J. Pharm. Pharmac., 1970, 22, 321–332 *Received November* 17, 1969

Infrared identification of some hallucinogenic derivatives of tryptamine and amphetamine

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The use of infrared spectroscopy for the identification of psychotomimetic derivatives of amphetamine and tryptamine is discussed. Numerous characteristic absorptions are assigned on the basis of spectra recorded from 123 bases and salts. These permit the recognition of compounds of these types even when no reference materials or spectra are available. Distinction between the spectra of optically active and racemic forms of some amphetamine derivatives is also possible.

The identification of hallucinogenic drugs can present difficulties, particularly when no reference data are available. The most important substance in this category is undoubtedly lysergide (LSD), which has been considered previously (Mesley & Evans, 1969), but there are potentially many other compounds having similar properties. Some of these are not recognized drugs, but have been synthesized with the deliberate intention of evading existing legislation. When a hitherto unknown compound is encountered, its identification may require the combined use of several analytical techniques, as in the case of the illicit drug known as "STP" (Martin & Alexander, 1968; Phillips & Mesley, 1969).

Of the individual methods available, mass spectrometry is especially suitable for handling small samples and can give valuable structural information (Bellman, 1968), while thin-layer chromatography is useful for distinguishing related substances, provided that the material has been previously examined (Phillips & Gardiner, 1969). Infrared spectroscopy, however, has the widest applicability since on the one hand it provides a fingerprint for a given substance which can be compared with reference standards, while on the other it can yield valuable information concerning functional groups present in an unknown compound, which should permit at least partial identification. It can also be used to examine both free bases and their salts in the form of solids, liquids or solutions. Spectra of crystalline solids are generally more complex, and therefore more characteristic, than those of the liquid phase, and can sometimes be used additionally to identify optical isomers.

Apart from lysergide, the psychotomimetic drugs fall mainly into two classes: (i) those derived from tryptamine [3-(2-aminoethyl)indole], of which LSD is perhaps an extreme case; and (ii) ring-substituted derivatives of phenethylamine, though with the exception of mescaline these are all amphetamine derivatives. The present study is intended to establish characteristic absorption frequencies which will enable these compounds to be identified from their spectra. For this purpose it has proved necessary to consider also the simple amphetamines having no substitution in the benzene ring, and also a number of substances related to the hallucinogens and with which they might be confused.

Substances examined and their legal status

In the United Kingdom the important hallucinogens and amphetamines are controlled under the Drugs (Prevention of Misuse) Act 1964 and its subsequent modification (S.I. 1966, No. 1001). Apart from lysergide and its salts the only tryptamine derivatives included are hydroxy-*NN*-dimethyltryptamines, their esters or ethers, and salts of any of these substances. The intention is thus to control the naturally occurring hallucinogens psilocin and bufotenine (4- and 5-hydroxy-*NN*-dimethyltryptamine) and psilocybin (the phosphate ester of psilocin). It may be noted that the 6- and 7-hydroxy-compounds, which are not known to be hallucinogenic, are also included whereas *NN*-dimethyltryptamine and its homologues, many of which have hallucinogenic properties, are not covered.* Table 1 lists the tryptamines and related substances, including some based on gramine (3-dimethylaminomethylindole), which were examined; in addition to the simple compounds, the naturally occurring substances harmine, harmaline and ibogaine were included on account of their reported psychotomimetic properties (Downing, 1962).

The legal status of the amphetamines is more complex, and has been summarized by Phillips (1967). The 1964 Act covered amphetamines substituted in the side-chain but not in the ring, these compounds being liable to abuse as stimulants, but specifically excluded certain compounds of the ephedrine type. With the identification of the illicit material known as "STP" as 2,5-dimethoxy-4-methylamphetamine (Martin & Alexander, 1968; Phillips & Mesley, 1969), following reports of similar properties for other related compounds (Shulgin, 1964), it was thought necessary to control ring-substituted amphetamines and these are included in the Poisons List (No. 2) Order 1968 (S.I. 1968 No. 1682). Similarly the entry for mescaline has been extended to include other derivatives of phenethylamine formed by substitution in the aromatic ring. The choice of ring-substituted amphetamines for inclusion in the present study was limited by availability; those without ring-substitution were selected to show the effects of most simple substituents. The complete list is given in Table 2, optical isomers being indicated only where more than one was examined (structural formulae of these compounds are given by Beckett, Tucker & Moffat, 1967).

EXPERIMENTAL

Materials used were mostly commercial samples of the salts, apart from a series of *N*-substituted tryptamine salts which were supplied by the Chemical Defence Establishment. Most of the samples were examined by thin-layer chromatography (Phillips & Gardiner, 1969) and found to be substantially pure. Free bases were generally obtained by solvent extraction from an alkaline solution of the salt. In some instances, where the original material was either the free base or a salt of an organic acid, the hydrochloride was prepared by careful treatment of the base with dilute hydrochloric acid and evaporation to dryness. Many of the materials, both bases and salts, were treated with a variety of solvents and the solutions evaporated under varying conditions as a check for the incidence of polymorphism.

* This position is likely to be reversed by the Misuse of Drugs Bill currently before Parliament. In Part I of Schedule 2 to that Bill *NN*-dimethyl- and *NN*-diethyltryptamine are explicitly cited, whereas the 6- and 7-hydroxy-derivatives are not specified. In the same Bill the control of amphetamine-like substances will be modified to make explicit reference to a limited number of those drugs for which there is evidence of misuse.

Infrared spectra were recorded using a Grubb Parsons GS2 grating spectrometer. Solid samples were examined as mulls in Nujol (liquid paraffin B.P.) or as pressed discs using potassium chloride (A.R. quality) or potassium bromide (E. Merck A.G.,

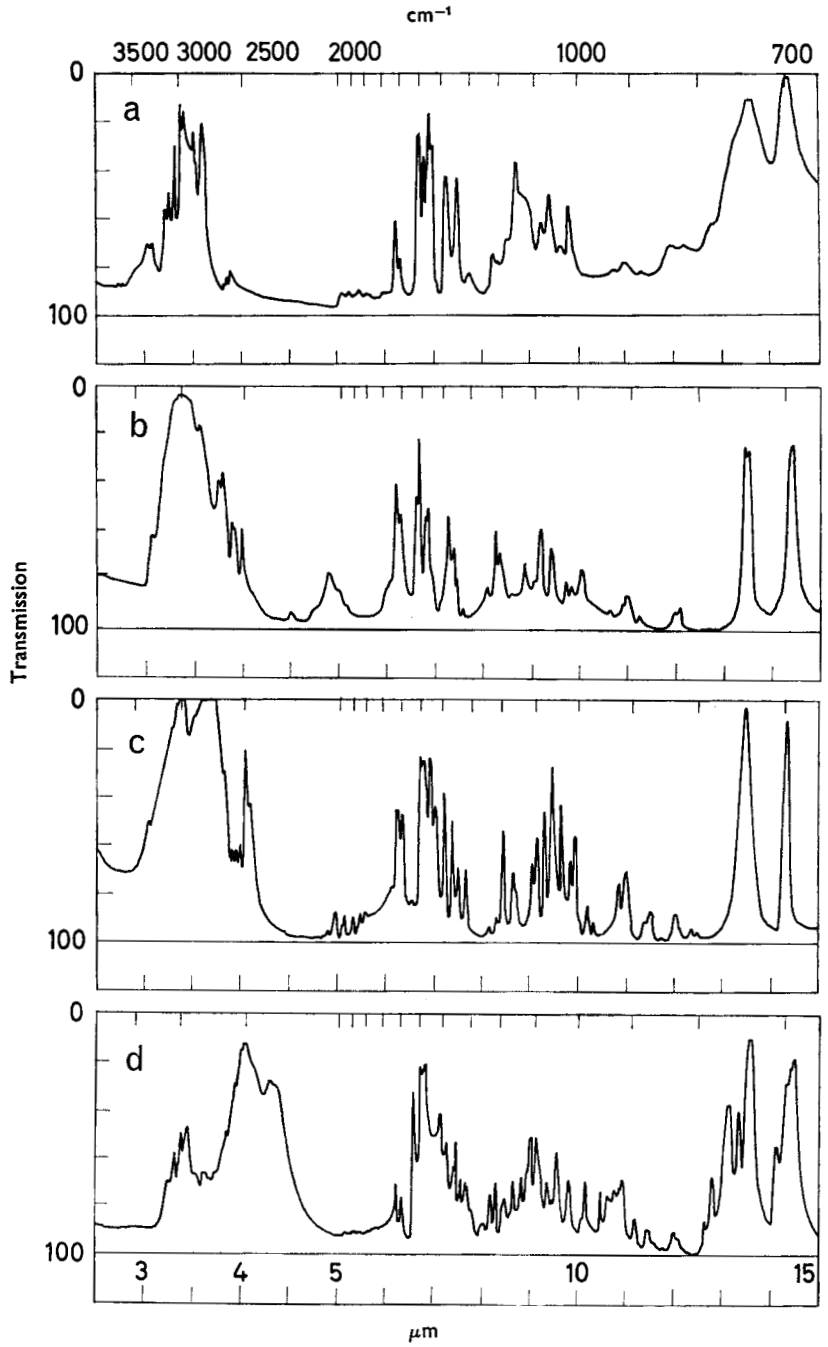

FIG. 1. Typical infrared spectra of amphetamines: (a) (+)-Methylamphetamine (liquid film). (b) (+)-Amphetamine hydrochloride (KCl disc). (c) (+)-Methylamphetamine hydrochloride (KCl disc). (d) Benzphetamine hydrochloride (KCl disc).

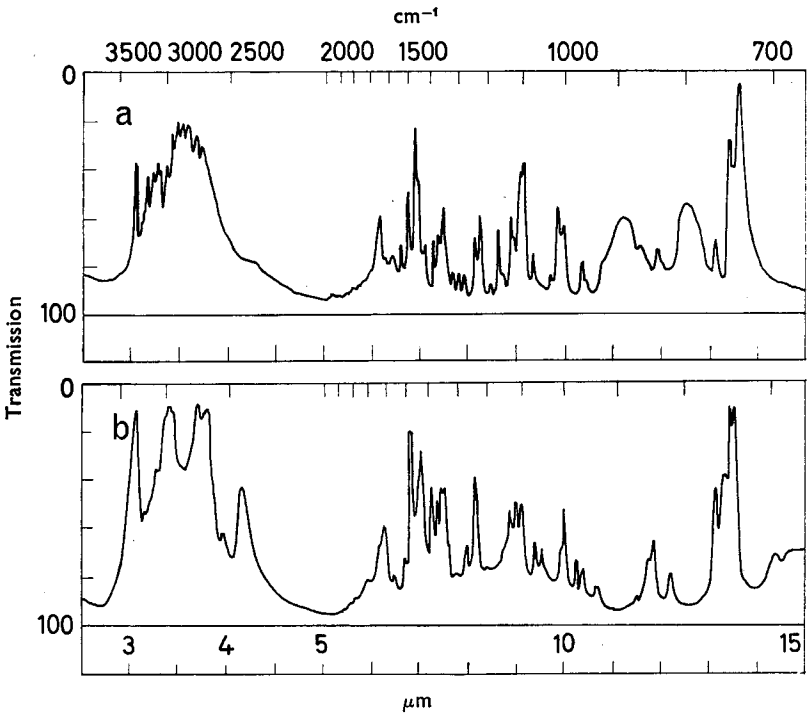

FIG. 2. Typical infrared spectra of tryptamines: (a) *N*-Methyltryptamine (KBr disc). (b) *N*-Methyltryptamine hydrochloride (KCl disc).

spectroscopic grade). Some typical spectra are shown in Figs 1 and 2. Spectra of many of the substances have been published elsewhere, details of which are given in Tables 1 and 2. Unless otherwise stated the spectra now obtained are in agreement with these published spectra.

RESULTS AND DISCUSSION

Characteristic absorptions of amphetamines

Aromatic absorptions (no ring substituent). The most prominent absorptions in the spectra of most of the simple amphetamines and their hydrochlorides are two strong bands at approximately 740 and 700 cm^{-1}, both of which may be slightly split in crystalline solids. These absorptions are characteristic of monosubstituted benzenes in general and are therefore not specific, but the amphetamines are the only significant group of drugs in which these are the strongest bands. From the examination of a large number of monoalkylbenzenes, all of which were liquid, Hawkes & Neale (1960) showed that the frequency of the 700 cm^{-1} band was not affected by the nature of the substituent, but that the higher frequency band (assigned to out-of-plane deformation of five adjacent C–H bonds) was sensitive to branching in the α-position of the alkyl chain; average frequencies were found to be 743, 761 and 764 cm^{-1} for CH_2R, CHR_1R_2 and $CR_1R_2R_3$ substituents respectively. In the present work, where the substituents are not simple alkyl groups, this effect is less predictable; all the compounds with a CH_2 group adjacent to the ring, with the exception of those mentioned below, absorb at 746–735 cm^{-1}, but the effect of hydroxyl substitution

Table 1. *Tryptamine derivatives examined*

Base	Salts	Published spectra: Base	Published spectra: Salt
Tryptamine	hydrochloride		a (21381)
5-Methyltryptamine	hydrochloride		
7-Methyltryptamine			
α-Methyltryptamine	hydrochloride		
N-Methyltryptamine	hydrochloride, hydrogen oxalate	a (31613)	
5-Hydroxytryptamine (serotonin, 5-HT)	hydrogen maleate	b	
5-Methoxytryptamine	hydrochloride	a (21683)	
5-Benzyloxytryptamine	hydrochloride		a (21272)
5-Hydroxy-*N*-methyltryptamine	hydrogen oxalate		
NN-Dimethyltryptamine	hydrogen oxalate	c, a (21676)	
5-Hydroxy-*NN*-dimethyltryptamine (Bufotenine)	hydrogen oxalate	d	a (10781)*
5-Methoxy-*NN*-dimethyltryptamine	hydrochloride		
5-Benzyloxy-*NN*-dimethyltryptamine	hydrochloride		a (29034)
4-Phosphoryloxy-*NN*-dimethyltryptamine (Psilocybin)			
Gramine		a (3824, 10608)	
5-Ethylgramine		a (33647)	
5-Methoxygramine	hydrochloride		
5-Benzyloxygramine		a (18488)	
N-Ethyltryptamine	hydrochloride		
N-n-Propyltryptamine	hydrochloride		
N-Isopropyltryptamine	hydrochloride		
N-n-Butyltryptamine	hydrochloride		
N-Benzyltryptamine	hydrochloride		
NN-Diethyltryptamine	hydrochloride	a (33656)	
NN-Di-n-propyltryptamine	hydrobromide		
NN-Di-isopropyltryptamine	hydrochloride		
NN-Di-n-butyltryptamine	hydrochloride		
NN-Pyrrolidinotryptamine	hydrochloride		
5-Benzyloxy-*NN*-pyrrolidinotryptamine	hydrochloride		a (29038)
Harmine	hydrochloride	c, a (3358)	
Harmaline	hydrochloride	a (2969)	a (2974)
Ibogaine	hydrochloride	a (909)*	a (923)

Notes (Tables 1 and 2):

* Published spectrum shows changes associated with preparation of KBr disc.

† Published spectrum is of a different optical isomer.

‡ Published spectrum not in agreement with that obtained in this work.

§ Base not isolated.

References: a—Sadtler Standard Spectra (serial number in parentheses); b—Clarke (1969); c—Cromp & Turney (1967); d—Stoll & others (1955); e—Chatten & Levi (1959); f—Sammul, Brannon & Hayden (1964); g—Hayden, Brannon & Yaciw (1966); h—Fazzari & others (1968); i—Phillips & Mesley (1969).

on the α-carbon is variable, giving frequencies in the range 761–738 cm^{-1}. Thus a band at 750 cm^{-1} or above indicates branching, but a frequency near 740 cm^{-1} does not necessarily imply an absence of branching.

Phentermine and mephentermine and their salts, which have two methyl groups on the second carbon from the ring, are anomalous in showing two bands at approximately 770 and 730 cm^{-1} in place of the expected 740 cm^{-1} band. The same effect was noted by Hawkes & Neale (1960) for hydrocarbons with two methyl groups on the β-carbon, and they concluded that the 770 cm^{-1} band was the aromatic C–H absorption. Whatever their origin, it appears that both bands are characteristic of

Table 2. *Phenethylamines examined*

Base	Salts	Published spectra	
		Base	Salt
(+)-Amphetamine	hydrochloride, sulphate		e, f, a (14721)*
(—)-Amphetamine	sulphate	a (34382)	a (34383)*
(±)-Amphetamine	hydrochloride, sulphate	a (134)	e, g, a (14722)*
(+)-Methylamphetamine ..	hydrochloride	g†	e, f, a (14723)
(±)-Methylamphetamine ..	hydrochloride		a (14724)‡
Benzphetamine	hydrochloride		f
Phentermine	hydrochloride	a (28933)	a (28934)
Mephentermine	hydrochloride, sulphate		
Phenylpropanolamine ((±)-norephedrine)	hydrochloride	g	f, a (27968)
(—)-Norephedrine	hydrochloride, sulphate		
Norisoephedrine	hydrochloride		
Ephedrine	hydrochloride	a (520)	e, a (7550)
Pseudoephedrine	hydrochloride		g
(—)-*N*-Methylephedrine	hydrochloride	a (15536)	
(±)-*N*-Methylephedrine	hydrochloride		
Phenylephrine	hydrochloride	g	f, a (15582)*
Noradrenaline	hydrogen tartrate	a (21296)†	a (1027)*
Adrenaline		b, a (7393)	
Isoprenaline§	sulphate		
Tranylcypromine	sulphate		
Phenmetrazine (*trans*)	hydrochloride	g	f
Phenmetrazine (*cis*)	hydrochloride		
Chlorphentermine	hydrochloride		h
Methoxyphenamine	hydrochloride		a (20485)
Methoxamine	hydrochloride		
3,4-Methylenedioxyamphetamine (MDA)	hydrochloride, sulphate	a (20160)	
3-Methoxy-4,5-methylenedioxy-amphetamine (MMDA) ..	hydrochloride		
2,5-Dimethoxy-4-methyl-amphetamine (DOM, "STP") ..	hydrochloride	i	i
Mescaline	hydrochloride, sulphate	c	f

benzenes with a single $CH_2 \cdot CMe_2 \cdot R$ substituent, and together with the 700 cm^{-1} band they are the most noticeable spectral features of such compounds.

Apart from these low-frequency absorptions, all the amphetamines have bands at approximately 1600, 1580, 1490 and 1450 cm^{-1}, due to ring stretching, and at least five sharp bands in the 1290–1015 cm^{-1} region due to C–H in-plane deformation.

Aromatic absorptions (ring-substituted). In place of the 740 and 700 cm^{-1} bands of the monosubstituted benzenes the following are found (values quoted are for individual compounds examined and are not necessarily typical).

1,2-Disubstitution (methoxyphenamine): very strong band near 750 cm^{-1} (four adjacent hydrogens).

1,3-Disubstitution (phenylephrine): strong band 780 cm^{-1} (three adjacent hydrogens), medium bands at 868 cm^{-1} (base) or 900 cm^{-1} (hydrochloride) due to isolated hydrogen, and at 700 cm^{-1} (ring deformation).

1,4-Disubstitution (chlorphentermine): strong band 810 cm^{-1} (pairs of adjacent hydrogens), also bands at 842 and 750 cm^{-1} (latter may correspond to 730 cm^{-1} band in phentermine).

1,2,4-Trisubstitution (adrenaline, isoprenaline, methoxamine, MDA): strong band 823–798 cm^{-1} (two adjacent hydrogens), other bands at 884–863 cm^{-1} (isolated hydrogen) and 782–772 cm^{-1} (latter replaced by 710 cm^{-1} in methoxamine).

1,2,3,5-Tetrasubstitution (mescaline, MMDA): Only isolated hydrogens, doublet at 813/803 cm^{-1} in MMDA, strong band 830 cm^{-1} in mescaline (two hydrogens equivalent in mescaline, not in MMDA).

1,2,4,5-Tetrasubstitution (DOM): Only isolated hydrogens, several bands around 870–840 cm^{-1}.

Absorptions associated with amine group. The nature of the bases is not readily determined from their spectra. The liquid amines, both primary and secondary, have broad N–H stretching bands near 3300 cm^{-1} in which NH and NH_2 absorptions are not distinguishable. In the solid phase the bands are generally sharper and as a rule the secondary amines show only one band, but the primary amines can have one, two or three bands. The liquid primary amines show a broad band near 850 cm^{-1}, but OH groups can also give similar bands; the liquid secondary amines have a broad band near 745 cm^{-1}, but this is generally obscured by the 740 cm^{-1} aromatic band. In the solid phase these bands cease to be recognizable, whilst tertiary amines have no characteristic absorptions at all, apart from those due to *N*-methyl groups (see below).

The amine salts are more clearly differentiated. All the primary amine hydrochlorides have a very strong broad band centred near 2950 cm^{-1} with several weaker bands between 2800 and 2450 cm^{-1} and frequently a band of medium intensity at 2060–1945 cm^{-1}. Secondary salts usually have two very strong bands near 2950 and 2730 cm^{-1}, a medium, sharp band at 2450 cm^{-1} and weaker bands at 2500 and 2030 cm^{-1}. The tertiary amine salts generally have a single strong, broad band in the range 2700–2450 cm^{-1}, sometimes accompanied by other weaker bands.

Methyl group absorptions. Methyl groups attached to carbon normally absorb at approximately 2960, 2870, 1460 and 1370 cm^{-1}, but the first three of these are liable to be obscured by CH_2 absorptions. However, the presence of the 1370 cm^{-1} band serves to distinguish amphetamines from the corresponding phenethylamines, provided there are no other *C*-methyl groups in the molecule (not applicable if examined as liquid paraffin mull). Thus mescaline and adrenaline, which contain *O*-methyl and *N*-methyl groups respectively but no *C*-methyl, have no band at 1370 cm^{-1}.

The presence of two methyl groups on the same carbon atom, as in the phentermine series, gives rise to two bands of equal intensity at about 1375 and 1360 cm^{-1}. There are also additional absorptions at 1180 cm^{-1} (liquids) or near 1170 and 1160 cm^{-1} (solids), but these are not very distinctive.

N-Methyl groups are clearly distinguishable by a fairly strong band at 2785–2770 cm^{-1}, absent in all other compounds (except MDA which has a weak band at 2780 cm^{-1} due to the $O–CH_2–O$ group). *O*-Methyl groups are not clearly distinguishable, the bands at 2825 and 1450 cm^{-1} being close to the normal CH_2 and CH_3 absorptions. The C–O absorptions, on the other hand, are very pronounced (see below).

Absorptions due to OH groups in side-chain. All the ephedrine-type compounds have a secondary hydroxyl group which gives characteristic absorptions in the salts. The O–H stretching absorption is a fairly strong band near 3300 cm^{-1}, and there is a second fairly strong band at 1055–1030 cm^{-1} (1080 cm^{-1} in phenylephrine hydrochloride) which is noticeably broader than the aromatic bands already present in this region.

In the free bases there is obviously strong intermolecular hydrogen bonding between

the OH group and the nitrogen atom, causing the O–H stretching band to appear as a very broad background extending from about 3300 to 2500 cm^{-1}, though phenylpropanolamine is exceptional in having two maxima at 3040 and 2725 cm^{-1}. There is another strong band, usually near 1080–1060 cm^{-1}, and the O–H out-of-plane deformation now appears as a broad band between 975 and 800 cm^{-1}, but there is often confusion between this and the corresponding N–H band.

Absorptions due to ether groups. Purely aliphatic ethers have a single very strong absorption near 1110 cm^{-1} (this is also true of cyclic ethers such as phenmetrazine), but when one of the two alkyl groups is replaced by benzene there are usually two bands at approximately 1250 and 1140 cm^{-1}, and these are largely due to stretching of the aromatic and aliphatic C–O bonds respectively. From the spectra of the various methoxy-substituted amphetamines it is apparent that the positions and intensities of these bands and of those in this region due to C–H deformation are affected by other substituents in the ring, and this has been confirmed by comparison with a large number of published spectra of aromatic ethers.

Thus methoxyphenamine, with a strong band at 1240 cm^{-1} and medium bands at about 1125, 1045 and 1025 cm^{-1}, is typical of *o*-substituted anisoles. Addition of a second methoxy group in the *para*-position relative to the alkyl group generally gives a strong band at 1210 cm^{-1} and a medium band at 1040 cm^{-1}, and of the intermediate bands that at 1150 cm^{-1} appears to be characteristic; methoxamine conforms to this pattern, though in the base the 1040 cm^{-1} band is enhanced by a contribution from the hydroxyl group, while the hydrochloride has two bands at 1048 and 1020 cm^{-1}. 2,5-Dimethoxy-4-methylamphetamine also has strong bands at 1210 and 1045 cm^{-1}, but with no intervening bands of appreciable intensity (for spectra see Phillips & Mesley, 1969).

Published spectra show that 1,3-dimethoxybenzene, with or without an additional 5-substituent, has a very strong absorption at about 1150 cm^{-1}, which is unusual for an aromatic ether. Mescaline follows this pattern with a very strong band at 1125 cm^{-1} attributable to the two methoxy groups which are *meta* to each other, but with an additional fairly strong band at 1240 cm^{-1} which may be due to the third methoxy group between the other two. MMDA, in which two of the methoxy groups are replaced by a methylenedioxy ring, also has its strongest band at 1130 cm^{-1} but without the 1240 cm^{-1} band (there are in addition medium bands at 1195, 1090 and 1040 cm^{-1}). MDA has the typical aromatic ether pattern of strong bands at 1240 and 1040 cm^{-1}, and is thereby distinguishable from 1,2-dimethoxy compounds which give two strong bands at 1265 and 1235 cm^{-1}. This is worth noting, as the presence or absence of *O*-methyl groups is difficult to establish directly.

General conclusions. The distinctive features noted above permit the identification of (i) the benzene ring, and the position of any other ring substituents; (ii) primary, secondary and tertiary amines (from spectra of the salts); (iii) methyl substitution on nitrogen, and on a side-chain carbon (distinction between phenethylamines and amphetamines); (iv) hydroxyl groups in the side-chain (distinction of ephedrines from amphetamines); (v) ether groups on the ring, and their position.

The only structural features not established with certainty are the length of the side-chain and the position of the amino-group. Thus the spectrum of norisoephedrine, in which the positions of the OH and NH_2 groups are interchanged, shows no anomalous features which might distinguish it from the ephedrine series.

Nevertheless, all the spectra examined (apart from those of optical isomers mentioned in the final section) are quite distinctive and could be used to identify any of these compounds by comparison with an authentic specimen.

Characteristic absorptions of tryptamines

Absorptions due to indole nucleus. The simple compounds with no substitution in the benzene ring all have a very strong band near 740 cm^{-1} (1,2-disubstituted benzene) and in most cases a prominent, fairly sharp band near 810 cm^{-1}. The latter is shown in the range 825–800 cm^{-1} by 18 of the 23 solid compounds examined, whilst three of the remainder have a similar peak at 789–783 cm^{-1}; the liquid bases all show a broad band near 800 cm^{-1}. Kanaoka, Ban & others (1960) have ascribed a band at 810–760 cm^{-1} in 3-substituted indoles to out-of-plane C–H bending in the 2-position. The 5-substituted compounds are less predictable, as the band due to two adjacent ring hydrogens also occurs near 810 cm^{-1}, giving either a single strong absorption or multiple bands. Elsewhere in the spectrum the indole nucleus is characterized by a multiplicity of bands between 1620 and 1300 cm^{-1}, particularly between 1400 and 1300 cm^{-1}.

NH absorptions. All the crystalline bases (except bufotenine, psilocybin and ibogaine), and also several of the liquids, are characterized by a remarkable broad absorption extending between approximately 3300 and 2500 cm^{-1}, on which may be superimposed as many as fifteen sharp peaks. This feature disappears in spectra of dilute solutions, being replaced by a single sharp peak at 3470 cm^{-1}, and is ascribed to the formation of a strong hydrogen bond linking the indole NH group with the side chain nitrogen of another molecule. The broad absorption thus represents the N–H stretching, the superimposed peaks being mainly overtones and combination bands intensified by Fermi resonance. This feature, though particularly noticeable in the tryptamine series, is also found in the gramines and in some compounds in which the substituent is on the benzene ring. It is absent in the salts, in which the lone pair of electrons on the side-chain nitrogen is no longer available as a proton-acceptor site, and these compounds show instead a single peak between 3400 and 3100 cm^{-1}. The actual position of this band depends upon the degree of substitution of the side-chain nitrogen: thus the primary amine salts absorb at 3290–3250 cm^{-1}, the secondary salts very close to 3400 cm^{-1} and the tertiary salts within the range 3320–3125 cm^{-1}. The reason for this dependence is not apparent.

The tryptamine bases containing NH or NH_2 in the side-chain show respectively one or two sharp peaks near 3300 cm^{-1}, which are well separated from the feature described above and are thus quite diagnostic. The hydrochlorides show the characteristic absorptions of primary, secondary and tertiary amine salts, as described for the amphetamine derivatives.

Other characteristic tryptamine absorptions. The spectra of the tryptamines are more complex than those of the amphetamines and it is therefore more difficult to assign individual absorptions, but certain bands may nevertheless be regarded as characteristic of the basic structure. Bands at 1330 (stronger than most neighbouring peaks), 1225, 1100 and 1010 cm^{-1} are prominent in the tryptamines with no ring substitution and in their salts. In the 5-substituted tryptamines the 1330 cm^{-1} band, though still present, ceases to be prominent, the 1225 cm^{-1} band is usually obscured by the strong ether absorption (see below) and the 1010 cm^{-1} band either disappears or becomes less prominent. The gramines, whether ring-substituted or not, all show

a prominent band near 990 cm^{-1} which is not found in the tryptamines, and this serves as a distinguishing feature.

Bands due to ring substituents. The methyl and benzyl ethers all have a prominent absorption near 1210 cm^{-1}, but the second ether band is not clearly defined. The benzyl group also gives additional absorptions at lower frequencies, particularly near 740 and 690 cm^{-1}. The corresponding phenols (5-hydroxytryptamine, bufotenine), also absorb near 1200 cm^{-1} in the amorphous forms usually obtained by extraction from neutralized solutions, though in crystalline bufotenine the strong band is at 1239 cm^{-1}. Bufotenine is readily distinguished from its ethers by a strong O–H stretching band at 3390 cm^{-1}, and in place of the complex band usually centred at 2900–2800 cm^{-1} there is a broad hump at 2560 cm^{-1}, presumably due to N–H . . . O bonds.

Psilocybin is exceptional as most of the strong absorptions are due to the phosphate group, and the spectrum is barely recognizable as that of a tryptamine derivative.

Bands characteristic of N-*alkyl groups.* In the series of *N*-alkyl and *NN*-dialkyltryptamines no correlations have been found which can be used to identify individual compounds, though all the spectra are clearly distinguishable from each other. The only identifiable alkyl substituent is the isopropyl group, which gives a band near 1165 cm^{-1} in a region usually free from absorption, though the anticipated double peak near 1370 cm^{-1} due to the CMe_2 group is obscured by other absorptions.

General conclusions. The features described permit the identification of an indole derivative containing a basic side-chain, and also indicate whether this base is primary, secondary or tertiary. The 810 cm^{-1} band appears to be specific for 3-substitution and the particular bands quoted above serve to distinguish the aminoethyl side-chain from others closely related. 5-Substituted derivatives can be distinguished without difficulty, so that the only groups not readily identifiable are the individual *N*-alkyl substituents. It should be noted that the correlations quoted here apply to the bases and their hydrochlorides, but the characteristic bands may be obscured in salts of organic acids, such as oxalates.

Polymorphism

Polymorphism can be a disturbing factor in the infrared identification of drugs (Mesley & Johnson, 1965; Mesley & Houghton, 1967; Mesley & Clements, 1968), but fortunately it seems to be rare amongst these compounds, the incidence in each class being greater in the salts than in the bases. 2,5-Dimethoxy-4-methylamphetamine was the only amphetamine base to give two forms (Phillips & Mesley, 1969), whilst phenylpropanolamine hydrochloride, tranylcypromine sulphate and phenmetrazine hydrochloride also exhibited the phenomenon. Potassium bromide discs of mescaline sulphate apparently show evidence of polymorphism: when prepared with a moderate amount of grinding the disc gives a spectrum consistent with mescaline hydrobromide and potassium sulphate, but on prolonged grinding further changes occur suggesting conversion to a second form of mescaline hydrobromide. This effect was not observed with potassium chloride discs.

Of the tryptamine bases only *NN*-dimethyltryptamine and 5-methoxy-*NN*-dimethyltryptamine yielded two forms. The hydrochlorides of 5-benzyloxytryptamine, 5-benzyloxy-*NN*-dimethyltryptamine and ibogaine all gave two forms, 5-methoxytryptamine hydrochloride and 5-hydroxytryptamine bimaleate three each and harmaline hydrochloride no less than five different forms.

Distinction between optical isomers

Samples of the salts of amphetamine, methylamphetamine, norephedrine and *N*-methylephedrine were available both in the optically active form and as the racemic mixture. As is to be expected, the (+)- and (−)-forms of amphetamine sulphate have identical spectra, but the (±)-form is significantly different. Obviously the (+)- and (−)-forms crystallize in lattices which have identical unit cell dimensions but which are mirror images of each other, and these cannot be distinguished by infrared spectroscopy. If these unit cells are not superimposable then the lattice structure of the racemic mixture is bound to be different, and this will cause differences in the infrared spectrum analogous to those caused by polymorphism. The (+)- and (±)-amphetamine hydrochlorides show similar differences, but on conversion to the respective bases, which are liquids, the differences disappear as the spectrum is no longer affected by any lattice constraints.

The hydrochlorides of (−)- and (±)-norephedrine and (−)- and (±)-*N*-methylephedrine are similarly distinguishable, as are the *N*-methylephedrine bases, which are both crystalline solids. In the case of the norephedrine bases the (±)-form (phenylpropanolamine) is crystalline but (−)-norephedrine remained liquid.

Methylamphetamine proved to be exceptional in that the (+)- and (±)-hydrochlorides gave the same infrared spectrum. Polarimetry confirmed that the two samples differed in optical activity and x-ray diffraction showed that they were crystallographically identical. It was therefore inferred that in this case the unit cells of the (+)- and (−)-forms can be superimposed, allowing the racemic form to crystallize with the same lattice structure, a conclusion which implies that the crystal symmetry is orthorhombic or higher.

The spectral differences between the (+)- and (±)-amphetamine salts are sufficient to allow them to be distinguished using as little as one milligram of material. Thus it should be possible to identify a single 5 mg dexamphetamine tablet, whereas the present B.P. test requires 20 tablets.

Acknowledgements

Thanks are due to Mr. J. A. Macnab and Mr. G. S. Sayers for assistance in this work, and to the Chemical Defence Establishment for supplying a number of samples.

REFERENCES

BECKETT, A. C., TUCKER, G. T. & MOFFAT, A. C. (1967). *J. Pharm. Pharmac.*, **19**, 273–294.

BELLMAN, S. W. (1968). *J. Ass. off. analyt. Chem.*, **51**, 164–175.

CHATTEN, L. G. & LEVI, L. (1959). *Analyt. Chem.*, **31**, 1581–1586.

CLARKE, E. G. C. (1969). *Isolation and Identification of Drugs*, London: Pharmaceutical Press.

CROMP, C. C. & TURNEY, F. G. (1967). *J. forens. Sci.*, **12**, 538–546.

DOWNING, D. F. (1962). *Q. Rev. chem. Soc.*, **16**, 133–162.

FAZZARI, F. R., SHARKEY, M. F., YACIW, C. A. & BRANNON, W. L. (1968). *J. Ass. off. analyt. Chem.*, **51**, 1154–1167.

HAYDEN, A. L., BRANNON, W. L. & YACIW, C. A. (1966). *Ibid.*, **49**, 1109–1153.

HAWKES, J. C. & NEALE, A. J. (1960). *Spectrochim. Acta*, **16**, 633–653.

KANAOKA, Y., BAN, Y., OISHI, T., YONEMITSU, O., TERASHIMA, M., KIMURA, T. & NAKAGAWA, M. (1960). *Chem. pharm. Bull., Tokyo*, **8**, 294–301.

MARTIN, R. J. & ALEXANDER, T. G. (1968). *J. Ass. off. analyt. Chem.*, **51**, 159–163.

MESLEY, R. J. & CLEMENTS, R. L. (1968). *J. Pharm. Pharmac.*, **20**. 341–347.

MESLEY, R. J. & EVANS, W. H. (1969). *Ibid.*, **21**, 713–720.
MESLEY, R. J. & HOUGHTON, E. E. (1967). *Ibid.*, **19**, 295–304.
MESLEY, R. J. & JOHNSON, C. A. (1965). *Ibid.*, **17**, 329–340.
PHILLIPS, G. F. (1967). *J. forens. Sci. Soc.*, **7**, 17–30.
PHILLIPS, G. F. & GARDINER, J. (1969). *J. Pharm. Pharmac.*, **21**, 793–807.
PHILLIPS, G. F. & MESLEY, R. J. (1969). *Ibid.*, **21**, 9–17.
Sadtler Standard Spectra, published by Sadtler Research Laboratories, Inc., Philadelphia, Pa.
SAMMUL, O. R., BRANNON, W. L. & HAYDEN, A. L. (1964). *J. ass. off. agric. Chem.*, **47**, 918–991.
SHULGIN, A. T. (1964). *Experientia*, **20**, 366–367.
STOLL, A., TROXLER, F., PEYER, J. & HOFMANN, A. (1955). *Helv. chim. Acta*, **38**, 1452–1472.