Mescaline and Related Compounds

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This review covers essentially derivatives of phenethylamine and phenylisopropylamine which contain three phenolic hydroxyl groups and their alkyl ethers. They comprise mescaline, its amphetamine analog and their position isomers. The chemistry, biochemistry and pharmacology of these compounds are the subject of sections of this review.

Compilation of these data has been stimulated by the growing interest in psychotomimetic substances for producing 'model psychosis' and for psychotherapy. Information gained from these studies may someday lead to the cause and eventually to the cure of various mental illnesses. The literature has been covered to include all entries through *Chemical Abstracts 64*, No. 7 (March 28, 1966) and selected articles have been added from journals up to that date.

Introduction

Peyote (from the Aztec peyotl) is a small, spineless cactus, *Anhalonium Lewinii* Hennings or *Lophophora Williamsii* Lemaire, which grows wild in North Mexico and the Southwestern United States. The main axis of the plant lies underground and from it arise a number of aerial shoots which are button-shaped or disc-like, from 20 to 50 mm in diameter. In the center of each disc is a tuft of hairs and usually one or more pink flowers. This dried disc is incorrectly called 'peyote button' or 'mescal button', since it does not come from the non-cactus succulent, the mescal proper, from whose fermented sap the brandy mescal is prepared. It is also erroneously called 'mescal bean' which is really the Red Bean, *Sophora secundiflora* (ortega) Lag. ex DC.

Historically peyote has long been used for 'doctoring', witchcraft and religious ceremonies by the American Indians. The Franciscan monk Bernardino de Sahagun in 1560 was the first person to describe peyotl in his writings concerning the conquest of Mexico by Cortez. Hennings of the Botanical Museum of Berlin classified the cactus as belonging to the Anhalonium species and named it *Anhalonium Lewinii* Hennings.

Lewin [1, 2] carried out the first pharmacological tests on the cactus *Anhalonium Lewinii* and the alkaloids present in it. Shortly after Prentiss and Morgan [3], Mitchell [4], Ellis [5], Dixon [6] and Mogilewa [7] described the physiological and hallucinogenic effects of peyote and its alkaloids. Heffter [8] succeeded in isolating a number of alkaloids from the dried peyotl discs. He named the chloroform soluble alkaloid mescaline, which was obtained in 6.3 per cent yield. From the pharmacological tests on animals and from personal experience he found out that mescaline was responsible for the hallucinogenic properties of the cactus [9].

Of the numerous studies on peyotl or mescaline intoxication and its possible relationship to mental disorders the classical publications of Beringer [10], Klüver [11] and La Barre [12] should be mentioned. In his monograph called 'Phantastica' Lewin [13] has described the history of peyotl, its current

and ancient cultic use and its psychic effects on the human beings. Mention should also be made of a recent publication of LA BARRE [14] in which the author discusses various aspects of peyotism and the use of mescaline in psychiatric research.

Occurrence

Mescaline is the principal alkaloid of the cactus *Anhalonium Lewinii* Hennings. HEFFTER [8], KAUDER [15] and SPÄTH and BECKE [16] isolated it from the dried discs of the cactus. It was also found to occur in other Cactaceae, such as *Gymnocalycium gibbosum* (Haw) PFEIFF [17], *Trichocereus terscheckii* (Parmentier) BRITTON and ROSE [18], *Opuntia Cylindrica* [19] and 'San Pedro' or 'Huachuma' cactus, possibly *Trichocereus pachanoi* [20]. Besides mescaline SPÄTH and BRUCK [21, 22] isolated *N*-methyl- and *N*-acetylmescaline from the cactus *Anhalonium Lewinii*. RETI and CASTRILLÓN [18] have isolated *N,N*-dimethylmescaline from *Trichocereus terscheckii*. None of these derivatives of mescaline has been reported as hallucinogenic.

Syntheses

HEFFTER [23–25] thought that mescaline was 3,4,5-trimethoxybenzylmethylamine, which he synthesized and found it to be different from the naturally occurring substance. In 1919, SPÄTH [26] proved the structure of mescaline to be 3,4,5-trimethoxyphenethylamine by the synthesis outlined below:

$$\mathrm{ArCOOH} \longrightarrow \mathrm{ArCOCl} \longrightarrow \mathrm{ArCHO} \longrightarrow \mathrm{ArCH{=}CHNO_2} \longrightarrow \begin{matrix} \mathrm{ArCH_2CH{=}NOH} \longrightarrow \mathrm{ArCH_2CH_2NH_2} \end{matrix}$$

There are many variations of SPÄTH's synthesis for obtaining mescaline and its analogues [27–42]. SLOTTA and HELLER [43] followed a different course for the preparation of mescaline:

$$\mathrm{ArCHO} \longrightarrow \mathrm{ArCH{=}CHCOOH} \longrightarrow \mathrm{ArCH_2CH_2COOH} \longrightarrow \begin{matrix} \mathrm{ArCH_2CH_2CONH_2} \longrightarrow \mathrm{ArCH_2CH_2NH_2} \end{matrix}$$

Trisubstituted phenethylamines have been synthesized from substituted benzyl alcohols by replacing the alcoholic OH by CN and reducing the resulting nitrile to the amine [44–47]. BLOCK [48] has used this method to obtain C^{14}-labeled mescaline.

KINDLER and PESCHKE [49] and AMOS [50] obtained mescaline by the following sequence:

$$\mathrm{ArCHO} \longrightarrow \mathrm{ArCH(OR)CN} \longrightarrow \mathrm{ArCH_2CH_2NH_2} \qquad R = \mathrm{H\ or\ COCH_3}$$

BANHOLZER, CAMPBELL and SCHMID [51] synthesized mescaline by treating trimethoxybenzoyl chloride with diazomethane to obtain a diazoketone which was allowed to react with ammoniacal silver nitrate to give trimethoxyphenylacetamide; $LiAlH_4$ reduction of the amide gave the amine. These investigators also prepared *N*-substituted derivatives of mescaline by using the appropriate amine in place of ammonia.

$$ArCOCl \longrightarrow \underset{(I)}{ArCOCHN_2} \longrightarrow ArCH_2CONH_2 \longrightarrow ArCH_2CH_2NH_2$$

HADÁČEK and coworkers [52] obtained mescaline by a longer route from the diazoketone (I).

$$ArCOCHN_2 \longrightarrow ArCH_2COOCH_3 \longrightarrow ArCH_2COOH \longrightarrow ArCH_2COCHN_2 \longrightarrow ArCH_2CH_2CONH_2 \longrightarrow ArCH_2CH_2NH_2$$

Ar = 3,4,5-trimethoxyphenyl

The trisubstituted phenethylamines listed in the literature are compiled in Tables 1–4.

Biogenesis

LEETE [87] administered DL-tyrosine-2-C^{14} to the cactus *Anhalonium Lewinii* by injection and root feeding. Three weeks later he isolated radioactive mescaline from the homogenized plant by a suitable solvent extraction procedure. His findings indicated that tyrosine may be a direct precursor of mescaline.

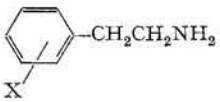
Physical Constants of Mescaline

Mescaline melts at 35–36 °C and boils at 180 °C/12 mm. It is moderately soluble in water, soluble in alcohol, chloroform and benzene. It is almost insoluble in petroleum ether and ether. It takes up carbon dioxide from the air and forms a crystalline carbonate. For the melting points of various derivatives of mescaline please refer to Tables 1–3.

Mescaline picrate in chloroform-toluene (1:1) has a maximum of absorption at 420 mμ. The extinction coefficient of mescaline is 0.028 ± 0.00077 [88]. Mescaline sulfate absorbs ultraviolot light maximally at 268 mμ [89].

BRIGGS et al. [90] have recorded the infrared spectra of a large number of compounds of pharmaceutical interest. The infrared spectrum of mescaline was determined in chloroform solution and five bands – 1456, 1333, 1176, 1125, 1000 cm^{-1} – were assigned for the methoxyl group. BERTRAND [91] has recorded fluorescence spectra of a number of amino acids and amines including mescaline.

Table 1. *Substituted β-Phenethylamines.*



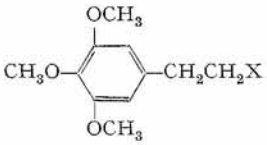
X	m.p. °C or b.p. °C/mm Hg	Salt, m.p. °C	[Ref.]
2,3,4-$(OH)_3$-		HCl, 162–163 °C	[53]
2,4,5-$(OH)_3$-		HBr, 216–218 °C	[54]
3,4,5-$(OH)_3$-		HCl, 213.5 °C	[30]
		Picrate, 193–194 °C	
2,4,5-$(OH)_3$-3,6-$(CH_3)_2$-		HBr, 227-228 °C (decomposed)	[55]
3-OH-4,5-$(OCH_3)_2$-		–	[56]
3-OH-4,5-$(OCH_3)_2$-		HCl, 180–181 °C	[40]
3,5-$(OCH_3)_2$-4-OH-		Picrate, 231–231.5 °C	[35]
		HCl, 258–259 °C	
3,5-$(OCH_3)_2$-4-OH-	153–154 °C	HCl, 256–279 °C	[41]
		Bisulfate, 143–144 °C	
3,5-$(OCH_3)_2$-4-OH-		Picrate, 217–218 °C (decomposed)	[57]
3,5-$(OCH_3)_2$-4-OH-		HCl, 250 °C	[47]
3,5-$(OCH_3)_2$-4-$OCO_2C_2H_5$-		Picrate, 200 °C (decomposed)	[56]
3,5-$(OCH_3)_2$-4-OC_2H_5-		HCl, 165 °C	[44]
3,5-$(OCH_3)_2$-4-OC_2H_5-		HCl, 165–166 °C	[35]
		Picrate, 182–183 °C	
3,5-$(OCH_3)_2$-4-OC_4H_9-		–	[27]
3,5-$(OCH_3)_2$-4-$OCH_2C_6H_5$-	173 °C/0.03	HCl, 156–158 °C	[47]
3,4-$(OCH_3)_2$-5-$OCH_2C_6H_5$-		Picrate, 163 °C	[56]
3,4-$(OCH_3)_2$-5-$OCH_2C_6H_5$-		Oxalate, 188 °C (decomposed)	[38]
		Formate.1 H_2O, 104 °C	
3,4-$(OCH_3)_2$-5-OC_6H_5-		Oxalate, 147–148.5 °C	[58]
3,4-$(OH)_2$-5-OCH_3-		Picrate, 222–223 °C	
		(decomposed)	[36]
		HCl, 206–207 °C	
3,4-$(OH)_2$-5-OCH_3-	173–174 °C	HCl, 198–199 °C	[41]
		Bisulfate, 107–108 °C	
3,4,5-$(OCH_3)_3$-	180–185 °C/12	Sulfate, 2 H_2O, 183–186 °C	[26]
		Picrate, 216–218 °C	
		Chloroplatinate, 187–188 °C	
		Chloroaurate, 1 H_2O, 140–141 °C	
		(decomposed)	
		Benzoate, 120–121 °C	
		m-Nitrobenzoate, 161–162 °C	
		Quaternary methiodide,	
		224–225 °C	
3,4,5-$(OCH_3)_3$-		HCl, 184 °C	[28]
3,4,5-$(OCH_3)_3$-	30–32 °C	HCl, 178–180 °C	[29]
		Picrate, 217–219 °C	
3,4,5-$(OCH_3)_3$-		Acid sulfate, 158 °C	[30]
		HCl, 182 °C	
		Picrate, 218 °C	
3,4,5-$(OCH_3)_3$-		Picrate, 216–218 °C	[31]
		HCl, 182–184 °C	
3,4,5-$(OCH_3)_3$-		Picrate, 214–216 °C	[32]
		HCl, 180–181 °C	

Table 1. (continued)

X	m.p. °C or b.p. °C/mm Hg	Salt, m.p. °C	[Ref.]
3,4,5-$(OCH_3)_3$-		HCl, 184 °C	[33]
3,4,5-$(OCH_3)_3$-	180 °C/12	HCl, 181 °C	[43]
3,4,5-$(OCH_3)_3$-		Acid sulfate, 183 °C Picrate, 217 °C (decomposed) Chloroplatinate, 184–185 °C	[45]
3,4,5-$(OCH_3)_3$-		HCl, 184 °C Picrate, 222 °C	[46]
3,4,5-$(OCH_3)_3$-	35–36 °C	HCl, 184 °C Picrate, 222 °C	[49]
3,4,5-$(OCH_3)_3$-	–	–	[50, 60, 61, 62]
3,4,5-$(OCH_3)_3$-		Picrate, 216 °C	[51]
3,4,5-$(OCH_3)_3$-		Picrate, 218–220 °C Sulfate, 185–186 °C	[52]
3,4,5-$(OCH_3)_3$-		Picrate, 219–220 °C	[59]
3,4,5-$(OCH_3)_3$-		HCl, 178–179 °C	[63]
3,4,5-$(OCH_3)_3$-		Picrate, 219–220 °C	[64]
3,4,5-$(OCH_3)_3$-		Acid sulfate, 1 H_2O, 183–186 °C	[48][1]
2-C_2H_5-3,4,5-$(OCH_3)_3$-		HCl, 148–150 °C	[65]
3,4,5-$(OC_2H_5)_3$-		–	[27]
3,4,5-$(OC_2H_5)_3$-	181 °C/10	HCl, 175 °C Picrate, 155 °C	[28]
3,4,5-$(OC_2H_5)_3$-		HCl, 172–173 °C	[66]
2,4,5-$(OCH_3)_3$-		–	[67]
2,4,5-$(OCH_3)_3$-	66–68 °C		[68]
2,4,5-$(OCH_3)_3$-		HCl, 190 °C Sulfate, 203–205 °C	[69]
2,4,5-$(OCH_3)_3$-		HCl, 187–188 °C (decomposed)	[54]
2,4,5-$(OCH_3)_3$-3,6-$(CH_3)_2$-		HCl, 266–267 °C (decomposed)	[55]
2,3,5-$(OCH_3)_3$-		Picrate, 102 °C	[37]
2,3,5-$(OCH_3)_3$-		Picrate, 158–159 °C	[39]
2,3,4-$(OCH_3)_3$-	170 °C/12	HCl, 167 °C Picrate, 137 °C	[28]
2,3,4-$(OCH_3)_3$-	167 °C/12		[43]
2,3,4-$(OCH_3)_3$-		Picrate, 136-137 °C HCl, 167 °C	[31]
2,3,4-$(OCH_3)_3$-	160–180 °C/1		[70]
2,3,4-$(OC_2H_5)_3$-	165 °C/11	HCl, 185 °C Picrate, 142 °C	[28]
2,3,6-$(OCH_3)_3$-		Picrate, 166-167 °C	[39]
2,4,6-$(OCH_3)_3$-		Picrate, 204–205 °C HCl, 234–235 °C	[34]
2,4,6-$(OC_2H_5)_3$-		Picrate, 206–207 °C HCl, 198–198.5 °C	[34]
2,3,4,5-$(OCH_3)_4$-		HCl, 155-156 °C	[71]
2,3,4,6-$(OCH_3)_4$-		Picrate, 189–190 °C HCl, 168–169 °C	[71]
2,3,5,6-$(OCH_3)_4$-		HCl, 136–137 °C	[71]
2,3,4,5,6-$(OCH_3)_5$-		HCl, 197–198 °C	[71]

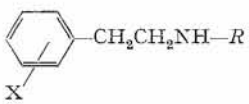
[1] C^{14}-Labeled mescaline.

Table 2. *N-Substituted β-(3,4,5-Trimethoxyphenyl) ethylamines.*



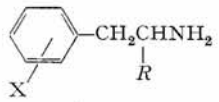
X	Salt, m.p. °C	[Ref.]
$-NHCH_3$	Picrate, 178 °C	[51]
$-N(CH_3)_2$	HCl, 203-205 °C Picrate, 170.5–171 °C	[51]
$-N(CH_3)_2$	Methiodide	[59]
$-N(CH_3)_2$	HCl, 207–208°C	[85]
$-NCH_2C_6H_4 \cdot OCH_3$(m) $\vert$ CH_3	166–166.5 °C	[73]
α,α-Dimethylmescaline	HCl, 219 °C	[86]

Table 3. *N-Substituted β-Phenethylamines.*



X	*R*	m.p. °C or b.p. °C/mm Hg	[Ref.]
3,4-$(OCH_3)_2$-5-OH-	$COCH_2C_6H_4 \cdot OCH_3$(p)	102 °C	[72]
3,4-$(OCH_3)_2$-5-$OCOCH_3$-	$COCH_2C_6H_4 \cdot OCH_3$(p)	135 °C	[72]
3,4-$(OCH_3)_2$-5-$OCH_2C_6H_5$-	$COCH_2C_6H_4 \cdot OCH_3$(p)	88 °C	[72]
3,4-$(OCH_3)_2$-5-OC_6H_5-	$COCH_2C_6H_4 \cdot OCH_3$(p)	88–89 °C	[58]
3,4,5-$(OCH_3)_3$-	COC_6H_5	123 °C	[49]
3,4,5-$(OCH_3)_3$-	COC_6H_5	121 °C	[64]
3,4,5-$(OCH_3)_3$-	COC_6H_5	123–124 °C	[74]
3,4,5-$(OCH_3)_3$-	$CH_2C_6H_4 \cdot OCH_3$(m)	154.5–155 °C	[73]
3,4,5-$(OCH_3)_3$-	2,4-$(NO_2)_2$-C_6H_3	168.5 °C	[69]
3,4,5-$(OCH_3)_3$-	2,4-$(NO_2)_2$-Naphthyl	148.5 °C	[69]
3,4,5-$(OCH_3)_3$-	$CH_2C_6H_5$	220 °C/0.5	[74]
3,4,5-$(OCH_3)_3$-	CH=S	92 °C	[75]
3,4,5-$(OCH_3)_3$-	CH=O	68–69 °C	[76]
3,4,5-$(OCH_3)_3$-	$COCH_2C_6H_3(OCH_3)_2$-3,4	138 °C	[77]
3,4,5-$(OCH_3)_3$-	$COCH_2CH(CH_3)_2$	92–93 °C	[78]
2-Br-3,4,5-$(OCH_3)_3$-	COC_6H_5	114–115 °C	[74]
2,3,4-$(OCH_3)_3$-	$COCH_2C_6H_4 \cdot OCH_3$(p)	77–78 °C	[42]
3,4,5-$(OC_2H_5)_3$	CH=O	67–69 °C	[76]
2,4,5-$(OCH_3)_3$-	2,4-$(NO_2)_2$-C_6H_3	158 °C	[69]
2,4,5-$(OCH_3)_3$-	2,4-$(NO_2)_2$-Naphthyl	150 °C	[69]

Table 4. *Substituted α-Alkyl-β-Phenethylamines.*



X	R	Salt, m.p. °C	[Ref.]
3,4,5-$(OCH_3)_3$-	CH_3	HCl, 220-221 °C	[66]
3,4,5-$(OCH_3)_3$-	CH_3	HCl, 219–220 °C	[79]
3,4,5-$(OCH_3)_3$-	CH_3	HCl, 209 °C	[80]
3,4,5-$(OCH_3)_3$-	CH_3	HCl, 208–209 °C Picrate, 171–173 °C	[81]
3,4,5-$(OCH_3)_3$-	CH_3	HCl, 200 °C	[82]
3,4,5-$(OCH_3)_3$-	C_2H_5	HCl, 192–193 °C Picrate, 177–181 °C	[81]
3,4,5-$(OCH_3)_3$-	n-C_3H_7	HCl, 214–218 °C Picrate, 182–184 °C	[81]
3,4,5-$(OCH_3)_3$-	n-C_4H_9	HCl, 182–184 °C Picrate, 168–170 °C	[81]
3,4,5-$(OCH_3)_3$-	n-C_5H_{11}	HCl, 155–158 °C Picrate, 162–163 °C	[81]
3,4,5-$(OCH_3)_3$-	n-C_6H_{13}	HCl, 132–134 °C Picrate, 149–151 °C	[81]
3,4,5-$(OCH_3)_3$-	n-C_7H_{15}	HCl, 112–116 °C Picrate, 148–149 °C	[81]
2,3,5-$(OCH_3)_3$-	CH_3	HCl, 119 °C	[80]
2,4,5-$(OCH_3)_3$-	CH_3	HCl, 181 °C	[80]
2,3,6-$(OCH_3)_3$-	CH_3	HCl, 125 °C	[80]
2,3,4-$(OCH_3)_3$-	CH_3	HCl, 149 °C	[80, 82]
2,4,6-$(OCH_3)_3$-	CH_3	Picrate, 212–213 °C HCl, 214–215° C	[5]
2,4,6-$(OCH_3)_3$-	CH_3	HCl, 214 °C	[80]
2,4,5-$(OCH_3)_3$-	CH_3	HCl, 181 °C	[82]
2,4,5-$(OCH_3)_3$-	CH_3	HCl, 187 °C	[83]
2,4,5-$(OCH_3)_3$-	CH_3	HCl, 186.5–187.2 °C	[84]
2,4,5-$(OCH_3)_3$-	C_2H_5	HCl, 206–207 °C	[84]
2,4,5-$(OH)_3$-	CH_3	HBr, –	[84]
2,4,5-$(OH)_3$-	C_2H_5	HBr, –	[84]

Color Reactions and Chromatographic Methods

A number of chemical methods are available for the detection and identification of mescaline and related substances [92–98]. Table 5 lists the effect of various reagents on mescaline.

2-Nitro-1,3-indandione has been found useful for the isolation and characterization of mescaline and various other organic bases. Addition of the reagent to the solution of an amine gives a precipitate which can be characterized readily [94]. A modified chromic acid reagent turns paper chromatographic spots of mescaline red [98].

A number of paper [99–104], thin-layer [105, 106] and gas [107] chromatographic methods have been reported for the separation and identification of mescaline; Rf values have been listed for several solvent systems [99, 102, 105, 106, 108]. Typical developing reagents include ninhydrin and Gibb's reagent [109]. The incorporation of C^{14}-labeled mescaline into liver proteins was demonstrated by BLOCK [110] and BLOCK and BLOCK [111] by means of paper chromatography and paper electrophoresis of tissue hydrolyzates. Table 6 lists color reactions and Rf values of mescaline and related substances.

Table 5. *Effect of Various Reagents on Mescaline* [93, 97].

Reagent	Color of Precipitate	Reagent	Observed Color
Bouchardt	Bluish	Erdmann	Deep red
Dragendorff	Red	Froehde	Yellow-green
Jarowski	White	Buckingham	Green-yellow
Mayer	White	Mandelin	Green
Millon	Yellow	Schlagdenhaufen	Green to gray to reddish
Tanret	White	Marquis	Orange
Picric acid	Yellow	Vitali's	Violet turning brown
$HClO_4$	Colorless	Selenium dioxide	Yellow-brown
H_2CrO_4	Gray	Ammonium vanadate	Orange
$HAuCl_4$	Yellow	Ammonium Molybdate	Green-blue
H_2PtCl_6	Yellow		
H_3PO_4	White		

Table 6. *Color Reactions and Rf Value of Substituted Phenethylamines* [109].

Phenethylamine	Ninhydrin	Gibb's Reagent	Rf Value on Paper[1]
3,4,5-$(OCH_3)_3$-	Purple	–	0.74
3,5-$(OCH_3)_2$-4-OH-	Purple	Green blue	0.55
4,5-$(OCH_3)_2$-3-OH-	Yellow	Blue	0.62
3,4-$(OH)_2$-5-OCH_3-	Yellow	Yellow blue	0.40
3,5-$(OH)_2$-4-OCH_3	Yellow	Yellow	0.50
3,4,5-$(OH)_3$-	Yellow	Yellow	0.28

[1] Solvent system: 1-Butanol: Glacial acetic acid: Water (4:1:5).

Analytical Procedures

A number of colorimetric and fluorimetric methods for the determination of mescaline have been described in the literature [112–117]. RICHTER [112] described a method for the determination of amines in human urine. The method depends on the fact that picric acid gives little color while amine

picrates are strongly colored in 50 per cent chloroform-toluene or chloroform-light petroleum solution. The clear yellow solution of amine picrate is compared colorimetrically with solutions prepared in a similar manner from standard amine solutions. DESSI and RIZZOLI [113] improved Richter's method for determination of mescaline in both blood and urine.

Mescaline can be extracted from aqueous solutions by isobutyl alcohol and the quantity estimated by measuring the intensity of absorption at the absorption peak [118]. DESSI and FRANCO [119] made use of Beyer and Skinner reaction for the photometric determination of mescaline. Aqueous solutions of mescaline are treated with *p*-nitrophenyldiazonium chloride, the mixture is made alkaline and the wave-length for maximum absorption is determined. Mescaline absorbs maximally at 510 mμ in aqueous solution and at 530 mμ in butanol solution. This method was improved by VISTOLI [115].

WOODS and coworkers [114] have described a colorimetric method for the estimation of amines in plasma, whole blood, urine and tissue, with special reference to mescaline and cocaine. The amine is extracted from the fluid or tissue with chloroform, the solution purified by passage through a column of powdered sucrose and then mixed with a chloroform solution of bromocresol purple. The optical density of the resulting yellow solution is then determined in a Beckman Du spectrophotometer at 410 mμ. The optical density of mescaline (5 μg/ml in chloroform) is 0.480. Only halogenated phenolsulfonephthalein dyes are useful for color development which depends upon quininoid formation from the dye.

SEILER and WIECHMANN [117] have described a fluorimetric method for the determination of mescaline on thin-layer chromatograms or in solution. This method is based on the conversion of mescaline into an isoquinoline derivative having an intense green fluorescence.

KALÁB [120] has suggested an analytical method for mescaline based on its oscillographic behavior. In N alkaline solution the oscillogram of mescaline showed one indentation at the anode lead and one at the cathode. Deformation occurred in N acid solution. CAVIEZEL and BAILLOD [121] described a device for estimating the motility of mice and thereby differentiate various psychotropic substances by examining their time-activity ratio.

MARINI-BETTÒLO and FRUGONI [122, 123] observed the influence of pH on the electrophoretic separation of the alkaloids. They found that although the separation was possible at a fixed pH in the majority of cases, complex mixtures were best separated by controlled variation of pH. The relative displacements for mescaline at pH 2.3, 4.3, 6.4, 8.2, 10.5 and 11.4 after three hours were: 74, 70.5, 102, 93, 82, 12. WITT [124, 125] and WITT and coworkers [126] developed a method of distinguishing substances with central nervous system action by their effect on the web production by the spider. Small doses of LSD improved exactitude of the angles of the web, while accuracy decreased under the influence of mescaline. This method is too complicated for routine use. From his findings WITT concluded that the similar effect which LSD and mescaline have on man is brought about by attacks from different points [125].

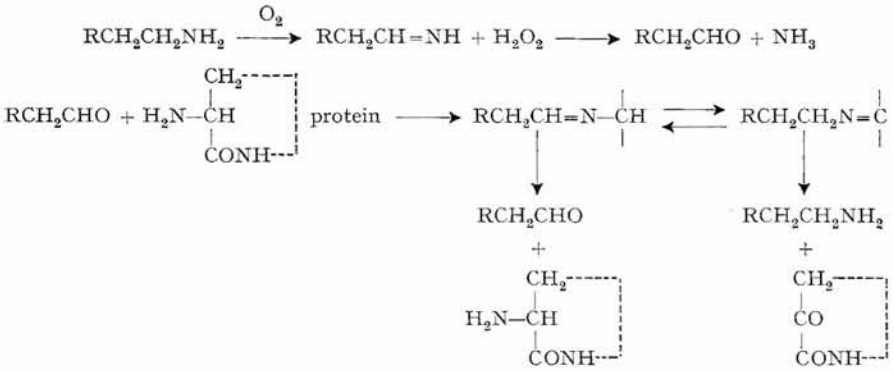
Distribution

Mescaline is readily absorbed from the intestinal tract. TARSITANO [127] injected mescaline into dogs and found the highest concentration in the liver and kidneys, much less in the brain and no appreciable amount in the blood and lungs. COCHIN, WOODS and SEEVERS [128] found that plasma levels reached a peak immediately after intravenous injection of mescaline into dogs, and the drug disappeared from the blood stream from 6 to 8 hours. The concentrations of mescaline in the liver, spleen and kidneys were 3 to 6 times those in the plasma. The level of mescaline in the brain and blood was of the same order of magnitude. VOGT [129] also found much higher levels in liver and kidneys than in blood or brain. She did not find any difference in concentration in the occipital and frontal cortex of monkeys.

BLOCK et al. [111, 130–133] studied the distribution of mescaline-α-^{14}C in mice. Shortly after intraperitoneal injection, highest radioactivity was found in the liver and kidneys, whereas brain and spinal cord were virtually devoid of radioactivity. Mescaline was rapidly incorporated in the liver proteins from which it could be recovered by hydrolysis. The maximum tissue concentration of mescaline coincided with the period of marked autonomic stimulation, while the highest concentration in liver protein corresponded to the period of hallucinations [133].

BLOCK [110, 134, 135] determined the *in vitro* incorporation of mescaline-α-^{14}C into tissue slices. Liver homogenates did not incorporate mescaline in nitrogen atmosphere. If the homogenates were kept under oxygen first and then under nitrogen, mescaline was incorporated. Warming the mixture for a short time to a temperature of 55 °C caused a tenfold increase in reaction rate; addition of tyramine had similar effect. BLOCK therefore concluded that there was an inhibitor, perhaps amine oxidase, for which tyramine had greater affinity. Tyramine blocked the action of the inhibitor competitively and thereby facilitated the incorporation of mescaline. Heating destroyed the inhibitor partially or totally depending upon the temperature. Further work indicated that the inhibitor was not amine oxidase since a number of known inhibitors of amine oxidase failed to increase mescaline incorporation [134]. Cathepsin, phosphorylation and dephosphorylation and glycolytic or respiratory systems had no effect on mescaline incorporation. Heavy metals had a definite influence, while the supernatant gas phase composition had a critical effect. These results indicated that mescaline is incorporated into proteins by some mechanism which is different from that involved in the case of amino acids [135]. Isolated cell nuclei incorporated mescaline readily and heating or tyramine had no effect. Mitochondria and microsomes behaved similarly to the total homogenate. These results led to the conclusion that the incorporation inhibiting factor was localized within mitochondria and microsomes, while cell nuclei did not possess it [136]. BLOCK [136] postulated that mescaline undergoes oxidation to an aldehyde which reacts with free amino groups of protein yielding a schiff base. This schiff base is hydrolyzed to an aldehyde which undergoes further oxidation

to an acid. Alternately, the schiff base may dissociate to mescaline and the oxidized protein.



FISCHER [137–139] used wool protein as a model surface simulating the neuroreceptors involved in drug-induced psychoses. Mescaline, methadrine, LAE and LSD exhibited increasing affinity (absorption) for wool protein, parallel with the decreasing amounts of these drugs required to produce a model psychosis of similar intensity and duration. High affinity of basic compounds for wool appeared to be associated with very potent biological activity. Sympathetic overtonus and subsequent adrenergic blockade seemed to contribute towards the precipitation of a model psychosis.

NEFF and ROSSI [109] administered intravenously mescaline into mongrel cats and observed peak intoxication after 30 min. Autoradiograms of cat brain sections indicated highest concentration of radioactivity in the hypophysis, relatively high levels in the cortical and subcortical gray matter and very little radioactivity in the areas composed largely of myelinated fibers. The biological half-life of mescaline in plasma and cerebrospinal fluid was 1.5 to 2 h. Maximum mescaline concentration in the brain attained between 0.5 to 2 h. roughly paralled the period of maximal intoxication determined by gross observation. CHARALAMPOUS et al. [108a], however, found significant concentrations of radioactivity in the human cerebrospinal fluid through $9^1/_2$ h. after the administration of C^{14}-mescaline.

Metabolism

a) *In vivo* Studies:

Rabbits are 70 times as tolerant to mescaline as man. The most striking effect of mescaline in rabbits and dogs is a strong retention of urine, lasting as long as 48 h. Rabbits excreted 40–50% of the ingested dose of mescaline as 3,4,5-trimethoxyphenylacetic acid. This acid was found to be inert pharmacologically [108, 140]. COCHIN, WOODS and SEEVERS [128] recovered 28–46% of

the administered mescaline from the dog urine. This range was of the same order of magnitude as that found in the human urine by investigators at the Public Health Service hospital in Lexington, Ky. After intramuscular injection mescaline appeared in the urine in detectable amounts 30 min. later with the maximum rate of excretion in 2 to 4 h.

BLOCK and coworkers [100] reported that mice and rats excreted 93% of the intraperitoneally injected mescaline-α-^{14}C in the urine and 5% in the feces. The urinary radioactivity was assigned as follows: In rats: 18.4% mescaline, 72.4% 3,4,5-trimethoxyphenylacetic acid and 9.1% unidentified material. In mice: 79.4% mescaline, 16.2% 3,4,5-trimethoxyphenylacetic acid and 4.4% of unidentified material. SPECTOR [141] injected mescaline-α-^{14}C (I.P.) into mongrel female dogs; peak urinary excretion of radioactivity was observed within 2 h., and 55-62% of the administered radioactivity was excreted during 13 h. He recovered 40% of mescaline and 60% of 3,4,5-trimethoxyphenylacetic acid.

GOLDSTEIN et al. [142] and FRIEDHOFF and GOLDSTEIN [143] isolated 2-(3,4,5-trimethoxyphenyl)ethanol from the urine of rats fed mescaline-1-^{14}C. Normally, mescaline is converted into 3,4,5-trimethoxyphenylacetic acid in rats and very little of the alcohol is formed. Pretreatment with iproniazid inhibits markedly the formation of this acid from mescaline, presumably by blockade of amine oxidase or a specific mescaline oxidase. Calcium carbimide pretreatment, on the other hand, increases the formation of the alcohol at the expense of the acid, because of the inhibition of aldehyde dehydrogenase. The combined effects of mescaline and iproniazid could not be distinguished from that of an equivalent dose of mescaline, indicating that the amine *per se* is not responsible for the effect. Rabbits which were insensitive to a dose of 10 mg/kg I.P. of mescaline developed severe reactions when pretreated with calcium carbimide. Thus aldehyde dehydrogenase inhibition markedly enhanced the pharmacological effect of mescaline. The administration of 2.5 mg/kg i.v. of 2-(3,4,5-trimethoxyphenyl)ethanol to rabbits resulted in a mild mescaline-like effect, which was potentiated considerably when the alcohol was given in combination with calcium carbimide. If the alcohol was ingested alone mild effects were observed after 30 min. Calcium carbimide (I.P.) immediately produced severe effects. From these data FRIEDHOFF and GOLDSTEIN [143] suggested that 3,4,5-trimethoxyphenylacetaldehyde is responsible for the pronounced pharmacological effects of mescaline.

MUSACCHIO and coworkers [144] fed mescaline-α-^{14}C to rats and isolated four substances from the 24-hour urine by means of paper chromatography. They identified *N*-acetyl-3,5-dimethoxy-4-hydroxyphenethylamine (I), *N*-acetyl-3,4-dimethoxy-5-hydroxyphenethylamine (II) and *N*-acetylmescaline (III). The fourth compound was thought to be *N*-acetyl-3,4-dihydroxy-5-methoxyphenethylamine (IV) from its chromatographic behavior. When rats were treated with *N*-acetylmescaline (III), they were able to isolate compounds I, II and IV. These results suggest that *N*-acetylation precedes *O*-demethylation in rats. Recently, NEFF et al. [109] have reported on their failure to isolate

any other metabolite of mescaline except 3,4,5-trimethoxyphenylacetic acid in the cat brain, plasma, cerebrospinal fluid and urine after the administration of C^{14}-labeled mescaline.

In 1935, MÖLLER [145] reported the recovery of 94% of ingested mescaline from the urine of normal subjects, whereas the recovery in psychopathic patients was significantly lower. These results have never been confirmed. SLOTTA and MÜLLER [140] were unable to find either free amine or the 3,4,5-trimethoxyphenylacetic acid in human urine after the ingestion of mescaline. The excretory product was an oil which took up three moles of hydrogen and yielded a substance with the formula $C_{10}H_{17}NO_3$, having one methoxyl and incapable of forming a picrate. RICHTER [112], however, recovered 52% of intravenous dose and 58% of the oral dose of mescaline from human urine in 24 h. Using a modification of Zeisel's method for determining methoxyl groups, SALOMON, GABRIO and THALE [146] recovered 9–39% of the administered oral dose of mescaline in 18 h. from human urine. MOKRASCH and STEVENSON [147] recovered 31% of intravenously injected mescaline from the urine within 6 h. after the administration; 7.4% of the drug was recovered as 3,4,5-trimethoxyphenyl-acetic acid.

HARLEY-MASON, LAIRD and SMYTHIES [148] have identified 3,4-dihydroxy-5-methoxyphenacetylglutamine in the urine of humans given mescaline. They recovered 35 ± 5% of mescaline and 1–2% of the metabolite from the urine, but failed to detect 3,4,5-trimethoxyphenylacetic acid. RATCLIFFE and SMITH [40] have recovered small amounts of 3-hydroxy-4,5-dimethoxyphenethylamine besides mescaline from the human urine. CHARALAMPOUS and coworkers [108] reported the excretion of 81.9% of the oral dose of C^{14}-labeled mescaline in the human urine during the first 12 h. An average of 26.2% of the given dose was excreted as 3,4,5-trimethoxyphenylacetic acid. Recent studies from this laboratory showed that 87 and 92% of the orally administered C^{14}-mescaline was excreted in the human urine during the first 24 and 48 h. respectively. The following compounds were identified in the urine: mescaline, 55–60%; 3,4,5-trimethoxyphenylacetic acid, 27–30%; *N*-acetyl-*β*-(3,4-dimethoxy-5-hydroxyphenyl)ethylamine, 5%; *N*-acetylmescaline, < 0.1%. All the four compounds were identified in the cerebrospinal fluid. One human subject given labeled *N*-acetylmescaline excreted 68% of the conjugated *N*-acetyl-*β*-(3,4-dimethoxy-5-hydroxyphenyl)ethylamine and only a trace amount of *N*-acetylmescaline, indicating that *N*-acetylation precedes *O*-demethylation [108a]. FRIEDHOFF and HOLLISTER [108b] recovered only 41.2% off the administered mescaline from the human urine in 24 h.; 23.1% as mescaline and 18.1% as 3,4,5-trimethoxyphenylacetic acid.

b) *In vitro* Studies:

In 1938, BERNHEIM and BERNHEIM [149] demonstrated that rabbit liver contains an enzyme system that oxidizes mescaline readily, rat and guinea pig liver and rabbit kidney very slowly, rat and guinea pig kidney and cat and dog liver and kidney not at all. In comparison with tyramine the rate of

oxidation of mescaline is slow but the corresponding acid is formed by enzyme preparations which form only small quantities of the acid from tyramine. Cyanide, pyrophosphate and borate inhibit mescaline oxidation in concentrations which do not affect the oxidation of tyramine. These findings indicate that some factor other than oxidase is essential. It is possible that some heavy metal is necessary for the oxidation of mescaline. The results of BERNHEIM and BERNHEIM confirmed the work of PUGH and QUASTEL [150] who also observed that mescaline was attacked feebly or not at all by an amine oxidase in brain. ALLES and HEEGARD [151] included mescaline in their studies on substrate specificity of amine oxidase and found that mescaline was not oxidized at all in comparison with the 100% oxidation of phenethylamine. BLASCHKO [152] doubted that amine oxidase takes part in the oxidation of mescaline. He suggested that this is the reason for the high tolerance of rabbits to mescaline. STEENSHOLT [153] claimed to have isolated mescaline oxidase from the rabbit liver which was different from monoamine oxidase. However, he failed to separate this enzyme from MAO.

POLONOVSKI et al. [154] believe that amines having a high affinity for amine oxidase inhibit dopa decarboxylase, while those which inhibit the enzyme very little or not at all have no affinity for amine oxidase. For dilute equimolar solution mescaline caused 35% inhibition of dopa decarboxylase.

SOURKES [155] has postulated that mescaline oxidase and diamine oxidase are identical. ZELLER and coworkers [156] investigated the oxidative deamination of mescaline by various tissue preparations from two ornithologic and seven mammalian species. They believe that mescaline is oxidized by either monoamine oxidase, diamine oxidase or both. CLARK, BENINGTON and MORIN [157, 158] found that the oxidative deamination of mescaline by rabbit liver enzyme was inhibited by semicarbazide, thus confirming the results of ZELLER and coworkers [156]. Mescaline has recently been reported to be a very poor substrate for highly purified human plasma MAO [159].

AXELROD [160] isolated enzyme systems capable of causing *O*-demethylation of mescaline and other aromatic ethers. He also described the presence of an enzyme in the soluble supernatant fraction of rabbit lung which caused *N*-methylation of mescaline [161, 162]. This enzyme was non-specific; *p*-chloromercuribenzoate inhibited the purified enzyme indicating the presence of an essential sulfhydryl group.

DALY, AXELROD and WITKOP [163] have carried out studies on *in vitro* demethylation of mescaline and *in vitro* methylation of its demethylated analogs. Enzymic *O*-demethylation of mescaline-α-^{14}C using a rabbit liver preparation of microsomes and supernatant fraction gave small amounts of 3,4-dimethoxy-5-hydroxyphenethylamine and 3,5-dimethoxy-4-hydroxyphenethylamine; 3,4,5-trimethoxyphenylacetic acid was recovered from the acid fraction. The formation of this acid was inhibited by iproniazid, semicarbazide and by nicotinamide and triphosphopyridine nucleotide; less inhibition was observed with 1-octanol. Enzymic *O*-methylation of 3,4,5-trihydroxyphenethylamine by rat liver catechol-*O*-methyltransferase resulted in the formation

of 3,5-dihydroxy-4-methoxyphenethylamine and small amounts of 3,4,-dimethoxy-5-hydroxy-phenethylamine and 3,4-dihydroxy-5-methoxyphenethylamine (I). Compound I on incubation with *O*-methyltransferase yielded 3,4-dimethoxy-5-hydroxyphenethylamine. Mescaline was reported to be a weak substrate for dopamine-β-oxidase [164].

YAMADA and coworkers [165] isolated crystalline amine oxidase from *Aspergillus niger* capable of oxidizing a wide variety of amines including mescaline. This enzyme was inhibited by metal chelating agents such as 8-hydroxyquinoline, diethyldithiocarbamate and cyanide, and by hydroxylamine, semicarbazide, isoniazid and iproniazid.

According to SEILER [166], who incubated freshly prepared mouse brain homogenates with a solution of mescaline sulfate at 37 °C for 18 h., the oxidation of mescaline is not caused by the diamine oxidase of other organs and plasma but by a monoamine oxidase. The enzyme is bound to the mitochondrial fraction. The principal product of oxidation is 3,4,5-trimethoxyphenylacetic acid.

Biochemical Effects

In 1933, QUASTEL and WHEATLEY [167] observed that mescaline strongly inhibited the oxidation of glucose, lactate, pyruvate and glutamate but not of succinate by minces of guinea pig brain when the substrates were added to the mixture of brain homogenate and mescaline preincubated for 2 to 3 h. Further studies revealed that the mescaline-induced inhibition of the rate of oxygen uptake by guinea pig brain could be reversed to the extent of 83% by washing [168]. SCHUELER [169] confirmed the work of QUASTEL and WHEATLEY. He used succinate as an antidote for mescaline intoxication in man and observed a decrease both in complexity of design and intensity of color of visions. Mescaline was found to be without effect on the oxygen uptake or on the associated phosphorylation in rat brain mitochondria preparation respiring *in vitro* on pyruvate as substrate [170]. It inhibited the oxidation of pyruvate by brain homogenates but produced negligible effect on succinic dehydrogenase, cytochrome oxidase and alkaline phosphatase [171, 172].

Normal tissue from guinea pig cerebral cortex became much more sensitive to mescaline upon electrical stimulation; $10^{-3}\,M$ mescaline caused 50% inhibition, whereas in the absence of electrical stimulation about a 30 times concentration was required to affect the metabolism. However, when the mescaline concentration was lowered to $10^{-4}\,M$ even the stimulated tissue was unaffected [173]. TSUNODA [174] observed that the respiration of unstimulated rat cortex tissue was slightly inhibited by $10^{-2}\,M$ mescaline but not by lower concentrations. There was no inhibition of extra uptake of oxygen of the tissue under electrical stimulation even at a mescaline concentration as high as $10^{-2}\,M$. Upon discontinuation of pulses $10^{-3}\,M$, $3 \times 10^{-3}\,M$ and $10^{-2}\,M$

mescaline inhibited respiration 22.7, 33.8 and 50% respectively. SHATZKO and SIM [175], however, have reported that 0.09 M of mescaline inhibited the respiration of rat brain homogenate in glucose, glutamate and succinate 64, 42 and 42% respectively; higher mescaline concentrations produced greater inhibition of respiration. 2,4-Dinitrophenols did not influence the inhibition of respiration of Ehrlich mouse ascites tumor cells by mescaline [176]. The oxidation of reduced diphosphopyridinenucleotide by subcellular particulate fractions from rat cerebral cortex was 33% inhibited by $1.7 \times 10^{-3} M$ mescaline [177]. The oxidation of serotonin by the rat cerebral amine oxidase was also slightly inhibited by mescaline [178].

BLOCK and coworkers [100] reported that mescaline did not inhibit enzymes of the citric acid cycle or transaminase. Rat brain phosphorylase was depressed *in vivo* [179], but serum glutamate-oxalacetate transaminase activity was enhanced by mescaline [180]. It diminished the rate of appearance of radioactivity in the brains of mice injected with glucose-C^{14} [181]. Synergism between thiamine and mescaline was observed in mice and rats; a combination of the two drugs resulted in death but mescaline alone was not lethal [182]. In normal subjects mescaline decreased the amount of hippuric acid excretion by the administration of glycine and sodium benzoate indicating disturbance of the liver function [183].

STEINER and SULMAN [184] observed that mescaline induced an anxiety reaction and produced notched waves on the EEG of conscious rabbits pretreated with iproniazid; such pretreatment, however, did not influence the lack of effect of mescaline on blood sugar level and urinary excretion of 5-hydroxyindoleacetic acid [185]. Small doses of mescaline caused bradycardia and hypoglycemia and fasting had a protective action. Pretreatment with epinephrine also gave partial protection against these changes but not death, while insulin enhanced hypoglycemia. Alternately, mescaline partially prevented hyperglycemia caused by epinephrine [186]. ELLIS and ANDERSON [187] have reported that mescaline sulfate (10 mg/kg I.P.) has $< 1/100$ the hyperglycemic activity of *l*-epinephrine in the rat.

Mescaline caused hyperglycemia, fall in blood potassium and leucocytosis with eosinopenia in some subjects. The increase in 17-keto steroids was irregular [188]. Within 1 h. after the intravenous injection in mental patients it produced a fall in total amino acids and eosinophils as well as a rise in blood glucose and leucocytes [189]. In the serum of schizophrenics marked decreases in the content of cystine, threonine, tryptophan and phenylalanine were observed [189a]. Chlorpromazine and thioperazine were the most effective in preventing the mescaline-induced fall in ninhydrin-positive substances in serum of psychotic patients. Haloperidol was moderately effective while amytal had no effect. Diethazine and amphetamine intensified the response to mescaline [190, 191]. Clinical results were related to this fall, the greatest fall accompanied the most severe reaction to mescaline. Delayed increase of glucose observed after mescaline injection was, however, unrelated to alterations in ninhydrin-positive substances [190].

Paper chromatographic studies of DESSI and GIANNI [192] indicated an increase in carbohydrate substances but no significant change in alanine and glutamic acid of the brain of rats fed mescaline. Others have reported a significant rise in free alanine in the rat brain after mescaline [193]. Mescaline caused a considerable leakage of glutamic acid from rat brain slices without significantly inhibiting oxygen consumption [194]. In rats it increased liver, diminished kidney and had no effect on the brain uptake of α-aminoisobutyric acid [195].

Mescaline has a very weak inhibitory activity on the norepinephrine uptake by the isolated heart [196]. It caused a slight release of epinephrine from rat adrenal medulla homogenates in the electrolyte medium but not in the sucrose medium [197]. However, it had no influence on rabbit medullary granules [198]. It also decreased glycogen phosphorylase a level in the rat brain *in vivo* [199].

According to WASER and ITZBICKI [200] mescaline decreased histamine concentration in the rat blood. It enhanced histamine responses on rat blood pressure and on the guinea pig ileum [201, 202]. Addition of $10^{-5}M$ mescaline to hog kidney diamine oxidase 3 h. prior to the addition of histamine afforded 90% protection against the administered histamine [202]. KAPELLER-ADLER and MACFARLANE [203] who separated the enzyme histaminase from hog kidney diamine oxidase preparation demonstrated that DAO had no effect on histamine, while histaminase was specifically active on histamine and its derivatives.

Mescaline had no effect on brain sulfhydryl levels but it depressed slightly the total nonprotein sulfhydryl concentration in the liver [204]. It enhanced plasma free fatty acids [205–207]. The degree of mobilization of free fatty acids was not related to the severity of the clinical reaction; other biochemical changes, such as diminished urinary creatinine clearance, increased serum phosphorus and reduced inorganic phosphorus clearance were attributed to stress.

There are conflicting reports in the literature regarding the effect of mescaline on human serum cholinesterase [208, 209]. Mescaline decreased the activity of erythrocyte cholinesterase and plasma pseudo-cholinesterase but was without effect on cerebral cholinesterase of the rat [210]. It also did not influence the cholinergic activity of the brain [211].

CRIGHEL and coworkers [212] observed significant changes in the amino acids of the cortex prior to the onset of epileptogenic focus at two and thirty minutes after topical application of mescaline to the cat cortex; glutaminase I activity was, however, unaffected [213]. Shortly after the topical application of mescaline to the cat cortex the level of ATP was markedly higher and the incorporation of ^{32}P into ATP was greater in the brain tissue of the epileptogenic focus in comparison with that in the contralateral gyrus [214]. According to LEWIS et al. [215] there appears to be some correlation between the behavioral stimulation in the rat and the increase in brain levels of phosphocreatine, ATP and ATP/ADP ratios produced by mescaline.

Neurophysiological Effects

MARRAZZI and coworkers [216–221] and MARRAZZI [222, 223] studied the effects of various substances on cerebral synaptic transmission by using the transcallosal pathway connecting symmetrical points in the right and left optic cortex of the cat and recording the postsynaptic electric response evoked by presynaptic submaximal stimulus. Mescaline-induced inhibition of synaptic transmission was partially prevented by chlorpromazine, reserpine and azacyclonol [218, 219, 222]. ROVETTA [224] applied mescaline to the cortex of anesthetized cats and observed a marked increase in amplitude and prolongation of the latency of the evoked cortical potentials to light flash or to direct cortical stimulation. When applied to the lateral geniculate it produced a two to four fold increase in all components of the response to light flash. Intravenous administration of mescaline slightly diminished the amplitude but enhanced the duration of cortical and geniculate potentials evoked by photic stimulation. PENNES [225], however, obtained results contradictory to those of ROVETTA. He found that topical mescaline had no constant effect, whereas intravenous injection of mescaline diminished or abolished the evoked potentials elicited by photic or electric stimulation. When applied to the cortex of cats it modified the evoked primary and secondary responses and amplified the negative retarded phase. Reserpine potentiated but chlorpromazine antagonized these changes [226, 227].

Mescaline injected intraperitoneally into cats induced spontaneous action potentials originating from the retina [228, 229]. SMYTHIES and coworkers [230] studied the effect of mescaline on the optic evoked potentials in rabbits. In large doses it caused an initial inhibition followed by a facilitation of the primary wave and a decreased latency; the later waves were progressively more susceptible to the inhibitory effect and less susceptible to inhibition.

Mescaline exhibited feebly depressant action on neurones in the cerebral cortex of cats excited by electrical stimulation or by the local application of glutamate [231]. It was relatively ineffective as a depressant of the orthodromic excitation of neurones of the lateral geniculate nucleus of the cat [232]. It prolonged the duration of the preganglionic and of the ganglionic action potentials and produced ganglionic block by virtue of its axonal depressant action. Chlorpromazine, azacyclonol and meprobamate tended to enhance the mescaline-induced block, but the latter was ineffective in reducing the block produced by chlorpromazine [233]. The blocking action of mescaline could be reversed partially or completely by repetitive stimulation [234].

RINALDI and HIMWICH [235, 236] demonstrated that mescaline produced an alert EEG arousal in the curarized, unanesthetized rabbit that could be restored to normal pattern by azacyclonol. Further studies from this laboratory showed that the EEG changes were produced at the medullary level [237]. In rats mescaline increased the low voltage, fast activity and bursts of spikes in the EEGs; chronic administration, however, enhanced only the low voltage, fast activity [238]. Epinephrine was ineffective but iproniazid diminished these

changes. Reserpine augmented the effects of mescaline if administered 24 h. earlier [238, 239]. A correlation between mescaline-induced behavioral and EEG changes has been observed by a number of investigators [240–243]. STERNER [244] has suggested a system of classification of psychotropic drugs based on the EEG changes produced at varying time intervals.

In man, mescaline caused a decrease in the amplitude of the alpha waves and an increase in the periods of quiet of the EEG; the effects persisted for several days [245]. It produced variable changes in the EEG of 25 schizophrenics. The alpha activity decreased or disappeared in 20, increased in 4 and showed relatively little change in one patient. No correlation between brain waves and clinical phenomena was observed in this study [246], although others have found such changes [245, 247–249]. It caused a decrease or disappearance of delta activity in the epileptic; spike wave patterns disappeared for variable periods [250]. It also suppressed the high voltage, slow wave activity induced by electro-convulsive treatment [251]. In post-addicts given mescaline the EEGs showed no change, intermittant or continuous replacement of alpha activity by low voltage, fast activity and/or increase in frequency of alpha rhythms [249, 252]. Morphine and tetraethylammonium chloride were ineffective in relieving the anxiety produced by mescaline, but intravenous injection of barbiturates abolished anxiety promptly [252]. Chloropromazine antagonized the effects of mescaline [248, 253]; prochlorperazine was much less effective and promazine was ineffective [254]. Pretreatment with promethazine, diethazine or chlorpromazine significantly reduced the clinical symptomatology due to mescaline [255]. However, some patients receiving diethazine before mescaline developed an acute state featured by muscular weakness, staggering gait, difficulty in verbalization and acute panic.

Toxicity

The LD_{50} of mescaline in the rat is 330–410 mg/kg I.P., 157 mg/kg i.v. and 534 mg/kg subcutaneously [186, 256]. These values fall within the ranges given by other investigators for mice, frogs and guinea pigs [257–259]. Flexor convulsions and respiratory arrest are the terminal events. Capillary damage in the liver and nitrogen retention in dogs fed mescaline have been reported [260]. The I.P. injection of 0.5 g/kg of sodium succinate in the mouse afforded complete protection against 0.2 g/kg of mescaline [257].

Tolerance and Cross-tolerance

Human subjects and animals receiving mescaline daily become tolerant to mescaline [261–267] and cross-tolerant to LSD [265–267]. The tolerance regresses rapidly and initial responsiveness is attained 3–4 days after the drug

is withdrawn. The tolerance for the vegetative phase does not develop to the same degree as for the psychic phase [268]. No tolerance to the hypoglycemia and bradycardia produced by mescaline was observed by SPECK [186]. Dogs given 5 g/kg of ground peyote buttons acquired tolerance to the emetic effects during the course of one year of daily ingestion [269]. Doses of mescaline producing acute tolerance have no effect on development of the chronic type [270].

Antagonism and Synergism

The systemic administration of the phenothiazine tranquilizers [271–273], reserpine [271, 273, 274], asarone [275], trioxazine [276], lithium carbonate [277], lysergic acid derivatives [278], benactyzine, methylnonyldioxolane, chlorphenoxamine, etc. [273] inhibit various components of the mescaline-induced effects in different animals. However, reserpine injected 24 h. before the mescaline potentiated the action of the latter in mice [279].

Effect on Animal Behavior

In rats mescaline exerted a biphasic effect, initially depressing the conditioned avoidance response and then giving rise to a prolonged excitatory phase. At lower doses, the latter effect was dominant [263]. HARMINE augmented the effect of mescaline [243]. MAFFI [280, 281] observed the effect of mescaline on the secondary conditioned response (SCR) in an experimental avoidance situation; the I.P. ED_{50} for blocking SCR was 32.5 mg/kg. Following an injection of 50 mg/kg only 10% of the animals showed a loss of conditioned response. Dogs under the influence of large doses of mescaline reacted to a conditioned stimulus as if it was the unconditioned one [282]. It offered some protection to albino rats bred to have a high incidence of seizures when exposed to a standard sound [283].

Mescaline produced experimental catatonia in mice, guinea pigs, cats, monkeys, pigeons, etc. [243, 284–291]. Chlorpromazine, reserpine and azacyclonol inhibited these catatonic manifestations [292, 293]. It caused reduction in the behavior patterns called contentment and sociability but increased excitement, aggressive and defensive hostility [294]. Inhibition of isolation-induced attack behavior of mice by mescaline was observed recently [295]. It produced a scratching response in mice, which was antagonized by tetrahydroberberine [296], various tranquilizers, 5-HT, *d*-amphetamine, etc. but not by barbiturates, meprobamate, azacyclonol and mephenesin [278, 297, 298]. Administration of mescaline by intracerebral injection induced aggressive tendencies and paroxysms of ear scratching in mice by doses which were ineffective by other routes [299]. It prolonged and enhanced morphine analgesia in mice [300].

Pharmacodynamic Effects

The effects of mescaline on the cardiovascular and respiratory systems have been studied by various investigators [186, 256, 258, 301–305]. Doses of 4 mg/kg of mescaline produced in dogs no change in blood pressure or either hypotension or hypertension; large doses (20–60 mg/kg) caused a fall in blood pressure, bradycardia, respiratory depression and vasodilation [186, 258, 301–303, 305]. The pressor and depressor effects persisted after section of the vagi, greater and lesser splanchnic nerves, adrenalectomy or atropinization. Moderate doses (8 mg/kg) markedly inhibited the pressor effect of epinephrine without affecting its accelerating effect on cardiac rate. GRACE [258], however, observed that the fall in blood pressure produced by mescaline in anesthetized cats was prevented by vagotomy, decapitation or atropine. Strong solutions of mescaline arrested the perfused frog heart in diastole due to a direct action on the cardiac muscle [258]. It exhibited some sensitization to the cardio-depressant action of Na_2EDTA [306]. Pretreatment of cats and dogs with reserpine enhanced its action on the cardiovascular system and on the nictitating membrane [307]. At a threshold dose of 152 γ/kg i.v. it slightly potentiated the effect of epinephrine on the nictitating membrane of the anesthetized cat [308]. The vasoconstriction produced by the perfusion of 5-HT through the isolated rabbit leg was slightly antagonized by mescaline [309].

The hyperthermic effect of mescaline in rabbits is potentiated by pretreatment with iproniazid or reserpine [310–312]. JACOB and coworkers [313, 314] have observed a correlation between the hyperthermia in rabbits, antianalgesia in mice and hallucinogenic activity in man produced by mescaline. In rats it lowered rectal temperature. It was an effective antipyretic against tetrahydro-2-naphthylamine-induced fever [315].

Mescaline raised the threshold of rats and rabbits to electro-shock [238, 316]. Hypophysectomy reversed this effect [317]. It lowered the threshold of the first twitch induced by intravenous infusion of strychnine [318]. Eserine and prostigmine facilitated the convulsant response produced by the topical application of mescaline to the cat cortex [319].

Mescaline facilitated 5-HT-induced contractions of the isolated rat uterus at lower concentrations and contracted the uterus at higher doses. Atropine had no effect but chlorpromazine inhibited these uterine contractions [320–323]. It caused vasoconstriction of the umbilical vessels of the human placenta [324]. In small doses it enhanced the potentiating effect of 5-HT but blocked the prolongating action of reserpine on hexobarbital hypnosis in mice [325]. It also augmented cerebral 5-HT level and suppressed the protective effect of reserpine against toxicity of amphetamine in mice grouped in small cages [325a]. The favorable results obtained after administration of mescaline in a few cases of amenorrhea were attributed to an antagonism to 5-HT [326].

Mescaline in concentrations over 1:500 produced gradual paralysis and shortening of the isolated gastrocnemius muscle of the frog. It stimulated the contractions of intestine and uterus *in situ* but not when excised [258]. Under

its influence the intestinal muscle was first contracted and later almost paralyzed [301]. HOSHIKAWA [256], however, reported that mescaline caused respiratory stimulation, increased the tone of excised intestine and slightly anesthetized the cornea. It decreased the tonus of the smooth muscle at a concentration of 20 parts per million [303]. The curare-like blockade of the dog peroneal tibialis anticus nerve-muscle preparation by mescaline was antagonized by epinephrine, prostigmine and potassium chloride [327, 328]. In the rabbit and the cat it had no direct effect but it potentiated the inhibition of muscular contractions due to *d*-tubocurarine, gallamine and succinyldicholine [329]. It also stimulated the escape reflexes in mice in low doses and inhibited them in high doses [330].

Effect on Humans

After a latency period depending upon the route of mescaline administration, a number of disagreeable symptoms are felt. After an intravenous dose of 0.5 g of mescaline sulfate nausea, vomiting, sweating, generalized discomfort, dizziness, headache, palpitation, feeling of hot or cold, chest, neck or abdominal cramps and pupillary dilatation occur within 10 min. [331]. There is a small rise in body temperature and systolic blood pressure [265]. Usually, the heart rate is accelerated somewhat, but sometimes a slight bradycardia is observed instead, as a reflex compensation of the hypertension. It increases the threshold for elicitation of the knee-jerk [265].

Although the subjective vegetative symptoms such as nausea and vomiting subside before the development of the psychic symptoms the objective vegetative symptoms like pupillary dilation generally follow the time course of the psychic effects. Abnormal mental states characterized by anxiety, difficulty in thinking, alteration in mood (usually euphoric), altered sensory perception (especially visual), elementary and true hallucinations and alterations of body image have been reported by subjects under the influence of mescaline [265]. These effects generally last from 8 to 12 h. but in some cases prolonged reactions have been reported [148, 332]. Descriptions of the effects of mescaline are given by various investigators [260, 331, 333–337].

Reactions induced by LSD, psilocybin and mescaline are qualitatively similar [265, 338], mescaline being the least potent of the three substances. Psychopathological and physiopathological studies with mescaline produced intoxications simulating schizophrenia [335, 339, 340]. Its effect has catatonic features [339, 341]. An experienced clinical observer can easily distinguish between schizophrenic reactions and the drug-induced psychoses [335]. The disorganization of psychic integration was much more apparent in schizophrenics than in normal subjects given mescaline [342]. It precipitated schizophrenic psychoses in persons suffering from latent schizophrenia and also reactivated the psychosis in patients who improved after psychosurgery [343].

Large doses of mescaline were associated with more vivid hallucinations than were small doses, but the greatest impairment of color vision was observed in subjects receiving small doses [146]. Mescaline and LSD and their combination produced an enhancement in primary suggestibility [344]. Chlorpromazine and meretran blocked the mescaline-induced model psychoses in man [345, 346].

SILVA and coworkers [347] compared the effects of taraxein, a protein fraction obtained from the serum of schizophrenics, with those of mescaline, LSD and psilocybin. There was more dysphoria, blocking and thought deprivation displayed after taraxein than with the three psychotomimetics. Secondary symptoms evoked by the protein fraction were typical of those seen in schizophrenics than the secondary symptoms induced by other substances.

FREDERKING [348] has made use of the mescaline-induced state of intoxication as an aid in psychotherapy. He recommends the use of mescaline when it is desirable to shorten a course of therapy, reactivate a stalled treatment of a neurosis and for the purpose of breaking down memory blocks. Recent studies of TURNS and DENBER [349] indicate that psychotherapy with mescaline is effective in carefully selected cases where other methods have failed.

Theories of Mode of Action of Mescaline

Within the past several years doubt has been raised whether mescaline *per se* is psychotomimetic or whether its action is produced by its breakdown product because of the following observations: (i) Mescaline inhibited the oxidation of glucose, lactate or pyruvate only if it was preincubated with the brain homogenates for two to three hours [167, 169]. (ii) In mice it was rapidly incorporated into liver proteins and during the phase of active C.N.S. effects the brain was almost devoid of it [132]. (iii) It stimulated the contractions of intestine and uterus *in situ* but not when excised [258]. (iv) No correlations were observed between the degree or type of behavioral responses and blood levels or rates of excretion of mescaline in man. The period of maximal behavioral changes followed the period of maximal blood level and excretion by 1–2 h. [147]. (v) The effective dose—400 mg—is much higher than that of other hallucinogens; the effects take from 1–2 h. to develop and 5–6 h. to reach a maximum [148]. (vi) The combined effect of mescaline and iproniazid could not be distinguished from that of an equivalent dose of mescaline [143].

FISCHER [350] suggested that mescaline is converted *in vivo* into a compound resembling LSD, which was responsible for its effect. He proposed that the hypothetical LSD-like compound may be formed from partially demethylated mescaline or through the condensation of very small amounts of mescaline with norepinephrine or 5-HT. GORDON [351] also postulated the formation of an indolic compound *in vivo* from it.

According to QUASTEL and WHEATLEY [167] malfunction of the liver may give rise to abnormal amine metabolites which would affect brain respiration and subsequently produce C.N.S. disturbances. It is not very likely that the hallucinogenic effect of mescaline is directly related to its sympathomimetic action on humans since a number of substances possessing both the C.N.S. and sympathomimetic properties are not hallucinogenic. The competition for adrenergic receptors leading to the disturbance of adrenergic mechanisms has been suggested by SPECK [186]. The disturbance of histamine catabolism in the brain was suggested by CARLINI et al. [202].

MARRAZZI and HART [221] postulated that 'cerebral synaptic inhibition plays a part in the action of hallucinogens either by the direct disruption of normal patterns of synaptic activity responsible for behavior or indirectly by inhibiting normal restraints and thereby releasing aberrant patterns of activity as a result of alteration in the normal balance between cholinergic excitation and adrenergic inhibition at susceptible cerebral synapses'.

SNYDER and MERRIL [352] made molecular orbital calculations for a variety of hallucinogenic and structurally similar nonhallucinogenic analogues in the phenethylamine, amphetamine and tryptamine series and for LSD. They observed a close correlation between the energy of the highest filled molecular orbital of compounds, an index of electron donation, and their hallucinogenic potency.

Studies of the mode of action of mescaline still remains a fertile field of research for those who are interested in it.

Mescaline Analogs

JANSEN [68] synthesized the first isomer of mescaline, the 2,4,5-trimethoxy analog. Experiments on frogs and cats indicated that it possessed pharmacological actions similar to those of mescaline. However, it did not bring about a euphoric state in man. DE JONG [353] and NOTEBOOM [284, 285] reported that several analogs of mescaline produced catatonia in cats. Replacement of the 3-OCH_3 group in mescaline by an OC_2H_5 group markedly increased the toxicity.

GRACE [258] compared the effects of mescaline with those of its 4-ethoxy- and 3,4-diethoxy analogs. Both compounds were about twice as toxic as mescaline when tested on frogs and mice. The symptoms produced by all three were qualitatively similar, motor paralysis due to depression of the C.N.S. and death from respiratory failure. These compounds produced a fall in blood pressure in anesthetized cats, which was prevented by vagotomy or atropine, stimulated the contractions of the intestine and uterus *in situ* and arrested the perfused frog heart in diastole due to a direct action on the cardiac muscle. ELPHICK and GUNN [349] found that substitution of a hydrogen atom on the β-carbon atom of mescaline by a methoxyl group diminished the physiological activity.

BENINGTON and coworkers [34–36, 66, 71, 355, 357] have synthesized several mescaline analogs and their deoxy congeners. CLARK et al. [157, 158, 171, 172] reported results of *in vitro* biochemical studies and behavioral studies of these compounds in cats. Substitution of 4-OCH_3 group in mescaline with CH_3 imparted rage producing properties to the compound, whereas mescaline itself did not induce rage [355]. Other compounds with similar effects were: 3,5-dimethyl-4-methoxy- and 3,4,5-trimethylphenethyl-amines [66, 158]. Amines which produced rage response in cats also caused hyperthermia and were readily deaminated by rabbit liver amine oxidase. Pretreatment with MAO inhibitors increased the rage response. Increasing the aliphatic side chain decreased or abolished the rage reaction [158].

2,4,6-Triethoxyphenethylamine is a strong inhibitor of succinic dehydrogenase and cytochrome c oxidase activity, while mescaline is almost without effect; 4-hydroxy-3,5-dimethoxyphenethylamine and *N*-methylmescaline are moderate inhibitors of these two systems [172]. The oxidation of the following compounds by rabbit liver amine oxidase was inhibited by semicarbazide: 3,4,5-triethoxy-, 3,4,5-trimethoxy-, 3,5-dimethoxy-4-hydroxy-, 3,5,-dimethoxy-4-ethoxy- and 3,5-dimethoxy-4-methylphenethylamines. The oxidation of the following amines was unaffected by semicarbazide: 2,4,5-trimethoxy-, 2,4,5-trimethyl-, 3,4,5-trimethyl- and 2,3,4,5-tetramethyl-phenethylamines. The following amines were not deaminated at a significant rate: 2,3,6-trimethoxy-, 2,4,6-trimethoxy-, and 2,4,6-trimethylphenethyl-amines, tetra- and pentamethoxyphenethylamines and their deoxy analogs. Compounds of this group did not interfere with the oxidation of mescaline by rabbit liver amine

Table 7. *Effect of Phenethylamine Analogs on Brain Alkaline Phosphatase Activity and Pyruvate Utilization* [171]

No.	Compound	AP activity (control = 100)	Pyruvate utilization (control = 100)
1.	4-OH-3,5-$(OCH_3)_2$-Phenethylamine	97	63
2.	4-C_2H_5O-3,5-$(OCH_3)_2$-Phenethylamine	105	29
3.	3,4,5-$(OCH_3)_3$-Phenethylamine	97	58
4.	3,4,5-$(OCH_3)_3$-Phenylisopropylamine	101	50
5.	2,4,6-$(CH_3)_3$-Phenethylamine	46	9
6.	2,4,6-$(C_2H_5)_3$-Phenethylamine	77	5
7.	2,4,6-$(OC_2H_5)_3$-Phenethylamine	57	10
8.	2,4,6-$(OCH_3)_3$-Phenethylamine	88	47
9.	2,4,6-$(OCH_3)_3$-Phenylisopropylamine	90	28
10.	2,3,4,6-$(OCH_3)_4$-Phenethylamine	90	45
11.	2,3,5,6-$(OCH_3)_4$-Phenethylamine	86	61
12.	2,3,4,5,6-$(OCH_3)_5$-Phenethylamine	81	50
13.	*N*-Methylmescaline	105	64
14.	*N*,*N*-Dimethylmescaline	102	–

oxidase. The deamination rate was found to be dependent upon the oxygen tension [158]. Table 7 shows the effect of a series of side-chain, *N*-substituted and ring analogs of mescaline on rat brain alkaline phosphatase (AP) activity and on brain respiration using pyruvate as substrate.

Following generalizations can be made from the foregoing Table: (i) 3,4,5-Trisubstituted compounds have only a slight effect on AP activity. These compounds have strikingly different effect on the pyruvate utilization system. In this case the nature of the substituent has a great influence. Replacement of OH by OCH_3 increases inhibitory action, with still further inhibition being brought about by OC_2H_5 substitution. (ii) The 2,4,6-trisubstituted compounds are strong inhibitors of pyruvate utilization system and AP activity. The AP inhibition decreases in the following order: $CH_3 > C_2H_5O > C_2H_5 > OCH_3$. (iii) Increasing the length of the side chain as seen by examining compounds 3 and 4 and 8 and 9 diminishes inhibition of AP activity but enhances the inhibition of pyruvate utilization. (iv) *N*-Methyl substitution decreases the inhibitory effects of the amines on both enzyme systems.

Mescaline and its amphetamine analog are slight stimulants of lactic dehydrogenase [171].

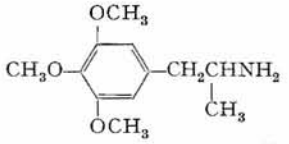
SMYTHIES and LEVY [358] compared the psychopharmacological behavior of some mescaline analogs using the rope climbing test. They found that the removal of the 5-OCH_3 group from mescaline caused a 50% decrease in activity, while demethylation of the 4-OCH_3 group resulted in complete loss of activity. Substitution of benzyloxy group for the 4-OCH_3 group increased the activity. Dopamine had very little behavioral effect but 5-hydroxydopamine had a moderate degree of activity.

Large doses of mescaline produce catatonia and hypokinetic rigid syndrome (HRS) in cats. From experiments with a number of methoxyphenethylamines on cats ERNST [359] confirmed that the occupation of *para* position of phenethylamine molecule by a methoxyl group was essential to produce HRS.

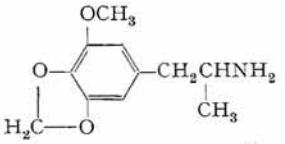
LUDUENA [360] found that trichocereine (*N*,*N*-dimethylmescaline) acts on the C.N.S. and produces convulsions in normal cats but not in decerebrated cats. It does not produce mental disturbances in man. SMYTHIES and SYKES [361, 362] found that unlike mescaline, trichocereine causes negligible inhibition of the conditioned avoidance response and marked excitation similar to that produced by amphetamine. Increasing the dosage delays the onset of the excitation.

HEY [79] synthesized α--methyl-3,4,5-trimethoxyphenethylamine (TMA), a compound structurally similar to amphetamine. PERETZ and associates [363] found that in man doses of 1.6–2.0 mg/kg of TMA produced visual hallucinations without having significant effect on the blood pressure or respiration and caused a mild increase in heart rate. The peak urinary excretion occurred between 2–5 h. and the drug was not detectable in the urine 22 h. after oral administration; 20 to 35% of the ingested dose was recovered unchanged in the urine. SHULGIN and coworkers [364] have confirmed these results. SHULGIN

[81, 82, 365] has synthesized and tested a number of α-alkyl-phenethylamines of the following type:



(I)



(II)

He found that lengthening of the aliphatic chain in I and the enlargement of the heterocyclic ring in II resulted in a decreased human effectiveness. On the other hand, repositioning of the meta methoxyl group, in either of the above compounds, to an available ortho position resulted in an increase in potency [365]. Table 8 lists the effective dose of amines in man, the LD_{50} in mice and the mescaline units in human.

Table 8. *Toxicity and Potency of Substituted Isopropylamines* [82]

No.	Isopropylamine	LD_{50} in mice mg/kg	Effective dose in man μg/kg	Mescaline units (potency compared to mescaline = 1)
1.	3,4,5-$(OCH_3)_3$-	260	1700	2.2
2.	3,4-(CH_2O_2)-5-OCH_3-	150	1400	2.7
3.	2,4,5-$(OCH_3)_3$-	120	220	17
4.	3,4-(CH_2O_2)-6-OCH_3-	130	180	21
5.	2,3,4-$(OCH_3)_3$-	120	>1900	< 2
6.	3,4-(CH_2O_2)-2-OCH_3-	40	210	18

All four isomers are somewhat more toxic than the 3,4,5-trisubstituted analogs. Compound No. 6 is the most toxic of the group and it alone produced clonic convulsions prior to death. In other compounds death occurred due to respiratory arrest. The intoxication syndrome produced by these substances in human is qualitatively similar to that resulting from mescaline, except that the color effects and nausea are absent. Generally, methoxymethylenedioxyamphetamines produce more emphatic and pleasant response; personal anxiety and restlessness are caused by compound No. 3; neither physical nor psychotropic effects are exhibited by it.

SCHOPP and WALSH [328] demonstrated that TMA resembles mescaline in causing an immediate depression of indirectly induced skeletal muscle contractions in the dog peroneal tibialis anticus nerve-muscle preparation. SCHWACHHOFER and coworkers [86, 366, 367] have synthesized a number of α,α-disubstituted derivatives of mescaline. Investigation of the pharmacological properties of these substances revealed that only α,α-dimethylmescaline and α-methyl-α-veratrylmescaline exhibit properties similar to the parent compound [368]. SUPNIEWSKI [369] has reported that β-apioleethylamine

(2,5-dimethoxy-3,4-methylenedioxyphenethylamine) exhibits pharmacodynamic properties similar to those of mescaline. FRIEDMAN and coworkers [259] studied the behavioral effects of mescaline, β-hydroxy-mescaline and N-methyl-β-hydroxymescaline in mice and found that substitutions on mescaline did not dramatically alter the biological activity of the parent substance.

N-Methyl-N-(3-methoxybenzyl)-2, 3, 4-trimethoxyphenethylamine is reported to raise slightly the threshold of electrically induced auricular fibrillation in cats [370].

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