The Chemistry of Peyote Alkaloids[1]

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The fact that several publications, reporting new constituents and biogenetic pathways of peyote, have appeared since the publication of our latest review article (1)—and surely more to come—and the organization of this Symposium all testify that interest in peyote is still far from extinguished. In the lapse of only the past 18 months, fifteen additional constituents of peyote have been reported, bringing the total number of identified constituents of this resourceful cactus to 56 at the time of writing this article.

The earliest chemical studies with peyote were made by Lewin (2) in 1888 who isolated the first crystalline constituent, namely the tetrahydroisoquinoline alkaloid anhalonine (**XXXVIII**; for structures, *cf.* table 1). With the realization that the latter compound possessed no hallucinatory effects, vigorous research was continued to discover the active principle. The studies of Heffter (3–8) towards the end of the century resulted in the discovery of three additional tetrahydroisoquinolines, pellotine (**XXXV**), anhalonidine (**XXX**), and lophophorine (**XLI**) and the identification of mescaline (**XVII**), a β-phenethylamine, as the hallucinogenic principle of the drug. In 1899, another alkaloid, anhalamine (**XXI**), was isolated by Kauder (9). Ernst Späth must be accredited for the structure elucidation and the synthesis of all these alkaloids, publishing his results in a series of reports from 1919 and extending the scope of his investigations to include alkaloids from other Cactaceae up to 1939 (10–28). Späth's contributions included the isolation of five further peyote constituents, namely anhalinine (**XXV**), anhalidine (**XXVII**) (22, 23), *N*-methylmescaline (**XVIII**) (26), *N*-acetylmescaline (**XX**) (27), and *O*-methylanhalonidine (**XXXIII**) (28).

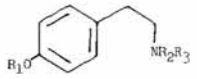
Revival of interest in peyote started in the early 1960's with a report on glc studies (29) of its constituents which revealed the complexity of the alkaloidal mixture and thus drew attention to the seemingly forgotten plant. This coincided with the constantly-growing interest in hallucinogenic drugs in general and with the almost-sudden flourish of activity in biogenetic study. All was much facilitated—and perhaps stimulated—by the availability of modern techniques such as glc, mass spectrometry and use of isotope tracers. The outcome was an avalanche of publications which, for the cactaceae plants, were extended to several species other than peyote, *Lophophora williamsii* (Lemaire) Coulter. The results of studies on peyote showed that this small-sized cactus is by far the richest in alkaloidal contents of all members of the family.

The total alkaloidal content has been estimated (30) to be 3.7% for dried "upper slices of mescal buttons" and 0.41% for fresh peyote heads. Table 2 lists the figures reported by various workers for the percentages of some alkaloids in the plant. A recent study (31), based on measurement of glc peak areas, revealed the percentages given in the same table for the separate components based on the alkaloidal fraction of greenhouse-grown peyote. Those alkaloids which are not listed in table 2 are reported (31) to exist in only trace amounts. Seasonal variations have also been observed (31), whereby the contents of *N*-demethylated compounds (e.g., **XXI** and **XXX**) were higher during late

[1]Presented 24 April 1972 at the Symposium on Peyote, Houston, Texas. The Symposium was sponsored by the Section on Pharmacognosy and Natural Products of the Academy of Pharmaceutical Sciences and the American Society of Pharmacognosy.

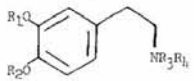
TABLE 1. *Peyote constituents.*

MONO-OXYGENATED PHENETHYLAMINES



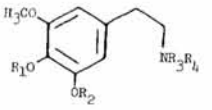
Number and Name	Formula	mp, bp/mm	Substituents			References
			R_1	R_2	R_3	
I. Tyramine	$C_8H_{11}ON$	161°	H	H	H	33, 34
II. *N*-Methyltyramine	$C_9H_{13}ON$	127–128°	H	H	CH_3	33
III. Hordenine	$C_{10}H_{15}ON$	117–118°	H	CH_3	CH_3	32–34
IV. Candicine[a]	$C_{11}H_{19}O_2N$	230–231° (As iodide)	H	CH_3	CH_3	33, 34, 135

DIOXYGENATED PHENETHYLAMINES



			R_1	R_2	R_3	R_4	
V. Dopamine	$C_8H_{11}O_2N$	241° (As HCl)	H	H	H	H	37
VI. Epinine	$C_9H_{13}O_2N$	188–189°	H	H	H	CH_3	37
VII. 4-Hydroxy-3-methoxyphenethylamine	$C_9H_{13}O_2N$		CH_3	H	H	H	37
VIII. *N*-Methyl-4-hydroxy-3-methoxyphenethylamine	$C_{10}H_{15}O_2N$	154–155° (As HCl)	CH_3	H	H	CH_3	37
IX. *N,N*-Dimethyl-4-hydroxy-3-methoxyphenethylamine	$C_{11}H_{17}O_2N$	190–191° (As HCl)	CH_3	H	CH_3	CH_3	37
X. 3,4-Dimethoxyphenethylamine	$C_{10}H_{15}O_2N$	188°/15	CH_3	CH_3	H	H	39

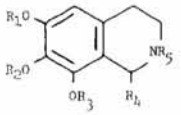
TRIOXYGENATED PHENETHYLAMINES AND THEIR AMIDES



				R_1	R_2	R_3	R_4	
XI.	3,4-Dihydroxy-5-methoxyphenethylamine	$C_9H_{13}O_3N$	207°	H	H	H	H	37
XII.	3-Hydroxy-4,5-dimethoxyphenethylamine (3-Demethylmescaline)	$C_{10}H_{15}O_3N$	178–179° (As HCl)	CH_3	H	H	H	41, 42
XIII.	*N*-Methyl-3-hydroxy-4,5-dimethoxyphenethylamine	$C_{11}H_{17}O_3N$	151–5° (As HCl)	CH_3	H	H	CH_3	43
XIV.	*N*-*N*-Dimethyl-3-hydroxy-4,5-dimethoxyphenethylamine	$C_{12}H_{19}O_3N$	180–185° (As HCl)	CH_3	H	CH_3	CH_3	43
XV.	*N*-Formyl-3-hydroxy-4,5-dimethoxyphenethylamine	$C_{11}H_{15}O_4N$	——[b]	CH_3	H	H	COH	44
XVI.	*N*-Acetyl-3-hydroxy-4,5-dimethoxyphenethylamine	$C_{12}H_{17}O_4N$	102–103°	CH_3	H	H	$COCH_3$	44
XVII.	Mescaline	$C_{11}H_{17}O_3N$	30–32° 180°/12	CH_3	CH_3	H	H	34, 80, 107
XVIII.	*N*-Methylmescaline	$C_{12}H_{19}O_3N$	177.5–178° (As picrate)	CH_3	CH_3	H	CH_3	26, 34
XIX.	*N*-Formylmescaline	$C_{12}H_{17}O_4N$	68–69°	CH_3	CH_3	H	COH	44
XX.	*N*-Acetylmescaline	$C_{13}H_{19}O_4N$	93–94°	CH_3	CH_3	H	$COCH_3$	27, 34, 44

TABLE 1. *Continued.*

TETRAHYDROISOQUINOLINES AND THEIR AMIDES



				R_1	R_2	R_3	R_4	R_5	
XXI.	Anhalamine	$C_{11}H_{15}O_3N$	189–191°	CH_3	CH_3	H	H	H	8, 9, 34
XXII.	*N*-Formylanhalamine	$C_{12}H_{13}O_4N$	——[b]	CH_3	CH_3	H	H	COH	44
XXIII.	*N*-Acetylanhalamine	$C_{13}H_{17}O_4N$	——[b]	CH_3	CH_3	H	H	$COCH_3$	44
XXIV.	Isoanhalamine	$C_{11}H_{15}O_3N$	213–215° (As HBr)	H	CH_3	CH_3	H	H	123
XXV.	Anhalinine	$C_{12}H_{17}O_3N$	61–63°	CH_3	CH_3	CH_3	H	H	22, 34
XXVI.	*N*-Formylanhalinine	$C_{13}H_{17}O_4N$	——[b]	CH_3	CH_3	CH_3	H	COH	44
XXVII.	Anhalidine	$C_{12}H_{17}O_3N$	131–133°	CH_3	CH_3	H	H	CH_3	23, 34
XXVIII.	Anhalotine (as iodide)	$C_{13}H_{20}O_3NI$	219–220°	CH_3	CH_3	H	H	$(CH_3)_2$	135
XXIX.	Isoanhalidine	$C_{12}H_{17}O_3N$	215–218° (As HCl)	H	CH_3	CH_3	H	CH_3	123
XXX.	Anhalonidine	$C_{12}H_{17}O_3N$	160–161°	CH_3	CH_3	H	CH_3	H	5, 34
XXXI.	*N*-Formylanhalonidine	$C_{13}H_{17}O_4N$	——[b]	CH_3	CH_3	H	CH_3	COH	44
XXXII.	Isoanhalonidine	$C_{12}H_{17}O_3N$	209–211° (As HBr)	H	CH_3	CH_3	CH_3	H	123
XXXIII.	*S*-(+)-*O*-Methylanhalonidine	$C_{13}H_{19}O_3N$	140°/0.05, +20.7° (MeOH)	CH_3	CH_3	CH_3	CH_3	H	28, 34
XXXIV.	*N*-Formyl-*O*-methylanhalonidine	$C_{14}H_{19}O_4N$	——[b]	CH_3	CH_3	CH_3	CH_3	COH	44
XXXV.	Pellotine	$C_{13}H_{19}O_3N$	111–112°	CH_3	CH_3	H	CH_3	CH_3	4, 9, 34
XXXVI.	Peyotine (as iodide)	$C_{14}H_{22}O_3NI$	185–186°	CH_3	CH_3	H	CH_3	$(CH_3)_2$	135
XXXVII.	Isopellotine	$C_{13}H_{19}O_3N$	212–222° (As HCl)	H	CH_3	CH_3	CH_3	CH_3	123
XXXVIII.	*S*-(−)-Anhalonine	$C_{12}H_{15}O_3N$	85.5°,−56.3° ($CHCl_3$)	CH_3	—CH_2—		CH_3	H	2, 5, 34, 139, 140
XXXIX.	*N*-Formylanhalonine	$C_{13}H_{15}O_4N$	——[b]	CH_3	—CH_2—		CH_3	COH	44
XL.	*N*-Acetylanhalonine	$C_{14}H_{17}O_4N$	——[b]	CH_3	—CH_2—		CH_3	$COCH_3$	44
XLI.	*S*-(−)-Lophophorine	$C_{13}H_{17}O_3N$	−47° ($CHCl_3$)	CH_3	—CH_2—		CH_3	CH_3	5, 34
XLII.	Lophotine (as iodide)	$C_{14}H_{20}O_3NI$	240–242°	CH_3	—CH_2—		CH_3	$(CH_3)_2$	135
XLIII.	Peyophorine	$C_{14}H_{19}O_3N$	155–156° (As picrate)	CH_3	—CH_2—		CH_3	C_2H_5	133

CONJUGATES WITH KREBS ACIDS

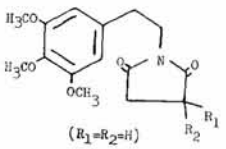
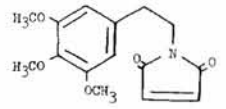
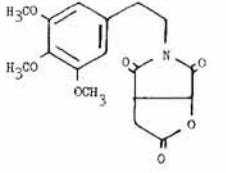
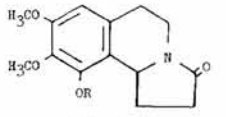
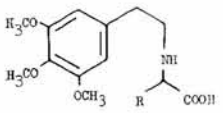
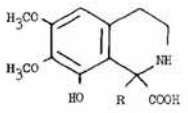
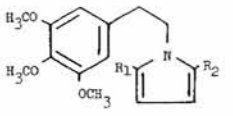
XLIV.	Mescaline succinimide	$C_{15}H_{19}O_5N$	125–126°	 (R_1=R_2=H)	44
XLV.	Mescaline malimide	$C_{15}H_{19}O_6N$	——[b]	XLIV, R_1=OH, R_2=H	44
XLVI.	Mescaline citrimide	$C_{17}H_{21}O_8N$	——[b]	XLIV, R_1=OH, R_2=CH_2COOH	147
XLVII.	Mescaline maleimide	$C_{15}H_{17}O_5N$	——[b]		44
XLVIII.	Mescaline isocitrimide lactone	$C_{17}H_{19}O_7N$	——[b]		147
XLIX.	Peyoglutam	$C_{14}H_{17}O_4N$	217–219°	 (R=H)	44

TABLE 1. *Continued.*

L.	Mescalotam	$C_{15}H_{19}O_4N$	———[b]	XLIX, R=CH_3	44
LI.	Mescaloxylic acid	$C_{13}H_{19}O_5N$	187–189°	 (R=H)	152, 153
LII.	Mescaloruvic acid	$C_{14}H_{21}O_5N$	235–236.5°	LI, R=CH_3	152, 153
LIII.	Peyoxylic acid	$C_{12}H_{15}O_5N$	237–238°	 (R=H)	144, 151
LIV.	Peyoruvic acid	$C_{13}H_{17}O_5N$	233–234°	LIII, R=CH_3	144, 151
PYRROLE DERIVATIVES					
LV.	Peyonine	$C_{16}H_{19}O_5N$	131–133.5°	 (R_1=H, R_2=COOH)	155
LVI.	Peyoglunal	$C_{17}H_{21}O_5N$	———[b]	LV, R_1=CHO, R_2=CH_2OH	147

[a]The presence of candicine was suggested (33) on the basis of tlc evidence but could not be substantiated in a later study (135).
[b]Products identified by glc-mass spectrometry in comparison with authentic preparations.

autumn and winter than the corresponding *N*-methyl derivatives (**XXVII** and **XXXV**, respectively).

The methods employed for isolation depend largely on the nature of the compounds which exist in considerable variety and specific conditions may, therefore, have to be devised for the selective isolation of a particular type. By far the greater bulk of peyote constituents are true alkaloids. Some of these however, are encountered in the nonbasic fractions as amides of formic and acetic acids or as conjugates with certain Krebs cycle acids, while others are amino acids of unique constitution. At least three of the tetrahydroisoquinoline alkaloids occur in the elusive quaternary state in trace amounts. Again, the

TABLE 2. *Alkaloid content in peyote.*

Alkaloid	Content[a] (%)	Ref.
Hordenine (III)	(8)	——
N-Methyl-4-hydroxy-3-methoxyphenethylamine (VIII)	(<0.5)	——
N,N-Dimethyl-4-hydroxy-3-methoxyphenethylamine (IX)	(0.5–2)	——
3-Demethylmescaline (XII)	(1–5)	——
N,N-Dimethyl-3-demethylmescaline (XIV)	(0.5)	——
Mescaline (XVII)	6 (30)	30
N-Methylmescaline (XVIII)	(3)	——
Anhalamine (XXI)	0.1 (8)	8
Anhalinine (XXV)	0.01 (0.5)	22,23
Anhalidine (XXVII)	0.001 (2)	22,23
Anhalonidine (XXX)	5 (14)	5
O-Methylanhalonidine (XXXIII)	(<0.5)	——
Pellotine (XXXV)	0.74 (17)	4
Isopellotine (XXXVII)	(0.5)	——
Anhalonine (XXXVIII)	3 (3)	5
Lophophorine (XLI)	0.5 (5)	5
Peyophorine (XLIII)	(0.5)	——

[a]The figures given in this column are based on the plant weight as reported by various authors. The figures given in parentheses are based on the alkaloidal fraction according to a report by Lundström (31).

procedure of isolation may be oriented by sub-fractionation into phenolic and nonphenolic mixtures. A good number of products have been identified in the gas chromatograms and the nature of products established by study of the mass spectrometric fragmentations and correlation to synthetic models. In much of these studies, it must be mentioned, work has been guided by biogenetic considerations; the existence of certain types (*vide infra*) was actually anticipated or assumed and it was a matter of proving or disproving their presence in given fractions. For convenience, the present discussion shall be given on basis of the structural types available.

THE PHENETHYLAMINES

The phenethylamine constituents of peyote may be classified according to oxygenation pattern (*cf.*, table 1) into derivatives of tyramine, dopamine and 3,4,5-trihydroxyphenethylamine. Their joint occurrence in the same plant tissue reflects the fact, now established, that they are biogenetically interrelated. By column and thin layer chromatographic methods, McLaughlin and Paul (32, 33) have identified in the phenolic fractions four tyramine drivatives, *viz.*, tyramine (I) itself, *N*-methyltyramine (II), hordenine (III), and candicine (IV), all of which were previously encountered in other cacti (34, 35). Hordenine

is by far the most abundant of this group (31) and the results of Todd (36) show that this alkaloid, unlike several other phenethylamine and tetrahydroisoquinoline constituents of peyote, occurs only in the roots where probably active *N*-methylation enzymes are operative.

Six dopamine derivatives have been isolated or identified by glc-mass spectrometric techniques and trapping experiments, and all are attributed to the Agurell-Lundström group (31). They are the diphenolic dopamine (V) (37) and epinine (VI) (31), and their *O*- and *N*-methyl derivatives VII (37), VIII (37, 38), IX (37), and X (39). Although *N*-methylated variants of 3,4-dimethoxyphenethylamine (X) are as yet unknown in peyote, though biogenetically feasible, their presence in another cactus, *Echinocereus merkeri* Hildm., has been established (31). It is remarkable that the *O*-methylation isomer of VII, namely 3-hydroxy-4-methoxyphenethylamine, has not been detected in peyote although it is the main phenolic alkaloidal constituent in *Pachycereus pecten-aboriginum* Backeberg and other cacti (40). Both dopamine (V) and its partial *O*-methylation product (VII), but not the dimethoxy analog (X), have established places in the biogenetic pathways of mescaline (XVII) (1, 31) in peyote.

In addition to mescaline (XVII) and its *N*-methyl (XVIII) and *N*-acetyl (XX) derivatives, reported in earlier years, the trioxygenated phenethylamines of peyote have been recently found to comprise seven additional products. These include the biogenetically-involved phenolic bases 3,4-dihydroxy-5-methoxyphenethylamine (XI) (37) and 3-demethylmescaline (XII) (41, 42), and five *N*-substituted derivatives. The latter are the *N*-methylated derivatives (XIII and XIV) of 3-demethylmescaline (XII) (43) and the *N*-formyl derivatives (XV and XIX) of XII and mescaline (XVII), respectively, and *N*-acetyl-3-demethylmescaline (XVI), which were identified by the Kapadia group (44) in the nonbasic fractions. Despite their presence in appreciable amounts, it appears that no specific biogenetic function has been verified for the various *N*-methylphenethylamines, and they may simply represent by-products of the methylation processes (45–47) which essentially affect phenolic groups. Despite the availability of a methoxy-methylenedioxy system in several tetrahydroisoquinolines (XXXVIII–XLIII), it is remarkable that a phenethylamine counterpart (homomyristicylamine) has not yet been found in peyote; its presence, however, has been anticipated by Kapadia *et al.* (41) from biogenetic considerations.

SYNTHETIC APPROACHES

A considerable number of syntheses are known today for mescaline, 3,4,5-trimethoxyphenethylamine (XVII), the main constituent of peyote. Several other interesting methods have been devised in recent years for the synthesis of analogs of mescaline (48) for the purpose of exploring their potential psychotomimetic activity. In the present review, however, all discussion shall be limited to the natural products of peyote.

In the earliest synthesis of mescaline, realized by Späth in 1919 (10), 3,4,5-trimethoxybenzaldehyde, prepared from the acid, was condensed with nitromethane in ethanol solution containing alkali and the resulting ω-nitrostyrene (LVII) was finally reduced to mescaline in two steps (fig. 1A). Späth and Röder (13) also realized a synthesis of 3-demethylmescaline (XII), needed as an intermediate toward anhalamine (XXI), using the same sequence after temporary protection of the phenol group. This approach has been utilized quite extensively by numerous later workers (49–74) in the synthesis of mescaline and several of its analogs, and it thus proved its versatility. Several modifications in the reaction conditions at individual steps have been suggested. These include the use of acetic acid containing ammonium acetate (56, 58, 61, 64, 75) or

an aliphatic primary amine (57, 58) in the stage leading to the nitrostyrene when higher yields have been reported. Reduction of the nitrostyrene to the corresponding phenethylamine has also been considerably improved through the use of lithium aluminum hydride (54, 56, 75, 76, 65–68, 70–72, 74) in a one-step transformation, a reagent which may cause partial demethylation in the benzenoid groups (77). The same reduction has also been effected electrolytically (50, 78), by modified catalytic hydrogenation (52, 79–81) and through the use

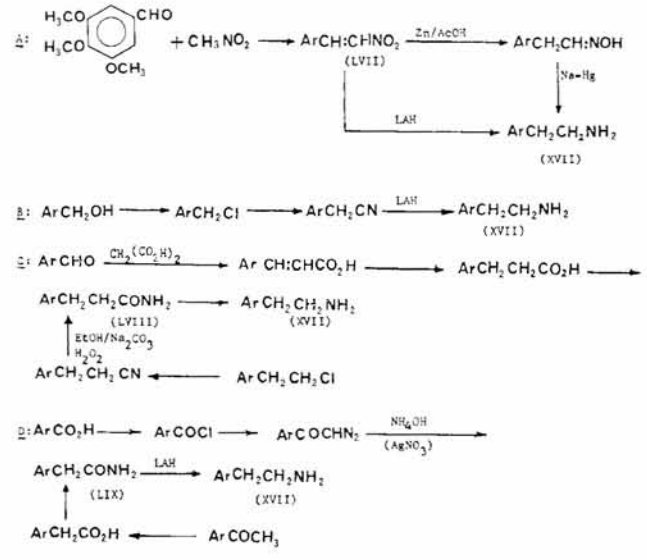


FIGURE 1

of amalgamated zinc and hydrochloric acid (73) or palladium (69). There is evidence (82) that the formation of the nitrostyrene (LVII) is preceded by a short-lived β-hydroxy-β-phenylnitroethane intermediate in which the benzylic alcohol group readily dehydrates under the prevailing reaction conditions. The reaction sequences indicated in fig. 1A was chosen by Lundström and Agurell (68) in several syntheses of phenethylamines labelled with carbon-14 and tritium in the side chain needed in biosynthetic studies. For this purpose, the appropriately substituted benzaldehyde was condensed with ^{14}C-nitromethane and the nitrostyrene reduction was accomplished with $LiAlH_4$-^3H.

Another useful approach (fig. 1B) for the construction of the side chain in mescaline, which seems to be of general utility in the preparation of analogous products, consists in the conversion of a substituted benzyl alcohol to the chloride, then to the phenylacetonitrile with final reduction to the desired amine using lithium aluminum hydride (83–89). In some recent reports, the utility of a variety of nonconventional reducing conditions for the final step, including Al/Ni (90) and Ni/Cr_2O_3 (91, 92), has been demonstrated. Improvisations in this approach include the use of selected reagents and reaction conditions in individual steps. For example, Abdel-Rahman *et al.* (88) used thionyl chloride in the benzyl chloride preparation and potassium cyanide in aqueous formic acid or dimethyl sulfoxide in the subsequent stage and achieved an overall yield of 40% of mescaline based on the initial gallic acid used. Benington *et al.* (58, 75, 93, 94) obtained the desired benzyl chloride derivatives by chloromethylation (using aqueous formaldehyde and concentrated hydrochloric acid

or chloromethyl ether in acetic acid) (75) of the suitably substituted benzene derivative.

The synthetic pathway in fig. 1C represents a different approach with good potential. It was originally devised by Slotta (95) and Slotta and Heller (96) for a mescaline synthesis in which the appropriately substituted phenylpropionamide (LVIII) was subjected to Hoffmann degradation. This approach has been further explored by recent investigators (97–100) for the preparation of suitably substituted phenethylamines, some of which possess unique synthetic potential (99). The desirable intermediate LVIII could be prepared from the corresponding phenylacrylic acid [obtainable from a benzaldehyde derivative (95, 96)] or β-phenylethyl chloride (98) as indicated in fig. 1.

A successful and versatile method (fig. 1D) for the construction of the ethylamine side chain (93, 101) involves transformation of the appropriately substituted benzoic acid into the corresponding phenylacetamide (LIX) by an Arndt-Eistert synthesis, followed by reduction with lithium aluminum hydride (89). The use of appropriate amines in place of ammonia, in the treatment of the diazoketone, affords *N*-substituted phenethylamines (101). This approach has recently been used by Kapadia *et al.* (41) in a synthesis of 3-demethylmescaline (XII). The intermediate LIX may also be obtained from the corresponding acetophenone by application of the Kindler modification of the Willgerodt reaction which gives a phenylacetic acid derivative *en route* (102).

In another approach towards mescaline (fig. 2E), originated by Kindler and Peschke (80) and later employed by Amos (103), the benzaldehyde derivative was condensed with potassium cyanide and the resulting mandelonitrile was acetylated and finally reduced by catalytic hydrogenation. It does not seem that this sequence has been utilized by later workers.

A longer route for mescaline, which now seems to be of only historical interest, was used by Hadácek *et al.* (104) where the diazoketone group in LX was transformed by a five-step sequence (fig. 2F) to the phenethylamine side chain. A specific synthesis (fig. 2G) of mescaline has also been reported by Hahn and Wassmuth (51) and Hahn (105) in which the desired trimethoxyphenylacetaldehyde, obtained from ozonolysis of elemecine (LXI), was trans-

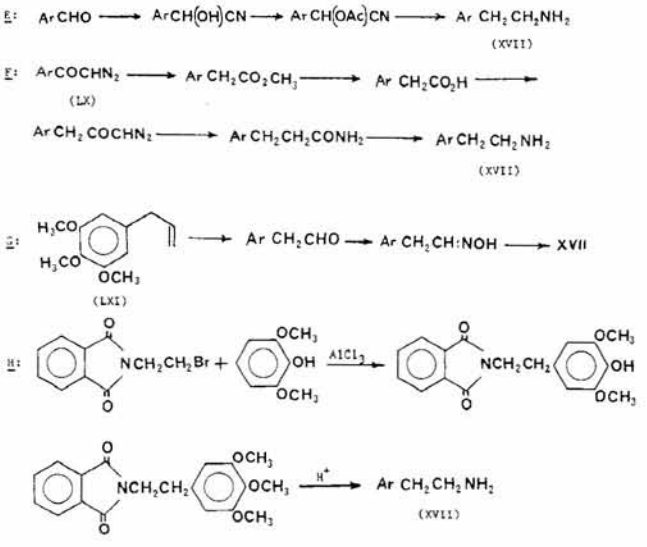


FIGURE 2

formed to the oxime and finally reduced. Another specific synthesis of mescaline has recently been reported by Rabusic and Gregor (106) (fig. 2H). The method constitutes a novel approach in this series with interesting sequence of reactions and apparent synthetic potential since it starts simply with a suitable benzene derivative. The recent review of Patel (107) on mescaline and its analogs gives a comprehensive listing of the various aromatic and *N*-substituted β-phenethylamines reported in the literature which have been obtained by some of the foregoing methods (50, 78, 96, 108–113). It may also be mentioned that other specific syntheses of mescaline analogs carrying substituents on the β-position of the side chain have been developed in recent years (48, 114–117).

Degradation work in mescaline and related phenethylamines is resorted to in current research only in biosynthetic studies to determine the location of an introduced label. The commonest reactions include potassium permanganate oxidative cleavage of the ethylamine side chain (fig. 3) to give, for example,

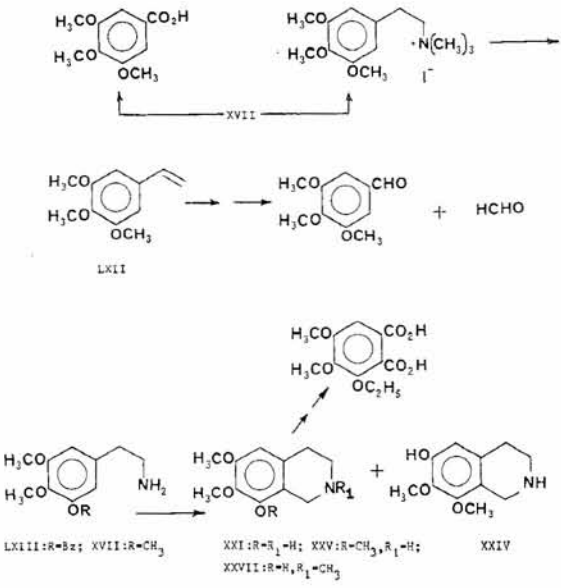


FIGURE 3

3,4,5-trimethoxybenzoic acid from mescaline (68, 118–122) and 4-acetoxybenzoic acid from *O*-acetylhordenine (121). Products accounting for both carbon atoms of the side chain have also been obtained, as illustrated in Leete's (119) systematic degradation of mescaline. In the latter, the *N,N*-dimethyl methiodide derivative was subjected to Hoffmann degradation; the resulting styrene (**LXII**) was oxidized to a diol with osmium tetroxide followed by cleavage with sodium metaperiodate, yielding 3,4,5-trimethoxybenzaldehyde and formaldehyde.

THE TETRAHYDROISOQUINOLINES

It is remarkable, and biogenetically significant, that all the tetrahydroisoquinolines of peyote are trioxygenated at the 6-, 7- and 8-positions, which is compellingly conducive to the assumption that they evolve by cyclization of trioxygenated phenethylamine progenitors. It is interesting, however, to note that other cactus sources are known which contain tetrahydroisoquinolines with different patterns of oxygenation as available in several known 5,6,7-trioxygen-

ated and 6,7-dioxygenated products. The simplest model among peyote tetrahydroisoquinolines is the dimethoxyhydroxylated anhalamine (XXI) and all other analogs are derived from it by *O*-, *N*- or C-1-methylation or combinations thereof. In fact all combination possibilities are now known to exist in peyote except for the *O*-methyl derivative of pellotine (XXXV). Another structural variety is represented by the methoxy-methylenedioxy system available in anhalonine (XXXVIII) and lophophorine (XLI) and their derivatives and analogs (*cf.* table 1). It is remarkable that the C-1 methylene (unsubstituted) counterparts of the latter type have not yet been found in peyote, although their presence is not unlikely from biogenetic reasoning as recently proposed (41). An interesting group of four phenolic tetrahydroisoquinoline alkaloids with an unusual pattern of *O*-methylation have recently been identified by Lundström (123) in peyote by preparative glc and glc-mass spectrometry, namely isoanhalamine (XXIV), isoanhalidine (XXIX), isoanhalonidine (XXXII) and isopellotine (XXVII). Biogenetically, they are considered to evolve from the same phenethylamine precursor, 3-demethylmescaline (XII), as do their counterparts XXI, XXVII, XXX, and XXXV, respectively, but with cyclization involving the position *para* to the phenol group.

SYNTHETIC APPROACHES

The principal approaches now available for the synthesis of the peyote tetrahydroisoquinoline alkaloids depend basically on the general Pictet-Spengler (124), Bischler-Napieralski (125), and Pomeranz-Fritsch (126) isoquinoline syntheses and their modifications. An appropriately substituted trioxygenated phenethylamine intermediate is condensed with an aldehyde, according to the first method, or the *N*-acyl derivative is cyclized, according to the second, thus providing the methylene group or two-carbon unit present at C-1 of the desirable tetrahydroisoquinoline. In both methods, the unsymmetrically 3,4,5-trisubstituted phenethylamines are likely to follow either, or both, of two possible directions of cyclization. It remains, therefore, as an additional task, to ascertain the exact disposition of the resulting tetrahydroisoquinoline. This problem is not encountered in the syntheses depending on the Pomeranz-Fritsch method and its modifications (127), since the starting material, an *N*-benzylaminoacetaldehyde diethylacetal, can be substituted as to give only one possible cyclization product. It is a fact that the structure elucidation of the principal tetrahydroisoquinolines of peyote—for which Späth must be credited—was realized largely by synthetic approaches, inspired by biogenetic considerations, rather than by degradative ones.

SYNTHESES DEPENDING ON THE PICTET-SPENGLER REACTION.—These seem to have been limited to approaches toward the C-1 methylene-containing tetrahydroisoquinolines, exemplified by anhalamine (XXI) and its *O*- and *N*-methyl analogs (XXV and XXVII, respectively). Thus the first synthesis of XXI was realized by Späth and Röder (13) through condensation of 3,4-dimethoxy-5-benzyloxyphenethylamine (LXIII) with formaldehyde (fig. 3). The direction of cyclization and, hence, location of the phenolic hydroxyl group were determined by permanganate oxidation of the *O,N*-diethyl derivative which gave 4,5-dimethoxy-3-ethoxyphthalic acid (20). Anhalinine (XXV) was also obtained by Späth and Becke (22) by the same method starting from mescaline; anhalidine (XXVII) was obtained (23) simply by *N*-methylation of anhalamine. In a later study, Brossi *et al.* (128) found that cyclization in the reaction LXIII→XXI proceeds in two directions giving isoanhalamine (XXIV) in addition to anhalamine (XXI).

SYNTHESES DEPENDING ON THE BISCHLER-NAPIERALSKI REACTION.—These have proven their greater versatility as illustrated by their application in all

types of peyote tetrahydroisoquinolines. Anhalonidine (XXX) and pellotine (XXXV) were the first peyote tetrahydroisoquinoline alkaloids to be synthesized and were obtained as early as 1921 by Späth (11) using this approach. Cyclodehydration of *N*-acetylmescaline (XX) followed by hydrogenation and quaternarization gave a product which was identical with *O*-methylpellotine methiodide. Anhalonidine was correlated to pellotine by complete methylation of both to the same product (fig. 4). In an independent synthesis of anhalonidine

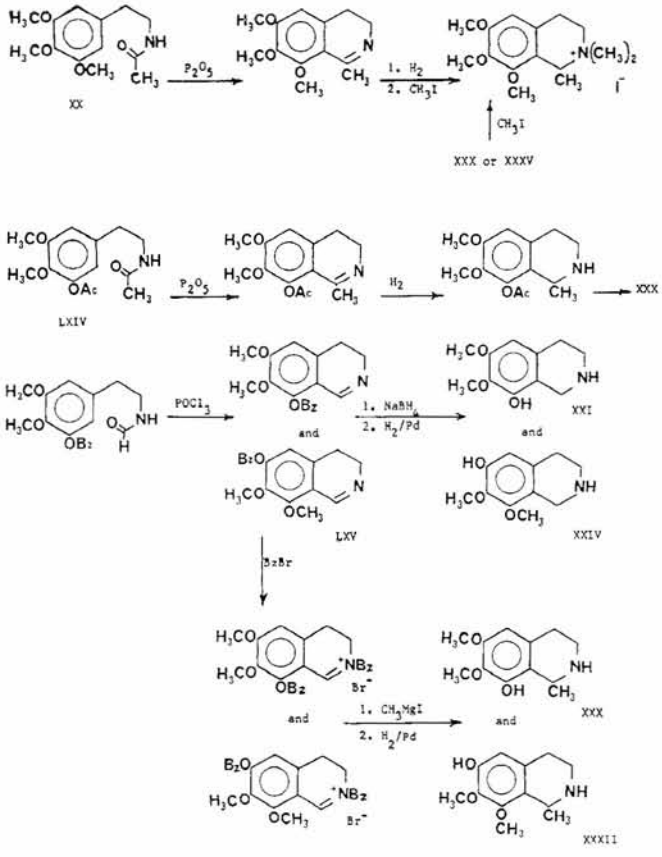


FIGURE 4

(XXX), Späth (14) followed the same route using *N*-acetyl-3,4-dimethoxy-5-hydroxyphenethylamine after a temporary protection of the phenol group by acetylation (LXIV) as shown in fig. 4. The direction of cyclization was determined (17) by permanganate oxidation of the *O*-ethyl derivative of pellotine, which gave 4,5-dimethoxy-3-ethoxyphthalic acid; this was also confirmed by an analytical approach (18).

In a relatively recent report by Brossi *et al.* (128), both anahalmine (XXI) and isoanhalamine (XXIV) resulted from a Bischler-Napieralski cyclodehydration of *N*-formyl-3,4-dimethoxy-5-benzyloxyphenethylamine—which occurs in both possible directions giving two dihydroisoquinolines (LXV)—followed by reduction and hydrogenolysis (*cf.* fig. 4). The same intermediate mixture (LXV) was utilized (128) in a synthesis of anhalonidine (XXX) and isoanhal-

onidine (XXXII) through quaternarization followed by treatment with methyl Grignard reagent and finally hydrogenation.

Brossi *et al.* (129) also utilized an interesting method, originally devised by Karady (130) for a synthesis of *O*-methylanhalonidine (XXXIII), in the construction of the heterocyclic system which bears some resemblance to the Bischler-Napieralski reaction. The urethane derivative (LXVI) of the suitable substituted phenethylamine is cyclized under the action of polyphosphoric acid and the resulting lactam is reduced to the tetrahydroisoquinoline system which is then subjected to appropriate treatments (*cf.* fig. 5) so as to yield the desirable

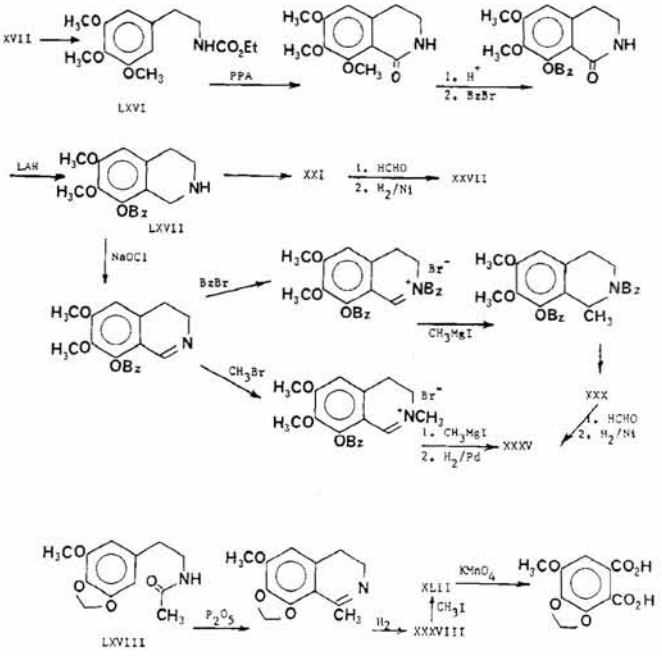


FIGURE 5

substituents. By application of this sequence, anhalamine (XXI) and anhalidine (XXVII) have been obtained by Brossi *et al.* (129) and by Kametani *et al.* (87). The same principle was utilized in a new synthesis of anhalonidine (XXX) and pellotine (XXXV) through dehydration of the 6,7-dimethoxy-8-benzyloxytetrahydroisoquinoline intermediate (LXVII) followed by quaternarization and treatment with methyl Grignard reagent to introduce the C-1 methyl group.

Bischler-Napieralski synthesis has also been employed by Späth and Gangl (15) in the preparation of the methylenedioxy-containing alkaloids anhalonine (XXXVIII) and lophophorine (XLI) through cyclodehydration of *N*-acetylhomomyristicylamine (LXVIII) followed by reduction and quaternarization (fig. 5). The structure was later confirmed by permanganate oxidation to 3,4-methylenedioxy-5-methoxyphthalic acid (22). This is the only approach hitherto used for the total synthesis of the methylenedioxy tetrahydroisoquinoline alkaloids.

SYNTHESES DEPENDING ON THE POMERANZ-FRITSCH REACTION.—These syntheses appear to offer considerable latitude and versatility and are amenable to adaptation to specific problems. Their earliest use in peyote alkaloids was due

to Späth and Becke (19) for the synthesis of pellotine (XXXV) starting from the Schiff base (LXIX), obtained by condensation of 2-benzyloxy-3,4-dimethoxyacetophenone with aminoacetaldehyde diethylacetal, followed by cyclization using sulfuric acid (fig. 6). During a Pomeranz-Fritsch acid-cyclization of the Schiff base LXX obtained as shown in fig. 6, Inubushi and Fujitani (60) found, unexpectedly, that the isoquinoline product had lost the C-1 substituent; they obtained anhalidine (XXVII) by subsequent quaternarization and reduction.

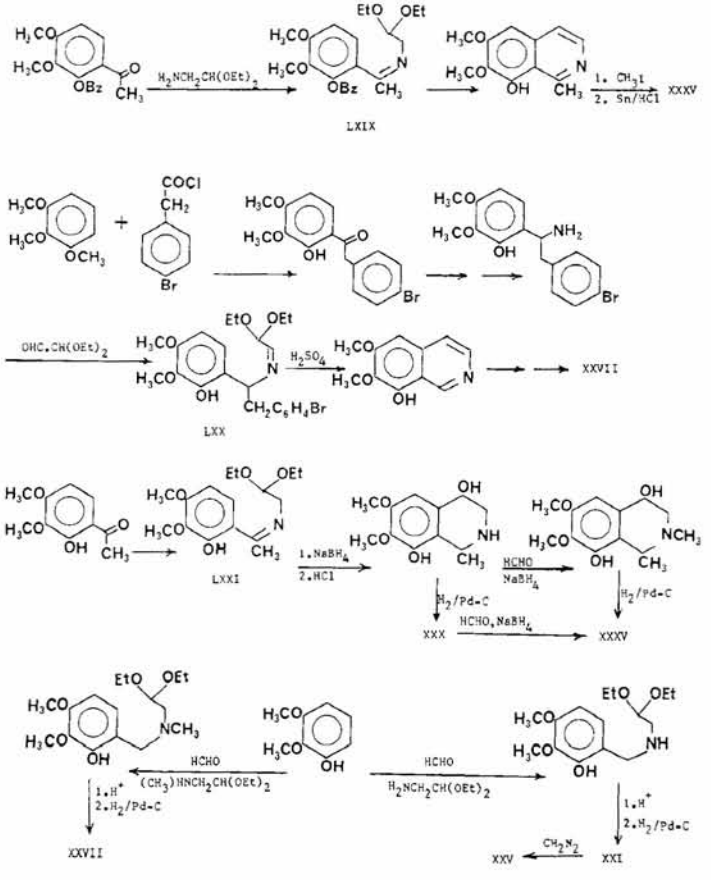


FIGURE 6

Useful modifications of the Pomeranz-Fritsch synthesis have been developed by Bobbitt *et al.* (127), involving the acid-catalysed cleavage, ring closure, and reduction of the intermediate benzylaminoacetals. Utilizing this modified procedure, Takido *et al.* (131) have recently achieved a new synthesis of anhalonidine (XXX) and pellotine (XXXV) proceeding from the requisite Schiff base (LXXI) *via* the corresponding 4-hydroxytetrahydroisoquinoline intermediates (*cf.* fig. 6). An interesting adaptation of the Pomeranz-Fritsch reaction has also been devised by Bobbitt and Dutta (132) in a novel synthesis of the C-1 methylene tetrahydroisoquinolines anhalamine (XXI), anhalinine (XXV), and anhalidine (XXVII). The required intermediate benzylaminoacetals—resulting by simple Mannich reaction of an appropriate phenol with formaldehyde and suitably substituted aminoacetals (*cf.* fig. 6)—are converted

into the desirable tetrahydroisoquinolines by acid treatment followed by hydrogenation.

INTERCONVERSIONS

Since several tetrahydroisoquinolines differ from one another only in the degree of methylation (*cf.* table 1), interconversions have been realized—and also utilized in structure determination of new compounds—simply by *O*- and *N*-methylations or demethylations by well-trodden methods. This is well illustrated in the syntheses discussed before (figs. 4–6). While *O*-methylation is simply induced with diazomethane, *N*-methylation requires special treatment if quaternarization is to be avoided. The latter has been conveniently achieved through reductive condensation with formaldehyde in the presence of Raney nickel catalyst or sodium borohydride.

The structure of peyophorine (XLIII), a minor alkaloid identified by Kapadia and Fales (133), was verified by synthesis through *N*-ethylation of anhalonine and lithium aluminum hydride reduction of *N*-acetylanhalonine. This is the only *N*-ethylated alkaloid so far found in peyote, and its presence is remarkable in view of the rarity of such moiety in nature (134).

The three quaternary tetrahydroisoquinoline bases as yet known in peyote, anhalotine (XXVIII), peyotine (XXXVI) and lophotine (XLII), have been isolated by Kapadia *et al.* (135) as the iodides and were synthesized simply by quaternarization of the corresponding alkaloids. Lophotine had been known earlier (15) as a product resulting during the synthesis of anhalonine and lophophorine (fig. 5). It is not unlikely that the quaternary base mixture of peyote contains additional products.

All the amides (*N*-formyl and *N*-acetyl) derivatives of the tetrahydroisoquinolines thus far known (*cf.* table 1) have been identified by combined glc-mass spectrometric studies of the nonbasic fractions by Kapadia and Fales (44). Synthesis of the formyl derivatives (XXII, XXVI, XXXI, XXXIV and XXXIX) was achieved by treatment of the corresponding base with triethylamine and formic acid, a method recommended by Durand *et al.* (136). The acetyl derivatives (XXIII and XL) were obtained by simple treatment with acetic anhydride. Where *O*-acetylation occurred, in the phenolic alkaloids, saponification was an additional step. The gas-liquid chromatograms (44) reflected the fact that more products are present in the nonbasic fractions. It appears that little attention has been given to the study of the nonbasic fractions of other alkaloid-bearing Cactaceae (and, in fact, most other alkaloid-bearing plants). The association of amides with true bases is quite expectable for biogenetic reasons and because of the simple fact that organic acids are co-existent.

The problem of introducing a methylenedioxy grouping in an already constructed tetrahydroisoquinoline system has been overcome very recently in an elegant study by Brossi *et al.* (137). Demethylation of *O*-methylanhalonidine (XXXIII) by controlled acid treatment afforded the diphenol (LXXII) (138) which, after conversion to the carbamate using ethyl chloroformate, was treated with dibromomethane in presence of cupric oxide to give the requisite methylenedioxy substituent as present, ultimately, in anhalonine (XXXVIII) and lophophorine (XLI) (fig. 7).

STEREOCHEMISTRY

Problems of stereoisomerism, encountered obviously only in the C-1 methyl-carrying tetrahydroisoquinolines, have confronted Späth and his coworkers since the early days of peyote chemistry. All synthetic methods used for these compounds were not stereo-selective and afforded the (±)-products; the optically active forms have been obtained for some of them by resolution of the racemic mixture using (+)- or (−)-tartaric acid, as a general procedure. Although

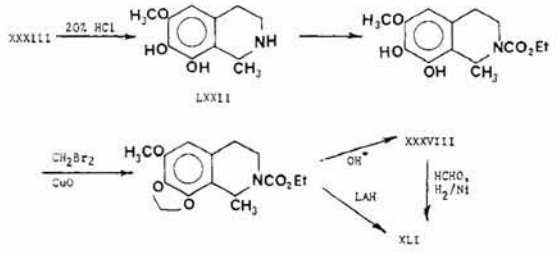


FIGURE 7

(+)-*O*-methylanhalonidine (**XXXIII**) was isolated from peyote (28) in optically active form, its *N*-methyl phenolic counterpart pellotine (**XXXV**) was obtainable (4, 9) only in racemic form. Späth and Kesztler (25) prepared the optically active forms of pellotine [by resolution of the racemic mixture using (+)-tartaric acid (28)] and, considering the facility with which they racemize, these authors thought that the natural product might be optically active and that racemization occurs by aging of the drug or during the process of isolation. The methylenedioxy alkaloids (−)-anhalonine (**XXXVIII**) (2, 139, 140) and (−)-lophophorine (**XLI**) (5) were both isolated in optically active form. Späth and Kesztler (24) resolved the synthetic racemic mixture of anhalonine (using (−)-tartaric acid) (15) and showed that natural lophophorine results by *N*-methylation of (−)-anhalonine.

From a consideration of the observed optical rotatory shifts, Battersby and Edwards (141) assigned the *S* configuration to both (−)-anhalonine (**XXXVIII**) and (−)-lophophorine (**XLI**). Very recently, Brossi *et al.* (137) reported the results of an X-ray crystallographic study of the hydrobromides of **XXXVIII** and (+)-*O*-methylanhalonidine (**XXXIII**). Their studies confirmed the previous findings of Battersby and Edwards and established the *S* configuration for all three compounds, which were found to give similar optical rotatory dispersion and circular dichroism spectra. The X-ray study (137) provided data for the bond lengths and angles involving the nonhydrogen atoms, and revealed the absolute configurations where the C-1 methyl group is pseudoequatorial in (−)-anhalonine (**XXXVIII**), but is axial in (+)-*O*-methylanhalonidine (**XXXIII**). The proven stereochemistry of the three compounds is illustrated in fig. 8. The stereochemistry of the remaining alkaloids anhalonidine (**XXX**), pellotine (**XXXV**) and peyophorine (**XLIII**) will still have to be proven.

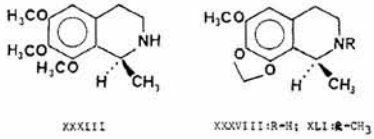


FIGURE 8

DEGRADATION

Chemical degradation of the heterocyclic system in tetrahydroisoquinolines was previously a means in structure determination work, but is currently resorted to for the location of the label in biosynthetic studies. An example of the latter use is the relatively recent degradation (142) of anhalamine (**XXI**), as the *O*, *N*-dimethyl derivative methiodide, to 3,4,5-trimethoxyphthalic anhydride (involving loss of C–3 of anhalamine), using the conditions described much

earlier by Späth and Becke (143). A useful degradative sequence (*cf.* fig. 9) of anhalonidine (XXX), reported by Leete (119), consists in an Emde reductive cleavage of the heterocyclic system in the *O,N*-dimethyl methiodide derivative followed by quaternarization and Hoffmann degradation. The resulting styrene derivative (LXXIII) was oxidized to a glycol with osmium tetroxide and finally cleaved with sodium metaperiodate, yielding 2-ethyl-3,4,5-trimethoxybenzaldehyde and formaldehyde; the latter accounting for C–3. The Kuhn-Roth oxidative degradation of such alkaloids carrying a methyl group on C–1 is also often resorted to as a diagnosis of the label present in this part of the molecule giving rise to acetic acid (144–146).

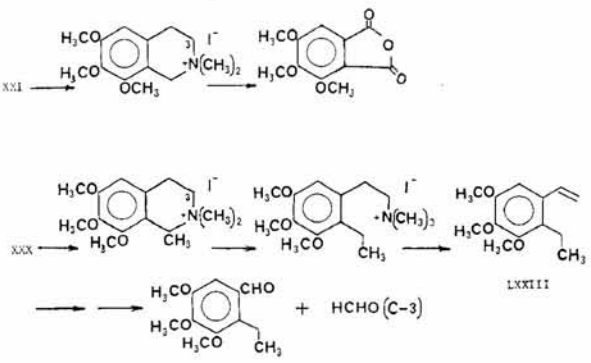


FIGURE 9

CONJUGATES WITH KREBS CYCLE ACIDS

THE AMIDES.—This group of peyote constituents represents products, the natural occurrence of which was predicted on biogenetic grounds as resulting by conjugation with the co-existing Krebs cycle acids. It appears that no other plant source is known in which a comparable array of alkaloidal conjugates has been identified. In addition to the phenethylamine and tetrahydroisoquinoline amides (formyl and acetyl) mentioned before (*cf.* table 1), recent glc-mass spectrometric studies by Kapadia and Fales (44) have shown that the nonbasic fractions of peyote contain more complex amide derivatives. The nature of several of these has been elucidated from mass spectral considerations and by comparison with synthetic models of the suspected structures. These include the succinimide (XLIV), malimide (XLV), and maleimide (XLVII) derivatives of mescaline, which were all synthesized simply by sublimation of the mescaline salts of the corresponding acids. More recently, Kapadia *et al.* (147) characterized two additional amides of mescaline in the same nonbasic fractions, namely the citrimide (XLVI) and the isocitrimide lactone (XLVIII) derivatives. Their structures were evidenced by mass spectral data and proven by synthesis from mescaline through treatment with citric anhydride and isocitric acid lactone, respectively.

The nonbasic fractions of peyote were also found (44) to contain two structurally interesting lactams, XLIX and L, related to 3-demethylmescaline (XII) and mescaline (XVII), which were named peyoglutam and mescalotam, respectively. Their constitutions, inspired by biogenetic considerations, were proven by synthesis from the corresponding bases by treatment with α-ketoglutaric acid followed by decarboxylation (fig. 10). The direction of cyclization in XLIX was established by nmr evidence (44, 148). Very recently, it has been found (149) that improved yields of peyoglutam and mescalotam are ob-

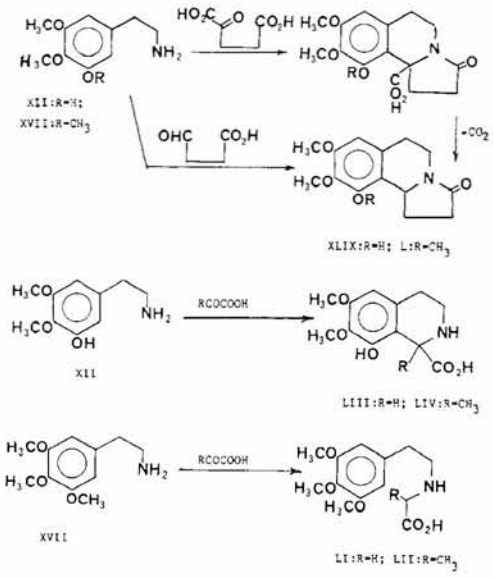


FIGURE 10

tainable when succinic acid semialdehyde is used in the condensation, which may imply that in the reaction with α-ketoglutaric acid (44) partial decarboxylation of the latter may afford the semialdehyde as the reactive species.

THE AMINO ACIDS.—It is surprising that no systematic study has hitherto been conducted on the general proteinic amino acid make-up of peyote, significant and relevant to the biosynthetic processes as they may be. The presence of proline in the amino acid fraction was, however, demonstrated lately by Kapadia *et al.* (150). The gas chromatogram (fig. 11) of the silylated (with bis(trimethylsilyl)trifluoroacetamide) mixture of peyote amino acid fraction (144) reflects the considerable complexity of the mixture. Prompted by biogenetic considerations suggesting their probable natural occurrence, Kapadia *et al.* (144, 151) synthesized two nonproteinic amino acids with the structures LIII and LIV (table 1) and demonstrated their presence in the natural mixture (*cf.* fig. 11). Synthesis of these two acids, named peyoxylic acid (LIII) and

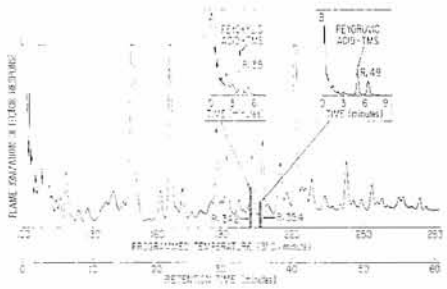


FIG. 11. *Gas-liquid chromatogram of the silylated peyote amino acid fractions.* Fractions A and B (inserts), obtained by preparative paper chromatography, were chromatographed on the same glc column at 190°. The unmarked peaks were not investigated further.

peyoruvic acid (LIV) was achieved by condensation of 3-demethylmescaline (XII) with glyoxylic acid and pyruvic acid, respectively, under physiological conditions (fig. 10). The condensation, a Pictet-Spengler-type reaction, is facilitated by the presence of an activating phenolic group. It has been demonstrated experimentally that both acids play an important intermediary role in the biogenetic transformation of phenethylamines into tetrahydroisoquinolines (144). The possibility of presence of *O*-methylpeyoxylic and *O*-methylpeyoruvic acids, which have already been synthesized by Kapadia *et al.* (82), in the natural mixture of peyote needs to be explored.

Kapadia *et al.* (152, 153) have also considered the possibility of natural occurrence of conjugates of mescaline resulting by reductive amination of glyoxylic acid and pyruvic acid where more than one possibility for the mode of conjugation is open. The products resulting by reductive amination leading to phenethylamine analogs of glycine and alanine have been synthesized (152, 153) by reacting mescaline with glyoxylic acid and pyruvic acid, respectively, in the presence of sodium cyanoborohydride, as a reducing agent, at pH 5. The latter compound was also prepared by reacting mescaline with α-chloropropionic acid (fig. 10). The presence of these two compounds, designated mescaloxylic acid (LI) and mescaloruvic acid (LII) in the amino acid mixture of peyote, as constituents, has been demonstrated (152, 153) by glc-mass spectrometric evidence. It does not appear too unlikely that both acids may participate, at least in part, in the biosynthesis of certain peyote alkaloids. Although other biosynthetic routes may be open for consideration, the specific relationships of mescaloruvic acid (LII) or its *O*-monodemethyl analog to peyophorine (XLIII), and mescaloxylic acid (LI) to *N*-methylmescaline (XVIII) appear to be particularly attractive. In both of these cases, the decarboxylation of such acids as LI and LII is obviously an essential step at some stage.

PYRROLE DERIVATIVES

Since the possibility of occurrence of indole derivatives, resulting by intramolecular oxidative cyclization of phenethylamines, appeared feasible, Kapadia *et al.* conducted specific search for such products. Although none was found

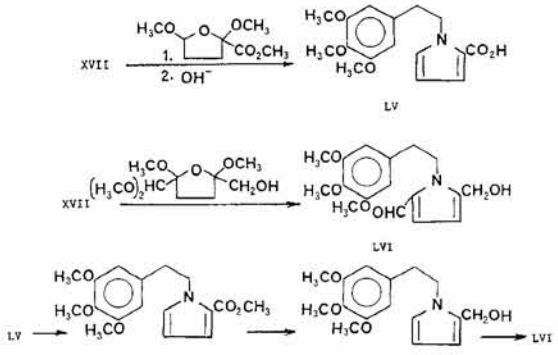


FIGURE 12

thus far, these workers were able, however, to isolate two products containing pyrrole residues as minor constituents from the nonbasic fractions of peyote, namely peyonine (LV) (154) and peyoglunal (LVI) (147). The structure of peyonine was determined (155) from spectral and mass spectrometric evidence and through synthesis by treatment of mescaline (XVII) with methyl 2,5-dimethoxytetrahydro-2-furoate followed by saponification (fig. 12). Peyonine

appears to be the first simple pyrrole-2-carboxylic acid derivative isolated from a natural source. The constitution of peyoglunal (the only aldehyde- and hydroxymethyl-containing product thus far encountered in peyote), also suggested by spectral and mass spectrometric evidence, was established (147) by synthesis from mescaline through condensation with 2,5-dimethoxy-5-hydroxymethyltetrahydrofurfuraldehyde dimethyl acetal (fig. 12). Better yields of peyoglunal (LVI) were obtained (147) from peyonine (LV) by reduction of the methyl ester with lithium borohydride followed by formylation under Riemer-Tiemann conditions. Peyonine and peyoglunal represent pyrrole derivatives of rare natural occurrence.

ANALYTICAL METHODS

Several reagents have been used in the detection and identification of mescaline and related products (156–161). Some are particularly useful in working with peyote alkaloid mixtures, e.g. on thin-layer chromatoplates, such as dansyl chloride for nonphenolic products and tetrazotized benzidine (33) and tetrazotized di-*O*-anisidine (135) for detection and identification of phenolic ones. Also, a number of paper (162–167), thin-layer (33, 36, 168–173), and gas (39, 168, 174–179) chromatographic methods have been reported for the separation and identification of mescaline and other cactus alkaloids. Kapadia and Rao (176) observed a relationship between the retention time and structure of peyote alkaloids and related bases.

Several methods have been recommended for the quantitation of mescaline in biological fluids. They include colorimetric methods depending on measurement of the color formed by interaction with picric acid (180, 181), bromocresol purple (182), and *p*-nitrophenyldiazonium chloride (183, 184). In a fluorometric method (185), mescaline is transformed into a fluorescent isoquinoline derivative; another method (186) is based on the characteristic oscillographic behavior of mescaline in acid and alkaline solutions.

The recent review of Nieforth (48) and those of Barbeau (187) and Friedhoff and Winkle (188) provide additional useful information on some specialized methods for analysis in biological fluids.

MASS SPECTRA OF PEYOTE CONSTITUENTS

The spectra of the phenethylamines and tetrahydroisoquinolines invariably exhibit molecular ions with very low intensities. The principal fragmentations result by cleavage of the β-bonds relative to the aromatic ring. The phenethylamines [such as X (175), XII (41) and XVII (189)] and their *N*-alkyl-substituted derivatives thus give the benzyl ions *a* (which may also have tropylium structures) and, through transfer of hydrogen atom from the departing fragment (as depicted by arrows in fig. 13), the equally important (and often stronger)ions *b*. Fragmentations of this type have been useful in the location of labels in the side chain (190). In tertiary amines, such as peyonine (LV), the same type of breakdown obviously does not take place, and the predominant fragment ion is due to species *a* (155). The spectra are complicated further only by combinations of losses from the aromatic substituent groups. The *N*-formyl- and *N*-acetylphenethylamines (191), as well as the related cyclic imide derivatives (XLIV, XLV and XLVII) (44), give as principal fragmentation products ions of species *a* in addition to styrene ions (c), resulting by scission of the C–N bond of the side chain with transfer of hydrogen (as depicted by the arrows in fig. 13) in a McLafferty rearrangement.

The primary reactions exhibited by the tetrahydroisoquinolines [typified by XXI, XXIII, XXVI, XXVII, XXXIV, XLI (191) and XLIII (133)] involve expulsion of the C–1 substituent (192), giving the highly stabilized dihydroisoquinolinium ion species *d* (fig. 13). The strongest peaks in the spectra are

due to ions (species e) formed by collapse of the heterocyclic system through the retro-Diels-Alder reaction. This type of breakdown does not seem to take place appreciably in those products carrying a methyl group on C–1, probably because the elimination of this substituent is more favored and becomes by far the most important reaction. Mescalotam (L) and peyoglutam (XLIX) (44) exhibit relatively strong M^+ ions and ones resulting by loss of the hydrogen atom on C–1 of the tetrahydroisoquinoline system. Fragmentation of the lactam ring by loss of CH_2CH_2CO gives ions with appreciable abundance which may have structure *f* (fig. 13).

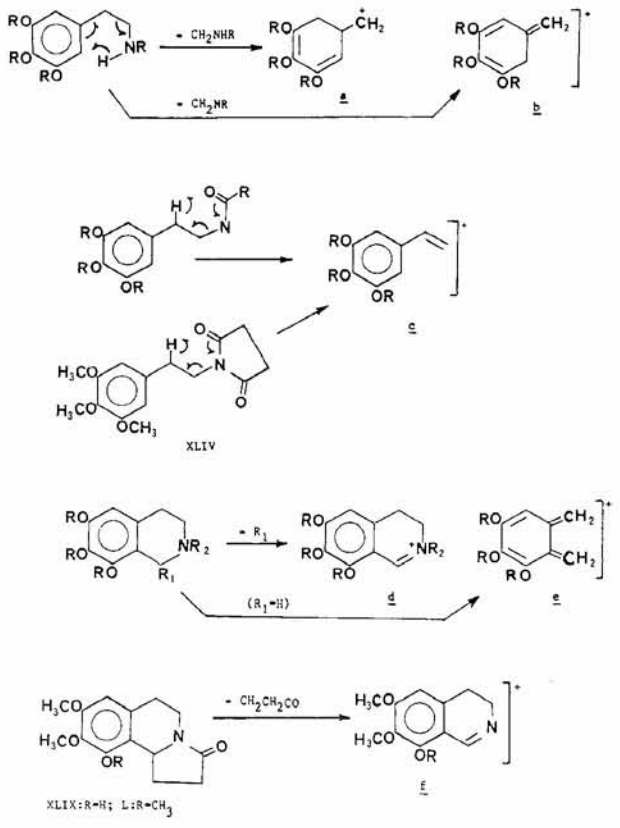


FIGURE 13

The mass spectra of the amino acids LI, LII (152, 153), LIII and LIV (144), determined for the trimethylsilyl derivatives, exhibited no special fragmentation pathways, and the patterns were complicated only by expulsions from the TMS residues.

A very useful analytical and diagnostic tool is combined glc-mass spectrometry which proved its practical value in the rapid identification of minute (1 μg) amounts of a compound in a complex mixture. This technique has been utilized by the present authors (44, 133, 144, 147) and by others, notably the Agurell-Lundström group (39, 42, 43, 123), in the study of trace constituents of peyote (*vide supra* under group titles) and was instrumental in revealing several intermediates of biosynthetic pathways. Mass fragmentography is another new

development, introduced by Hammar *et al.* (193) and later modified by Hammar and Hessling (194), where the mass spectrometer is used as a gas chromatographic detector continuously monitoring 1–3 selected mass numbers of compounds eluted from the gas chromatographic column. It has been utilized with considerable advantage for the identification of trace substances in complex mixtures in biosynthetic studies (38).

NOTE ADDED IN PROOF: After this review had been submitted, the occurrence of *O*-methylpeyoxylic acid and *O*-methylpeyoruvic acid in peyote was demonstrated by glc-mass spectrometry and reported (KAPADIA, G. J., G. S. RAO, M. H. HUSSAIN and B. K. CHOWDHURY. 1973. Peyote and related alkaloids. XV. *O*-Methylpeyoxylic acid and *O*-methylpeyoruvic acid, the new cyclic amino acid analogs of mescaline. *J. Heterocycl. Chem.* **10:** 135).

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LITERATURE CITED

1. KAPADIA, G. J. and M. B. E. FAYEZ. 1970. Peyote constituents. Chemistry, biogenesis, and biological effects. *J. Pharm. Sci.* **59:** 1699.
2. LEWIN, L. 1888. Ueber Anhalonium Lewinii und andere Cacteen. *Arch. Exp. Pathol. Pharmakol.* **24:** 401.
3. HEFFTER, A. 1894. Ueber Pellote. Ein Beitrag zur pharmakologischen Kenntniss der Cacteen. *Arch. Exp. Pathol. Pharmakol.* **34:** 65.
4. HEFFTER, A. 1894. Ueber Zwei Cacteenalkaloide. *Chem. Ber.* **27:** 2975.
5. HEFFTER, A. 1896. Ueber Cacteenalkaloide. *Chem. Ber.* **29:** 216.
6. HEFFTER, A. 1898. Ueber Pellote. *Arch. Exp. Pathol. Pharmakol.* **40:** 385.
7. HEFFTER, A. 1898. Ueber Cacteenalkaloide. *Chem. Ber.* **31:** 1193.
8. HEFFTER, A. 1901. Ueber Cacteenalkaloide. *Chem. Ber.* **34:** 3004.
9. KAUDER, E. 1899. Ueber Alkaloide aus *Anhalonium lewinii*. *Arch. Pharm.* **237:** 190.
10. SPÄTH, E. 1919. Ueber die Anhalonium Alkaloide. *Monatsh. Chem.* **40:** 129.
11. SPÄTH, E. 1921. Die Konstitution des Pellotins, des Anhalonidins und des Anhalamins. *Monatsh. Chem.* **42:** 97.
12. SPÄTH, E. 1921. Konstitution des Anhalins. *Monatsh. Chem.* **42:** 263.
13. SPÄTH, E. and H. RÖDER. 1922. Die Synthese des Anhalamins. *Monatsh. Chem.* **43:** 93.
14. SPÄTH, E. 1922. Die Synthese des Anhalonidins und des Pellotins. *Monatsh. Chem.* **43:** 477.
15. SPÄTH, E. and J. GANGL. 1923. Anhalonin und Lophophorin. *Monatsh. Chem.* **44:** 103.
16. SPÄTH, E. 1929. Ueber das Carnegin. *Chem. Ber.* **62:** 1021.
17. SPÄTH, E. and J. PASSL. 1932. Ueber die Konstitution von Pellotin und Anhalonidin. *Chem. Ber.* **65:** 1778.
18. SPÄTH, E. and F. BOSCHAN. 1933. Ueber Kakteenalkaloide. 10. Die Konstitution des Pellotins und des Anhalonidins. *Monatsh. Chem.* **63:** 141.
19. SPÄTH, E. and F. BECKE. 1934. Eine neue Synthese des Pellotins. *Chem. Ber.* **67:** 266.
20. SPÄTH, E. and F. BECKE. 1934. Die Konstitution des Anhalamins. *Chem. Ber.* **67:** 2100.
21. SPÄTH, E. and F. BECKE. 1935. Ueber die Trennung der Anhaloniumbasen. *Monatsh. Chem.* **66:** 327.
22. SPÄTH, E. and F. BECKE. 1935. A new cactus alkaloid, anhalinine, and the constitution of anhalonine. *Chem. Ber.* **68:** 501.
23. SPÄTH, E. and F. BECKE. 1935. Anhalidine. *Chem. Ber.* **68:** 944.
24. SPÄTH, E. and F. KESZTLER. 1935. Synthesis of anhalonine and of lophophorine. *Chem. Ber.* **68:** 1663.
25. SPÄTH, E. and F. KESZTLER. 1936. The optical activity of pellotine. *Chem. Ber.* **69:** 755.
26. SPÄTH, E. and J. BRUCK. 1937. Ueber ein neues Alkaloid aus den Mezcal buttons. *Chem. Ber.* **70:** 2446.
27. SPÄTH, E. and J. BRUCK. 1938. N-Acetylmezkalin als Inhaltsstoff der Mezcal buttons. *Chem. Ber.* **71:** 1275.
28. SPÄTH, E. and J. BRUCK. 1939. *O*-Methyl-*d*-anhalonidine. *Chem. Ber.* **72:** 334.
29. KAPADIA, G. J. and G. S. RAO. 1964. Preparation, gas-liquid chromatography and structure-retention relationship of anhalonium and related alkaloids. *Lloydia* **27:** 271.
30. Anonymous. 1959. Peyotl. *Bull. Narcotics* **11:** 16.
31. LUNDSTÖM, J. 1971. Biosynthetic studies on mescaline and related cactus alkaloids. *Acta Pharm. Suecica* **8:** 275.
32. MCLAUGHLIN, J. L. and A. G. PAUL. 1965. Presence of hordenine in *Lophophora williamsii*. *J. Pharm. Sci.* **54:** 661.
33. MCLAUGHLIN, J. L. and A. G. PAUL. 1966. Identification of *N*-methylated tyramine derivatives in *Lophophora williamsii*. *Lloydia* **29:** 315.
34. RETI, L. 1950. Cactus alkaloids and some related compounds. *Fortsch. Chem. Org. Naturstoffe* **6:** 242.
35. WILLAMAN, J. J. and SCHUBERT, B. G. 1961. Alkaloid Bearing Plants and Their Contained Alkaloids. *U.S. Dept. of Agr. Tech. Bull. No.* 1234, *U. S. Government Printing Office, Washington, D.C.*
36. TODD, J. S. 1969. Thin-layer chromatography analysis of Mexican population of *Lophophora* (Cactaceae). *Lloydia* **32:** 395.
37. LUNDSTRÖM, J. 1971. Biosynthesis of mescaline and tetrahydroisoquinoline alkaloids in *Lophophora williamsii* (Lem.) Coult. Occurrence and biosynthesis of catecholamine and other intermediates. *Acta Chem. Scand.* **25:** 3489.
38. LINDGREN, J. E., S. AGURELL, J. LUNDSTRÖM and U. SVENSSON. 1971. Detection of biochemical intermediates by mass fragmentography: Mescaline and tetrahydroisoquinoline precursors. *Febs Letters* **13:** 21.
39. LUNDSTRÖM, J. and S. AGURELL. 1968. Gas chromatography of peyote alkaloids. A new peyote alkaloid. *J. Chromatog.* **36:** 105.
40. AGURELL, S., J. G. BRUHN, J. LUNDSTRÖM and U. SVENSSON. 1971. Cactus alkaloids. X. Alkaloids of *Trichocereus* species and some other cacti. *Lloydia* **34:** 183.

41. KAPADIA, G. J., Y. N. VAISHNAV and M. B. E. FAYEZ. 1969. Peyote alkaloids. IX. Identification and synthesis of 3-demethylmescaline, a plausible intermediate in the biosynthesis of the cactus alkaloids. *J. Pharm. Sci.* **58**: 1157.
42. AGURELL, S. and J. LUNDSTRÖM. 1968. Apparent intermediates in the biosynthesis of mescaline and related tetrahydroisoquinolines. *Chem. Commun.* **1968**: 1638.
43. LUNDSTRÖM, J. 1971. Biosynthesis of tetrahydroisoquinoline alkaloids in *Lophophora williamsii* (Lem.) Coult. *Acta Pharm. Suecica* **8**: 485.
44. KAPADIA, G. J. and H. M. FALES. 1968. Krebs cycle conjugates of mescaline. Identification of fourteen new peyote alkaloid amides. *Chem. Commun.* **1968**: 1688.
45. MUDD, S. H. 1960. S-Adenosylmethionine requirement for plant transmethylations. *Biochim. Biophys. Acta* **37**: 164.
46. MUDD, S. H. 1960. S-Adenosylmethionine formation by barley extracts. *Biochim. Biophys. Acta* **38**: 354.
47. MANN, J. D. and S. H. MUDD. 1963. Alkaloids and plant metabolism. IV. The tyramine methylpherase of barley roots. *J. Biol. Chem.* **238**: 381.
48. NIEFORTH, K. A. 1971. Psychotomimetic phenethylamines. *J. Pharm. Sci.* **60**: 655, and references cited therein.
49. Soc. Anon. Pour Lind. a Bâle. 1930. British Patent 360, 266; Jan. 8; *Chem. Abstr.* 27, 513 (1933).
50 SLOTTA, K. H. and G. SZYSKA. 1933. Ueber β-phenylaethylamine. 3. Neue Darstellung von Mescalin. *J. Prakt. Chem.* **137**: 339.
51. HAHN, G. and H. WASSMUTH. 1934. Ueber β-(oxyphenyl)-aethylamine und ihre Umwandlungen. I. Synthese des Mescalins. *Chem. Ber.* **67**: 696.
52. HAHN, G. and F. RUMPF. 1938. Kondensation von Oxyphenyl-aethyaminen mit α-Ketonsäuren. *Chem. Ber.* **71**: 2141.
53. ERNE, M. and F. RAMIREZ. 1950. Ueber die Reduktion von β-Nitrostyrolen mit Lithiumaluminiumhydrid. *Helv. Chim. Acta* **33**: 912.
54. BENINGTON, F. and R. D. MORIN. 1951. An improved synthesis of mescaline. *J. Amer. Chem. Soc.* **73**: 1353.
55. DORNOW, A. and G. PETSCH. 1951. Synthesis of 2-hydroxy-2-(3,4,5-trimethoxyphenyl)ethylamine (hydroxy-mescaline), bis[2-(3,4,5-trimethoxyphenyl)ethylamine (dimescaline), and 2-(3,4,5-trimethoxyphenyl)ethylamine (mescaline). *Arch. Pharm.* **284**: 160.
56. BENINGTON, F., R. D. MORIN and L. C. CLARK, JR. 1954. Mescaline analogs. I. 2,4,6-Trialkoxy-β-phenethylamines. *J. Org. Chem.* **19**: 11.
57. BENINGTON, F., R. D. MORIN and L. C. CLARK, JR. 1954. Synthesis of 4-hydroxy- and 4-ethoxy-3,5-dimethoxy-β-phenethylamines. *J. Amer. Chem. Soc.* **76**: 5555.
58. BENINGTON, F., R. D. MORIN and L. C. CLARK, JR. 1955. Mescaline analogs. III. 2,4,6-Trialkyl- and 3,4-dihydroxy-5-methoxy-β-phenethylamines. *J. Org. Chem.* **20**: 1292.
59. MERCHANT, J. R. and A. J. MOUNTWALA. 1957. Some new phenethylamines. *Curr. Sci.* **26**: 211.
60. INUBUSHI, Y. and K. FUJITANI. 1958. An unexpected reaction in a Pomeranz-Fritsch isoquinoline synthesis. *Yakugaku Zasshi* **78**: 486.
61. MERCHANT, J. R. and A. J. MOUNTWALA. 1958. Synthesis of some β-phenethylamine derivatives. *J. Org. Chem.* **23**: 1774.
62. RATCLIFFE, J. and P. SMITH. 1959. Metabolism of mescaline. *Chem. Ind. (London)* **1959**: 925.
63. DYUMAEV, K. M. and I. S. BELOSTOTSKAYA. 1962. Synthesis of trisubstituted phenethylamines by catalytic reduction of β-nitrostyrenes. *Zh. Obshch. Khim.* **32**: 2661.
64. KUBOTA, S., T. MASUI, E. FUJITA and S. M. KUPCHAN. 1966. The structure and total synthesis of takatonine. *J. Org. Chem.* **31**: 516.
65. SHULGIN, A. T. 1968. The ethyl homologs of 2,4,5-trimethoxyphenylisopropylamine. *J. Med. Chem.* **11**: 186.
66. SHULGIN, A. T. 1964. Psychotomimetic amphetamines. II. Methoxy 3,4-dialkoxyamphetamines. *Experientia* **20**: 366.
67. HO, B. T., W. M. MCISAAC, R. AN, W. TANSEY, K. E. WALKER, L. ENGLERT and M. B. NOEL. 1970. Analogs of α-methylphenethylamine (amphetamine). I. Synthesis and pharmacological activity of some methoxy and/or methyl analogs. *J. Med. Chem.* **13**: 26.
68. LUNDSTRÖM, J. and S. AGURELL. 1970. Synthesis of specifically labelled substituted β-phenethylamines. *Acta. Pharm. Suecica* **7**: 247.
69. VORONIN, V. G., G. D. KULIKOVSKAYA and L. D. MAGDA. 1965. Substituted β-phenethylamines. *Zh. Org. Khim.* **1**: 719.
70. HOLLAND, G. F., C. J. BUCK and A. WEISSMAN. 1963. Anorexigenic agents: aromatic substituted 1-phenyl-2-propylamines. *J. Med. Chem.* **6**: 519.
71. WIEGREBE, W. 1964. Synthesis of 1-(4-methoxybenzoyl)-*N*-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline. *Arch. Pharm.* **297**: 362.
72. MERCHANT, J. R. and M. S. KHAN. 1962. Some β-phenylethylamine derivatives. I. *J. Indian Chem. Soc.* **39**: 227.
73. TOMITA, M. 1968. Synthesis of *dl*-cepharanthine. *Chem. Pharm. Bull.* **16**: 217.
74. SHULGIN, A. T. 1966. The six trimethoxyphenylisopropylamines (trimethoxyamphetamines). *J. Med. Chem.* **9**: 445.
75. BENINGTON, F., R. D. MORIN and L. C. CLARK, JR. 1955. Mescaline analogs. II. Tetra- and pentamethoxy-β-phenethylamines. *J. Org. Chem.* **20**: 102.
76. BENINGTON, F., R. D. MORIN and L. C. CLARK, JR. 1956. *p*-Dialkylamino-β-phenethylamines and 9-(β-aminoethyl)-julolidine. *J. Org. Chem.* **21**: 1470.
77. KAPADIA, G. J. and N. J. SHAH. 1968. Peyote alkaloids. V. Preparation of mescaline and selective ether cleavage of pyrogallol trimethyl ethers with lithium aluminum hydride. 115th Annual Meeting of the American Pharmaceutical Association (Miami Beach, Fla.); Abstract no. 16, p. 104.
78. SLOTTA, K. H. and G. SZYSKA. 1934. Synthese des Mescalins. *Chem. Ber.* **67**: 1106.
79. KINDLER, K. and W. PESCHKE. 1932. Syntheses of tyramine and epinine. *Arch. Pharm.* **270**: 340.
80. KINDLER, K. and W. PESCHKE. 1932. Ueber neue u. ueber verbesserte Wege zum Aufbau von pharmakologisch wichtigen Aminen. VI. Ueber den Synthesen des Meskalins. *Arch. Pharm.* **270**: 410.
81. KINDLER, K. 1927. New and improved methods of synthesizing pharmacologically important amines. *Arch. Pharm.* **265**: 389.
82. KAPADIA, G. J., M. H. HUSSEIN, B. K. CHOWDHURY and G. S. RAO. 1971. Some new tetrahydroisoquinoline and β-phenethylamine analogs of the cactus alkaloids. 31st International Congress of Pharmaceutical Sciences (Washington, D.C.).
83. TSAO, M. U. 1951. A new synthesis of mescaline. *J. Amer. Chem. Soc.* **73**: 5495.
84. DORNOW, A. and G. PETSCH. 1952. Synthesis of hydroxymescaline and mescaline. *Arch. Pharm.* **285**: 323.
85. BROSSI, A., M. BAUMANN and R. BORER. 1965. Zur Aetherspaltung 6,7,8-trimethoxy-substituierter Isoquinolinverbindungen mit waesseriger Salzsaeure. *Monatsh. Chem.* **96**: 25.
86. BLOCK, W. and K. BLOCK. 1952. Synthese von ^{14}C-radioaktivem Mescalin. *Chem. Ber.* **85**: 1009.
87. KAMETANI, T., N. WAGATSUMA and F. SASAKI. 1966. Selective demethylation of 3,4-dihydro-6,7,8-trimethoxyisoquinoline and modified total synthesis of anhalamine. *J. Pharm. Soc. Jap.* **86**: 913.

88. ABDEL-RAHMAN, M. O., M. N. ABOUL-ENEIN and R. M. TAHA. 1968. An improved method for the synthesis of mescaline. *J. Chem. U. A. R.* **11:** 401.
89. BEASLEY, J. G. and A. BURGER. 1964. Methyl analogs of papaverine. *J. Med. Chem.* **7:** 686.
90. SLOBODSKI, A. G. and V. G. TUPIKINA. 1969. β-(3,4-Dimethoxyphenyl) ethylamine. *Otkrytinya Izobret., Prom. Obraztsy, Tovarnye Znaki,* **46:** 176; *Chem. Abstr.* **71,** 12819 (1969).
91. MNDZHOYAN, A. L., A. A. AROYAN and T. R. OVSEPYAN. 1961. Amines and derivatives. XI. The preparation of some chloracetamides and urethans. *Izv. Akad. Nauk Arm. SSR, Khim. Nauki,* **14:** 157.
92. AROYAN, A. A. and T. R. OVSEPYAN. 1962. Syntheses from chloromethyl derivatives of esters of *o*- and *p*-cresols. *Izv. Akad. Nauk Arm. SSR, Khim. Nauki* **15:** 263.
93. BENINGTON, F., R. D. MORIN, L. C. CLARK, JR. and R. P. FOX. 1958. Psychopharmacological activity of ring- and side chain-substituted β-phenethylamines. *J. Org. Chem.* **23:** 1979.
94. BENINGTON, F., R. D. MORIN and L. C. CLARK, JR. 1958. Tetra- and pentamethyl-β-phenethylamines. *J. Org. Chem.* **23:** 2034.
95. SLOTTA, K. H. 1932. Preparation of 3,4,5-trimethoxybenzaldehyde. *J. Prakt. Chem.* **133:** 129.
96. SLOTTA, K. H. and H. HELLER. 1930. Ueber β-phenylaethylamine. I. Mezcalin und mezcalin-ähnlicher Substanzen. *Chem. Ber.* **63:** 3029.
97. KULKARNI, S. N., S. B. PATIL, P. V. PANCHANGAM and K. S. NAGUND. 1967. Substituted methoxyphenethylamines. *Indian J. Chem.* **5:** 471.
98. SCHWACHHOFER, G. and J. Chapin. 1962. Synthesis of some α-disubstituted derivatives of mescaline. *Bull. Soc. Chim. Fr.* 835.
99. MCCARTY, F. J., R. D. ROSENSTOCK, J. P. PAOLINI, D. MICUCCI, L. ASHTON, W. W. BENNETTS and F. P. PALAPOLI. 1968. Synthesis and pharmacology of a series of 1-aralkyl-3-butenylamines. *J. Med. Chem.* **11:** 534.
100. HABERMEHL, G. and A. KHALIQUE. 1967. Homopiperonylamine. *Pak. J. Biol. Agr. Sci.* **10:** 46.
101. BANHOLZER, K., T. W. CAMPBELL and H. SCHMID. 1952. Notiz ueber eine neue Synthese von Mezcalin, N-methyl- und N-dimethylmezcalin. *Helv. Chim. Acta* **35:** 1577.
102. BENINGTON, F., R. D. MORIN and L. C. CLARK, JR. 1957. Mescaline analogs. VII. 3,4,5-Trimethylphenethylamines. *J. Org. Chem.* **22:** 332.
103. AMOS, D. 1964. The preparation of mescaline from eucalypt lignin. *Aust. J. Pharm.* **45:** S8.
104. HADÁČEK, J., J. MICHALSKY and L. MACHOLÁN. 1955. Synthesis of mescaline. *Chem. Listy* **49:** 271.
105. HAHN, G. 1934. Synthese des Mescalins. *Chem. Ber.* **67:** 1210.
106. RABUSIC, E. and M. GREGOR. 1967. Aminoalkylation of phenol ethers. *Spisy Prirodoved. Fak. Univ. Brne,* **480:** 85; *Chem. Abstr.* **68:** 86944 (1968).
107. PATEL, A. R. 1968. Mescaline and related compounds. *Fortschr. Arzneimittelforsch.* **11:** 11.
108. JANSEN, M. 1929. β-2,4,5-Trimethoxyphenethylamine. *Chem. Weekbl.* **26:** 421.
109. JANSEN, M. 1931. β-2,4,5-Trimethoxyphenethylamine, an isomer of mescaline. *Rec. Trav. Chim. Pays-Bas Belg.* **50:** 291.
110. SLOTTA, K. H. and J. MÜLLER. 1936. Ueber den Abbau des Mescalins und meskalin-ähnlicher Stoffe in Organismus. *Hoppe Seyler's Z. Physiol. Chem.* **238:** 14.
111. GRACE, G. S. 1934. The action of mescaline and some related compounds. *J. Pharmacol. Exp. Ther.,* **50:** 359.
112. IWAMOTO, K. H. and W. H. HARTUNG. 1944. Methoxyl derivatives of phenylpropanolamine and 3,5-dihydroxyphenylpropanolamine. *J. Org. Chem.* **9:** 513.
113. HEY, P. 1947. Synthesis of a new homolog of mescaline. *Quart. J. Pharm. Pharmacol.* **20:** 129.
114. BINOVIC, K., S. VRANCEA, D. GRANDET, J. M. LEBOURG and R. PORQUET. 1968. Anorexic derivatives. *Chim. Ther.* **3:** 313.
115. KLOSA, J. 1966. New synthesis of diphenylisopropylamines. *J. Prakt. Chem.* **34:** 335.
116. SHCULZ, H. 1967. Preparation of cardiac- and circulatory-active compounds. I. *Pharmazie* **22:** 19.
117. PINDER, R. M. and A. BURGER. 1967. Trifluoromethyl analogs of amphetamine and norephedrine. *J. Pharm. Sci.* **56:** 970.
118. LEETE, E. 1959. Biogenesis of mescaline. *Chem. Ind. (London)* **1959:** 604.
119. LEETE, E. 1966. Biosynthesis of the peyote alkaloids. The incorporation of tyrosine-2-C^{14} into mescaline and anhalonidine. *J. Amer. Chem. Soc.,* **88:** 4218.
120. AGURELL, S., J. LUNDSTRÖM and F. SANDBERG. 1967. Biosynthesis of mescaline in peyote. *Tetrahedron Lett.* **1967:** 2433.
121. MCLAUGHLIN, J. L. and A. G. PAUL. 1967. Biosynthesis of hordenine and mescaline in *Lophophora williamsii. Lloydia* **30:** 91.
122. ROSENBERG, H., J. L. MCLAUGHLIN and A. G. PAUL. 1967. Phenylalanine, DOPA and DOPAmine as precursors to mescaline in *Lophophora williamsii. Lloydia* **30:** 100.
123. LUNDSTRÖM, J. 1972. Identification of new peyote alkaloids. Isomers to the main phenolic tetrahydroisoquinolines. *Acta Chem. Scand.* **26:** 1295.
124. WHALEY, W. M. and T. R. GOVINDACHARI. 1960. *Organic Reactions.* Ed.: R. ADAMS. Wiley, New York. p. 151.
125. WHALEY, W. M. and T. R. GOVINDACHARI. 1960. *Organic Reactions.* Ed.: R. ADAMS. Wiley, New York. p. 74.
126. GENSLER, W. J. 1960. *Organic Reactions.* Ed.: R. ADAMS. Wiley, New York. p. 191.
127. BOBBITT, J. M., J. M. KIELY, K. L. KHANNA and R. EBERMANN. 1965. A new synthesis of 1,2,3,4-tetrahydroisoquinolines. *J. Org. Chem.* **30:** 2247.
128. BROSSI, A., F. SCHNENKER, R. SCHMIDT, R. BANZIGER and W. LEIMGRUBER. 1966. Zur Darstellung 6,7,8-Hydroxy-dimethoxy-substituierter 1,2,3,4-Tetrahydro-isoquinoline aus 3-Benzyloxy-4,5-dimethoxy, phenaethylamin und Bericht ueber die Resultate der pharmakologischen Pruefung von Anhalamin, Anhalidin, *rac.* Anhalonidin und *rac.* Pellotin. *Helv. Chim. Acta* **49:** 403.
129. BROSSI, A., F. SCHENKER and W. LEIMGRUBER. 1964. Synthesen in der Isochinolinreihe. Neue Synthesen der Kaktusalkaloide Anhalamin, Anhalidin, *rac.* Anhalonidin und *rac.* Pellotine. *Helv. Chim. Acta* **47:** 2089.
130. KARADY, S. 1962. Synthesis of 5-ethyl-8-methoxycorydaline. *J. Org. Chem.* **27:** 3720.
131. TAKIDO, M., K. L. KHANNA and A. G. PAUL. 1970. A new synthesis of *rac.* anhalonidine and *rac.* pellotine. *J. Pharm. Sci.* **59:** 271.
132. BOBBITT, J. M. and C. P. DUTTA. 1969. 1,2,3,4,-Tetrahydroisoquinolines *via* the Mannich condensation. *J. Org. Chem.* **34:** 2001.
133. KAPADIA, G. J. and H. M. FALES. 1968. Peyophorine, a tetrahydroisoquinoline cactus alkaloid containing an *N*-ethyl group. *J. Pharm. Sci.* **57:** 2017.
134. SMALL, L. 1943. *Organic Chemistry.* Ed.: H. GILMAN. Wiley, New York. p. 1171.
135. KAPADIA, G. J., N. J. SHAH and T. B. ZALUCKY. 1968. Anhalotine, lophotine and peyotine, the quaternary alkaloids of *Lophophora williamsii. J. Pharm. Sci.* **57:** 254.
136. DURAND, S., X. LUSINCHI and R. C. MOREAU. 1961. Preparation de l'hydroxy-5 tetrahydro-1,2,3,4 isoquinoleine et de quelques-uns de ses derives. *Bull. Soc. Chim. Fr.* **1961:** 270.
137. BROSSI, A., J. F. BLOUNT, J. O'BREIN and S. TEITEL. 1971. New synthesis and absolute configuration of tetrahydroisoquinoline cactus alkaloids. *J. Amer. Chem. Soc.* **93:** 6248.
138. BROSSI, A. and S. TEITEL. 1970. Preferential cleavage of trimethoxy-substituted 1,2,3,4-tetrahydroisoquinoline alkaloids. *Chem. Commun.* **1970:** 1296.

139. LEWIN, L. 1894. Ueber Anhalonium Lewinii und andere Cacteen. *Arch. Exp. Pathol. Pharmakol.* **34**: 374.
140. LEWIN, L. 1894. Ueber Anhalonium Lewinii und andere giftige Cacteen. *Ber. Deut. Bot. Ges.* **12**: 283.
141. BATTERSBY, A. R. and T. P. EDWARDS. 1960. Chemical correlation of the absolute configurations of salsolidine, salsoline, and calycotomine with the amino-acid. *J. Chem. Soc.* **1960**: 1214.
142. LUNDSTRÖM, J. and S. AGURELL. 1968. Biosynthesis of mescaline and anhalamine in peyote. *Tetrahedron Lett.* **1968**: 4437.
143. SPÄTH, E. and F. BECKE. 1934. The constitution of anhalamine. *Chem. Ber.* **67**: 2100.
144. KAPADIA, G. J., G. S. RAO, E. LEETE, M. B. E. FAYEZ, Y. N. VAISHNAV and H. M. FALES. 1970. On the origin of carbon 1 in tetrahydroisoquinoline alkaloids. *J. Amer. Chem. Soc.* **92**: 6943.
145. BATTERSBY, A. R., R. BINKS and R. HUXTABLE. 1967. Biosynthesis of cactus alkaloids. *Tetrahedron Lett.* **1967**: 563.
146. BATTERSBY, A. R. 1961. Alkaloid biosynthesis. *Quart. Rev. Chem. Soc.* **15**: 272.
147. KAPADIA, G. J., M. B. E. FAYEZ, B. K. CHOWDHURY and H. M. FALES. 1970. Structure and synthesis of peyoglunal, a new cactus β-phenethylpyrrole. *Lloydia* **33**: 492.
148. HIGHET, R. J. and P. F. HIGHET. 1965. The characterization of complex phenols by nuclear magnetic resonance spectra. *J. Org. Chem.* **30**: 902.
149. KAPADIA, G. J. and B. K. CHOWDHURY. 1972. Unpublished results.
150. KAPADIA, G. J., M. B. E. FAYEZ, Y. N. VAISHNAV, G. S. RAO and H. M. FALES. 1969. The origin of the C–1 carbon of the tetrahydroisoquinoline alkaloids. Peyoxylic acid and peyoruvic acid. *Lloydia* **32**: 525.
151. KAPADIA, G. J., Y. N. VAISHNAV, H. M. FALES and M. B. E. FAYEZ. 1969. Identification and synthesis of 3-demethylmescaline, a plausible intermediate in the biosynthesis of the cactus alkaloids. *116th Annual Meeting of the American Pharmaceutical Association*, Montreal, Canada, May 18–22.
152. KAPADIA, G. J., B. K. CHOWDHURY, M. L. SETHI, G. S. RAO and M. H. HUSSEIN. 1971. Some newer synthetic cactus alkaloid analogs. *118th Annual Meeting of the American Pharmaceutical Association*, San Francisco, Calif., March 27–April 2.
153. KAPADIA, G. J., M. H. HUSSEIN and G. S. RAO. 1972. Mescaloxylic acid and mescaloruvic acid, the novel amino acid analogs of mescaline. *J. Pharm. Sci.* **61**: 1172.
154. KAPADIA, G. J. and N. J. SHAH. 1967. Isolation and synthesis of peyonine, a novel β-phenethylpyrrole from *Lophophora williamsii*. *Lloydia* **30**: 287.
155. KAPADIA, G. J. and R. J. HIGHET. 1968. Structure of peyonine, novel β-phenethylpyrrole from *Lophophora williamsii*. *J. Pharm. Sci.* **57**: 191.
156. ROSENTHALER, L. 1931. Détection de composes organiques. Réactions microchimiques de la mescaline. *Pharm. Ztg.* **76**: 653.
157. DUCLOUX, E. H. 1931. Some microchemical reactions of mescaline. *Rev. Farm.* (*Buenos Aires*) **74**: 87.
158. WNAG, G. and A. DOMBROWSKI. 1942. Verwendung von 2-Nitro-indandion-(1.3) fur die Isolierung und Identifizierung organischer Basen. *Chem. Ber.* **75**: 82.
159. KINSKA, E. 1947. Mescaline. *Chem. Obz.* **22**: 77.
160. CLARKE, E. G. C. 1957. Microchemical identification of some less common alkaloids. *J. Pharm. Pharmacol.* **9**: 187.
161. BASTOS, M. L. 1956. Applications of a modified chromic acid reagent in toxicological chemistry. *Bol. Inst. Quim. Agr. Rio de Janeiro* **45**: 7.
162. MUNIER, I. R. and M. MACHEBOEUF. 1949. Microchromatographie de partage des alcaloides et de diverses bases azoties biologiques. *Bull. Soc. Chim. Biol.* **31**: 1144.
163. BLOCK, W., K. BLOCK and B. PATZIG. 1952. Zur Physiologie des ^{14}C-radioaktiven Mescalins im Tierversuch. I. Fermentversuche und Ausscheidungsprodukte. *Hoppe Seyler's Z. Physiol. Chem.* **290**: 160.
164. PALMIERI, V. M. and C. ROMANO. 1952. Paper chromatography in forensic medicine. *Arch. Ital. Sci. Farmacol.* **2**: 345.
165. REIO, L. 1960. Supplementary data for the paper-chromatographic separation and identification of phenol derivatives and related compounds of biochemical interest, using a reference system. *J. Chromatogr.* **4**: 458.
166. RESPLANDY, A. 1961. Paper chromatography of alkaloids with aqueous solutions of electrolytes. *Mem. Inst. Sci. Madagascar* **10**: 1; *Chem. Abstr.* **60**, 13885 (1961).
167. FISCHER, R. 1958. Pharmacology and metabolism of mescaline. *Rev. Can. Biol.* **17**: 389.
168. AGURELL, S. 1969. Cactaceae alkaloids. I. *Lloydia* **32**: 206.
169. COCHIN, J. and J. W. DALY. 1962. Rapid identification of analgesic drugs in urine with thin-layer chromatography. *Experientia* **18**: 294.
170. STEELE, J. A. 1965. Solvent systems for the identification of opiates in narcotic seizures by thin-layer chromatography. *J. Chromatogr.* **19**: 300.
171. JART, A. and A. J. BIGLER. 1967. Thin-layer chromatographic separation of primary and secondary amines as 4-(phenylazo) benzenesulfonamides. *J. Chromatogr.* **29**: 255.
172. WALDI, D., K. SCHNACKERZ, and F. MUNTER. Systematic analysis of alkaloids on thin-layer plates. *J. Chromatogr.* **6**: 61.
173. LUNDSTRÖM, J. and S. *Agurell*. 1967. Thin-layer chromatography of the peyote alkaloids. *J. Chromatogr.* **30**: 271.
174. PARKER, K. D., C. R. FONTAN and P. L. KIRK. 1963. Rapid gas-chromatographic method for screening toxicological extracts for alkaloids, barbiturates, sympathomimetic amines, and tranquilizers. *Anal. Chem.* **35**: 356.
175. AGURELL, S. 1969. Identification of alkaloid intermediates by gas chromatography-mass spectrometry. I. Potential mescaline precursors in *Trichocereus* species. *Lloydia* **32**: 40.
176. KAPADIA, G. J. and G. S. RAO. 1965. Gas-liquid chromatography and structure-retention time relationship of Anhalonium alkaloids and related bases. *J. Pharm. Sci.* **54**: 1817.
177. BROWN, S. D., J. L. MASSINGILL, JR. and J. E. HODGKINS. 1968. Cactus alkaloids. *Phytochemistry* **7**: 2031.
178. CLARKE, E. G. C. 1967. The identification of some prescribed psychedelic drugs. *Forensic Sci. Soc. J.* **7**: 46.
179. VANDEN HEUVEL, W. J. A. 1968. Gas-liquid chromatography of the trimethylsilyl derivatives of several amines of biological interest. *J. Chromatogr.* **36**: 354.
180. RICHTER, D. 1938. Elimination of amines in man. Biochem. J. **32**: 1763.
181. DESSI, P. and C. RIZZOKI. 1968. Testing of 3,4,5-trimethoxyphenylethylamine in aqueous solutions, urine and blood. *Boll. Soc. Ital. Biol. Sper.* **24**: 1250.
182. WOODS, L. A., J. COCHIN, E. J. FORNEFELD, F. G. MCMAHON and M. H. SEEVERS. 1951. Estimation of amines in biological materials with critical data for cocaine and mescaline. *J. Pharmacol. Exp. Ther.* **101**: 188.
183. VISTOLI, G. 1955. Application of a color reaction to the photometric determination of sympathomimetic amines of pharmaceutical importance. *Boll. Chim. Farm.* **94**: 133.
184. DESSI, P. and T. FRANCO. 1949. Application of the Beyer and Skinner reaction to photometric determination of mescaline and histamine. *Boll. Soc. Ital. Biol. Sper.* **25**: 1368.

185. SEILER, N. and M. WIECHMANN. 1964. Die fluorimetrische Bestimmung des Mezcalins und einiger β-Phenaethylamine. *Hoppe Seyler's Z. Physiol. Chem.* **337**: 229.
186. KALÁB, D. 1956. Oscillographic behavior of mescaline. *Pharmazie* **11**: 268.
187. BARBEAU, A. 1967. The "pink spot", 3,4-dimethoxyphenylethylamine and dopamine relation to Parkinson's disease and to schizophrenia. *Rev. Can. Biol.* **26**: 55.
188. FRIEDHOFF, A. J. and E. V. WINKLE. 1963. The role of catecholamines in specific psychiatric disorders. *Res. Publ. Ass. Res. Nerv. Ment. Dis.* **43**: 366.
189. BELLMAN, S. W. 1968. Mass spectral identification of some hallucinogenic drugs. *J. Ass. Offic. Anal. Chem.* **51**: 164.
190. LUNDSTRÖM, J. and S. AGURELL. 1970. Synthesis of specifically labelled substituted β-phenethylamines. *Acta Pharm. Suecica* **7**: 247.
191. KAPADIA, G. J. and H. M. FALES. 1968. Peyophorine, a tetrahydroisoquinoline cactus alkaloid containing an *N*-ethyl group. *Lloydia* **31**: 430.
192. BUDZIKIEWICZ, H., C. DJERASSI and D. H. WILLIAMS. 1964. *Structure Elucidation of Natural Products by Mass Spectrometry, vol.* 1. Holden-Day, Inc., San Francisco, Calif. p. 173.
193. HAMMAR, C. G., B. HOLMSTEDT and R. RYHAGE. 1968. Mass fragmentography. Identification of chlorpromazine and its metabolites in human blood by a new method. *Anal. Biochem.* **25**: 532.
194. HAMMAR, C. G. and R. HESSLING. 1971. Novel peak matching technique by means of a new and combined multiple ion detector-peak matcher device. *Anal. Chem.* **43**: 298.