessful. The expected amide was isolated in very low yield which was insufficient for complete identification. However, bis(4-phenyl-1-piperazinyl)phosphinic chloride (**4**) was obtained in 32% yield. Compound **4** was identical with the product obtained from the reaction of 2 equiv of 1-phenylpiperazine with 1 equiv of $POCl_3$ in the presence of Et_3N. This was the only instance where compounds of type **4** were isolated from the reaction mixture in our synthesis of numerous lysergamides.

4
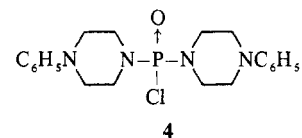
The 9,10-dihydrolysergamides **2** (Table II) were obtained by the catalytic reduction of the corresponding lysergamides **1** following the method previously described.[7] Catalytic reduction of the normal amide has been shown by Stoll and Hofmann[7,8] to yield only one isomer; hydrogen adds from the backside resulting in a C/D trans fusion.[9,10]
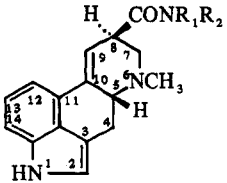
It was not possible to prepare **2i** by the catalytic reduction of *N*-(2-propynyl)lysergamide because of the presence of the acetylenic function. Instead, **2i** was obtained in poor yield from *d*-9,10-dihydrolysergoyl chloride hydrochloride and 2-propynylamine in the presence of pyridine.

The 2,3-dihydrolysergamides **3** (Table III) were obtained by a general procedure previously described by Stadler and coworkers[11,12] involving reduction of the corresponding lysergamide maleate with Zn dust and HCl. This reduction

---

Table I. Lysergamides (as Maleates)

| Compd	R_1	R_2	Method of prepn	Mp, °C (maleate)	Lit. mp, °C	$[\alpha]^{20}D$, concn 0.5 in MeOH	Recrystn solvent	Yield,[a] %
1a	H	$n\text{-}C_4H_9$	A	204–206 dec	216[b]			65[c]
1b	H	$tert\text{-}C_4H_9$	B	216–218 dec	220 dec[d]	+64[e]	MeOH–EtOAc	41
1c	H	$c\text{-}C_6H_{11}$	A	223 dec	225 dec[f]	−30.6[g]	MeOH–Et$_2$O	43
1d[h]	$n\text{-}C_4H_9$	$n\text{-}C_4H_9$	B	165–167 dec		−10	MeOH	30
1e	H	$i\text{-}C_3H_7$	B	206–208 dec	209–210 dec[i]	+38	MeOH	47
1f	H	$n\text{-}C_3H_7$	B	191–193 dec	207 dec[j]			28[c]
1g[k]	H	$CH(CH_3)(CH_2)_3CH(CH_3)_2$	B	206–208 dec		−5[l]	MeCN	50
1h[h,k]	H	$CH(CH_3)C(CH_3)_3$	B	215–217 dec		−25[m]	MeOH	45

[a]Unless otherwise stated all yields are of recrystallized material. [b]Reference 3. [c]Material was sufficiently pure for subsequent reactions and was not recrystallized. [d]Reference 17. [e]Concentration 0.6 in 50% EtOH. Reference 17 reports +60°. [f]A. Hofmann, R. Bruner, H. Kobel, and A. Brach, *Helv. Chim. Acta*, **40**, 1358 (1957). [g]Concentration 0.5 in pyridine at 25°. M. Semonsky, V. Zikan, and Z. Votava, *Chem. Listy*, **51**, 592 (1957) report −33.3°; see also *Chem. Abstr.*, **51**, 10545 (1957). [h]New compounds gave satisfactory C, H, and N analyses. [i]R. P. Pioch, U. S. Patent 2,997,470 (1961). [j]A. Stoll and A. Hofmann, *Helv. Chim. Acta*, **38**, 421 (1955). [k]Showed two components on tlc which were not separable by solid-phase column chromatography. We believe that the two components represent diastereoisomers differing at the asymmetric carbon in R_2. [l]Concentration 0.8 in pyridine at 26°. [m]Concentration 0.5 in pyridine.

can result in the formation of two diastereoisomers because of the generation of an asymmetric center at position 3. Stadler and coworkers[11] claim that the reduction is stereospecific based on the argument that addition of a proton from the front side results in intermediate **5** which is energetically favored over the alternative **6**. These workers did indeed isolate a single isomer from this reduction although some epimerization at position 8 was noted.
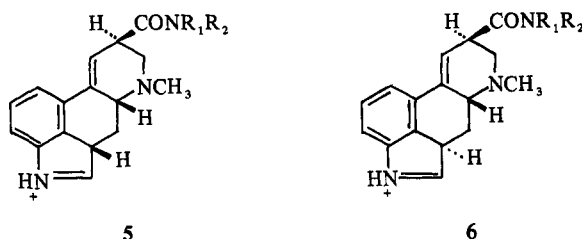
For the preparation of the 2,3,9,10-tetrahydrolysergamides **7** and **8**, alternative routes 1 and 2 are possible. *N-n*-Butyl-2,3,9,10-tetrahydrolysergamide (**7a**) was obtained as the product from the reduction sequence designated as route 1 and the isomeric tetrahydrolysergamide **8a** from the alternative route 2. Compounds **7a** and **8a** exhibited identical uv spectra and only very minor differences in their ir spectra. Their nmr spectra were extremely similar except for the presence of two singlet NCH$_3$ peaks in the spectrum of **8a** at δ 2.41 and 2.30 with an area ratio of 2:1. Only the former signal was exhibited by **7a**. This led to the belief that **8a** was a mixture of the two possible diastereoisomers from the reduction of **2a**. Furthermore, it was felt that one of the isomers in the mixture **8a** might prove to be identical with **7a**. Efforts to resolve **8a** by tlc were unsuccessful. There was no difference in the behavior of **7a** and **8a** in numerous tlc systems employed except on Adsorbisil 5 plates with MeOH as eluent. In this case **7a** had R_f 0.5 and **8a** had R_f 0.4. Although both compounds showed one or two trace impurities in this system, **8a** was not separable into two or more major components.

Similar differences in the physical properties of isomeric compounds **7b** and **8b** have been reported.[11,12] The physical
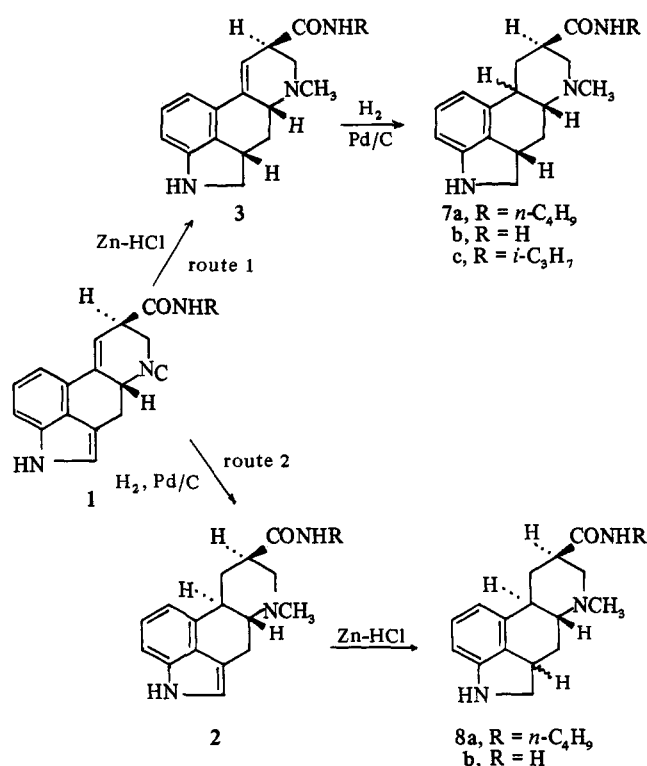
properties of the tetrahydrolysergamides are summarized in Table IV.

It is not possible to make any definitive assignment of the stereochemistry of **7a,b** and **8a,b** either on the basis of published data or on our present findings. However, it is strongly suspected that the **3 → 7** reduction is highly stereoselective whereas the **2 → 8** reduction is weakly stereoselective.‡

Thus, although it has been previously shown that reduction of the 2,3 and 9,10 double bonds are stereospecific for normal lysergamides,[8,10,12] the data clearly indicate that this is true only when the reduction is carried out on a fully un-

‡A. Hofmann, personal communication.

Table II. 9,10-Dihydrolysergamides

2

Compd	R₁	R₂	Mp, °C (free base)	Lit. mp, °C	$[\alpha]^{25}D$, concn 0.5 in MeOH	Recrystn solvent	Yield,[a] %	Formula	Analyses
2a	H	n-C₄H₉	222-223 dec	224-225 dec[b]	-81[c]	MeOH-EtOAc	74	C₂₀H₂₇N₃O	C, H, N
2b	H	tert-C₄H₉	207-209 dec[d]		-88[c,d]	MeOH-EtOAc	61	C₂₀H₂₇N₃O·C₄H₄O₄	C, H, N
2c	H	c-C₆H₁₁	244-246 dec	251[e]	-122[f]	Me₂CO	75	C₂₂H₂₉N₃O·C₄H₄O₄	C, H, N
2d	n-C₄H₉	n-C₄H₉	152-154 dec		-71.5	MeCN	77	C₂₄H₃₅N₃O	C, H, N
2e	H	i-C₃H₇	251-254 dec	255 dec[g]	-143[g]	EtOAc	55	C₁₉H₂₅N₃O	C, H, N
2f	H	n-C₃H₇	228-230 dec	236-237 dec[b]	-82	MeCN[h]	22	C₁₉H₂₅N₃O	C, H, N
2g	H	CH(CH₃)(CH₂)₃CH(CH₃)₂	206-210 dec		-53[i]	MeCN	19	C₂₄H₃₅N₃O	C, H, N[j]
2h	H	CH(CH₃)C(CH₃)₃	225-227 dec[d]		-64[d]	MeOH	53	C₂₂H₃₁N₃O·C₄H₄O₄	C, H, N
2i	H	CH₂C≡CH	220-222 dec			MeOH-Et₂O	5	C₁₉H₂₁N₃O	C, H, N

[a] All yields are of recrystallized material. [b] Reference 17. [c] Concentration 0.5 in EtOH. [d] Maleate. [e] M. Semonsky and V. Zikan, *Collect. Czech. Chem. Commun., 25,* 1190 (1960); see also *Chem. Abstr., 54,* 14288 (1960). [f] Concentration 0.4 in pyridine at 27°. [g] Reference in footnote e reports -133° at 20°. [g] See Table I, footnote j. These workers report $[\alpha]^{20}D$ -140°, concentration 0.5 in pyridine. [h] Crude product was chromatographed on column of alumina prior to recrystallization. [i] Concentration 0.3 in CHCl₃. [j] N: calcd, 11.01; found, 11.57.
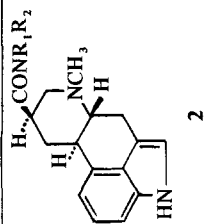
saturated lysergamide. The stereochemistry of the reduction of the second double bond which creates the tetrahydro system remains to be defined.

The introduction of substituents into the indole portion of the lysergic acid moiety was limited to the N-n-butyl and N-isopropyl amides since animal studies showed that these were potent emetics (Table VII). The reaction of the 9,10-dihydrolysergamides with a slight excess of N-bromosuccinimide[13] afforded the corresponding 2-bromo derivatives 9 and 10 (Table V). Treatment of the same 9,10-dihydrolysergamides with 2 equiv of bromine in AcOH yielded the 2,13-dibromo derivatives 11 and 12. The use of elemental bromine gave a much cleaner reaction product than did NBS. However, as expected, NBS is more specific than Br₂ for substitution at the 2 position of indoles as shown by the fact that treatment of 9,10-dihydro-N-isopropyllysergamide with only 1 equiv of Br₂ yielded a mixture of the 2-bromo and 2,13-dibromo derivatives.

Treatment of N-n-butyl-2,3,9,10-tetrahydrolysergamide 7a with elemental bromine or pyridinium bromide perbromide failed to yield a well-defined product. However, when the basic nitrogen at position 1 of 7a was masked with an acetyl (13) or 2,2,2-trichloroethoxycarbonyl group (14), bromination proceeded smoothly to yield the 12-bromo compounds 15 and 16, respectively. Removal of the labile protecting group[14] from 16 afforded 17.

Low-temperature nitration of 7a gave a 40% yield of the 13-nitro derivative 18 but attempts to nitrate 9 gave an intractable tar. Compound 18 was readily reduced (82% yield) to the corresponding 13-amino compound 19 which was highly crystalline and stable inspite of the presence of three basic functions.

Attempts were made to obtain 9,10-dihydro derivatives containing a substituent in ring A by dehydrogenation of the appropriate 2,3,9,10-tetrahydro precursor. Unfortunately, all such attempts on 17, 18, and 19 were unsuccessful.
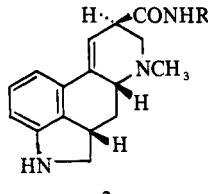
Finally, a number of 1-alkyl and substituted alkyl derivatives of 9,10-dihydro-N-isopropyllysergamide were prepared following previously described procedures[15-17] (Table VI).

Pharmacology. Compounds were examined for their emetic activity by intravenous administration to mongrel dogs of either sex weighing 10-14 kg. Three to four animals were medicated at each dose, at 0.3 log dose intervals. A few of the compounds were soluble in aqueous solution but most required the use of PEG 200 or dilute lactic acid for solubilization. Animals were observed continuously for up to 60 min following medication and only the actual expulsion of gastric contents was scored as emesis.[18]

For each compound, the lowest tested dose able to elicit emesis in any of the animals tested at that dose was recorded as the minimum effective dose. The minimum effective emetic dose thus was an observed value, not a statistically derived value. For potency comparisons, minimum effective dose values serve to show the existence of large potency differences.

A comparison of the results (Table VII) obtained for LSD, ergocristine, ergocryptine, and the individual components of dihydroergotoxine with simple lysergamides, their di- and tetrahydro derivatives, and compounds bearing substituents in the indole ring showed that the ergot alkaloids ergocristine and ergocryptine as well as their 9,10-dihydro derivatives exhibited potent emetic activity. However, in the case of simple lysergamides emetic activity comparable to that of the ergot alkaloids was observed only with the 9,10-dihydrolysergamides of primary amines bearing no substituent on the indole ring. An exception to this finding

Table III. 2,3-Dihydrolysergamides

3

Compd	R	Mp, °C	Recrystn solvent	[α]²⁴D	Yield,ᵃ %	Formula	Analyses
3a	n-C₄H₉	203–205 dec	EtOH	+20ᵇ	75	C₂₀H₂₇N₃O	C, H, N
3b	c-C₆H₁₁	242–244 dec	MeOH	+7ᵇ	54	C₂₂H₂₉N₃O	C, H, N
3c	i-C₃H₇	208–210 dec	MeCN	−7ᶜ	69	C₁₉H₂₅N₃O	C, H, N

ᵃRepresents yield of recrystallized material. ᵇConcentration 0.35 in CHCl₃. ᶜConcentration 0.4 in MeOH.
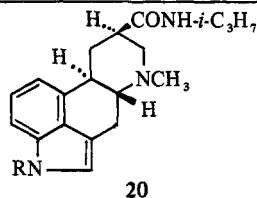
Table IV. Tetrahydrolysergamides 7 and 8

Compd	Mp, °C	Lit. mp, °C	Recrystn solvent	[α]²⁶D	Lit. [α]²⁰D	Formula	Analyses
7a	204–205 dec		MeCN	+12.2ᵃ		C₂₀H₂₉N₃O	C, H, N
8a	187–189 dec		MeCN	−38ᵃ		C₂₀H₂₉N₃O	C, H, N
7b		228–230ᵇ			+8ᶜ		
8b		239–241 decᵈ			−90ᶜ		
7c	222–225 dec		MeCN	e		C₁₉H₂₇N₃O	C, H, N

ᵃConcentration 0.4 in CHCl₃. ᵇReference 11. ᶜConcentration 0.5 in CHCl₃. ᵈReference 12. ᵉSolutions were too colored for accurate measurement of optical rotation.

Table V. Bromo Derivatives of R₃
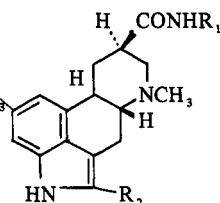
Compd	R₁	R₂	R₃	Mp, °C	Recrystn solvent	[α]²⁵Dᵃ	Yield,ᵇ %	Formula	Analyses
9	n-C₄H₉	Br	H	234–236 dec	MeCN	−90	46	C₂₀H₂₆BrN₃O	C, H, Br, N
10	i-C₃H₇	Br	H	225–227 dec	MeCN	−90.5	47	C₁₉H₂₄BrN₃O	C, H, Br, N
11	n-C₄H₉	Br	Br	248–253 dec	MeCN		26	C₂₀H₂₅Br₂N₃O	C, H, Br, N
12	i-C₃H₇	Br	Br	245–248 dec	MeCN		50	C₁₉H₂₃Br₂N₃O	C, H, Br, N

ᵃConcentration 0.4 in MeOH. ᵇRepresents yield of recrystallized material.

Table VI. 1-Substituted 9,10-Dihydro-N-isopropyllysergamides

20

Compd	R	Method of prepn	Mp, °C	Recrystn solvent	Yield,ᵃ %	[α]²⁴Dᵇ	Formula	Analyses
20a	CH₃	C	149–151	Me₂CO-n-heptane	36	−91	C₂₀H₂₇N₃O	C, H, N
20b	n-C₃H₇	C	243–245	Me₂CO	62		C₂₂H₃₁N₃O	C, H, N
20c	CH₂OCH₃	c	237–239	EtOAc-petroleum ether	64		C₂₁H₂₉N₃O₂	C, H, N
20d	CH₂N(CH₃)₂	D	201–203 dec	Me₂CO-n-hexane	46	−68	C₂₂H₃₂N₄O	C, H, N
20e	CH₂-c-N(CH₂CH₂)₂NCO₂Et	D	199–201	Me₂CO-n-heptane	38	−68	C₂₇H₃₉N₅O₃	C, H, Nᵈ

ᵃRepresents yield of recrystallized material. ᵇConcentration 0.5 in EtOH. ᶜSee Experimental Section. ᵈN: calcd, 14.54; found, 14.08.

was the 2-bromo derivative **10** of **2e** which possessed emetic activity comparable to that of the parent compound **2e**.

Experimental Section

Melting points are uncorrected and were determined on a Mel-Temp apparatus. The structures of all novel compounds were confirmed by nmr, ir, and uv spectroscopy. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn. Where analyses

are indicated only by symbols of the elements, these were within ±0.4% of the theoretical values.

Amidation of Lysergic Acid. Method A. d-N-Cyclohexyllysergamide Maleate (1c). A stirred slurry of 3.15 g (11 mmol) of d-lysergic acid monohydrate and 9.5 g (96 mmol) of cyclohexylamine in 150 ml of CHCl₃ was heated to reflux. The heat was removed and 2 ml (3.4 g, 22 mmol) of POCl₃ was added over a 2-min period at such a rate as to maintain reflux. At the end of the addition, the mixture was kept at reflux for 4–5 min until an amber-colored solution resulted. The solution was cooled to room temperature and washed with 200 ml of 1 M NH₄OH. The CHCl₃ solution was dried

Table VII. Emetic Activity of Lysergamides

Compd	Dog emesis, min effective dose, mg/kg iv	Compd	Dog emesis, min effective dose, mg/kg iv
LSD maleate	>1	2h	0.01
Ergocristine	0.012	3a	>1.0
Ergocryptine	0.01	3b	>0.1
9,10-Dihydroergo-cornine	0.003	3c	>0.1
		7a	>1.0
9,10-Dihydroergo-cristine	0.025	7c	>0.1
		9	>0.1
9,10-Dihydroergo-cryptine	0.006	10	0.03
		11	>0.1
1a	>1.0	12	>0.1
1e	>0.1	17	>0.1
2a	0.025	18	>0.1
2b	0.025	20a	1.0
2c	0.050	20b	>1.0
2d	>0.1	20c	1.0
2e	0.05	20d	1.0
2f	0.003	20e	>1.0
2g	0.1		

(MgSO₄), filtered, and concentrated *in vacuo* (no higher than 40°). Last traces of solvent were removed at 2–5 mm. The viscous residue was dissolved in a minimum amount of MeOH and acidified with a freshly prepared 20% solution of maleic acid in MeOH. Crystallization occurred spontaneously. The fluffy needles were filtered, washed with cold MeOH, and air-dried. The product (2.2 g) was used without further purification.

Method B. *d-N-tert-*Butyllysergamide Maleate (1b). A refluxing slurry of 3.15 g of *d*-lysergic acid in 150 ml of CHCl₃ was treated with 7.1 g (96 mmol) of *tert*-butylamine in 25 ml of CHCl₃ and 2 ml of POCl₃ which were added simultaneously from separate dropping funnels over 2–3 min. The reaction mixture was kept at reflux for another 3–5 min until a clear, amber solution resulted. The solution was cooled to room temperature and worked up in the same manner as described above giving 2 g of 1b. The reactants were scaled up eight times for the preparation of 1e.

Isolation of the Free Base. The maleate (2 g) was dissolved in a mixture of 25 ml of MeOH and 10 ml of 1 *M* NH₄OH. Upon the slow addition of 100 ml of water to the solution, the lysergamide crystallized as the free base. It was filtered and air-dried. If the lysergamide oiled out, it was extracted into CH₂Cl₂ and recovered by evaporation of the solvent under reduced pressure. If the free base thus obtained was homogeneous on tlc (SiO₂, 15% MeOH/CHCl₃) it was used without further purification. Otherwise it was recrystallized from the appropriate solvent.

*d-N,N-*Di-*n*-butyl-9,10-dihydrolysergamide (2d). A solution of 1.95 g of *d-N,N-*di-*n*-butyllysergamide in 150 ml of absolute EtOH was mixed with 0.8 g of 10% Pd/C and shaken under hydrogen at room temperature for 3 hr at an initial pressure of 2.8 kg/cm². The catalyst was removed by filtration and the filtrate concentrated *in vacuo*. The resulting solid residue was recrystallized from MeCN yielding 1.5 g of 2d.

All compounds listed in Table II (except 2i) were prepared by this general procedure. Other suitable catalysts were 5% Pd/C and 5% Pd–Al₂O₃.

*d-*9,10-Dihydro-*N*-(2-propynyl)lysergamide (2i). A solution of 1.2 ml of 2-propynylamine in 5 ml of pyridine was added during 5 min to a stirred slurry of 1.2 g of 9,10-dihydrolysergoyl chloride hydrochloride[4] in 30 ml of CH₂Cl₂ at 0°. The reaction mixture was kept under N₂ at 0° for 15 min and then the temperature was allowed to rise to 20° during the next 90 min. The reaction mixture was extracted with 3 *M* NH₄OH; the CH₂Cl₂ solution was dried and concentrated under reduced pressure. Trituration of the residue with MeCN caused the crystallization of 2i. The solid was recrystallized by solution in a minimum amount of MeOH followed by the addition of four volumes of Et₂O.

*d-N-n-*Butyl-2,3-dihydrolysergamide (3a). While the reaction temperature was maintained at 10–20°, 200 ml of concentrated HCl was added dropwise (3 hr) to a vigorously stirred suspension of 1.0 g of 1a and 10 g of Zn dust in 100 ml of absolute EtOH under N₂. During this time an additional 90 g of Zn dust was added at intervals in about 20-g portions. Because the van Urk–Smith color test[19,20] on the reaction mixture was still positive after 5 hr, the reaction mixture was stirred at room temperature overnight; the indole test was then negative. Excess Zn was filtered off and concentrated

NH₄OH was added to the filtrate at 10–20° until the white Zn salts initially formed were completely dissolved by excess base. The aqueous solution was extracted with CH₂Cl₂; the organic extract was washed, dried (Na₂SO₄), and evaporated to dryness under reduced pressure at 30–40°. Recrystallization from EtOH gave 0.55 g of 3a as pale-yellow felted needles.

Bis(4-phenyl-1-piperazinyl)phosphinic Chloride (4). During 1–2 min 1.0 ml (11 mmol) of POCl₃ was added to a refluxing solution of 3.9 g (24 mmol) of *N*-phenylpiperazine and 3.0 ml (22 mmol) of redistilled Et₃N in 100 ml of CHCl₃. The solution was refluxed for 15 min, cooled to room temperature, and washed with water. Concentration of the dried CHCl₃ solution to dryness under reduced pressure left 3.85 g of a colorless crystalline residue. Recrystallization from MeOH gave 2.55 g (57%) of 4, mp 154–156°. The compound was identical with the substance isolated from attempted amidation of *d*-lysergic acid with *N*-phenylpiperazine. *Anal.* (C₂₀H₂₆ClN₄OP) C, H, Cl, N, P.

*d-*2-Bromo-*N-n-*butyl-9,10-dihydrolysergamide (9). A solution of 1.3 g (7.2 mmol) of *N*-bromosuccinimide in 40 ml of dry dioxane was added to a stirred solution of 1.95 g (6 mmol) of 2a in 100 ml of dioxane. The resulting amber-colored solution was placed in a preheated oil bath (65–70°) for 15 min. The partially cooled solution was diluted with water and made basic by the addition of 10% Na₂CO₃ solution. The milky solution was extracted with CHCl₃; the extract was washed with water, dried, and evaporated to give a pale-orange solid residue which was chromatographed on a column of neutral Al₂O₃ (Activity II) using CHCl₃ as eluent. This gave 1.1 g of 9 as a tan solid after one recrystallization from MeCN. In a similar manner, 10 was prepared.

*d-*2,13-Dibromo-9,10-dihydro-*N*-isopropyllysergamide (12). A solution of Br₂ in AcOH (5 mmol in a 5% solution) was added to a solution of 160 mg (0.5 mmol) of 2e in 5 ml of AcOH. The mixture was stirred at room temperature for 4 hr, poured onto ice, and made basic by addition of 10% aqueous K₂CO₃. The product was extracted into CH₂Cl₂; the extract was washed with water, dried, and evaporated to dryness under vacuum to give a solid residue. The residue was recrystallized twice from MeCN to yield 930 mg of 12 as a cream-colored solid, mp 245–248° dec. Compound 11 was obtained in a similar fashion.

*d-*1-Acetyl-*N-n-*butyl-2,3,9,10-tetrahydrolysergamide (13). To 200 mg of 7a was added 2.0 ml of cold Ac₂O. The mixture was refrigerated for 1 hr, filtered, and washed with Et₂O. Recrystallization of the solid from MeCN gave 170 mg (75%) of the 13, mp 250–252°. *Anal.* (C₂₂H₃₁N₃O₂) C, H, N.

*d-N-n-*Butyl-2,3,9,10-tetrahydro-1-(2,2,2-trichloroethoxycarbonyl)lysergamide (14). A suspension of 1.11 g of 7a in 40 ml of 1 *N* NaOH was stirred and cooled in an ice–salt bath while 4.0 ml of 2,2,2-trichloroethoxycarbonyl chloride was added. The suspension was stirred at 0° for 3.5 hr, then was diluted with water, and extracted with CH₂Cl₂. The combined extracts were washed with water, dried, filtered, and evaporated to dryness under reduced pressure. The solid residue was recrystallized twice from EtOH yielding 833 mg (52%) of 14 as a cream-colored solid, mp 234–237° dec. *Anal.* (C₂₃H₃₀Cl₃N₃O₃) Cl.

*d-*12-Bromo-*N-n-*butyl-2,3,9,10-tetrahydro-1-(2,2,2-trichloroethoxycarbonyl)lysergamide (16). A solution of 1.0 g of 14 in 20 ml of glacial AcOH was treated at room temperature with an equimolar quantity of Br₂ added as a 5% AcOH solution. The solution was stirred for 4.5 hr and then was poured onto ice to give a flocculent precipitate. The mixture was made basic with 10% NaOH (with cooling). The mixture was then extracted with CH₂Cl₂. The combined extracts were washed with water, dried, filtered, and evaporated to dryness. The solid residue was recrystallized from EtOH giving 823 mg (71%) of 16, mp 210–211° dec. *Anal.* (C₂₃H₂₉BrCl₃N₃O₃) Br; Cl: calcd, 18.28; found, 17.80. Compound 15 was prepared following the same procedure, mp 258–260° dec. *Anal.* (C₂₂H₃₀BrN₃O₂) C, H, Br, N.

*d-*12-Bromo-*N-n-*butyl-2,3,9,10-tetrahydrolysergamide (17). A solution of 820 mg of 16 in 8 ml of glacial AcOH was stirred at room temperature with 820 mg of Zn dust for 1 hr; the course of the reaction was followed with tlc. When starting material had disappeared completely, the reaction mixture was filtered; the filtrate was diluted with cold water and raised to pH 11 by addition of 2 *N* NaOH. The precipitate that formed was extracted into CH₂Cl₂; the extract was washed with water, dried, filtered, and evaporated to dryness. The solid residue was recrystallized from EtOAc giving 343 mg (60%) of 17 as a cream-colored solid, mp 220–222° dec. *Anal.* (C₂₀H₂₈BrNO₃) C, H, Br, N.

*d-N-n-*Butyl-13-nitro-2,3,9,10-tetrahydrolysergamide (18). A mixture of 652 mg (2 mmol) of 7a and 6 ml of cold concentrated

H_2SO_4 was immersed in an ice-salt bath and stirred vigorously for 5-10 min to effect rapid solution. Fuming HNO_3 (0.1 ml, d 1.5) was added from a microsyringe and the solution was stirred at 0-5° for 1 hr. The dark amber-colored solution was poured onto 50 g of ice, and the mixture was made basic by the addition of saturated Na_2CO_3 solution while the temperature was kept at or below 10°. The basic mixture containing a flocculent yellow precipitate was extracted with CH_2Cl_2. The combined extracts were washed twice with saturated NaCl, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The orange semisolid residue was crystallized from MeCN, giving 0.3 g (40%) of fine orange crystals of **18**, mp 252-254° dec. *Anal.* ($C_{20}H_{28}N_4O_3$) C, H, N.

d-13-Amino-*N*-*n*-butyl-2,3,9,10-tetrahydrolysergamide (19). A solution of 280 mg of **18** in 50 ml of absolute EtOH was hydrogenated at room temperature at 1.8 kg/cm² for 1.5 hr over 150 mg of 10% Pd/C. The catalyst was filtered off, the colorless filtrate was evaporated to dryness under vacuum, and the residue was recrystallized from Et_2O-MeOH giving 210 mg (82%) of **19**, mp 228-231° dec. *Anal.* ($C_{20}H_{30}N_4O$) C, H, N.

Preparation of 1-Substituted Lysergamides. Method C. 9,10-Dihydro-*N*-isopropyl-1-*n*-propyllysergamide (20b). A mixture of 730 mg (31.5 mg-atoms) of Na, 15 mg of $Fe(NO_3)_3 \cdot 9H_2O$, and 200 ml of liquid NH_3 was stirred until the blue color disappeared (40 min). **2e** (1 g, 3.2 mmol) was added and stirring was continued for 1 hr, with occasional addition of liquid NH_3 to keep the volume at 200 ml. Then a solution of 4.95 g (30 mmol) of *n*-propyl iodide in 25 ml of Et_2O was added dropwise during 20 min. After another 75 min of stirring, 1 g of NH_4Cl was added and the NH_3 was allowed to evaporate completely. The residue was shaken with a mixture of 100 ml of $CHCl_3$ and 400 ml of water. The $CHCl_3$ solution was dried ($CaSO_4$) and evaporated to dryness under vacuum. The residue was recrystallized from boiling Me_2CO (decolorizing C) to give 715 mg (62%) of **20b** as colorless crystals, mp 243-245°.

9,10-Dihydro-*N*-isopropyl-1-methoxymethyllysergamide (20c). A mixture of 92 mg (4 mg-atoms) of Na sand, 40 ml of dry THF, and 530 mg (4.13 mmol) of dry naphthalene was stirred for 4 hr at room temperature; the final color of the solution was dark green. The solution was cooled to 0° and 1.15 g (3.7 mmol) of **2e** dissolved in 25 ml of THF was added dropwise during 15 min. The resulting clear brown solution was heated to reflux and treated with 350 mg (4.35 mmol) of freshly distilled chloromethyl methyl ether in 10 ml of THF. The mixture was refluxed for 1 hr and stirred at room temperature overnight. The reaction mixture was shaken with 200 g of ice and 100 ml of $CHCl_3$. The organic phase was dried ($CaSO_4$) and concentrated, and the solid residue recrystallized twice from EtOAc-petroleum ether (bp 30-60°) giving 840 mg (64%) of **20c**, mp 237-239°.

Method D. 9,10-Dihydro-1-dimethylaminomethyl-*N*-isopropyllysergamide (20d). A mixture of 1.5 g (0.005 mol) of **2e**, 25 ml of

AcOH, 15 ml of MeOH, and 25 ml of 32% aqueous dimethylamine was stirred at 50° while 12 ml of 40% aqueous formaldehyde was added. The mixture was then stirred at 65-75° for 1 hr, cooled, mixed with an equal volume of saturated aqueous NaCl, and made basic by the addition of K_2CO_3 to the cold solution. The mixture was extracted with $CHCl_3$ and the dried extract was evaporated to dryness. The residue was recrystallized three times from Me_2CO-*n*-hexane (decolorizing C) to give 850 mg (46%) of **20d** as an off-white powder, mp 201-203° dec.

References

(1) A. Hofmann in "Drugs Affecting the Nervous System," A. Burger, Ed., Marcel Dekker, New York, N. Y., 1968, Chapter 5.
(2) S. C. Wang and V. V. Glaviano, *J. Pharmacol. Exp. Ther.*, **111**, 329 (1954).
(3) A. Stoll and A. Hofmann, *Helv. Chim. Acta*, **26**, 944 (1943).
(4) A. Frey, U. S. Patent 3,084,164 (1963).
(5) R. P. Pioch, U. S. Patent 2,736,728 (1956).
(6) W. L. Garbrecht, *J. Org. Chem.*, **24**, 368 (1959).
(7) A. Stoll and A. Hofmann, *Helv. Chim. Acta*, **26**, 2070 (1943).
(8) A. Stoll, A. Hofmann, and Th. Petrzilka, *ibid.*, **29**, 635 (1946).
(9) R. C. Cookson, *Chem. Ind. (London)*, 337 (1953).
(10) A. Stoll, Th. Petrzilka, J. Rutschmann, A. Hofmann, and Hs. H. Gunthard, *Helv. Chim. Acta*, **37**, 2039 (1954).
(11) P. A. Stadler, A. J. Frey, F. Troxler, and A. Hofmann, *ibid.*, **47**, 756 (1964).
(12) A. Hofmann, P. Stadler, F. Troxler, A. Frey, and H. Ott, French Patent 1,298,156 (1962) and Swiss Patent 396,024 (1966).
(13) F. Troxler and A. Hofmann, *Helv. Chim. Acta*, **40**, 2160 (1957).
(14) T. B. Windholz and D. B. R. Johnston, *Tetrahedron Lett.*, 2555 (1967).
(15) F. Troxler and A. Hofmann, *Helv. Chim. Acta*, **40**, 1706 (1957).
(16) F. Troxler and A. Hofmann, *ibid.*, **40**, 1721 (1957).
(17) A. Hofmann and F. Troxler, British Patent 996,062 (1965).
(18) H. L. Borison and S. C. Wang, *Pharmacol. Rev.*, **5**, 193 (1953).
(19) H. W. van Urk, *Pharm. Weekbl.*, **66**, 473 (1929).
(20) M. I. Smith, *Pub. Health Rep.*, **45**, 1466 (1930).

6-Substituted 5-Chloro-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyrazin-2-ones with Hypotensive Activity

James H. Jones,* Wilbur J. Holtz, and Edward J. Cragoe, Jr.

Merck Sharp and Dohme Research Laboratories, Division of Merck and Company, Inc., West Point, Pennsylvania 19486. Received September 1, 1972

The thermal Curtius reaction of a 3-aminopyrazine-2-carboxylic acid azide proceeds with intramolecular cyclization to provide a versatile synthetic route to a wide variety of 1,3-dihydro-2*H*-imidazo[4,5-*b*]-pyrazin-2-ones. Many compounds in this series are potent hypotensive agents in animals; they are also inhibitors of the enyzme cyclic AMP phosphodiesterase *in vitro*.

Very few imidazo[4,5-*b*]pyrazines have been reported in the literature[1-3] and no good general method has been available for preparing compounds in this most interesting heterocyclic class. We have found that the Curtius reaction of a 3-aminopyrazine-2-carboxylic acid azide (Scheme I) proceeds with intramolecular cyclization to provide, in good yield, a wide variety of the subject compounds. We will report here only the 6-substituted 5-chloro-1,3-dihydro-2*H*-

imidazo[4,5-*b*]pyrazin-2-ones.[†] Most of these compounds are potent inhibitors[4] of cyclic AMP phosphodiesterase *in vitro*, and *in vivo* these compounds lower blood pressure because of peripheral vasodilatory properties. Most of the compounds also possess bronchodilatory and cardiac-stim-

---

†This tautomer most probably represents the true structure of the compounds and is named according to Chemical Abstracts nomenclature.