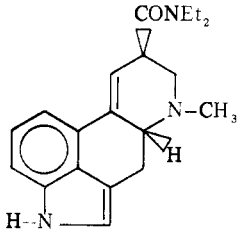
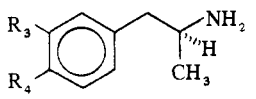
ture views LSD as having the ethylamine side chain arising from the 3 position of the indole nucleus, a closer structural analogy exists when the side chain is joined at the 4 position.[2,3]

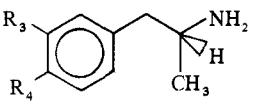
If this is a valid analogy in evaluating optically active mescaline-type agents, one might anticipate *a priori* that the isomer whose absolute configuration was the same as the C-5 position of (+)-LSD (natural, 5*R*, 8*R*)[4,5] (**1**) would possess the psychotomimetic activity. The absolute configurations of phenylisopropylamines are *S*-(+) (**2**) and *R*-(−) (**3**), respectively.[6] Schrecker[7] proved by total synthesis that (+)- and (−)-3,4-dimethoxyphenylisopropylamines (3,4-DMA) are *S*-(+) and *R*-(−), respectively. On such a stereochemical basis, the *R*-(−)-3,4-DMA would be expected to have the mescaline-like actions, while its enantiomer, *S*-(+)-3,4-DMA, would be expected to be much less active. In contrast, unsubstituted phenylisopropylamine has its central effects primarily in the *S*-(+) isomer.



1



2



3

Pharmacology. The compounds and quasiracemate mixtures were tested for an effect on the conditioned avoidance response in the rat as detailed previously.[8] Tables I and II summarize the results of the testing.

At 12.5 mg/kg racemic 3,4-DMA is reported to be equivalent to 25 mg/kg of mescaline in its effects on the rat.[9] The similarity of effects was confirmed in our laboratories.[8] The characteristic effect of racemic 3,4-DMA and mescaline was not observed with either (+)- or (−)-3,4-DMA at doses from 4 to 16 mg/kg. Each enantiomer caused an effect similar to amphetamine, enhanced performance at low doses and toxicity at higher doses. The *R*-(−) isomer was approximately one-third as active as the *S*-(+) isomer.

Since neither enantiomer was able to produce the characteristic effect in rats, it may be necessary for both enantiomers to be present. This hypothesis was tested by simultaneously administering (−)-3,4-DMA · HCl (6–12 mg/kg) and (+)-amphetamine sulfate (1–4 mg/kg). It was found that such quasiracemates could qualitatively reproduce the effect of racemic 3,4-DMA in the rat. The relationship between these studies and psychotomimetic effects in humans is unclear, since the hallucinogenic activity of 3,4-DMA in humans is questionable.[1,‡] However, the results indicate that further work on the effects of psychotomimetic phenylisopropylamine isomers is warranted.

Experimental Section

The 3,4-DMA di-*O*-(*p*-toluoyl)-*d*- or -*l*-tartrate salt was prepared by the method of Kidd,[10] followed by repeated recrystn from 95% EtOH to const sp rotn. The free base was liberated from the complex and neutralized with HCl, and the salt was recrystallized from *i*-PrOH–Et_2O.

‡A. T. Shulgin, personal communication.

Table I. Effect of Enantiomers in the Rat

Drug	Dose	Effect
(+)-3,4 DMA	0.55	None
	2.1	None
	8.1	Amphetamine-like
	16.2	Onset of amphetamine-like toxicity
(−)-3,4-DMA	6.25	Amphetamine-like (similar to 1 mg/kg of amphetamine sulfate)
	25.0	Amphetamine-like (similar to 4 mg/kg of amphetamine sulfate)
	50.0	Onset of amphetamine-like toxicity

Table II. Effect of Quasiracemate Mixtures in the Rat

Dose, mg/kg		
(−)-3,4 DMA · HCl	(+)-Amphetamine sulfate	Effect
6.25	1.0	Activity similar to 12.5 mg/kg of (±)-3,4-DMA
12.5	1.0	Activity and toxicity similar to ~50 mg/kg of (±)-3,4-DMA
25.0	1.0	Activity and toxicity similar to ~50 mg/kg of (±)-3,4-DMA. Followed by death
8.0	4.0	Activity and toxicity greater than that from 50 mg/kg of (±)-3,4-DMA. Followed by death.

Conditioned Avoidance Studies in Rats. Detailed procedure was published previously.[8]

Acknowledgments. The technical assistance of James L. Leseney and James A. Spoden is appreciated.

References

(1) A. T. Shulgin, T. Sargent, and C. Naranjo, *Nature (London)*, **221**, 537 (1969).
(2) B. B. Brodie, S. Spector, and P. A. Shore, *Pharmacol. Rev.*, 11, 548 (1959).
(3) E. Costa, G. L. Gessa, C. Hirsch, R. Kuntzman, and B. B. Brodie, *Ann. N. Y. Acad. Sci.*, **96**, 118 (1962).
(4) H. G. Leemann and S. Fabbri, *Helv. Chim. Acta*, **42**, 2696 (1959).
(5) A. Stoll and A. Hofmann, *Alkaloids*, **3**, 742 (1965).
(6) P. Karrer and E. Ehrhardt, *Helv. Chim. Acta*, 34, 2202 (1951).
(7) A. W. Schrecker, *J. Org. Chem.*, **22**, 33 (1957).
(8) C. F. Barfknecht, J. M. Miles, and J. L. Leseney, *J. Pharm. Sci.*, **59**, 1842 (1970).
(9) J. R. Smythies, V. S. Johnston, R. J. Bradley, F. Benington, R. D. Morin, and L. C. Clark, Jr., *Nature (London)*, **216**, 128 (1967).
(10) D. A. A. Kidd, *J. Chem. Soc.*, 4675 (1961).

4-Amino-2-buten-1-ol Esters†

Robert E. Willette* and Richard C. Driscoll
School of Pharmacy, University of Connecticut, Storrs, Connecticut 06268. *Received July 6, 1971*

In the general structure for the toxic pyrrolizidine alkaloids (**1**) it was noted that the essential feature for toxicity was the presence of an allylic alcohol esterified with a

†This work was supported by grants from the National Cancer Institute, U. S. Public Health Service (CA 10316) and the University of Connecticut Research Foundation. Taken from the dissertation submitted by R. C. Driscoll, in partial fulfillment of the requirements for a Ph.D. degree, University of Connecticut, Storrs, Conn., 1971. Presented at Division of Medicinal Chemistry, 162nd National Meeting of the American Chemical Society, Washington, D.C., Sept 1971.

Table I

R_2N	R'	Isomer	Bp (mm), °C[a]	Mp, °C[b]	Yield, %[a]	pK_a[c]	Formula[d]
			$R_2NCH_2CH=CHCH_2OCOR'$				
C_4H_8NO[e]	CH_3	trans	79-82 (0.06)	127-130.5	70	6.61 ± 0.06	$C_{10}H_{18}ClNO_3$
	$C(CH_3)_3$	trans	81-83 (0.075)	174-177	63	6.64 ± 0.03	$C_{13}H_{24}ClNO_3$
	CH_3	cis	81-83 (0.125)	143-145	52	6.44 ± 0.06[f]	$C_{10}H_{18}ClNO_3$
	$C(CH_3)_3$	cis	87-89 (0.16)	183-185	79	6.41 ± 0.05	$C_{13}H_{24}ClNO_3$
$(CH_3)_2N$[g]	CH_3	trans	30-32 (0.6)	69-71	89	8.97 ± 0.05	$C_8H_{16}ClNO_2$
	$C(CH_3)_3$	trans	43-45 (0.4)	162-164	70	8.98 ± 0.03	$C_{11}H_{22}ClNO_2$

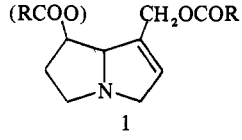
[a]Free base. [b]HCl salt, recrystd from EtOAc, taken in open capillaries and are cor. [c]Average of duplicate detns. [d]All compds were analyzed for C, H, N and are within ±0.3%. [e]Morpholino. [f]Free base titrated with 0.25 *N* HCl. [g]Olomucki[8] reports methiodide, mp 105-106°.

Table II

R_2N	R'	Bp (mm), °C[a]	Mp, °C[b]	Yield, %[a]	Formula[c]
		$R_2NCH_2C\equiv CCH_2OCOR'$			
C_4H_8NO[d]	CH_3	87-89 (0.125)	183-184.5	64	$C_{10}H_{15}NO_3$[e]
	$C(CH_3)_3$	99-102 (0.10)	157-159	63	$C_{13}H_{21}NO_3$[f]
$(CH_3)_2N$	$C(CH_3)_3$	53-54 (0.10)	145-146	62	$C_{11}H_{20}ClNO_2$
C_4H_8N[g]	$C(CH_3)_3$	76-77 (0.15)	142-143	83	$C_{13}H_{22}ClNO_2$
	$CH_3C=CCH_3(H)$[h]	90-92 (0.075)	99-100	69	$C_{13}H_{20}ClNO_2$

[a,b]See footnotes *a* and *b* of Table I. [c]See footnote *d* of Table I. [d]Morpholino. [e]High-resolution mass spectra, *m/e* 197.1047 (calcd 197.1052). [f]Free base. [g]1-Pyrrolidinyl. [h]Methyl groups are cis to one another.

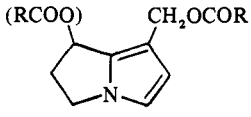
hindered acid.[1] These alkaloids also demonstrated some antitumor activity.[2] The open-chain aminobutenyl esters (**2**) were prepared as one series of models. Since the toxicity has been found to result from a biological activation wherein the tetrahydropyrrolizine ring is dehydrogenated to give highly reactive dihydropyrrolizine esters (**3**),[3] the title com-



1

$R_2NCH_2CH=CHCH_2OCOR'$

2

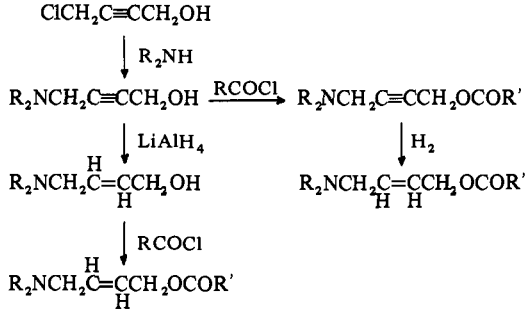


3

pounds, therefore, appear to be poor pyrrolizidine models, and we would like to report their synthesis and properties.

The trans series was prepared by condensation of the desired amine with 4-chloro-2-butyn-1-ol,[4] followed by LAH reduction and esterification (Scheme I). The cis esters were

Scheme I



prepared by esterification of the aminobutynol followed by catalytic reduction.

The configurational assignment is based on classic chemical grounds, *i.e.*, the catalytic reduction of triple bonds and LAH reduction of propargyl alcohols to trans allyl alcohols.[5] The pmr spectra of these were quite unusual and unexpected as detailed in the Experimental Section. Further studies are in progress to verify the apparent reversal in coupling constants between cis and trans olefin protons.[6]

Ionization constants (Table I) for the cis esters are somewhat lower than for the trans esters. Apparently the cis arrangement sterically hinders solvation of the protonated amine as opposed to H-bond formation between the protonated amine and the ester carbonyl, which would be base strengthening.

Preliminary hepatotoxicity studies in mice showed no abnormal liver effects over a range of 100 mg/kg per week for 8 weeks. None of the compds so far reported by CCNSC showed activity over 100% *T/C* in the mouse L 1210 assay.‡

Two new pyrrolidinyl esters are included in Table II. They were not worked with further.

Experimental Section§

trans-4-Morpholino-2-buten-1-ol. To a stirred suspn of 8 g (0.211 mole) of LAH in dry THF (400 ml) was added dropwise over 15 min a soln of 16 g (0.103 mole) of 4-morpholino-2-butyn-1-ol[7] in dry THF (20 ml). The mixt was refluxed for 2 hr, cooled, and treated with NaOH (20%, 4 ml) and H_2O (16 ml). The filtrate and Et_2O washings were dried (Na_2SO_4) and evapd *in vacuo*. The residue was distd to give 11.20 g (70%) of the product as a colorless oil, collected at 92-98° (0.06 mm). The main fraction had bp 93-96° (0.06 mm); high-resolution mass spectra, *m/e*: (M^+) 157.1094 (calcd for $C_8H_{15}NO_2$ 157.1103); nmr ($CDCl_3$) δ 5.70 (quintet, 2, half-bandwidth 10 Hz, vinyl H).

trans-4-Dimethylamino-2-buten-1-ol. From 25 g (0.187 mole) of 4-dimethylamino-2-butyn-1-ol[8] and 12.4 g (0.330 mole) of LAH in dry THF (635 ml), in the same manner as described above, was obtd 17.2 g (69%) of the product as a colorless oil, bp 50-52.5°

‡Liver toxicity studies were conducted in our laboratories by Mr. John Verhulst and histological examinations by Dr. Sven Nielsen, Department of Animal Diseases. L 1210 testing was kindly performed by CCNSC, National Cancer Institute.

§Analyses by Baron Consulting Co., Orange, Conn. High resolution mass spectra by Arthur D. Little, Cambridge, Mass. (NIH contract). The ir and nmr, except where noted, spectra of all compds were as expected. Isomer purity was established by glc. Ionization constants were detd at 25° with a Radiometer Titrimeter, Model TTT1 using 0.25 *N* NaOH as titrant on 0.01 *M* aqueous solutions of the HCl salt contg 0.1 *N* KCl. The values were calcd by standard methods for at least 8 points on the titration curve.

(0.35 mm) [lit.[9] 73°,(2.0 mm), 37% yield by Na reduction].

Trans Esters. The trans esters in Table I were all prepd in the usual manner by addn of the acid chloride in PhH to the alcohol and Et_3N in PhH. Nmr ($CDCl_3$) spectra of all trans esters were similar to that of the alcohol. Under triple irradiation, decoupling both CH_2 groups, the vinyl protons of the morpholino pivalate appeared as a singlet (half-bandwidth 3 Hz).

4-Amino-2-butyn-1-ol Esters. The esters in Table II were prepd as above for the trans esters from the corresponding alcohol and acid chloride.

Cis Esters. The cis esters in Table I were prepd by redn with H_2 and 5% Pd/C in EtOH at room temp and atm pressure to the theoretical amt. Usual work-up and distn; nmr ($CDCl_3$) δ 6.04 (octet, 2, half-bandwidth ~28 Hz). Triple irradiation, as above, showed a quartet (J_{AB} = 11.5 Hz).

Acknowledgment. We wish to thank Mr. John Verhulst for his technical assistance, the University of Connecticut Research Foundation for partial support of this work, and the National Cancer Institute for its support (CA 10316).

References

(1) A. T. Dann, C. C. J. Culvenor, and A. T. Dick, "The Pyrrolizidine Alkaloids," North-Holland, New York, N. Y., 1968.
(2) C. C. J. Culvenor, *J. Pharm. Sci.*, **57**, 1112 (1968).
(3) A. R. Mattocks, *J. Chem. Soc. C*, 1155 (1969); M. V. Jago, J. A. Edgar, L. W. Smith, and C. C. J. Culvenor, *Mol. Pharmacol.*, **6**, 402 (1970); D. N. Black and M. V. Jago, *Biochem. J.*, 118, 347 (1970).
(4) W. J. Bailey and E. Fuglivara, *J. Amer. Chem. Soc.*, 77, 165 (1955); J. H. Biel, E. P. Sprengeler, and H. L. Friedman, *ibid.*, 79, 6184 (1957).
(5) E. B. Bates, E. R. H. Jones, and M. C. Whiting, *J. Chem. Soc.*, 1854 (1954).
(6) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, New York, N. Y., 1969, p 301.
(7) J. H. Biel, E. P. Sprengeler, and H. L. Freidman, *J. Amer. Chem. Soc.*, **79**, 6184 (1957).
(8) M. Olomucki, *Ann. Chim. (Paris)*, **5**, 845 (1960).
(9) M. Olomucki, *C. R. Acad. Sci.*, **237**, 192 (1953).

Directional Nature of Hydrophobic Bonding in Phenethanolamine *N*-Methyl Transferase Inhibitors†

Corwin Hansch* and W. R. Glave
Department of Chemistry, Pomona College, Claremont, California 91711. *Received July 14, 1971*

When a substrate or an inhibitor is bound by an enzyme it is possible that only part of the small molecule makes contact with the macromolecule. Those parts of the small molecule which do not make contact do not contribute to hydrophobic bonding. While relatively few such examples have been established in quantitative terms for sets of congeners, the example of the emulsin hydrolysis of phenyl glucosides is clear-cut.[1] The recent study of Fuller, *et al.*,[2] provides another example. Table I contains their biological data and substituent constants for a series of ring-substituted amphetamines causing 50% inhibition of phenethanolamine *N*-methyl transferase (PNMT) using norepinephrine as the substrate. Fuller, *et al.*, showed[2] that by omitting 5 derivatives (3-Br, 4-OH; 3-Cl, 4-OH; 3,4-$(OH)_2$; 4-OH; 3-OH) the rest of the data could be correlated in 2 equations each containing a linear term in π and σ. For the equation correlating the 17 3,4 derivatives they obtained a correlation coefficient of 0.843 and for the equation correlating the 12 2 derivatives, r was 0.894. The unsubstituted compound was included in each set.

In reexamining this study in the light of our experience with the emulsin work,[1] it was decided to consider the simple monosubstituted meta and para isomers separately. This yielded eq 1 and 2. In the case of eq 1, dropping the σ term yields an equation with the single variable π having r = 0.734. While adding the term in σ is not justified by an F test (we feel this is due to the small number of data points), the coefficient is reasonably close to that of eq 2. Adding a term in π to eq 2 does not give a significant improvement in correlation and the coefficient with the π term in the two-variable equation is quite small (0.22). Hence we assume no hydrophobic interaction from the 4 position and assign π = 0 for all 4 substituents. Further preliminary work suggested that substituents in the 5 and 6 positions were also not involved in hydrophobic binding. Only 3 derivatives are in this category. For these positions π was also taken to be zero.

meta isomers

	n	r	s	
$pI_{50} = 1.54\pi + 1.98\sigma + 2.51$	5	0.863	0.591	(1)

para isomers

	n	r	s	
$pI_{50} = 1.39\sigma + 3.18$	8	0.861	0.256	(2)

Our model, then, for the fit of the inhibitors into a hydrophobic cleft is that only one side is accommodated. The 4, 5, and 6 positions of the inhibitor stand clear of hydrophobic regions of the enzyme. As far as the 5 and 6 positions are concerned, this is a very tentative conclusion since it is based on only 3 molecules having relatively small variance in π. In order to fit the 2-substituted inhibitors into the same equation we have included a steric term for these substituents (E_{s-2}). In addition to these extrathermodynamic postulates it was found that the 3-MeO function behaves in an anomalous manner. To account for this a dummy parameter of 1.00 was assigned to all 3-MeO functions; other molecules were assigned a value of zero for this parameter. Under these conditions we are able to include all but one of the molecules (3,4-$(OH)_2$) of Table I in the single equation

	n	r	s	
$pI_{50} = 0.485(\pm0.23)E_{s-2} + 0.991(\pm0.36)\pi_{-2,3} + 1.408(\pm0.37)\Sigma\sigma - 1.009 \times (\pm0.33)D + 2.550(\pm0.28)$	32	0.940	0.288	(3)

Equation 3 not only includes all of the data in a single equation instead of 2 equations, but it also has the advantage that we have only had to omit one data point instead of the 5 omitted by the Lilly group. In addition, the correlation with eq 3 is much better (r of 0.940 *vs.* r of 0.843 and 0.894) than either of the 2 equations used in the previous effort to correlate these data.

The directional nature of hydrophobic bonding stands out clearly for the 4 position. For example, the 4-CF_3 and 4-OC_6H_5 are well fit by eq 3 assigning π = 0 to these very lipophilic functions.

In designing more potent inhibitors, one would want to place strong electron-withdrawing groups in the 4 position regardless of their lipophilic nature. In fact, nonlipophilic functions such as NO_2 and CN might be best. The largest possible lipophilic function (with due consideration of

†This research was supported by Grant CA 11110 from the National Institutes of Health.