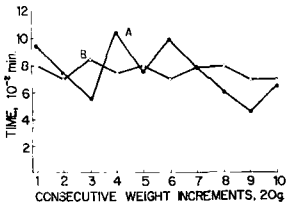


Fig. 6—Increment time measurements showing the effect of particle size of an ingredient comprising 12% of a powder mixture on the uniformity of flow. Key: A, < 40 mesh; B, 16–40 mesh.

formulations were subsequently tableted on the single-rotary press. Tablet weight data using the F test at 95% confidence limits indicated the more uniform flowing formulation had significantly less tablet weight variation.

SUMMARY

Instrumentation has been described for the qualitative and quantitative evaluation of the uniformity of flow of powders through a hopper orifice. For the qualitative evaluation, a recording powder flowometer was utilized in which a recorder tracing identifies fluctuating or inconsistently flowing materials. For quantitative measurement, a print out of the time for preselected weight increments of powder to flow is obtained and the variation in time is a measure of the uniformity of flow. Examples were presented to illustrate the utility of the instrumentation in identifying and evaluating nonuniform flow.

REFERENCES

(1) Gunsel, W. C., and Lachman, L., *J. Pharm. Sci.*, **52**, 178(1963).
(2) Augsburger, L. L., and Shangraw, R. F., *ibid.*, **55**, 418(1966).
(3) Knoechel, E. L., Sperry, C. C., and Lintner, C. J., *ibid.*, **56**, 116(1967).
(4) Gold, G., Duvall, R. N., and Palermo, B. T., *ibid.*, **55**, 1133(1966).
(5) Gold, G., Duvall, R. N., Palermo, B. T., and Slater, J. G., *ibid.*, **57**, 667(1968).

Keyphrases

Powder flow studies
Instrumentation—powder flow
Flow, powders—uniformity
Tablet weight variation—powder flow effect
Diagram—powder flowmeter

Notes

LSD Analogs II. *N*-[2-(3-Pyridyl)ethyl]-β-alanine Derivatives

By KENNETH J. LISKA and ANJANEYULU S. TADEPALLI

As a continuation of the study of structure-activity relationships in LSD analogs, the ethyl esters and *N,N*-diethylamides of *N*-[2-(3-pyridyl)ethyl]-β-alanine and *N*-methyl-*N*-[2-(3-pyridyl)ethyl]-β-alanine were prepared and evaluated for antiserotonin activity in the isolated rat fundus. All four compounds and one of the intermediates were found to be devoid of activity. SAR implications are discussed.

THE THEORY OF a biochemical etiology of mental illness, especially of schizophrenia, expounded by Woolley (1) and others, has not gained general acceptance. Yet complete rejection of this theory is not justified, for it appears that insufficient data have been accumulated on all aspects of the problem. Among the various kinds of data needed are those on structure-activity relationships in the various chemical types of psychotomimetics. With these data, it might be possible to draw conclusions regarding the mechanism of action of both natural and unnatural neurochemicals and neurohormones.

The aim of this investigation was to continue the preparation of relatives of lysergic acid diethylamide (LSD). In part I (2), serotonin inhibition was utilized as an index of LSD-like activity, and three β-alanine derivatives were found to possess significant pharmacological properties. In the present work, four additional β-alanine derivatives have been prepared and evaluated, again utilizing serotonin inhibitory activity as the criterion.

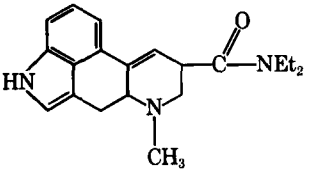
Woolley believed that serotonin was a key substance in any consideration of a biochemical etiology of schizophrenia, and it is true that all of the psychotomimetic indoles antagonize serotonin (3). Past criticisms of the use of serotonin inhibition as an index of LSD-like activity were based in part on the

Received June 17, 1968, from the Departments of Pharmaceutical Chemistry and Pharmacology, School of Pharmacy University of Pittsburgh, Pittsburgh, PA 15213
Accepted for publication August 6, 1968.
Supported in part by grant I-41, Health Research and Services Foundation, Pittsburgh, Pa.
The authors are indebted to Prof. Joseph P. Buckley, Department of Pharmacology, School of Pharmacy, University of Pittsburgh.

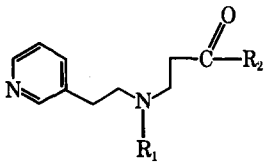
failure of 2-bromolysergic acid diethylamide (BOL) as a psychotomimetic even though it was a serotonin inhibitor. This criticism appears to be less valid when it is realized that substances such as BOL which antagonize serotonin in smooth muscle preparations need not necessarily have the same actions as LSD on the central nervous system. Thus, as Crossland points out (3), the sedative effect of serotonin, injected into cerebral ventricles, is antagonized by LSD but not by bromo-LSD, and there is evidence that bromo-LSD may not reach LSD-sensitive areas as easily as does LSD itself (3).

DISCUSSION

The relationship between LSD and this new type of β-alanine derivative is apparent from a consideration of their structures:



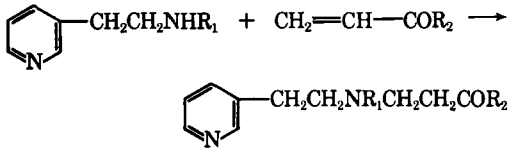
LSD



β-Alanine Derivatives

In place of the pyrrole ring in LSD, the analogs possess a pyridine ring. The simple ester (R_2 = OEt) and the *N,N*-diethylamide (R_2 = NEt_2) were prepared in both the N–H (R_1 = H) and the *N*-methyl (R_1 = CH_3) series.

Addition of primary or secondary amines to acrylic acid derivatives was utilized in all four preparations:



Hydrogenation of 3-pyridineacetonitrile in the presence of alcoholic ammonia afforded 3-(2-aminoethyl)pyridine (Compound I in *Experimental* section). Without the presence of ammonia to suppress secondary amine formation, the yield of the product was reduced by half. Even under optimum conditions, an average yield of 8% of the secondary amine, di-2-(3-pyridyl)ethyl amine (Compound II in *Experimental*) was obtained.

Formylation of the primary amine followed by lithium aluminum hydride reduction of the formaamide gave 3-(2-methylaminoethyl)pyridine (Compound IV). Yields of the *N*-methyl amine were poor owing to the insolubility of the formyl derivative in ether. The formylation was accomplished using formic acid and the primary amine, followed by heating to dehydrate; in each reaction, the simple formate salt could be isolated and recrystallized from *n*-butyl alcohol. It was found to be extremely hygroscopic.

TABLE I—EFFECT OF COMPOUNDS IV, VI, VII, VIII, AND IX IN RESPONSE OF ISOLATED RAT FUNDUS TO SEROTONIN

Compd.	Dose, mcg./ml.	No. of Expt.	Potentiation, %[a] Mean ± *SE*
IV[b]	50	5	117.9 + 6.1
	100	5	130.3 ± 5.2
VI	50	6	159.0 ± 14.15
	100	6	174.0 ± 14.53
VII	50	5	144.0 ± 17.6
	100	5	163.2 ± 23.2
VIII	50	1	121.0
	100	1	110.5
IX	50	1	127.8
	100	1	141.7

[a] Control response to serotonin is taken as 100%. [b] *p* values: Compd. IV, $p > 0.05$; Compd. VI, $p < 0.01$; Compd. VII, $p < 0.05$.

The addition of the primary and secondary amines to ethyl acrylate and to *N,N*-diethylacrylamide proceeded well without the inclusion of any glacial acetic acid. No yield, however, was obtained when 3-(2-aminoethyl)pyridine was allowed to react with acrylamide *per se*. The failure of this specific type of addition has been noted before, and it is assumed that while the desired compound may form initially, it readily decomposes under the conditions of isolation by distillation. All of the new compounds reported herein are water soluble; the tendency to form hygroscopic salts was pronounced.

The pharmacological procedures used were those described in the first paper in this series (2). The results, as summarized in Table I indicate that contrary to expectation, all of the compounds tested were devoid of serotonin inhibitory activity on the isolated rat fundus. Indeed, a slight but significant potentiating action was demonstrated for compounds VI and VII. The active serotonin inhibitors in Series I (2) possessed a group of high electron density on the aromatic ring, whereas the present compounds do not and are devoid of serotonin inhibitory activity. Thus it appears that one of the structural requirements for serotonin inhibition in these β-alanine derivatives, is the presence of groups of high electron density on the N-aromatic portion of the molecule.

EXPERIMENTAL[1]

3(2-Aminoethyl)pyridine (I)—W-2 Raney nickel reduction of commercial 3-pyridine acetonitrile, following the work of Robison and Robison (4), but using absolute alcoholic ammonia in place of aqueous, afforded 3-(2-aminoethyl)pyridine in 71% yield. n_D^{24}1.5379, b.p. 126–128° (24 mm.) [Lit. (4) 114–119° (15 mm.)]; picrate, from ethanol, m.p. 213.5–215° dec. (lit. 213–214° dec.); diHCl, from alcohol, m.p. 207.5–208.5° (lit. 206–207°). Primary amine NH (str.) 3413, 3333 cm.$^{-1}$.

Di-2-(3-pyridyl)ethylamine (II)—This secondary amine was isolated as a by-product in the preparation of Compound I by distillation of the pot residue. It was obtained in an average 8% yield as a yellow, mobile oil, b.p. 174–180° (0.1 mm.), n_D^{28} 1.5631. Secondary amine NH (str.) 3356 cm.$^{-1}$.

[1] M.p. and b.p. are not corrected. M.p.'s were determined in a Thiele apparatus. Analyses by Galbraith Labs. IR data from liquid films taken on an Infracord.

Anal.—Calcd. for $C_{14}H_{17}N_3$: C, 73.97; H, 7.54; N, 18.49. Found: C, 74.10; H, 7.59; N, 18.67.

N-[2-(3-Pyridyl)ethyl]formamide (III)—To Compound I (18.9 g., 0.15 mole), formic acid (7.2 g., 0.15 mole) was added dropwise with stirring in an open beaker. The solid formate salt which resulted was heated on a hotplate until most of the water was driven off as evidenced by cessation of fuming. The 22 g. crude yield was distilled directly, and after discarding a forerun, the fraction b.p. 170—172° (0.7 mm.) was collected as a colorless oil, n_D^{25} 1.5468, amide CO (str.) 1681 cm.$^{-1}$. Obtained 17.9 g. (77%).

Anal.—Calcd. for $C_8H_{10}N_2O$: C, 63.98; H, 6.71; N, 18.66. Found: C, 63.91; H, 6.70; N, 18.67.

3-(2-Methylaminoethyl)pyridine (IV)—Reduction of the formyl derivative (III) was accomplished using $LiAlH_4$, following the general procedure of Baumgarten *et al.* (5), and the work-up given by Mićović and Mihailović (6). The liquid formamide was added dropwise and the reaction mixture was stirred 4 hr. after addition was complete. Repeated ether extractions were found to be essential in the work-up owing to the water solubility of the product. In a typical reaction, the yield was 38% of a colorless oil, b.p. 124–128° (24 mm.), n_D^{29} 1.5185. Secondary amine NH (str.) 3356 cm.$^{-1}$.

Anal.—Calcd. for $C_8H_{12}N_2$: C, 70.55; H, 8.88; N, 20.57. Found: C, 70.49; H, 9.05; N, 20.67. Picrate, from absolute ethanol, m.p. 190–190.5°

N,N-Diethylacrylamide (V)—This was prepared according to the literature (7, 8), b.p. 90–95° (16 mm.), n_D^{26} 1.4655 [lit. 95° (19 mm.), n_D^{20} 1.4672].

N-[2-(3-Pyridyl)ethyl]-β-alanine Ethyl Ester (VI)—Commercial ethyl acrylate (14.4 g., 0.14 mole) was added with swirling to the primary amine (I) (17.6 g., 0.14 mole). The mixture was refluxed gently for 3 hr. and allowed to stand for 20 hr., after which it was distilled directly. After discarding a 1-g. forerun, an amber oil was collected, b.p. 160–170° (2–2.5 mm.), 13.7 g. (43%). n_D^{23} 1.5100, carbonyl CO (str.) 1725 cm.$^{-1}$.

Anal.—Calcd. for $C_{12}H_{18}N_2O_2$: C, 64.83; H, 8.16, N, 12.60. Found: C, 64.72; H, 8.24; N, 12.65.

Picrate, from alcohol, m.p. 138.5–140.5°. The HCl salt could not be obtained crystalline.

3-[2-(3-Pyridyl)ethylamino]-N',N'-diethylpropionamide (VII)—*N,N*-Diethylacrylamide (V) (6.35 g., 0.05 mole) was added dropwise to the primary amine (I). The mixture, protected with a drying tube, was heated under reflux on a steam bath for 4 hr. and then allowed to stand for 16 hr. Distillation yielded a main fraction, 7.9 g., b.p. 155–162° (0.08 mm.), which was redistilled to give 4.5 g. (36%) of a colorless oil, b.p. 160–170° (0.5 mm.). n_D^{29} 1.5083, tertiary amide CO (str.) 1625 cm.$^{-1}$.

Anal.—Calcd. for $C_{14}H_{23}N_3O$: C, 67.43; H, 9.30, N, 16.85. Found: C, 67.49; H, 9.17; N, 17.02.

The HCl salt was prepared crystalline but was very hygroscopic. The picrate crystallized after 4 days standing and was recrystallized from absolute alcohol, m.p. 102–103°, hygroscopic.

N-Methyl-N-[2-(3-pyridyl)ethyl]-β-alanine Ethyl Ester (VIII)—Commercial ethyl acrylate (3.2 g., 0.03 mole) was added with swirling to the secondary amine (IV) (4.2 g., 0.03 mole), and the mixture heated, as in the previous preparation, for 5 hr. and then allowed to stand overnight. Direct distillation gave a main fraction, b.p. 142–147° (0.2 mm.), which was redistilled to give 3.8 g. (52%) of yellow oil, b.p. 141–145° (0.1 mm.). n_D^{29} 1.4938, carbonyl CO (str.) 1727 cm.$^{-1}$.

Anal.—Calcd. for $C_{13}H_{20}N_2O_2$: C, 66.07; H, 8.53; N, 11.85. Found: C, 65.89; H, 8.55; N, 11.79. Picrate, from absolute ethanol, m.p. 143–145°.

3-[N-Methyl-N-2-(3-pyridyl)ethylamino]-N',N'-diethylpropionamide (IX)—*N,N*-Diethylacrylamide (2.8 g., 0.02 mole) was added to the secondary amine (IV) (3.0 g., 0.02 mole) as described in the preparation of VII. The reaction mixture was distilled directly, and after discarding a 2-g. forerun, collected 2.8 g. (48%) of a pale yellow oil, b.p. 170–177° (0.08 mm.). n_D^{25} 1.5089, tertiary amide CO (str.) 1655 cm.$^{-1}$.

Anal.—Calcd. for $C_{15}H_{25}N_3O$: C, 68.40; H, 9.57; N, 15.95. Found: C, 68.20; H, 9.77; N, 15.85. The picrate could not be obtained in a crystalline state.

PHARMACOLOGY

All experimental procedures were the same as for the previous series (2), except for the following. A Grass polygraph model No. 7WC8PA was used instead of a kymograph; the sensitivity of the polygraph was maintained constant for all experiments. The minimum amount of serotonin required to give a response of 7–10 mm. was determined to be 0.5–1.0 ng./ml. of bathing solution.

REFERENCES

(1) Woolley, D. W., "The Biochemical Bases of Psychoses," Wiley, New York, N. Y., 1962.
(2) Liska, K. L., Johnson, J. L., Mastraian, J. P., and Steenberg, M., *J. Pharm. Sci.*, **55**, 1045(1966).
(3) Crossland, J., "Progress in Medicinal Chemistry," Vol. 5, Butterworths, London, 1967, p. 307.
(4) Robison, M. M., and Robison, B. L., *J. Am. Chem. Soc.*, **77**, 6554(1955).
(5) Baumgarten, H. E., Bower, F. A., Setterquist, R. A., and Allen, R. E., *ibid.*, **80**, 4588(1958).
(6) Mićović, V. M., and Mihailović, M. Lj., *J. Org. Chem.*, **18**, 1190(1953).
(7) Norris, P. E., and Blicke, F. F., *J. Am. Pharm. Assoc., Sci. Ed.*, **41**, 637(1952).
(8) Stempel, G. H., Jr., Gross, R. P., and Mariella, R. P., *J. Am. Chem. Soc.*, **72**, 2299(1950).

Keyphrases

LSD analogs—synthesis
Structure-activity relationship—LSD analogs
Antiserotonin activity—LSD analogs
IR spectrophotometry—identity
Refractive index—identity