THE CHEMISTRY OF THE PSYCHOTOMIMETIC SUBSTANCES

By D. F. Downing

(Chemical Defence Experimental Establishment, Porton Down, Salisbury, Wilts.)

1. Introduction

A psychotomimetic* drug may be defined as one which will consistently produce changes in thought, perception, and mood, occurring alone or in concert, without causing major disturbances of the autonomic nervous system or other serious disability. The term was first used by Gerard[2] and the definition is modified from that of Osmond.[3]

Dewsbery,[4] in remarks on the value of these substances, considers them important for three reasons: (i) because they can give the investigator an approximate subjective experience of what mental disorder is like; (ii) because model psychoses can be studied in the same way as mental disorders; and (iii) because a study of their chemical nature can be expected to throw some light on the nature of the hypothetical substances believed to cause mental disorders.

It is, however, frequently emphasised (for example, by Rothlin[5]) that psychotomimetics, as the word implies, are substances which, in the animal body, cause symptoms similar to those of schizophrenia and are not necessarily similar to, and do not even act in a similar manner to, those substances which may be responsible for causing mental disorder. Nevertheless the stimulation of schizophrenic-like states by intoxication with psychotomimetic drugs has been one of the causes of the renewed interest in the idea that schizophrenia can be due to a chemical abnormality in the brain.

It is the purpose of this Review to collect the more important information on the organic chemistry of this group of compounds, whose members differ widely in structure. The present state of knowledge regarding the chemical aspects of their mode of action is also surveyed.

2. Phenethylamines

Mescaline (3,4,5-*Trimethoxyphenethylamine*) (2).—The chewing of "mescal buttons" ("peyotl," "peyote"), the dried tops of the dumpling

* Other terms have been used in the same sense: schizogen, psychotica, psychotogen, phantastica, hallucinogen, psychedelic. Confusion exists as to whether some of these terms include the tranquillising substances (ataractics). "Psychotropic" is a general term which usually is meant to include analgesics, euphorics, sedatives, tranquillisers, hypnotics, inebriants, stimulants, and psychotomimetics.[1]

[1] Hofmann, *Svensk kem. Tidskr.*, 1960, **72**, 12.

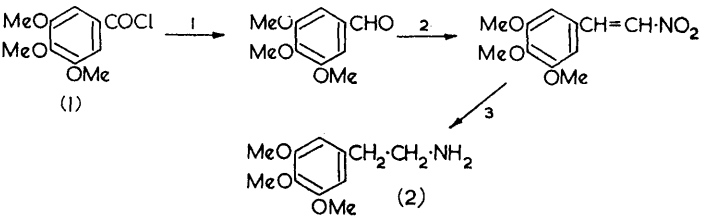
[2] Gerard, "Neuropharmacology," Transactions of the 2nd Conference, Jos. Macy, Jr. Foundation, New York, 1956.

[3] Osmond, *Ann. New York Acad. Sci.*, 1957, **66**, 418.

[4] Dewsbery, *Endeavour*, 1960, **19**, 20.

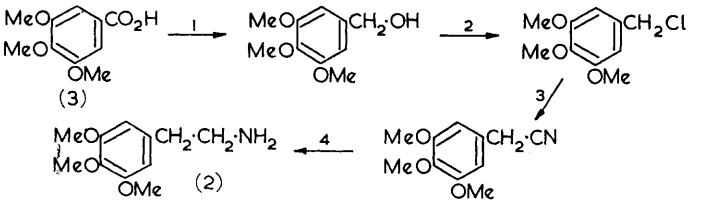
[5] Rothlin, in "Neuro-psychopharmacology," ed. Bradley, Deniker, and Radouco-Thomas, Elsevier, Amsterdam, 1959, p. 1.

cactus *Lophophora williamsii* (*Anhalonium lewinii*), to produce a ritual ecstatic state has long been the practice of the Indians living near to the Mexico–U.S.A. border. More recently what was a pagan rite has tended to be incorporated into the Christian liturgy of the Indian tribes (Peyotism).[6] This practice was first documented by Lewin[7] in 1888. The constituents of *L. williamsii* and similar cacti were initially investigated chemically by Heffter who reported his results in a series of papers.[8] He suggested that the chief constituent of *L. williamsii* was mescaline, which he suggested was 3,4,5-trimethoxy-*N*-methylbenzylamine. This formula was corrected by Späth[9] who proved by synthesis, from 3,4,5-trimethoxybenzoyl chloride (1), that mescaline was, in fact, 3,4,5-trimethoxyphenethylamine (2).



Reagents: 1, H_2–Pd. 2, $MeNO_2$. 3, Zn–AcOH, then Na–Hg.

Probably because of this early interest and its simple formula, mescaline has become the most widely known psychotomimetic, both scientifically[10] and popularly.[11] The interest in mescaline is illustrated by the number of syntheses (at least nine) of the compound reported since Späth's original



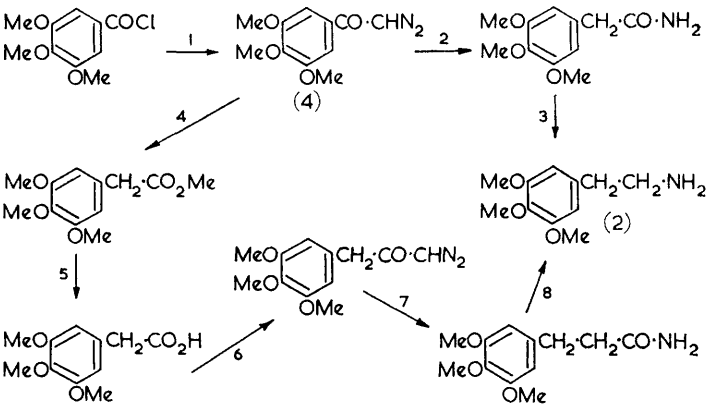
Reagents: 1, $LiAlH_4$. 2, HCl. 3, KCN. 4, $LiAlH_4$.

[6] La Barre, McAllester, Slotkin, Steward, and Tax, *Science*, 1951, **114**, 582.
[7] Lewin, *Arch. exp. Path. Pharmak.*, 1888, **24**, 401; 1894, **34**, 377.
[8] Heffter, *Ber.*, 1894, **27**, 2976; 1896, **29**, 223; 1898, **31**, 1194; 1901, **34**, 3008; 1905, **38**, 3634.
[9] Späth, *Monatsh.*, 1919, **40**, 129.
[10] For reviews see: (*a*) Beringer, "Der Meskalinrausch," Springer, Berlin, 1927; (*b*) Stockings, *J. Mental Sci.*, 1940, **86**, 29; (*c*) Mayer-Gross, *Brit. Med. J.*, 1951, II, 317; (*d*) Stafford, *J. Amer. Med. Assoc.*, 1921, **77**, 1278; (*e*) Reutter, *Schweiz. Apoth.-Ztg.*, 1924, **62**, 441; (*f*) Orlowski, *Apoth.-Ztg.*, 1952, **4**, 124; (*g*) Ronhier, "Le Peyolt," Doin et Cie, Paris, 1927.
[11] Huxley, "The Doors of Perception," Chatto and Windus, London, 1945; "Heaven and Hell," Chatto and Windus, London, 1956.

method. Some of these[12] are variations of Späth's method, but recently[13] advantage has been taken of lithium aluminium hydride reduction, as in the following synthesis from 3,4,5-trimethoxybenzoic acid (3).

This method has also been used[14] in the preparation of [^{14}C]mescaline from K^{14}CN.

A further development was the utilisation of the diazo-ketone (4), which provided two routes to mescaline.[15] Hahn and Wassmuth[16] have investigated further synthetic routes.



Reagents: 1, CH_2N_2. 2, $AgNO_3$–NH_3. 3, $LiAlH_4$. 4, Ag_2O–MeOH. 5, KOH. 6, $SOCl_2$, then CH_2N_2. 7, $AgNO_3$–NH_3. 8, Br_2–NaOH.

Lophophora williamsii has been shown[17] to produce *N*-methyl- and *N*-acetyl-mescaline, and mescaline has been isolated from other *Lophophora* species and from *Trichocereus terschekii*[18] and *T. pachoni*,[19] and it is also reported from the cacti *Gymnocalycium gibbosum*[20] and *Opuntia cylindrica*.[21] Trichocereine, from *T. terschekii*,[18] has been shown to be *NN*-dimethylmescaline and has been synthesised.[15,17] It has been found to have no sensory effect.[22] Many other mescaline analogues have been prepared

[12] Slotta and Heller, *Ber.*, 1930, **63**, 3029; Slotta and Szyzka, *J. prakt. Chem.*, 1933, **137**, 339; Bennington and Morin, *J. Amer. Chem. Soc.*, 1951, **73**, 1353; Erne and Ramirez, *Helv. Chim. Acta*, 1950, **33**, 912; Dornow and Petsch, *Arch. Pharm.*, 1951, **284**, 160; Kinder and Petschke, *ibid.*, 1932, **270**, 410.

[13] Tsao, *J. Amer. Chem. Soc.*, 1951, **73**, 5495; Dornow and Petsch, *Arch. Pharm.*, 1952, **285**, 323.

[14] Block and Block, *Chem. Ber.*, 1952, **85**, 1009

[15] Barnholzer, Campbell, and Schmid, *Helv. Chim. Acta*, 1952, **35**, 1577; Hádácek, Michalsky, and Macholán, *Chem. Listy*, 1955, **49**, 271.

[16] Hahn and Wassmuth, *Ber.*, 1934, **67**, 696.

[17] Späth and Bruek, *Ber.*, 1937, **70**, 2446; 1938, **71**, 1275.

[18] Reti and Castrillón, *J. Amer. Chem. Soc.*, 1951, **73**, 1767.

[19] Poisson, *Ann. Pharm. franç.*, 1960, **18**, 764.

[20] Ducloux, *Rev. Fac. Cienc. quim., Univ. nac. La Plata*, 1930, **6**, 75; *Chem. Abs.*, 1930, **24**, 4077.

[21] Turner and Heyman, *J. Org. Chem.*, 1960, **25**, 2250.

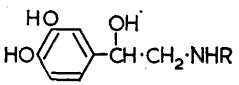
[22] Luduenva, *Compt. rend. Soc. Biol.*, 1936, **121**, 368.

(see ref. 23*a* for references up to 1954) and Bennington and his co-workers have been particularly active in this field.[23]

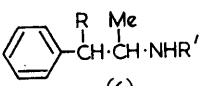
Mescaline has usually been taken in an oral dose of about 350 mg. and consequently is very much less active per mg. than most of the other well-known psychotomimetics. Vivid accounts of the effect are recorded by Mayer-Gross[10c] and Morselli.[24] The outstanding result of mescaline ingestion is visual hallucination, but depersonalisation and time distortion frequently occur. Many other symptoms have been recorded but these vary with the individual. Depression and euphoria may alternate. The effects usually last for 10—12 hours, although reactions up to eleven days in duration have been reported.[25]

The available analogues of mescaline which have been tested have, in general, less psychotomimetic activity than mescaline itself. Smythies[26] has started an investigation of mescaline analogues and has mentioned that 3,4-dimethoxyphenethylamine has half the activity of mescaline, whereas 4-hydroxy-3,5-dimethoxyphenethylamine has none and 4-benzyloxy-3,5-dimethoxyphenethylamine has greater activity than mescaline. 3,4,5-Trimethoxy-α-methylphenethylamine has been found to produce hallucinations with doses smaller than those required for mescaline.[27] Bennington[23c] has shown that a series of methyl-substituted phenethylamines cause rage reactions in cats.

Adrenaline and Adrenochromes.—Some of the symptoms (fear, anxiety,



(5)

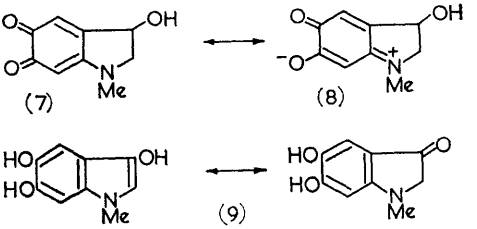


(6)

tenseness) of adrenaline (5; R = Me) and noradrenaline (5; R = H) poisoning following intravenous administration resemble those of a psychotomimetic. In larger doses ephedrine (6; R = OH, R′ = Me) and amphetamine (benzedrine) (6; R = R′ = H) have similar effects.[28] Large doses of methedrine (6; R = H, R′ = Me) have been reported as producing symptoms similar to those of lysergic acid diethylamide when given to mentally abnormal subjects.[29] These observations when combined with those recording the occurrence of adrenaline and noradrenaline in the brain caused Hoffer, Osmond, and Smythies[30] to search for a link between

[23] Bennington, Morin, and Clark, *J. Org. Chem.*, (*a*) 1954, **19**, 11; (*b*) 1955, **20**, 102, 1292, 1454; 1956, **21**, 1470, 1545; 1958, **23**, 19; (*c*) 1958, **23**, 2034.
[24] Morselli, *J. Psychologie normal et path.*, 1936, **33**, 368.
[25] Stevenson and Richards, *Psychopharmacologia*, 1960, **1**, 241.
[26] Smythies, *Lancet*, 1960, I, 1287.
[27] Shulgin, Bunnel and Sargent, *Nature*, 1961, **189**, 1011; Peretz, Smythies, and Gibson, *J. Mental Sci.*, 1955, **101**, 317, 423.
[28] Goodman and Gilman, "The Pharmacological Basis of Therapeutics," Macmillan, 2nd edn., 1955, p. 553.
[29] Liddel and Weil-Malherbe, *J. Neurology, Neurosurgery, and Psychiatry*, 1953, **16**, 7.
[30] Hoffer, Osmond, and Smythies, *J. Mental Sci.*, 1954, **100**, 29.

adrenaline and mescaline on the one hand and the hallucinogenic indoles on the other. These workers first reported the psychotomimetic activity of adrenochrome [(7) or (8); (8) may be considered to be a more satisfactory representation[31]]. Adrenolutin (9) and adrenochrome, which are isomeric, are normal constituents of the blood and it is believed that schizophrenic subjects are less able to control the destruction of injected adrenochrome than are normal subjects.[32] It has previously been indicated that phenethylamines and hydroxyindoles may well be biochemically equivalent since transformation of the former into indoles is certainly possible.[33]



The status of adrenochromes as psychotomimetics is, however, still a matter of debate and the work could not be repeated by others.[31,34] Recent opinion suggests[26] that adrenochromes are not psychotomimetic, at least in the usual sense. The instability of these compounds may, however, account for the varying results obtained.

The chemistry of adrenochrome and related compounds (aminochromes) has been reviewed recently.[35] The red oxidation product of adrenaline has been known for some time but it was not characterised as adrenochrome (7) until 1937 when it was prepared by enzymic (catechol oxidase) oxidation of adrenaline.[36] The oxidation of adrenaline to adrenochrome has also been carried out with silver oxide in methanol.[37] Purification of the product involved the removal of silver ions by ion exchange[38] and a product, which was reported to be stable at room temperature, was obtained. The silver oxide method has been used[39] to prepare racemic

[31] Harley-Mason, *Experientia*, 1948, **4**, 307.

[32] (*a*) Hoffer and Osmond, *J. Mental Sci.*, 1959, **105**, 653; (*b*) Hoffer, in "Psychotropic Drugs," ed. Garattini and Ghetti, Elsevier, Amsterdam, 1957, p. 10; (*c*) Hoffer, in "Hormones, Brain Function and Behaviour", ed. Hoagland, Academic Press, New York, 1957, p. 181.

[33] Osmond and Smythies, *J. Mental Sci.*, 1952, **98**, 309.

[34] (*a*) Feldstein, *Amer. J. Psychiatry*, 1959, **116**, 454; Szára, Axelrod and Perlin, *ibid.*, 1958, **115**, 162; (*b*) van Cauvenberge and Lecompte, *Lancet*, 1953, **264**, 98; (*c*) Smythies, *ibid.*, 1958, II, 308.

[35] (*a*) Heacock, *Chem. Rev.*, 1959, **59**, 181; (*b*) Tatai, *Seitai no Kagaku*, 1956, **7**, 296; *Chem. Abs.*, 1959, **53**, 20567; (*c*) Sobotka, Borsel, and Chanley, *Fortschr. Chem. org. Naturstoffe*, 1957, **14**, 217.

[36] Green and Richter, *Biochem. J.*, 1937, **31**, 596.

[37] Veer, *Rec. Trav. chim.*, 1942, **61**, 638; Harley-Mason, *J.*, 1950, 1276.

[38] Heacock, Nerenberg, and Payza, *Canad. J. Chem.*, 1958, **36**, 853; Feldstein, *Science*, 1958, **128**, 28.

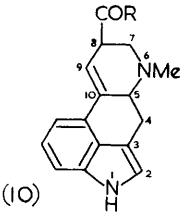
[39] Schayer, *J. Amer. Chem. Soc.*, 1952, **74**, 2441.

[3-^{14}C]adrenochrome. Other oxidations have been carried out with potassium iodate[40] and with oxygen on a palladium–charcoal catalyst.[40a] A large bibliography of the methods used for the preparation of adrenochromes is given in the review by Heacock.[35a]

Adrenolutin (9) is another of the oxidation products of adrenaline and was characterised by Lund[41] in 1949 and synthesised[42] in 1953. The monosemicarbazone of adrenochrome is also psychotomimetic and is known as adrenoxyl.[43] Noradrenolutin has been synthesised by Heacock and Scott.[44]

3. Lysergic acid diethylamide (LSD-25)

The most potent psychotomimetic substance known, so far, is (+)-lysergic acid diethylamide (*NN*-diethyl-lysergamide) (LSD-25) (10; R = NEt_2).

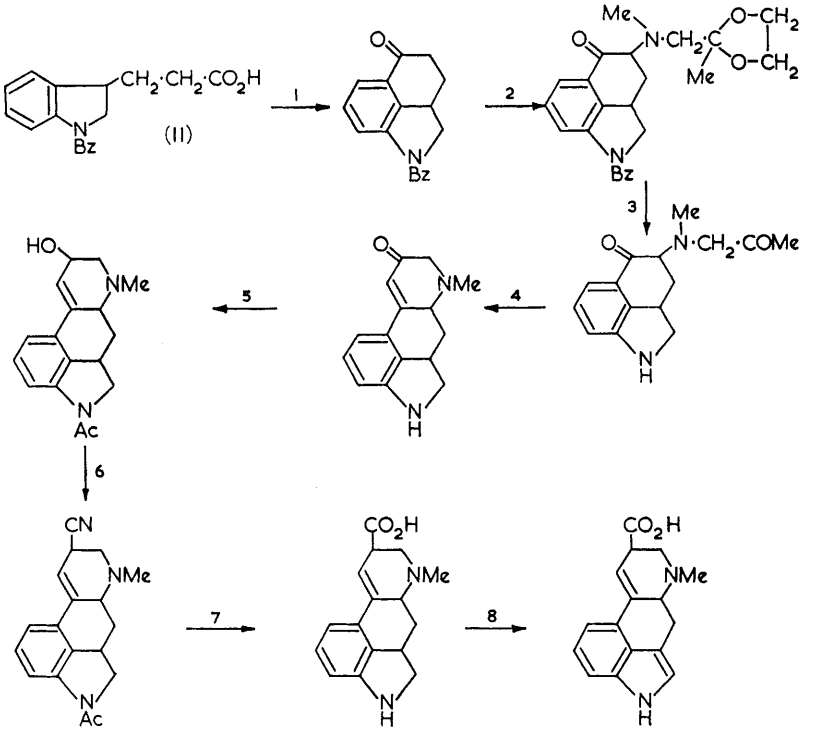


(10)

A lysergic acid (10; R = OH) residue occurs in the ergot alkaloids[45] from which it may be obtained by hydrolysis of the link between the acid and the peptide chains. The simplest ergot alkaloid is ergonovine (10; R = NH·CHMe·CH_2·OH) and the others have more complex polypeptide fragments[46] at C-8. Isolysergic acid differs[47] from lysergic acid only in the configuration at position 8.

(±)-Lysergic acid was synthesised by Woodward and his co-workers at the Eli Lilley Co.[48] by a route starting from *N*-benzoyl-3-2′-carboxyethylindoline (11). This synthesis differed from previous attempts to prepare the compound in one important characteristic—the maintenance of the dihydroindole nucleus in the intermediates until the final dehydrogenation step. Since the (±)-acid (10; R = OH) had previously been resolved,[49] this synthesis constituted a total synthesis of the natural product.

[40] (*a*) Bergel and Morrison, *J.*, 1943, 48; (*b*) Richter and Blaschko, *J.*, 1937, 601.
[41] Lund, *Acta Pharmacologica et Toxicologica*, 1949, **5**, 75, 121.
[42] Balsiger, Fischer, Hirt, and Giovannini, *Helv. Chim. Acta*, 1953, **36**, 708.
[43] Hukki and Seppäläinen, *Acta Chem. Scand.*, 1958, **12**, 1231.
[44] Heacock and Scott, *Experientia*, 1961, **17**, 347.
[45] (*a*) Stoll, "Progress in the Chemistry of Natural Products," Vol. IX, Springer Verlag, Vienna, 1952, p. 114; (*b*) Glenn, *Quart. Rev.*, 1954, **8**, 192.
[46] Stoll, Petrzilka, and Becker, *Helv. Chim. Acta*, 1950, **33**, 57; Stoll and Hofmann, *ibid.*, p. 1705; Stoll, Hofmann, and Petrzilka, *ibid.*, 1951, **34**, 1544.
[47] Stoll, Hofmann, and Troxler, *Helv. Chim. Acta*, 1949, **32**, 506.
[48] Kornfeld, Fornefeld, Kline, Mann, Jones and Woodward, *J. Amer. Chem. Soc.*, 1954, **76**, 5256.
[49] Stoll and Hofmann, *Helv. Chim. Acta*, 1943, **26**, 944.



Total synthesis of lysergic acid.

Reagents: 1, $SOCl_2$ then $AlCl_3$. 2, Br_2, then 2-methyl-2-methylaminomethyl-1,3-dioxolan. 3, Acid. 4, NaOMe. 5, Ac_2O, then $NaBH_4$. 6, $SOCl_2$, then NaCN. 7, MeOH, then HCl. 8, Deactivated Raney Ni.

This and previous methods directed towards the synthesis of lysergic acid together with the theories of its biogenesis are discussed by Saxton.[50] Earlier reviews on the ergot alkaloids by Stoll,[45a] Glenn,[45b] and Saxton[51] include the extensive work of Jacobs's and Stoll's groups. Another recent review is by Kornfield.[52] The stereochemistry of lysergic acid has also been investigated.[53]

Because of its relation to the structure of nicotinic acid diethylamide ("coramin"), which has analeptic properties, Stoll and his co-workers prepared, in 1938, the diethylamide of lysergic acid (10; R = NEt_2) from the naturally occurring acid.[54] At this time the substance was found to have

[50] Saxton, in "The Alkaloids," Vol. VII, ed. Manske, Academic Press, New York, 1960, p. 4.
[51] Saxton, *Quart. Rev.*, 1956, **10**, 108.
[52] Kornfield, *Record Chem. Progr.*, 1958, **19**, 23.
[53] Schreier, *Helv. Chim. Acta*, 1958, **41**, 1984; Leeman and Fabbri, *ibid.*, 1959, **42**, 2698.
[54] Stoll and Hofmann, *Z. physik. Chem.* (*Leipzig*), 1938, **251**, 155.

the typical contraction effects of an ergot alkaloid on the uterus and vagina (of the rabbit), but it was not until 1943 that Hofmann[55] noticed that a profound psychotomimetic effect occurs on ingestion of the compound and a dramatic account of this observation has been given by him.[56] The results of the first systematic psychiatric investigation of the effects produced by lysergic acid diethylamide were published[57] in 1947; it was clear that it is an extremely active compound. As little as 0·5—1 μg./kg. of (+)-lysergic acid diethylamide has been said to produce behavioural changes in man [the (−)-isomer is more than 100 times less active]. Very marked changes occur at higher dose levels. The effects vary greatly with the individual but optical hallucinations, a sense of depersonalisation, and schizoid states are particularly characteristic though there is some insight into personal condition.[58] The compound also possesses a wide range of other systemic effects in animals, including mydriasis, piloerection, hyperthermia, and antiserotonin activity, and these have been reviewed.[1,55]

Stoll and Hofmann[59] have synthesised over forty other amides of lysergic acid. The same group have introduced substituents into the ring system,[60] investigated the saturation of the 9,10-double bond,[61] and altered the spatial arrangement of the atoms within the molecule.[59] Published information indicates[1] that these compounds all have less behavioural activity than LSD-25 itself except the 1-acetyl derivative, which has about the same activity. It has been shown[1] that, in many instances, the production of hyperthermia in the animal body parallels the behavioural activity of these compounds related to LSD-25.

Three methods of synthesis for lysergic acid amides have been used. The original method of Stoll and Hofmann proceeds *via* the methyl ester (10; R = OMe), hydrazide (10; R = $NH{\cdot}NH_2$), and azide (10; R = N_3), the last giving the required amide on treatment with a suitable amine. This method has the disadvantage that the reaction conditions for the preparation of the hydrazide are such that a racemised and isomerised product (±)-isolysergic acid hydrazide, is obtained. Since (+)-lysergic acid is available from the ergot alkaloids[62] this is inconvenient. Recent methods have used trifluoroacetic acid[63] and sulphur trioxide in dimethyl formamide[64] to effect direct condensation between the optically active acid and an amine without racemisation or isomerisation.

[55] See Rothlin, in "Psychotropic Drugs," ed. Garrattini and Ghetti, Elsevier, Amsterdam, 1957, p. 36.
[56] Hofmann, quoted in "Research Today," Eli Lilley and Company, Indianapolis, U.S.A., 1957, **13**, 3.
[57] Stoll, *Schweiz. Archiv für Neurologie Psychiatrie*, 1947, **60**, 279.
[58] Rothlin, *Ann. New York Acad. Sci.*, 1957, **66**, 668.
[59] Stoll and Hofmann, *Helv. Chim. Acta*, 1955, **38**, 421.
[60] Troxler and Hofmann, *Helv. Chim. Acta*, 1957, **40**, 1706, 1721, 2160.
[61] Stoll and Schlientz, *Helv. Chim. Acta*, 1955, **38**, 585.
[62] Jacobs and Craig, *J. Biol. Chem.*, 1934, **104**, 547.
[63] Pioch, U.S.P., 2,736,728, 1956.
[64] Garbrecht, *J. Org. Chem.*, 1959, **24**, 368.

4. Tryptamine derivatives

Bufotenine (*5-Hydroxy-*NN*-dimethyltryptamine*) (13).—This compound was first isolated from many toad species,[65] together with the related bufotenidine (16).

The structure (13) of bufotenine was proposed by Wieland and his co-workers[66] and confirmed by synthesis shortly afterwards by Hoshino and Shimodaira.[67]

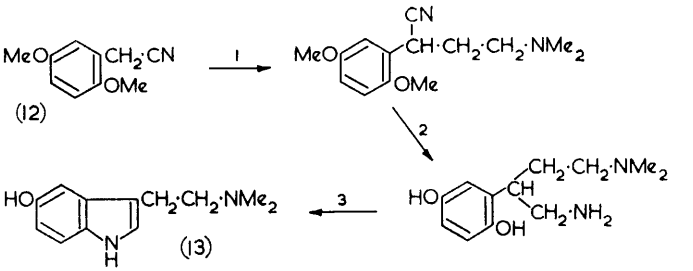
The dried secretion (Ch'an Su) of the Chinese toad[65a] has long been known to be biologically active and bufotenine is a constituent of this material. However, in 1954 bufotenine was shown[68] to occur in the seeds of the leguminous shrubs *Piptadenia peregrina* and *P. macrocarpa* which when ground up to give a snuff ("cohoba" or "nopo") is used in rituals in the West Indies and South America to produce hallucinations in man.[69] Later experiments[70] demonstrated that pure bufotenine has a psychotomimetic effect in man (2—16 mg./kg. i.v.), although this observation has since been questioned.[71]

Bufotenine was later shown to be identical with the "mappine" of the fungus *Amanita mappa*[72] and to occur widely in animals and higher plants.[73] The small amount of bufotenine occurring in *A. muscaria* is insufficient to account for the psychotomimetic effect of this fungus, even if allowance is made for the activity of muscarine.[1,74] The knowledge of the biological activity of bufotenine and its widespread incidence increased the interest in the compound and further syntheses were developed.

Harley-Mason and Jackson's method[75] is of interest because cyclisation takes place to yield the tryptamine directly. 2,5-Dimethoxybenzyl cyanide (12) on reaction with *NN*-dimethylaminoethyl chloride in the presence of sodamide gives 1-(2,5-dimethoxyphenyl)-3-dimethylaminopropyl cyanide, converted by hydrogenation and demethylation into a product which, on oxidation with potassium ferricyanide, cyclises to give bufotenine.

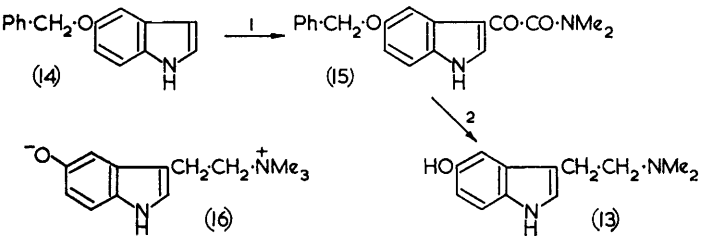
Stoll *et al.*[76] used the more usual route *via* 5-benzyloxygramine. However, the third of these recent methods, that of Speeter and Anthony,[77] is one which provides an alternative to the gramine route as a general method for the preparation of tryptamines. Oxalyl chloride reacts readily with indoles

[65] (*a*) Jensen and Chen, *J. Biol. Chem.*, 1936, **116**, 87; (*b*) Deulofeu and Mendive, *Annalen*, 1938, **534**, 288; (*c*) Deulofeu and Duprat, *J. Biol. Chem.*, 1944, **153**, 459.
[66] Wieland, Konz, and Mittasch, *Annalen*, 1934, **513**, 1.
[67] Hoshino and Shimodaira, *Annalen*, 1935, **520**, 19; *Bull. Chem. Soc. Japan*, 1936, **11**, 221.
[68] Stromberg, *J. Amer. Chem. Soc.*, 1954, **76**, 1707.
[69] Stafford, *J. Washington Acad. Sci.*, 1916, **6**, 547.
[70] Fabing and Hawkins, *Science*, 1956, **123**, 886.
[71] Turner and Merlis, *A.M.A. Arch. Neurology and Psychiatry*, 1959, **81**, 121.
[72] Wieland, Motzel, and Merz, *Annalen*, 1953, **581**, 10.
[73] Stowe, *Fortschr. Chem. org. Naturstoffe*, 1959, **17**, 248.
[74] Eugster, *Rev. Mycologie.*, 1959, **24**, 369.
[75] Harley-Mason and Jackson, *Chem. and Ind.*, 1952, 954.
[76] Stoll, Troxler, Peyer and Hofmann, *Helv. Chim. Acta*, 1955, **38**, 1452.
[77] Speeter and Anthony, *J. Amer. Chem. Soc.*, 1954, **76**, 6208.



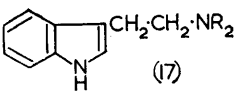
Reagents: 1, $NaNH_2$–Cl·CH_2·CH_2·NMe_2. 2, H_2–Raney Ni, then HBr. 3, $K_3Fe(CN)_6$.

to give indol-3-ylglyoxylyl chlorides and, in the preparation of bufotenine, 5-benzyloxyindole (14) was treated with oxalyl chloride followed by dimethylamine, yielding the glyoxylamide (15). Reduction of this amide with lithium aluminium hydride followed by catalytic debenzylation gave bufotenine.



Reagents: 1, $(COCl)_2$, then $NHMe_2$. 2, $LiAlH_4$, then Pd–C–H_2.

NN-*Dialkyltryptamines* (17).—Like bufotenine, *NN*-dimethyltryptamine (17; R = Me) occurs together with its *N*-oxide in the shrubs *Piptadenia peregrina* and *P. macrocarpa*,[78] and it is also present in the hallucinogenic drink prepared by some South American Indians from *Prestonia*

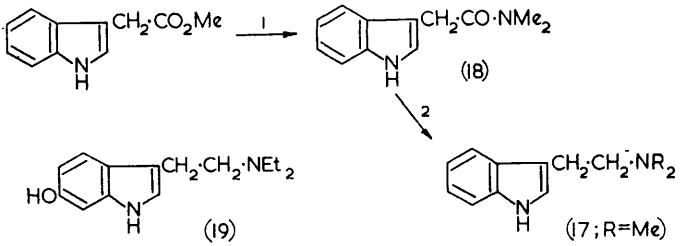


amazonicum[79] and in *Mimosa hostilis*[80] and *Lespedeza bicolor* var. *japonica*.[81] The hallucinogenic effect of the pure compound is similar to that of bufotenine (E.D. 1 mg./kg. i.m.).[82] An *N*-methylating enzyme has

[78] Fish, Johnson, and Horning, *J. Amer. Chem. Soc.*, 1955, **77**, 5892.
[79] Hochstein and Paradies, *J. Amer. Chem. Soc.*, 1957, **79**, 5735.
[80] Pachter, Zacharias, and Ribeiro, *J. Org. Chem.*, 1959, **24**, 1285.
[81] Goto, Noguchi, and Watanabe, *Yakugaku Zasshi*, 1958, **78**, 464; *Chem. Abs.*, 1958, **52**, 14083.
[82] (*a*) Szára, *Experientia*, 1956, **12**, 441; (*b*) Halasz, Brunecker, and Szára, *Psychiatrie et Neurologie*, 1958, **138**, 285; (*c*) Szára, in "Psychotropic Drugs," ed. Garrattini and Ghetti, Elsevier, Amsterdam, 1957, p. 460.

been found (in rabbit lung) which can convert 5-hydroxytryptamine into bufotenine and tryptamine into *NN*-dimethyltryptamine.[83]

NN-Dimethyltryptamine was prepared by Manske[84] by the separation of the products of the reaction between tryptamine and methyl iodide in chloroform. This method was later improved[85] but a more satisfactory method[86] is by the reaction between dimethylamine and methyl indol-3-ylacetate and reduction of the amide obtained (18) with lithium aluminium hydride.



NN-Diethyltryptamine (17; R = Et) has about the same psychotomimetic activity as the *NN*-dimethyl compound,[87] though different in quality.[82b] It has not been found in Nature, but has been prepared[88] by a route *via* the glyoxylamide similar to that used by Speeter and Anthony in the preparation of bufotenine. An alternative method[89] is from chloromethyl indol-3-yl ketone which on reaction with diethylamine followed by reduction with lithium aluminium hydride gives *NN*-diethyltryptamine.

The corresponding *NN*-dipropyl (17; R = Pr^n), *NN*-dibutyl (17; R = Bu^n), and *NN*-dihexyl (17; R = hexyl) compounds have also been prepared and shown to decrease in hallucinogenic activity with increase in the size of the dialkyl group.[90] Szára[91] has shown that a metabolite of *NN*-diethyltryptamine, *NN*-diethyl-6-hydroxytryptamine (19), is in fact more active in causing behavioural changes in animals than the parent substance. He has, further, demonstrated that the intensity of the reaction produced in man by *NN*-diethyltryptamine parallels the amount of the 6-hydroxy metabolite excreted in the urine.[91b]

Psilocybin (3-2′-*Dimethylaminoethylindol*-4-*yl phosphate*) (20).—This substance and the corresponding phenol, psilocin (21), are responsible for the psychotomimetic activity of some Mexican mushrooms. The Mexican Indian name "teonanácatl" is employed collectively for the

[83] Axelrod, *Science*, 1961, **134**, 343.
[84] Manske, *Canad. J. Res.*, 1931, **5**, 592.
[85] Hoshino and Kotake, *Annalen*, 1935, **516**, 76.
[86] Fish, Johnson, and Horning, *J. Amer. Chem. Soc.*, 1956, **78**, 3668.
[87] Boszormányi, Der, and Nagy, *J. Mental Sci.*, 1959, **105**, 171.
[88] Nógrádi, *Monatsh.*, 1957, **88**, 768.
[89] U.S.P., 2,814,625/1957; *Chem. Abs.*, 1958, **52**, 11948.
[90] Szára, *Biochem. Pharmacol.*, 1961, **8**, 32.
[91] (*a*) Szára and Putney, *Fed. Proc.*, 1961, **20**, 172; (*b*) Szára, *ibid.*, p. 885.

species, mostly *Psilocybe*, employed by the Indians in their religious ceremonies. Psilocin is isomeric with bufotenine, having the hydroxy-group in the 4- instead of the 5-position. Both psilocybin and psilocin were first isolated[92] in 1958. Previous work[93] on small amounts of fungi was thought to exclude the presence of an alkaloid.

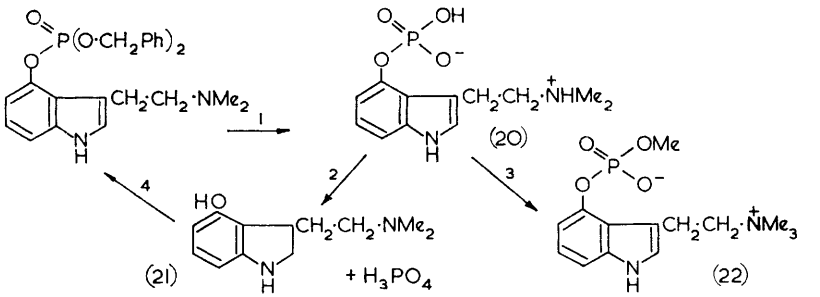
Pure psilocybin and psilocin have been shown to produce psychotomimetic symptoms (oral dose 4—8 mg./man) similar to those of mescaline and lysergic acid diethylamide,[94] and they have been isolated[95] from many *Psilocybe* spp. and from *Stropharia cubensis* (which occurs in Mexico and in Thailand). Of the fungi tested, *P. mexicana* Heim was found to contain the most psilocybin when grown in the laboratory.[96] Hofmann[1] has vividly described, from his own experience, the effect of eating the mushrooms. Some *Psilocybe* spp. (*P. yungensis*, *P. hooshageni* and *P. caerulescens*), used by the Indians, are hallucinogenic but do not contain psilocybin or psilocin.[1,97]

The structures of psilocybin and psilocin were elucidated by Hofmann and his co-workers.[94,97] It was shown that methylation of psilocybin with diazomethane gave a dimethyl derivative (22) which produced trimethylamine on pyrolysis. Hydrolysis of psilocybin resulted in equimolecular amounts of 4-hydroxy-*NN*-dimethyltryptamine (psilocin) and phosphoric acid. Psilocybin could be regenerated from psilocin by reaction with dibenzyl phosphorochloridate, followed by hydrogenation of the resultant dibenzyl derivative. Psilocin was synthesised[94] from 4-benzyloxyindole by reaction with oxalyl chloride followed by dimethylamine, and reduction of the resultant glyoxylamide with lithium aluminium hydride. Subsequent catalytic hydrogenation removed the benzyl group to give the required 4-hydroxy-*NN*-dimethyltryptamine.

The cultivation, chemistry, pharmacology, and clinical aspects of the "teonanácatl" group of fungi is the subject of a monograph.[98] Psilocybin has attracted pharmacological study.[99] It produces similar vegetative symptoms to LSD-25 (including the hyperthermia effect) in the intact animal. The phosphorylation of psilocin to psilocybin has been reported.[100]

A large number of compounds related to the hydroxytryptamines have been synthesised by the Hofmann group.[101] It is not yet known whether

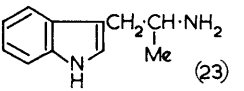
[92] Hofmann, Heim, Brack, and Kobel, *Experientia*, 1958, **14**, 107.
[93] Santesson, *Arch. Botan.*, 1939, **28**, *A*, 1.
[94] Hofmann, Heim, Brack, Kobel, Frey, Ott, Petrzilka, and Troxler, *Helv. Chim. Acta*, 1959, **42**, 1557.
[95] Heim, *Compt. rend.*, 1956, **242**, 965, 1389; 1957, **244**, 695.
[96] Heim and Cailleux, *Compt. rend.*, 1957, **244**, 3109.
[97] Hofmann, Frey, Ott, Petrzilka, and Troxler, *Experientia*, 1958, **14**, 397.
[98] Heim and Wasson, "Les Champignons hallucinogène du Mexique," Ed. du Muséum National d'Histoire Naturelle, Paris, 1958.
[99] Gnirss, *Schweiz. Arch. Neurologie Psychiatrie*, 1959, **34**, 346; Rimmle, *ibid.*, p. 348; Delay, Pichot, Lemperière, and Nicolas-Charles, *Compt. rend.*, 1958, **247**, 1235; Weidmann, Taeschler, and Konzett, *Experientia*, 1958, **14**, 378.
[100] Horita and Weber, *Proc. Soc. Exp. Biol. Med.*, 1961, **106**, 37.
[101] Troxler, Seeman, and Hofmann, *Helv. Chim. Acta*, 1959, **42**, 2073.



Reagents: 1, Pd–H_2. 2, H_2O; 150°. 3, CH_2N_2. 4, $(Ph{\cdot}CH_2{\cdot}O)_2POCl$.

any of these show psychotomimetic activity, but some pharmacology of many of them has been reported.[102]

α-*Methyltryptamine* (23).—(±)-α-Methyltryptamine is recorded[103] as producing an effect like that of LSD-25 in man and to be about three times



as active as *NN*-diethyltryptamine.[104] The biochemical effects of α-methyltryptamine on 5-hydroxytryptamine metabolism have been studied.[105]

5. Harmine and its derivatives

The literature on the chemistry of the biologically active constituents of *Banisteria caapi* ("Ayahausca") and *Prestonia amazonicum* (*Haemadictyon amazonicum*) ("Yagé") has been confused because of the use of the same trivial local South American Indian names for extracts of different plants. In particular the names "Ayahausca," "Yagé," and "Huanto" have been used indiscriminately for the extracts of either plant and for mixtures of extracts of both. All these preparations have been used amongst South American Indians for the production of ritual hallucinations. A bibliography of the literature concerning them up to 1939 exists.[106]

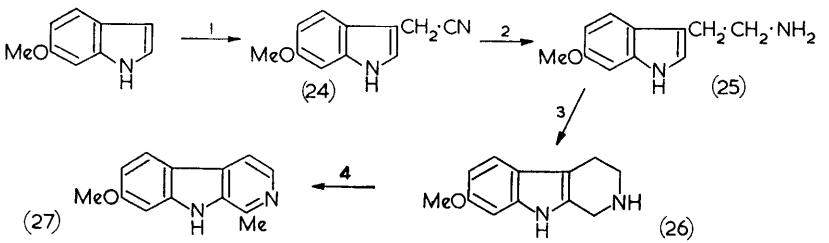
The names telepathine,[107] yageine,[108] and banisterine[109] for the alkaloids extracted from these sources have been used until quite recently (for

[102] Weidmann and Cerletti, *Helv. Physiol. Pharmacol. Acta*, 1959, **17**, C 46; 1960, **18**, 174.
[103] Murphee, Jenney, and Pfeiffer, *The Pharmacologist*, 1960, **2**, 64.
[104] Szára, *Experientia*, 1961, **17**, 76.
[105] Van Meter, Ayala, Costa, and Himwich, *Fed. Proc.*, 1960, **19**, 265; Grieg, Walk, and Gibbons, *J. Pharmacol.*, 1959, **127**, 110; Yuwiler, Geller and Eiduson, *Arch. Biochem. Biophys.*, 1959, **80**, 162.
[106] Henry, "The Plant Alkaloids," 4th edn., Blakiston, Philadelphia, 1949, p.488.
[107] Perrot and Raymond-Hamet, *Compt. rend.*, 1927, **184**, 1266; Villalba, *Boletin Lab. Sumber-Martinez, Bogota*, 1927, p. 9.
[108] Villalba, *J. Soc. Chem. Ind.*, 1925, **44**, 205.
[109] Lewin, *Arch. exp. Path. Pharm.*, 1928, **129**, 133; *Compt. rend.*, 1928, **186**, 469.

example, ref. 110). It was subsequently thought[109,111] that all these substances were the same and that the only alkaloid present in *B. caapi* was harmine (27). Hochstein and Paradies,[79] however, have shown that three alkaloids are present in *B. caapi* and have identified them as harmine (27), harmaline (28), and 1,2,3,4-tetrahydroharmine (26). Harmaline has previously been reported as present in *B. caapi* by Oryekhov.[112] Leptaflorine from *Leptactina densiflora* has recently been shown[113] to be racemic 1,2,3,4-tetrahydroharmine (26). Hochstein and Paradies[79] found that *P. amazonicum* yielded only *NN*-dimethyltryptamine (see p. 142). Other *Banisteria* spp. have been shown to contain harmine.[114]

Harmine has been known for more than a hundred years[115] as a constituent of *Peganum harmala* where it occurs together with harmaline[116] and the *O*-demethylated derivative of the latter, harmalol.[117] Other alkaloids are also present.[118] The formulæ for harmine (27) and harmaline (28) were originally suggested by Perkin and Robinson[119] and the substances were the subjects of extensive research by these workers and by O. Fischer.

The structure of harmaline was confirmed by synthesis[120] and two convenient syntheses of harmine appeared simultaneously. Akabori and Saito[121] used 6-methoxyindole which was converted into 6-methoxytryptamine (25) by reaction with methylmagnesium iodide followed by chloroacetonitrile to give 6-methoxyindol-3-ylacetonitrile (24), reduction

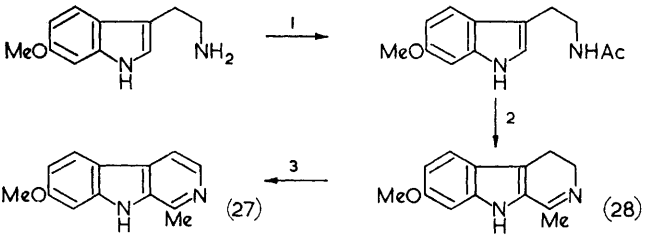


Reagents: 1, MeMgI, then Cl·CH_2·CN. 2, Na–EtOH. 3, H_2SO_4–AcOH. 4, Pd–maleic acid.

[110] Costa, *Rev. brasil. Farm.*, 1956, **37**, 481; *Chem. Abs.*, 1958, **52**, 1550.
[111] Elger, *Helv. Chim. Acta*, 1928, **11**, 162; Wolfes and Rumpf, *Arch. Pharm.*, 1928, **266**, 188; Chen and Chen, *Quart. J. Pharm.*, 1939, **12**, 30.
[112] Oryekhov, *Byull-Nauch Issledovatel Khim.-Farm. Inst.*, 1930, 3; *Chem. Abs.*, 1932, **26**, 5699.
[113] Paris, Percheron, Mainil, and Goutarel, *Bull. Soc. chim. France*, 1957, 780.
[114] Iberico, *Boletin del museo de historia natural "Javier Prado" (Lima)*, 1941, **5**, 313; *Chem. Abs.*, 1942, **36**, 1389; O'Connel and Lynn, *J. Amer. Pharmaceut. Assoc. (Sci. Edn.)*, 1953, **42**, 753.
[115] Fritsche, *Annalen*, 1847, **64**, 360.
[116] Goebel, *Annalen*, 1841, **38**, 363.
[117] Fischer, *Ber.*, 1885, **18**, 400.
[118] Karetskaya, *Zhur. obshchei Khim.*, 1957, **27**, 3361; Ovejiro, *Farmacognosia (Madrid)*, 1947, **6**, 103.
[119] Perkin and Robinson, *J.*, 1919, **115**, 933, 967.
[120] Perkin, Robinson, and Manske, *J.*, 1927, 1.
[121] Akabori and Saito, *Ber.*, 1930, **63**, 2245.

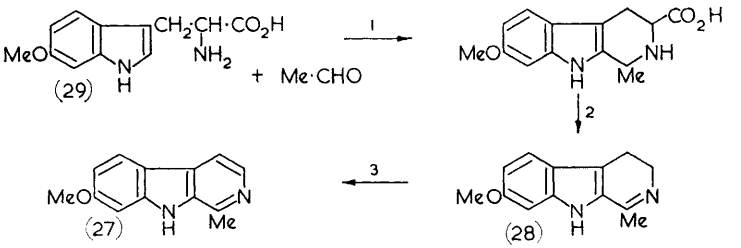
of which produced the amine (25). Heating with acetic acid and sulphuric acid resulted in 1,2,3,4-tetrahydroharmine (26), which was dehydrogenated by maleic acid and palladium black to harmine (27).

Späth and Lederer[122] also used 6-methoxytryptamine (25) which they prepared, however, by a modification of the Fischer indole synthesis. Acetylation of the amine (25) and cyclisation with phosphoric anhydride in xylene gave harmaline (28). Catalytic dehydrogenation gave harmine (27).



Reagents: 1, Ac_2O. 2, P_2O_5. 3, Pd.

A further synthesis[123a] of interest is that from 6-methoxytryptophan (29), which condenses with acetaldehyde at pH 6·7 to give 1,2,3,4-tetrahydroharmine-3-carboxylic acid; on decarboxylation and oxidation this produces harmaline (28) which may then be dehydrogenated to harmine (27). This synthesis is of biogenetic interest in relation to the conversion of tryptamines into harmans.[123]

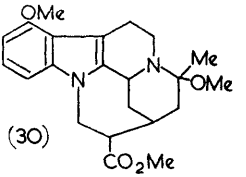


Reagents: 1, pH 6·7. 2, $-CO_2$, then CrO_3. 3, Pd.

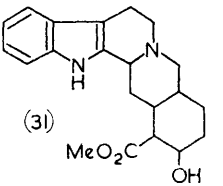
The psychotomimetic activity of harmine has been investigated by Lewin[109] and by Pennes and Hoch[124] and the pure substance is apparently less active than the crude extract of *B. caapi*. This has led to the suggestion[79] that harmaline and 1,2,3,4-tetrahydroharmine may also have this type of activity but, since the tetrahydroharmine may be considered structurally related to *N*-ethyl-6-methoxytryptamine, such psychotomimetic activity would not be surprising.

[122] Späth and Lederer, *Ber.*, 1930, **63**, 120, 2102.
[123] (*a*) Harvey and Robson, *J.*, 1938, 97; (*b*) Hopkins and Cole, *J. Physiol.*, 1903, **29**, 451; Kermack, Perkin, and Robinson, *J.*, 1921, **119**, 1617.
[124] Pennes and Hoch, *Amer. J. Psychiatry*, 1957, **113**, 887.

It has been suggested[125] that the structure of mitragynine, the major alkaloid of the intoxicant *Mitragyna speciosa* of Borneo, is (30), which is related to 1,2,3,4-tetrahydroharmine and incidentally to a 4-methoxyindole (in which it is similar to psilocin). It is not known if mitragynine is a true psychotomimetic, but yohimbine (31) which also contains a 1,2,3,4-tetrahydroharmine residue, is said[126] to give pronounced psychic effects

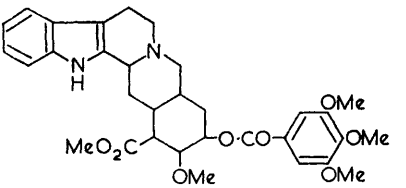


(30)



(31)

in doses of 0·5 mg./kg. i.v. Reserpine (32) also has this residue but is, on the other hand, a potent tranquilliser.

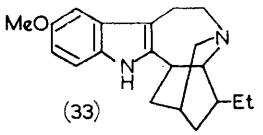


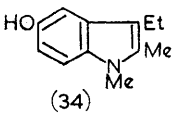
(32)

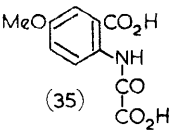
6. Iboga alkaloids

The root bark of the African shrub *Tabernanthe iboga* has proved a rich source of a group of at least twelve alkaloids, the principal member of which is ibogaine, first reported[127] in 1901. Extracts of the root are used by some inhabitants of West Africa and of the Congo to increase resistance to fatigue and tiredness.[128] It is also reported[129] to cause excitement, drunkenness, mental confusion, and, possibly, hallucinations in higher doses. These reported effects attracted Schneider and Sigg to investigate the central stimulant properties of the pure alkaloid ibogaine,[130] and typical fear and escape responses suggestive of hallucinations were obtained with cats (2—10 mg./kg. i.v.). No experiments with ibogaine on man have been reported. Previous pharmacological studies were carried out by Raymond-Hamet and Rothlin.[131]

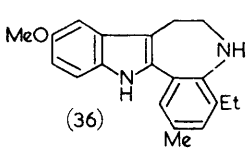
[125] Hendrickson, *Chem. and Ind.*, 1961, 713; Schlittler, *Experientia*, 1960, **16**, 244.
[126] Holmberg and Gershon, *Psychopharmacologia*, 1961, **2**, 93.
[127] Dybowski and Landrin, *Compt. rend.*, 1901, **133**, 748; Heller and Heckel, *ibid.*, p. 850.
[128] Aubry-Lecompte, *Arch. méd. navale*, 1864, **2**, 264; Baillon, *Bull. mens. Soc. Linnénne*, (Paris), 1869, **1**, 782 (quoted by Schneider and Sigg, see ref, 130); Raymond-Hamet and Perrott, *Bulletin de l'académie de médecine*, 1941, **124**, 243.
[129] Le Roy, quoted by Schneider and Sigg (ref. 130).
[130] Schneider and Sigg, *Ann. New York Acad. Sci.*, 1957, **66**, 765.
[131] Raymond-Hamet and Rothlin, *Arch. internat. pharmacodynamie*, 1939, **63**, 27.

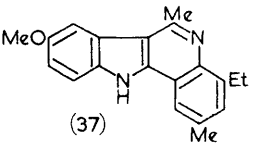

(33)

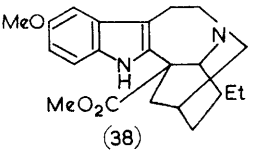

(34)


(35)

Work on the structure of the iboga alkaloids has been concentrated on ibogaine. The formula (33) suggested by Taylor and his co-workers[132] for this compound has been confirmed by *X*-ray analysis.[133] Ibogaine has long been thought an indole on the basis of colour tests[134] and, in 1953, 3-ethyl-5-hydroxy-1,2-dimethylindole (34) was isolated after potash fusion of the compound.[135] The *N*-oxalo-derivative (35) had previously been obtained by permanganate oxidation.[136] Taylor and his co-workers[132a] repeated the potash fusion and noticed that 3-ethyl-5-methylpyridine was a further product of the reaction. The same workers carried out a selenium dehydrogenation of ibogaine and obtained compounds (36) and (37), from which they deduced the structure (33) for ibogaine.


(36)


(37)


(38)

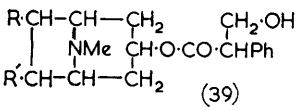
The structures of several of the other alkaloids occurring in *T. iboga* and containing the ibogaine skeleton were deduced readily. Another alkaloid from *T. iboga*, voacangine, was first isolated from *Voacanga africana*, thus stressing the relation between the alkaloids of the *Tabernanthe* and *Voacanga* spp.,[137] which was first observed when voacangine was hydrolysed and decarboxylated to give ibogaine.[138] Voacangine is 18-methoxycarbonylibogaine (38). The same compound has also been isolated from *Stemmadenia* spp.[139] and similar alkaloids from the African medicinal plant *Conopharyngia durissima*.[140]

Thus, recent work has discovered many alkaloids related to ibogaine which, however, is the only member of the group to have been investigated for psychotomimetic activity. Like LSD-25, bufotenine, psilocybin, 1,2,3,4-tetrahydroharmine, and similar compounds discussed earlier in this Review, ibogaine contains the tryptamine nucleus.

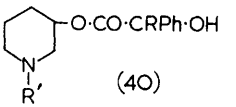
[132] (*a*) Bartlett, Dickel, and Taylor, *J. Amer. Chem. Soc.*, 1958, **80**, 126; (*b*) Taylor, *ibid.*, 1957, **79**, 3298.
[133] Jeffery, Arai, and Coppola, Abst. Amer. Cryst. Assoc., Cornell, 1959, quoted by Saxton, *Ann. Reports*, 1959, **56**, 278.
[134] Raymond-Hamet, *Bull. Sci. pharmacol.*, 1926, **33**, 518; *Bull. Soc. chim. France*, 1943, **25**, 205.
[135] Schlittler, Burckhardt, and Gellért, *Helv. Chim. Acta*, 1953, **36**, 1337.
[136] Janot, Goutarel, and Sneedon, *Helv. Chim. Acta*, 1951, **34**, 1205.
[137] Dickel, Holden, Maxfield, Paszek, and Taylor, *J. Amer. Chem. Soc.*, 1958, **80**, 123.
[138] Janot and Goutarel, *Compt. rend.*, 1955, **241**, 286.
[139] Walls, Collera, and Sandoval, *Tetrahedron*, 1958, **2**, 173.
[140] Renner, Prins, and Stoll, *Helv. Chim. Acta*, 1959, **42**, 1572.

7. Piperidyl glycollates

The production of an intoxicated state frequently accompanied by hallucinations and delirium following poisoning by atropine [(±)-hyoscyamine] (39; R = R′ = H) and the epoxide scopolamine [(−)-hyoscine)] (39; R–R′ = O<) has long been known. Acute schizophrenia has been sometimes diagnosed mistakenly in these cases.[28] Russian workers have reported the use of an atropine-induced psychosis as a model for schizophrenia,[141] and large doses are said to induce marked psychic disturbance.[142]



(39)



(40)

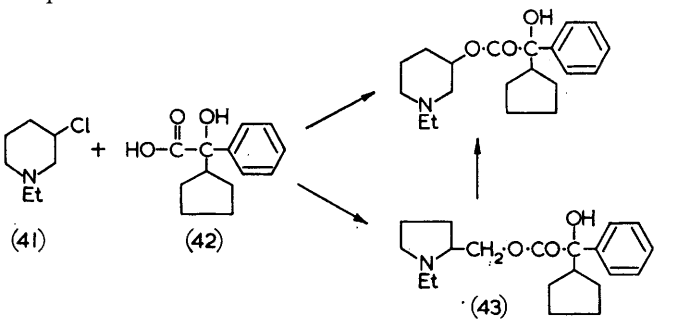
The atropine molecule has been used as a model for the preparation of a large number of potential drugs. In general, interest has centred on the mydriatic and spasmolytic properties of these compounds rather than on their effect on behaviour. In 1958, however, the psychotomimetic effect of 1-methyl-3-piperidyl benzilate (40; R = Ph, R′ = Me) and substances of related structure was described.[143] A relationship of these piperidine derivatives to part of the atropine molecule is apparent. They cause auditory and visual hallucinations, mood changes, disorientation, and hypochondriacal and paranoid delusions in man.

More recent work[142] has demonstrated that the most effective of a large number of compounds of this series are 1-ethyl-3-piperidyl cyclopentylphenylglycollate ("Ditran") (40; R = cyclopentyl, R′ = Et) and the corresponding 1-methyl compound (40; R = cyclopentyl, R′ = Me). The corresponding cyclohexyl (40; R = cyclohexyl, R′ = Me) and cyclobutyl (40; R = cyclobutyl, R′ = Me) and cyclopropyl (40; R = cyclopropyl, R′ = Me) compounds have been named[144] as having about the same psychotomimetic activity as the ester (40; R = cyclopentyl, R′ = Me). The 4-piperidyl isomers, which are closer to atropine in structure, are practically inactive as psychotomimetics. Recently 1-methyl-3-piperidyl esters of substituted benzilic acids[145] and a series of analogous compounds[146] have been prepared for evaluation as psychotomimetics.

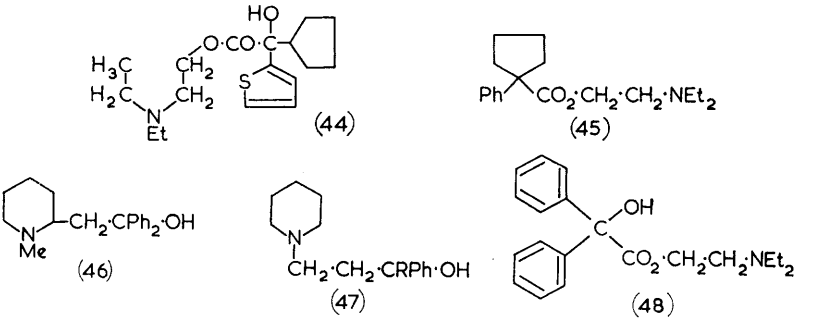
The piperidyl glycollates have been synthesised[147] either by reaction of 1-alkyl-3-hydroxypiperidine with the acid chloride or the methyl ester

[141] Goldenberg, *Novosibersk Govt. Med. Inst. Publ.*, 1957, **29**, 7.
[142] Abood, Ostfeld, and Biel, *Arch. Internat. Pharmacodynamie*, 1959, **120**, 186.
[143] Abood, Ostfeld, and Biel, *Proc. Soc. Exp. Biol. Med.*, 1958, **97**, 483; Ostfeld, Abood, and Marcus, *A.M.A. Arch. Neurology and Psychiatry*, 1958, **79**, 317; Abood and Meduna, *J. Nervous and Mental Disease*, 1958, **127**, 546.
[144] Cannon and Kadin, *J. Org. Chem.*, 1962, **27**, 240.
[145] Cannon, *J. Org. Chem.*, 1960, **25**, 959.
[146] Biel, Abood, Hoya, Leiser, Nuhfer, and Kluchesky, *J. Org. Chem.*, 1961, **26**, 4096.
[147] Biel, Sprengeler, Leiser, Horner, Drukker, and Friedmann, *J. Amer. Chem. Soc.*, 1955, **77**, 2250.

of an appropriate acid, or by reaction between a 1-alkyl-3-chloropiperidine and an acid. It has been noted[148] that the reaction between 3-chloro-1-ethylpiperidine (41) and cyclopentylphenylglycollic acid (42) results in a mixture of the expected product (40; R = cyclopentyl, R′ = Et) (30%) and the ring-contracted isomer 1-ethyl-2-pyrrolidinylmethyl cyclopentylphenylglycollate (43) (70%). Distillation of the latter causes ring expansion to the former. This type of ring contraction, which takes place under acid conditions, has previously been noticed only under basic conditions.[149] 1-Ethyl-3-piperidyl cyclopentylphenylglycollate (40; R = cyclopentyl, R′ = Et) is stated[148b] to induce a temporary psychosis most nearly imitative of schizophrenia.



The structurally related compound, 2-diethylaminoethyl cyclopentyl-2-thienylglycollate (44) has a harmine-like psychotomimetic action,[150] and similar effects are reported for compounds (45) ("Pentaphen"),[151] (46), (47; R = cyclohexyl) ("Artane," "Pipanol"), (47; R = cyclopentyl) ("Cycrimine," "Pagitane"), and some other synthetic atropine-mimetics.[151b]



[148] (*a*) Biel, Abood, Hoya, and Leiser, Abs. 138th Amer. Chem. Soc. Meeting, New York, 1960, p. 19-O; (*b*) Biel, *Chem. Eng. News*, 1960, **38**, No. 38, p. 50.

[149] Reitsema, *J. Amer. Chem. Soc.*, 1949, **71**, 2041.

[150] (*a*) Pennes and Hoch, *Amer. J. Psychiatry*, 1957, **113**, 887; (*b*) Himwich, van Meter, and Owens, in "Neuro-psychopharmacology," ed. Bradley, Deniker, and Radouco-Thomas, Elsevier, Amsterdam, 1959, p. 329.

[151] (*a*) Kagan, *Farmakologiya i Toxikologiya*, 1956, **19**, 49; (*b*) Pfeiffer, *Internat. Rev. Neurobiology*, 1959, **1**, 195; Pfeiffer, Murphee, Jenney, Robotson, and Bryan, *Fed. Proc.*, 1958, **17**, 403.

A closely related compound is 2-diethylaminoethyl benzilate ("Benactzine") (48). This substance and compounds related to it are known as ataractics. Russian workers have recently been particularly interested in them[152] and 2-diethylaminoethyl benzilate has been reported as causing hallucinations in (accidentally) high dose (1·4 g. per man)[153] and subsequently at a lower dose (40—70 mg./man)[154].

8. Cannabinols

Hemp (*Cannabis sativa* L.) produces, on its female flowering tops, a greenish resin containing an active principle or principles having a profound effect on the central nervous system and including the exhibition of psychotomimetic symptoms. The leaves and seeds also contain the same active constituents, but in smaller concentration. The names used for this resinous product vary with its origin in the world. Marihuana (The Americas), hashish (Middle East), bhang (India), charas, ganja (Far East), dagga (South Africa), and kif (North Africa) are the better-known names for the different local products.

The usual effect of smoking or ingestion of cannabis has been described[155] as a feeling of well-being alternating with depression, distortion of time and space, and double consciousness. Personal experiences have been recorded in detail[156] and the "use of hemp drugs for euphoric purposes" discussed.[157]

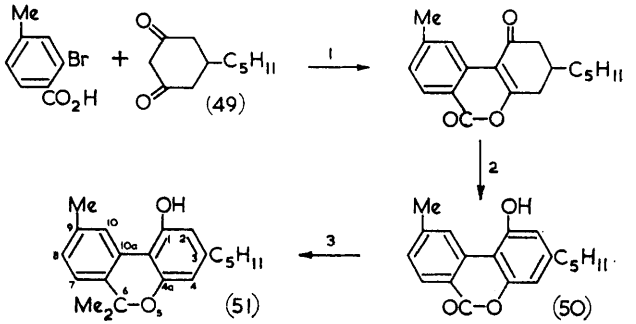
The euphoric activity in hashish was found to be due to an alkali-insoluble* nitrogen-free principle in the middle of the nineteenth century, but it was not until the beginning of the present century that a pure compound was isolated from this active fraction.[159] Until the research of Cahn[160] this substance (cannabinol) was accepted as the active principle of hashish. Cahn, however, established the structure of cannabinol in all but the orientation of the substituent groups and also cast doubt on the euphoric activity of the substance.

The structure of cannabinol was proved at the same time by both Adams's[161] and Todd's[162] groups to be 1-hydroxy-6,6,9-trimethyl-3-pentyldibenzopyran (51). Adams's synthesis was from dihydro-olivetol

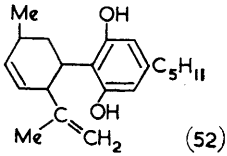
* Recently it has been claimed that, although the constituents of the alkali-soluble fraction of cannabis resin are inactive, they become active on storage or, more rapidly, if heated.[158]

[152] Anichkov, *Ann. Rev. Pharmacology*, 1961, **1**, 21.
[153] Vojtechovsky, Vitek, Ryšánek and Bultasová, *Experientia*, 1958, **14**, 422.
[154] Bultasová, Grof, Horáčková, Kuhn, Ryšánek, Vitek and Vojtechovsky, *Ideggyogaszati Szemle*, 1960, **13**, 225; *Chem. Abs.*, 1961, **55**, 9662.
[155] Cf. Todd, *Endeavour*, 1943, **2**, 69.
[156] Adams, *Harvey Lectures*, 1942, **37**, 168.
[157] Chopra, Chopra, Handa, and Kapur, "Indigenous Drugs of India," Dhur and Sons, Calcutta, 2nd edn., 1958, p. 87.
[158] Grlié and Andree, *Experientia*, 1961, **17**, 325.
[159] Wood, Sprivey and Easterfield, *J.*, 1896, **69**, 539; 1899, **75**, 20.
[160] Cahn, *J.*, 1930, 986; 1931, 630; 1932, 1342; 1933, 1400.
[161] Adams, Baker, and Wearn, *J. Amer. Chem. Soc.*, 1940, **62**, 2204.
[162] Ghosh, Todd, and Wilkinson, *J.*, 1940, 1121, 1393.

(5-pentylcyclohexane-1,3-dione) (49) which was prepared by catalytic reduction of olivetol. Condensation of this diketone with 2-bromo-4-methylbenzoic acid in the presence of sodium ethoxide and cupric acetate, and dehydrogenation of the product with sulphur, gave the pyrone (50) which was converted into cannabinol (51) with methylmagnesium iodide.



Reagents: 1, $Cu(OAc)_2$–NaOEt. 2, S. 3, MeMgI.

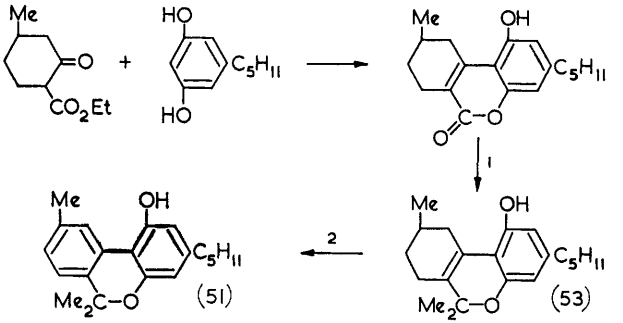


Todd's synthesis was of especial interest since the intermediate tetrahydrocannabinol (53) had considerable marihuana activity, unlike cannabinol (51) and the cannabidiol (52) [isolated by both Adams (from marihuana)[163] and Todd (from Indian hemp resin)[164]]. Condensation of olivetol with ethyl 4-methyl-2-oxocyclohexanecarboxylate, followed by the reaction of methylmagnesium iodide with the resultant dibenzopyrone, gave the tetrahydrocannabinol allocated the formula (53) which was dehydrogenated by palladium or selenium to cannabinol (51). A similar method was reported by Adams's group.[165]

The primary purification of hemp extracts and resin gives "red-oil" of hemp. Acetylation of the "red oil" facilitated the isolation of tetrahydrocannabinol acetate from this source.[166] This was the first isolation of an active compound from *Cannabis*. Deacetylation of tetrahydrocannabinol acetate from "red oil" gave (—)-tetrahydrocannabinol.

Most work has been done with extracts of *Cannabis sativa indica*. Recently German workers have extracted the indigenous variety *Cannabis sativa non-indica* and have used chromatographic and counter-current distribution methods to isolate from it crystalline cannabidiol and probably

[163] Adams, Hunt, and Clark, *J. Amer. Chem. Soc.*, 1940, **62**, 196, 735; Adams, Cain, and Wolff, *ibid.*, p. 732.
[164] Jacob and Todd, *Nature*, 1940, **145**, 350.
[165] Adams and Baker, *J. Amer. Chem. Soc.*, 1940, **62**, 2401.
[166] Wollner, Matchett, Levine, and Loewe, *J. Amer. Chem. Soc.*, 1942, **64**, 26.



Reagents: 1, MeMgI. 2, Pd or Se.

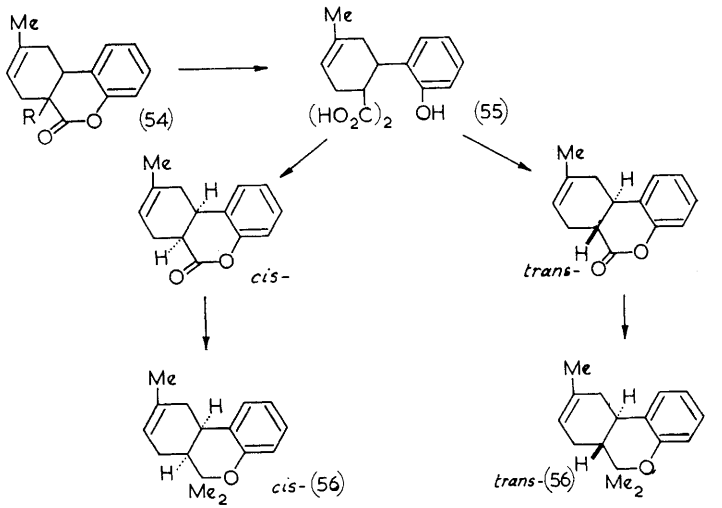
tetrahydrocannabinol. They have used these techniques to acquire two crystalline isomers from synthetic tetrahydrocannabinol resin.[167] A cannabidiolcarboxylic acid has also been isolated from *C. sativa non-indica*. Cannabinol, cannabidiol, and tetrahydrocannabinol have also been obtained from this source by distillation. [168]

Synthetic tetrahydrocannabinol, as normally prepared, is optically inactive and has less (1/10) marihuana activity than the natural optically active tetrahydrocannabinol. In addition to exhibiting *cis—trans*-stereoisomerism, tetrahydrocannabinols may exist as double-bond isomers, depending on whether the double bond in the left-hand ring of (53) occupies the conjugated position as shown in the formula or any of the other possible positions in that ring.

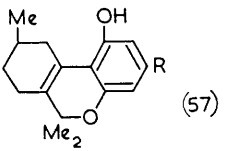
Adams *et al.*[169] showed that heating cannabidiol with an acid catalyst converted it into a mixture of highly biologically active tetrahydrocannabinol stereoisomers and double-bond isomers. It is probable that the psychotomimetic activity of *Cannabis* preparations is due to such a mixture.[155] The structure of these tetrahydrocannabinols have not been fully elucidated. Adams *et al.*[170] attempted the unambiguous synthesis of the tetrahydrocannabinol which has an 8,9-double bond. Although Adams's group failed, recent workers[171] have successfully adapted this method in the preparation of tetrahydrocannabinol model compounds. It was found that isoprene reacts readily with coumarins substituted with an electronegative group in the 3-position (CO_2Et, CN) to give the adduct (54; R = CO_2Et or CN). Hydrolysis then gives the stable dicarboxylic acid (55) which on lactonisation produces a separable mixture of *cis*- and *trans*-lactones. Treatment of each lactone with methylmagnesium iodide and subsequent cyclisation with toluene-*p*-sulphonic acid in xylene

[167] Korte and Sieper, *Annalen*, 1960, **630**, 71.
[168] Schultz and Haffner, *Arch. Pharm.*, 1958, **291**, 391; *Z. Naturforsch.*, 1959, **14b**, 98,
[169] Adams, Pease, Cain, and Clark, *J. Amer. Chem. Soc.*, 1940, **62**, 2402.
[170] Adams and Carlin, *J. Amer. Chem. Soc.*, 1943, **65**, 360; Adams, McPhee, Carlin. and Wicks, *ibid.*, p. 356; Adams and Bockstahler, *ibid.*, 1952, **74**, 5346.
[171] Taylor and Strojny, *J. Amer. Chem. Soc.*, 1960, **82**, 5198.

resulted in the *cis*- and *trans*-6a,7,10,10a-tetrahydro-6,6,9-trimethyldibenzopyrans (56) which lack the 1-hydroxy- and the 3-pentyl groups of the corresponding tetrahydrocannabinols.



A large number of homologues of tetrahydrocannabinol have been prepared, especially compounds (57; R = alkyl).[172] These compounds usually have been tested by one or both of the two tests used in the pharmacological work on marihuana. These are the "dog ataxia" test[173] and the Gayer "corneal anæsthesia" test.[174] Loewe[175] has claimed a close parallel between the "dog ataxia" test and psychotomimetic activity, but the connection between either test and psychotomimetic activity is doubted by other workers.[176]



In the series (57; R = n-alkyl), the hexyl compound is apparently the most active member according to the animal tests[172a,177] though its activity

[172] (*a*) Russell, Todd, Wilkinson, MacDonald, and Woolfe, *J.*, 1941, 826 and refs. therein; (*b*) Adams, Harfenist, and Loewe, *J. Amer. Chem. Soc.*, 1949, **71**, 1624 and refs. therein.

[173] Liutaud, *Compt. rend.*, 1844, **18**, 149; Walton, Martin, and Keller, *J. Pharmacol.*, 1938, **62**, 239.

[174] Gayer, *Arch. exp. Path. Pharm.*, 1928, **129**, 312; Marx and Eckhardt, *ibid.*, 1933, **170**, 395.

[175] Loewe, *Arch. exp. Path. Pharm.*, 1950, **211**, 175.

[176] Avison, Morison, and Parkes, *J.*, 1949, 952.

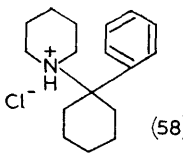
[177] Adams, Loewe, Jelinek, and Wolff, *J. Amer. Chem. Soc.*, 1941, **63**, 1971; Adams, Chen, and Loewe, *ibid.*, 1945, **67**, 1534.

is surpassed by (57; R = 1-methylheptyl) and by the 1′,2′-dimethylheptyl compound which is about seventy times as potent as natural tetrahydrocannabinol in the "dog ataxia" test.[178]

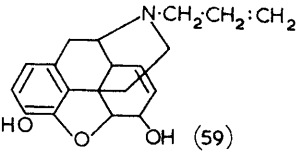
The compound (57; R = hexyl) is known as "Parahexyl" or "Synhexyl" and is one of the few members of this series tested for psychotomimetic activity in man,[179] where the effective oral dose was found to be 5—15 mg. per man. Loewe[180] puts the psychotomimetic threshold at the considerably higher level of 200 mg. per man.

9. Miscellaneous compounds

1-(1-*Phenylcyclohexyl*)*piperidine Hydrochloride* ("*Sernyl*," "*PCP*," "*Phenylcyclidine*") (58).—The compound was first reported as an anæsthetic drug but with the possibility of the production of delirium at higher doses.[181] Later work has shown that it has an effect different from most other psychotomimetics.[182] The secondary characteristics (hallucinations, delusions, etc.) of schizophrenia are absent, whereas the primary characteristics (loss of ability to sustain directed thought, fluctuations in experiencing time and space, etc.) are marked. Trials in psychoneurotic subjects have been recorded.[183] No information regarding the method of its synthesis has been published.



(58)



(59)

Opium Alkaloids.—Many of the morphine alkaloids obtained from the opium poppy (*Papaver somniferum*) and their synthetic analogues are known to produce euphoria in doses less than those required for analgesia. There is, however, little evidence, apart from mood changes, of a psychotomimetic action as a side effect. Recent reviews and monographs of the chemistry of this group are available.[184]

The morphine antagonist, *N*-allylmorphine ("Nalorphine") (59) does, however, cause effects comparable to those of marihuana, including uninhibited behaviour and visual hallucinations.[150a,185]

[178] Adams, MacKenzie, and Loewe, *J. Amer. Chem. Soc.*, 1948, **70**, 664.
[179] Stockings, *Brit. Med. J.*, 1947, I, 918.
[180] Loewe, *J. Pharmacol.*, 1946, **88**, 154.
[181] Chen, *Fed. Proc.*, 1958, **17**, 338; Catenacci, *ibid.*, p. 357.
[182] Luby, Cohen, Rosenbaum, Gottlieb and Kelly, *A.M.A. Arch. Neurology and Psychiatry*, 1959, **81**, 363.
[183] Bodi, Share, Levy, and Moyer, *Antibiotic Medicine and Clinical Therapy*, 1959, **6**, 79.
[184] Bentley, "Chemistry of the Morphine Alkaloids," Oxford Univ. Press, 1954; Manske and Holmes (eds.), "The Alkaloids," Academic Press, New York, Vol. II, 1952; Ginsburg, *Bull. Narcotics*, 1957, **9**, 18; 1958, **10**, 1.
[185] Isbell, *Fed. Proc.*, 1956, **15**, 442; Goodman and Gilman, "The Pharmacological Basis of Therapeutics," Macmillan, 2nd Edn., 1955, p. 255.

"*Ololiuqui*".—The plant known to the Aztecs as "Ololiuqui" ("Bador", "Coatlxoxouhqui", "Piuli", etc.) has long been referred to as containing an active principle with psychotomimetic properties[186] and is still used in Southern Mexico for the production of hallucinations. The plant has been identified with both *Rivea corymbosa* and *Datura meteloides*, but Schultes (quoted by Kinross-Wright[187]) has demonstrated that it is the former of these.

The reported behavioural disturbances caused by oral administration of the macerated seeds of *R. corymbosa* were confirmed by Osmond.[188] The more extensive tests of Kinross-Wright[187] did not confirm the observation and no effect was obtained from the leaves, roots, or seeds and this author suggests that the crushed seeds of *R. corymbosa* are adulterated with *Datura* spp., known to produce behavioural changes.

The constituents of "ololiuqui" have been little investigated chemically. The glucoside of an unknown alkaloid was reported[189] but more recently Hofmann and Tscherter[190] have shown that lysergic acid derivatives may be isolated from "ololiuqui" and that lysergamide, isolysergamide, and chanoclavine are present.[191]

"*Kava-Kava*".—On some South Sea Islands the root of *Piper methysticum* is called "kava-kava" and is used to prepare a ritual drink thought to contain a psychotomimetically active principle. This principle has not yet been identified although methysticin, kavain, and other related α-pyrones have been obtained, all of which proved to be inactive.[192]

Organophosphorus Compounds.—Some of the toxic organophosphorus anticholinesterase compounds have been shown to cause mental as well as functional disturbance. Di-isopropyl phosphorofluoridate (DFP) has produced behavioural changes.[193] Tetraethyl pyrophosphate (TEPP) and parathion are less and more active, respectively, in this fashion than DFP.[194] These observations are chiefly of interest with regard to a possible role for acetylcholine in psychotomimetic action.

10. Theories of the mode of action of psychotomimetics

The biochemical theories of schizophrenia have been reviewed recently[26,34c,195] and the following brief survey will be confined to the current

[186] Guerra and Olivera, "Las Plantas Fantasticas de Mexico," Diaro Espanol, Mexico, D.F., 1954.

[187] Kinross-Wright in "Neuro-psychopharmacology," ed. Bradley, Deniker, and Radouco-Thomas, Elsevier, Amsterdam, 1959, p. 453.

[188] Osmond, *J. Mental Sci.*, 1955, **101**, 526.

[189] Santesson, *Arch. Pharm.*, 1937, **275**, 532.

[190] Hofmann and Tscherter, *Experientia*, 1960, **16**, 414.

[191] Hofmann quoted in *Indian Med. J.*, 1961, 84.

[192] Borsche and Peitzsch, *Ber.*, 1927, **60**, 113; 1930, **63**, 2414; Klohs, Keller, Williams, Tolkes, and Cronheim, *J. Medicin. Pharmaceut. Chem.*, 1959, **1**, 95.

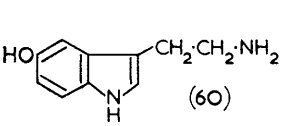
[193] Grob, Lilienthal, Harvey, Jones, Langworthy, and Talbot, *Bull. Johns Hopkins Hosp.*, 1947, **81**, 257; Rowntree, Nevin, and Wilson, *J. Neurology, Neurosurgery and Psychiatry*, 1950, **13**, 47.

[194] Grob and Harvey, *Bull. Johns Hopkins Hosp.*, 1949, **84**, 532; Grob, Garlick, and Harvey, *ibid.*, 1950, **87**, 106.

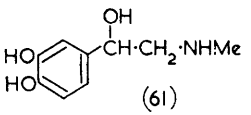
[195] Kety, *Science*, 1959, **129**, 1528, 1590.

theories of the mode of action of psychotomimetics. This, as has been mentioned previously, may or may not bear some relation to the biochemistry of endogenous psychosis.

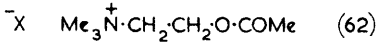
The chief proposals for the mode of action of psychotomimetics concern their role as substances which interfere with the normal action in the body of three compounds, 5-hydroxytryptamine (serotonin) (60), adrenaline (61), and acetylcholine (62).



(60)



(61)



(62)

5-*Hydroxytryptamine.*—5-Hydroxytryptamine has been the subject of symposia[196] and of many review articles.[197]

The creatinine sulphate of this vasoconstrictive substance was isolated[198] from serum in 1947 and characterised two years later.[199] 5-Hydroxytryptamine was synthesised shortly afterwards.[200] Since that date there has been much interest in the substance as is shown by the large numbers of syntheses available.[201]

Its importance was increased when it was found that, in addition to its vasoconstrictor activity, it had a constrictive effect on all smooth muscle and was important in the maintenance of the movements of the intestine (peristalsis).[202] Furthermore, it was present in high concentration (3 mμmoles/g.) in the brain.[203] It was found to be especially prevalent in the basal ganglia, which are thought to be the area of the brain concerned with emotion.[204]

(+)-Lysergic acid diethylamide, in very low concentration (10^{-9} g./l.), was shown to antagonise the effect of 5-hydroxytryptamine in contracting smooth muscle.[205] Other psychotomimetic substances were shown to have a similar antagonistic effect (anti-serotonin activity) and it was suggested

[196] "Symposium on 5-Hydroxytryptamine," ed. Lewis, Pergamon, London, 1958; *Ann. New York Acad. Sci.*, 1957, **66**, 592.

[197] Page, *Physiol. Rev.*, 1958, **38**, 277 and refs. (up to 1957) therein; Cerletti, *Helv. Med. Acta*, 1958, **25**, 330; Maupin, *La Biologie*, 1960, **49**, 75.

[198] Rapport, Green, and Page, *Fed. Proc.*, 1947, **6**, 184.

[199] Rapport, *J. Biol. Chem.*, 1949, **180**, 961.

[200] Hamlin and Fischer, *J. Amer. Chem. Soc.*, 1951, **73**, 5007.

[201] Harley-Mason and Jackson, *J.*, 1954, 1165; Speeter and Anthony, *J. Amer. Chem. Soc.*, 1954, **76**, 6208; Young, *J.*, 1958, 3493; Ash and Wragg, *ibid.*, p. 3887; Noland and Hovden, *J. Org. Chem.*, 1959, **24**, 895; Abramovitch and Shapiro, *Chem. and Ind.*, 1955, 1255; Bucount, Valls, and Joly, U.S.P. 2,920,080/1960; *Chem. Abs.*, 1960, **54**, 13018.

[202] Erspamer and Asero, *Nature*, 1952, **169**, 800; Vane, *Brit. J. Pharmacol.*, 1957, **12**, 344.

[203] Amin, Crawford, and Gaddum, *J. Physiol.*, 1954, **126**, 596.

[204] Bogdanski, Weissbach, and Udenfriend, *J. Neurochem.*, 1957, **1**, 272; Costa and Aprison, *J. Nervous and Mental Disease*, 1958, **126**, 289.

[205] Gaddum, *J. Physiol.*, 1953, **121**, 15.

that psychotomimetic action was due to the disturbance of 5-hydroxytryptamine balance in the brain.[203,206] The tranquilliser reserpine was shown to have the effect of reducing the brain 5-hydroxytryptamine concentration.[207]

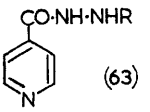
5-Hydroxytryptophan decarboxylase, the enzyme responsible for the synthesis of 5-hydroxytryptamine from 5-hydroxytryptophan, and monoamine oxidase, which converts 5-hydroxytryptamine into 5-hydroxyindole-3-ylacetic acid, are both present in highest concentration in those areas of the brain which have the highest concentration of 5-hydroxytryptamine.[208] 5-Hydroxytryptamine itself does not produce central effects unless administered intravenously at very high dosage or intraventricularly, since it passes only with difficulty from the blood to the brain.[209] However, 5-hydroxytryptophan causes marked elevation of the cerebral 5-hydroxytryptamine content and produces typical central effects (rage, fear, catatonia). It has, therefore, been suggested that the effects of 5-hydroxytryptophan are due to an increased amount in the brain of 5-hydroxytryptamine produced by a decarboxylation process.[210]

These considerations resulted in the suggestion that 5-hydroxytryptamine is an important chemical mediator in the nervous system, interference with which could result in mental changes.[211] The action of 5-hydroxytryptamine is visualised as an excitant one on the cerebral neurones in the brief period between its formation from 5-hydroxytryptophan and its decomposition by monoamine oxidase.[204,212]

Iproniazid (1-isonicotinoyl-2-isopropylhydrazine) (63; R = Pr^i) is known to give, in some cases, psychotic reactions on administration. It is a monoamine oxidase inhibitor and there will be, therefore, an increased amount of 5-hydroxytryptamine in the brain,[210] with characteristic central effects.[213] However, isoniazid (isonicotinoylhydrazine) (63; R = H), which does not inhibit monoamine oxidase, also produces similar psychoses.[214] There is other evidence against the theory that psychotomimetic activity is due to the disturbance of 5-hydroxytryptamine balance. 2-Bromolysergic acid diethylamide has 50% more antiserotonin activity than lysergic acid diethylamide itself and it can be demonstrated in the brain after systemic

[206] Woolley and Shaw, *Science*, 1954, **119**, 587; *Proc. Nat. Acad. Sci. U.S.A.*, 1954, **40**, 228.
[207] Shore, Pletscher, Tomich, Carlsson, Kuntzmann, and Brodie, *Ann. New York Acad. Sci.*, 1957, **66**, 607.
[208] Himwich, *Science*, 1958, **127**, 70.
[209] McIlwain, "Biochemistry and the Central Nervous System," 2nd edn., Churchill, 1959, p. 224.
[210] Udenfriend, Weissbach, and Bogdanski, *Ann. New York Acad. Sci.*, 1957, **66**, 402.
[211] Brodie and Shaw, *Ann. New York Acad. Sci.*, 1957, **66**, 631.
[212] Arioka and Tanimaki, *J. Neurochem.*, 1957, **1**, 311; Blaschko, *Pharmacol. Rev.*, 1952, **4**, 415.
[213] Paasonen, MacLean and Giarman, *J. Neurochem.*, 1957, **1**, 326; Davison, *Biochem. J.*, 1957, **67**, 316.
[214] Jackson, *Brit. Med. J.*, 1957, II, 743; Pleasure, *A.M.A. Arch. Neurology and Psychiatry*, 1954, 313.

administration: however, it produces none of the psychotomimetic effects of the parent compound.[215]



(63)

Nevertheless, the theory has remained attractive because of the similarity in chemical structure between 5-hydroxytryptamine and many of the known psychotomimetics. Lysergic acid derivatives, tetrahydroharmine, psilocybin, bufotenine, *NN*-dimethyltryptamine, and ibogaine all contain the tryptamine residue. Mescaline and adrenochrome have structures not far removed from the indole portion of tryptamine. Disturbance of cerebral 5-hydroxytryptamine balance could, in fact, be caused by monoamine oxidase inhibition, by antimetabolic action by compounds of a similar structure, or by release of it from its storage sites by reserpine, for example.

Some synthetic serotonin antimetabolites having indole structures have, in fact, been shown[216] to cause behavioural changes in man and in animals, though the effects usually are small compared with those of the psychotomimetic substances which have been discussed.

Adrenaline.—The realisation of the resemblance in structure between 5-hydroxytryptamine and the indole psychotomimetics has been an important factor in the development of theories of psychotomimetic action involving 5-hydroxytryptamine. It was the structural similarity of mescaline and adrenaline which indicated the possible significance of the latter in psychotomimetic action.[30,33] It was further realised that both adrenaline and mescaline could be the precursors of indoles (*in vitro* or *in vivo*) and that many psychotomimetics are indoles.[32b]

This suggested that an antimetabolite, possibly having a structure related to indole, may be psychotomimetic in action and resulted in the work with adrenochrome discussed above (p. 136). The doubt surrounding the reported psychotomimetic activity of adrenochrome and its derivatives has meant that work relative to the possible importance of adrenaline in this connexion has tended to concentrate on experiments designed to disclose differences in the adrenaline metabolism of schizophrenics and normal subjects. Possible competition between psychotomimetics and adrenaline requires further study.

In addition to the adrenochrome hypothesis it has been proposed[217] that *O*-methylation of adrenaline or a similar compound may be connected with the production of mental disorder, since by this means a compound close in structure to mescaline may be produced. *O*-Methylation is the main method of adrenaline metabolism when the substance is injected (though

[215] Cerletti and Rothlin, *Nature*, 1955, **176**, 785.
[216] Shaw and Woolley, *J. Pharmacol.*, 1954, **111**, 43; *J. Amer. Chem. Soc.*, 1957, **79**, 3561.
[217] Harley-Mason, quoted by Osmond and Smythies (ref. 33).

it may not be for endogenous adrenaline).[218] Since very little mescaline reaches the brain the suggestion has been made[26] that it produces its effect by an antimetabolic action on, for example, adrenaline in the body. Both 3,4-dihydroxy-5-methoxy- and 3-hydroxy-4,5-dimethoxy-phenethylamine have been isolated from human urine after the consumption of mescaline,[219] but only in amounts which account for less than half of the mescaline taken.

Finally, under this heading, the reported psychotomimetic effects of amphetamine,[220] which is said to produce symptoms often indistinguishable from schizophrenia, may be mentioned.

Acetylcholine.—Acetylcholine occurs together with adrenaline, noradrenaline, and 5-hydroxytryptamine in the brain. Its highest concentration is in the caudate, amygdaloid hippocampus and hypothalmus and it is the third substance for which evidence is available supporting the theory that its balance in the brain is necessary for mental stability.[151b,221]

The psychotomimetic effect of some anticholinesterases (for example, DFP) has been mentioned above (p. 157) and this fact combined with the occurrence of acetylcholine esterase and choline acetylase together with acetylcholine in the brain requires that a possible role of acetylcholine be examined. The original suggestions implicating acetylcholine have been expanded recently by Biel and his co-workers[146,148] as a result of their work with the piperidyl glycollates. They consider the proposal that in the "lower brain" the sympathetic centre (excitatory), controlled by noradrenaline, and the parasympathetic centre (depressant), controlled by acetylcholine or a similar substance, are in a balance. Disturbance of this balance allows either the excitatory or the depressant centre to dominate. Such a balance would be similar to that existing between the sympathetic and the parasympathetic nervous system in the rest of the body.

Blockage of noradrenaline action allows the depressant centre to dominate the brain. Tranquillisers may act in this way. Likewise, monoamine oxidase inhibitors (which prevent the metabolic destruction of noradrenaline) permit the excitatory centre to dominate, accounting for their action as psychic energisers.

The experiments of Biel and his co-workers[146,148] with the piperidyl glycollates (see p. 150), have shown that, in this series, potent anticholinergic action is necessary for good stimulation of the central nervous system. This observation is in agreement with their proposal that acetylcholine (or a similar substance) has an action in the parasympathetic centre of the

[218] Axelrod, *Science*, 1957, **126**, 400.

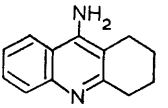
[219] Ratcliffe and Smith, *Chem. and Ind.*, 1959, 925; Harley-Mason, Laird, and Smythies, *Confin. Neurologica*, 1958, **18**, 152.

[220] Connell, *Biochem. J.*, 1957, **65**, 7 P; "Amphetamine Psychosis," Maudsley Monograph No. 5, Chapman and Hall, London, 1958; Stromgren, in "Neuro-psychopharmacology," ed. Bradley, Deniker, and Radouco-Thomas, Elsevier, Amsterdam, 1959, p. 183; Tolentino, in "Psychotropic Drugs," ed. Garattini and Ghetti, Elsevier, Amsterdam, 1957, p. 585.

[221] (*a*) Hoffer, *J. Clinical and Experimental Psychopathology*, 1957, **18**, 27; (*b*) Pfeiffer and Jenney, *Ann. New York Acad. Sci.*, 1957, **66**, 753.

brain similar to that of noradrenaline in the sympathetic centre, since an anticholinergic action will allow the excitatory centre to be dominant.

Abood[222] has discussed the possible mode of action of the piperidyl glycollates and also points out that they are potent anticholinergic agents and are thus related to acetylcholine. With this group, retention of coplanarity within the molecule seems necessary for both high anticholinergic activity and psychotomimetic potency. It has been shown[223] that tritium-labelled 1-ethyl-3-piperidyl benzilate is localised predominantly in a cytoplasmic granular fraction consisting largely of mitochondria. Abood[222] believes that the piperidyl glycollates are actually bound to mitochondria and that they act in the biological system at this level of the cell. The binding of piperidyl glycollates to mitochondria can be interfered with by chlorpromazine, reserpine, acetylsalicylic acid, meprobamate, and 9-amino-1,2,3,4-tetrahydroacridine (64). Gershon[224] has shown that the last compound (64) is a specific antagonist of the psychotomimetic action of the piperidyl glycollates in man. This acridine derivative prevents the metabolic destruction of acetylcholine and, therefore, may act by restoring the balance of acetylcholine which has been disturbed by the action of an anticholinergic piperidyl glycollate. Although some connexion between



(64)

anticholinergic potency and psychotomimetic activity has been demonstrated for the piperidyl glycollates there is not, as yet, a precise explanation of the mechanism of their action. All that is evident is that acetylcholine may have an important role in the interpretation of the mechanism of some psychotomimetic substances.

It may be concluded that work on the mode (or modes) of action of the psychotomimetic substances is at present only at an early stage. It is not possible to judge the relative importance, in this sense, of the three substances reviewed here and other substances may be found later to have more importance. In addition, the more neglected hypothesis that the psychotropic substances, in general, may exert a direct action at receptor sites has been indicated as deserving greater attention.[222]

The author thanks Drs. A. L. Green and W. D. Ollis for helpful comments on the manuscript.

[222] Abood, *J. Medicin. Pharmaceut. Chem.*, 1961, **4**, 469.
[223] Abood and Rinaldi, *Psychopharmacologia*, 1959, **1**, 117.
[224] Gershon, *Nature*, 1960, **186**, 1072.