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# Identification of the Major Impurities in the Illicit Manufacture of Tryptamines and Related Compounds

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**ABSTRACT:** *N*-[1-hydroxy-2-(3-indolyl)ethyl] pyrrolidine was detected as an impurity in *N*-[2-(3-indolyl)ethyl] pyrrolidine (tetramethylene tryptamine). 1-(*N,N*-diethlyamino)-2-(3-indolyl)ethan-1-ol together with 2-(3-indolyl)ethan-1-ol were detected as impurities 1-(*N,N*-diethylamino)-2-(3-indolyl)-ethane (*N,N*-diethyl tryptamine). These impurities indicate that the synthetic route was that of Misztal and such information is important.

**KEYWORDS:** toxicology, chemical analysis, tryptamine

Previous workers [*1-13*] have shown that the identification of intermediates in illicit preparations is a valuable guide to the synthetic route employed. In this paper we wish to present evidence concerning the method of synthesis of two tryptamines obtained from the identification of their intermediates. Analytical data are presented for these together with synthetic details of how they were produced.

The work was stimulated by receipt of a yellow powder that was submitted for analysis. Preliminary tests using thin-layer chromatography (TLC) and ultraviolet spectroscopy showed the powder to consist of two components, both being of the tryptamine type. Preparative TLC was used to prepare pure samples of each component that were then examined by gas chromatography/mass spectrometry (GC/MS) and shown to be *N*-[1-hydroxy-2-(3-indolyl)ethyl]pyrrolidine (III) and *N*-[2-(3-indolyl)ethyl]pyrrolidine (IV). (Details on the intermediates and reaction products designated Substances I to VIII are given in Fig. 1 and Table 1.) The identities of these components were confirmed by synthesis, and characterization of the synthetic products was achieved by using a combination of mass spectrometry, nuclear magnetic resonance spectroscopy, and infrared spectroscopy.

The nature of these compounds strongly suggested that the yellow powder was the product obtained from the illicit production of a substance [*14*] closely related to the hallucinogen diethyl tryptamine. The above mixture is entirely consistent with what would be obtained from the synthesis of tryptamines using indole as the starting material and following the reaction sequence shown in Fig. 2. Substance IV has been studied by various workers [*15-18*]; its synthesis by the method shown in Fig. 2 is based on the work of Speeter and Anthony

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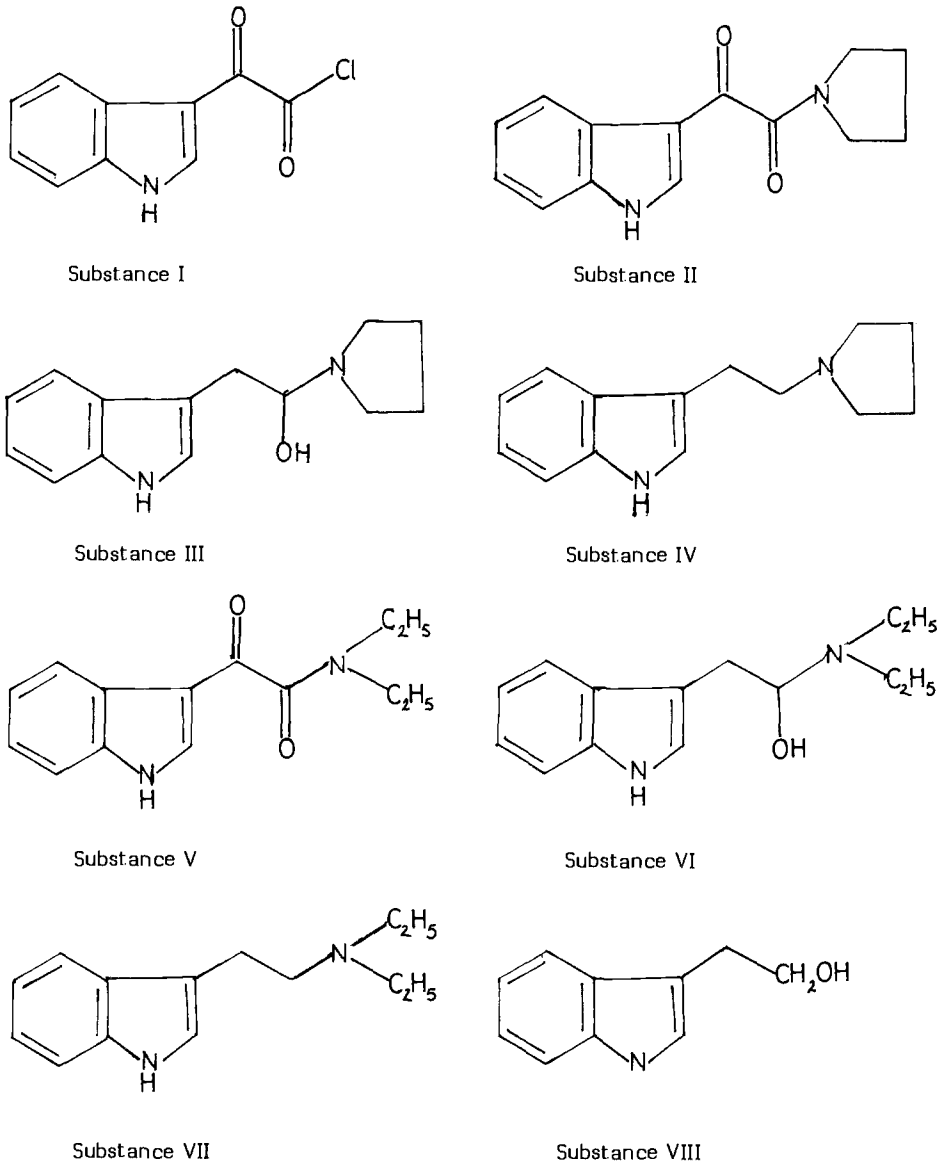



FIG. 1—*Tryptamines and their reaction intermediates (for compound names see Table 1).*

[*19*]. Incomplete reduction of 3-indolylglyoxylpyrrolidide (II) accounts for the presence of Substance III in the mixture analyzed.

As a result of these observations the analogous reactions using diethylamine in place of pyrrolidine were studied (see Fig. 3). The incomplete reduction of 3-indolylglyoxyldiethylamide (V) resulted in the formation 1-(*N,N*-diethylamino)-2-(3-indolyl)-ethan-1-ol (VI). Characterization of the products from the above reaction was carried out in the same way as for the yellow powder.

TABLE 1—*Tryptamines and their reaction intermediates.*[a]

| Compound | Substance Number | Molecular Weight |
|---|---|---|
| 3-Indolylglyoxyl chloride | I | 207.5 |
| 3-Indolylglyoxylpyrrolidide | II | 242 |
| *N*-[1-hydroxy-2-(3-indolyl)ethyl]pyrrolidine | III | 230 |
| *N*-[2-(3-indolyl)ethyl)pyrrolidine | IV | 214 |
| 3-Indolylglyoxyldiethylamide | V | 244 |
| 1-(*N,N*-diethylamino)-2-(3-indolyl)ethan-1-ol | VI | 232 |
| 1-(*N,N*-diethylamino)-2-(3-indolyl)ethane | VII | 216 |
| 2-(3-indolyl)ethan-1-ol | VIII | 161 |

[a]For diagrams of molecular structure see Fig. 1.

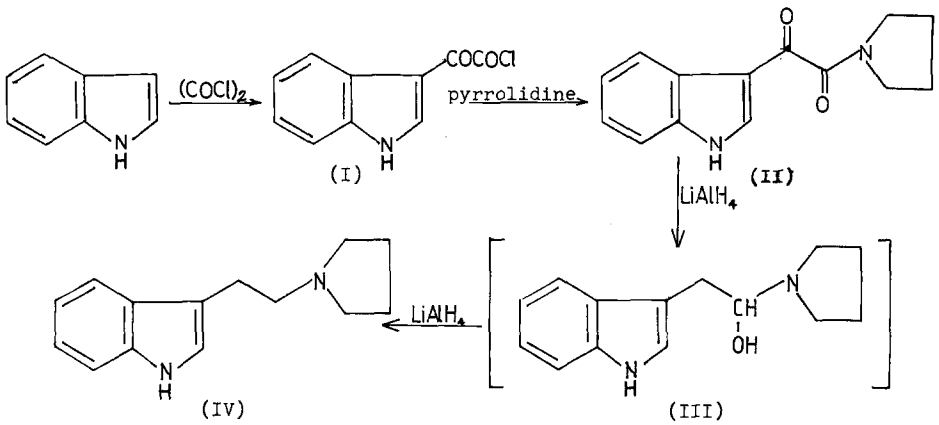



FIG. 2—*Reaction sequence in synthesis of tryptamines with indole as starting material.*

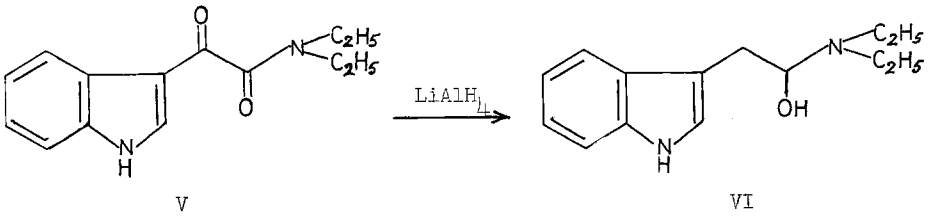
## Experimental Apparatus

### *Gas Chromatography/Mass Spectrometry*

The gas chromatographic conditions were 1.8-m (6-ft) glass column with an outside diameter of 6.3 mm (¼ in.) packed with 3% OV-17 on Chromosorb HP 80-100 mesh and operated isothermally at 260°C. The GC was interfaced to a VG 1212F quadrupole mass spectrometer (with a combined electron impact/chemical ionization source) via a single-stage glass jet separator held at a temperature of 230°C. The pertinent MS parameters were source temperature of 200°C and 70 eV used in the electron impact mode; chemical ionization spectra were obtained by using isobutane. Acquisition and processing of mass spectra were achieved automatically with a VG 2135 data system.

### *Proton Magnetic Resonance Spectra*

Proton magnetic resonance spectra were recorded on a Perkin Elmer R12B machine (60 MHz) locked via the double resonance accessory to tetramethysilane at 35°C. Samples were run in deuterochloroform except where otherwise stated.




V VI

FIG. 3—*Reaction sequence with diethylamine in place of pyrrolidine.*

*Infrared Spectra*

Infrared spectra were obtained from 13-mm KBr disks by using a Perkin Elmer 157 spectrophotometer.

*Thin-Layer Chromatography*

The chromatograms were run on silica gel plates (100 by 200 mm) that had previously been dipped in 10% 2*N* sodium hydroxide in methanol solution and oven-dried. The eluant consisted of a mixture of cyclohexane, toluene, and diethylamine in a 12:5:3 ratio; the components were visualized using Van Urk reagent.[3]

**Syntheses**

*N-[2-(3-Indolyl)ethyl]pyrrolidine*

Indole was dissolved in anhydrous diethyl ether and oxalyl chloride was added to the solution over 1/2 h while the temperature was maintained between 0 and 5°C. The precipitated yellow product of 3-indolylglyoxyl chloride (I) was stirred for a further hour in the cold, washed twice with 50 mL of dry ether, and then suspended in 50 mL of dry ether.

Pyrrolidine was added to the suspension over 1/2 h and stirring was continued until the yellow color disappeared. The product was collected by filtration, washed with ether and cold water, and recrystallized from ethanol to yield 7.0 g (68%) of Substance II (melting point, 221 to 223°C).

Lithium aluminum hydride (0.7 g) was suspended in 150 mL of dry ether and a suspension of Substance II in dry ether (20 mL) was added while stirring. The mixture was refluxed for 1 h; after this period water was added to decompose the unreacted lithium aluminum hydride. The inorganic precipitate was filtered off, made basic with 2*N* sodium hydroxide, and washed with ether; the combined ethers were then dried over anhydrous sodium sulfate. The crude product was examined by GC/MS and shown to be Substance IV contaminated with Substance III. The yield of Substance IV after preparative TLC and recrystallization from ethanol was 0.54 g (61%) (melting point, with sublimaton, 109 to 110°C). Sixty milligrams of Substance III were isolated from this preparation.

The above reduction was repeated using 0.4 g of lithium aluminum hydride and 2 g of Substance II. Working up as before gave Substance III as the major product contaminated with Substance IV.

The gas chromatogram showed the ratio of the two components to be on the order of 85% Substance III to 15% Substance IV. Preparative TLC was used to isolate a pure sample of Substance III.

[3]5 g of *p*-dimethylamino benzaldehyde in 250 mL of ethanol mixed with 170 mL of concentrated hydrochloric acid and made up to 500 mL with water.

N,N-*Diethyl Tryptamine*

Indole was dissolved in anhydrous ether (75 mL) and cooled to 0 to 5°C and oxalyl chloride was added over ½ h. The cold mixture containing the yellow crystalline product was stirred for an hour, then washed as before.

The washed product was suspended in fresh dry ether and diethylamine was added, stirring being continued until the yellow color had disappeared. The crystalline product was washed as before and recrystallization from ethanol afforded 7.6 g of Substance V (yield, 86%; melting point, 172 to 173°C).

Lithium aluminum hydride (0.4 g) was suspended in dry ether (50 mL) and a suspension of Substance V (2 g) in 10 mL of dry ether was added while stirring. The mixture was refluxed for 1 h; working up in the usual way gave Substance VI as the major product, together with minor amounts of *N,N*-diethyl tryptamine (VII) and 2-(3-indolyl)ethan-1-ol (VIII).

## Results and Discussion

*3-Indolylglyoxylpyrrolidide (II)*

The ultraviolet spectra of 3-indolylglyoxylamides II and V are highly characteristic; since they have high extinction coefficients, their presence may be readily detected in illicit mixtures. At acidic pH the spectrum exhibits three maxima at 247, 265, and 316 nm; in alkaline media two maxima occur, at 269 and 338 nm (Fig. 4).

The mass spectrum of Substance II (Fig. 5) exhibits a weak molecular ion at *m/e* 242 with the base peak (*m/e* 144) arising from β cleavage to the pyrrolidine nitrogen. A further loss of carbon monoxide produces the indolyl ion *m/e* 116. The infrared spectrum of Substance II (Fig. 6) is in good agreement with those obtained by Kram et al [*6*] for 3-indolylglyoxyldimethylamide and Substance V.

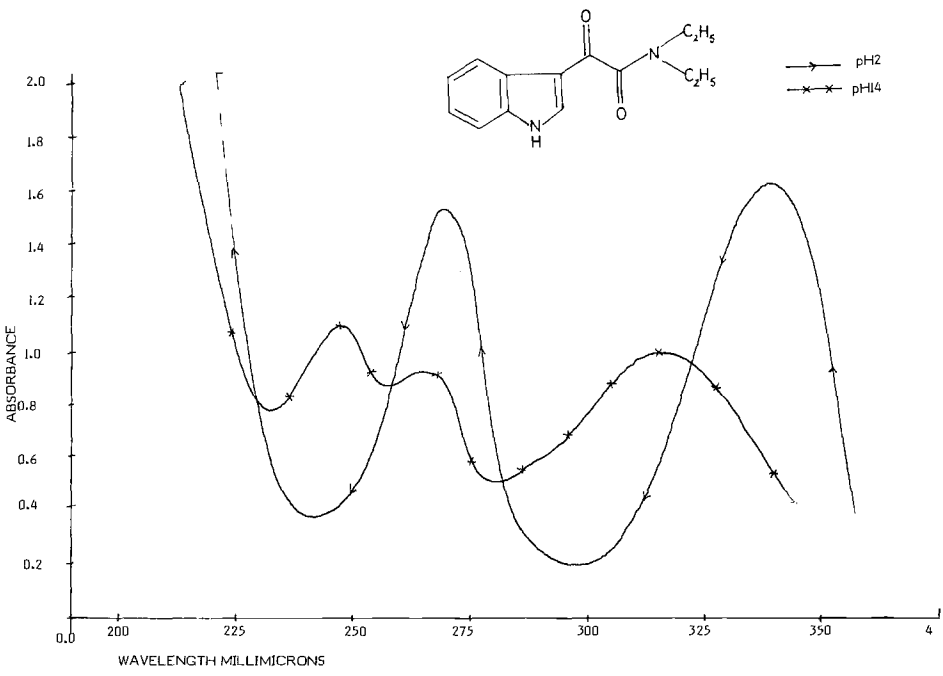



FIG. 4—*Ultraviolet spectra of Substance V at differing pH values.*

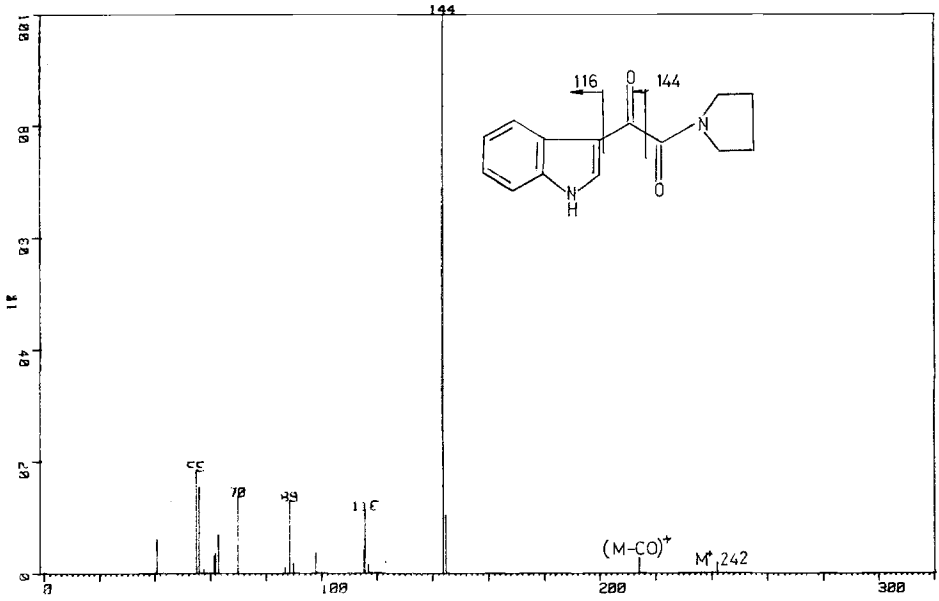



FIG. 5—*Mass spectrum of Substance II.*

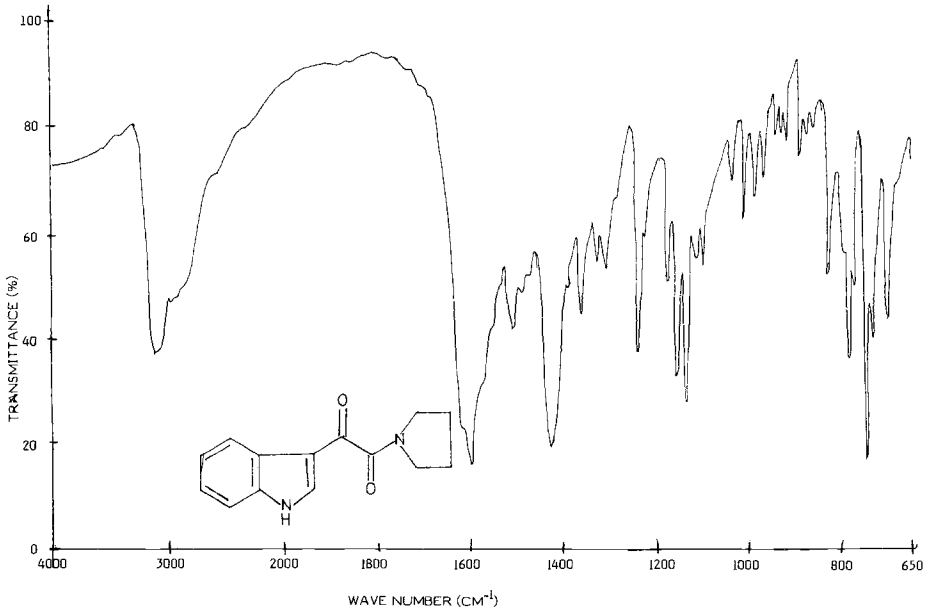



FIG. 6—*Infrared spectrum of Substance II.*

A simple proton magnetic resonance spectrum (Fig. 7) was obtained from Subtance II in dimethyl sulfoxide (DMSO). The single proton singlet at 8.23 ppm is due to the proton $\alpha$ to the indolyl nitrogen, and the single proton multiplet centered at 8.15 ppm arises from the benzene ring proton $\beta$ to the indolyl nitrogen. The three-proton multiplet at 7.2 to 7.7 ppm represents the remaining aromatic protons. The four-proton quartet centered at 3.45 ppm is due to the protons $\alpha$ to the pyrrolidine nitrogen. The remaining four protons of the pyrrolidine moiety gives rise to the complex multiplet centered at 1.82 ppm.

N-*[2-(3-Indolyl)-ethyl]pyrrolidine (IV)*

The mass spectrum of Substance IV (Fig. 8) exhibits the ions *m/e* 130 and *m/e* 144, corresponding to the loss of the *N*-methylene pyrrolidine and the pyrrolidine moieties, respec-

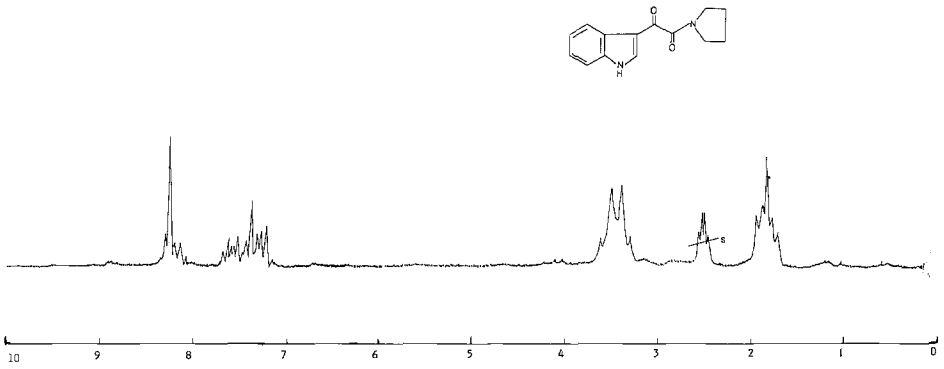



FIG. 7—*Proton magnetic resonance spectrum of Substance II (s = impurity in dimethyl sulfoxide—hexadeuterated).*

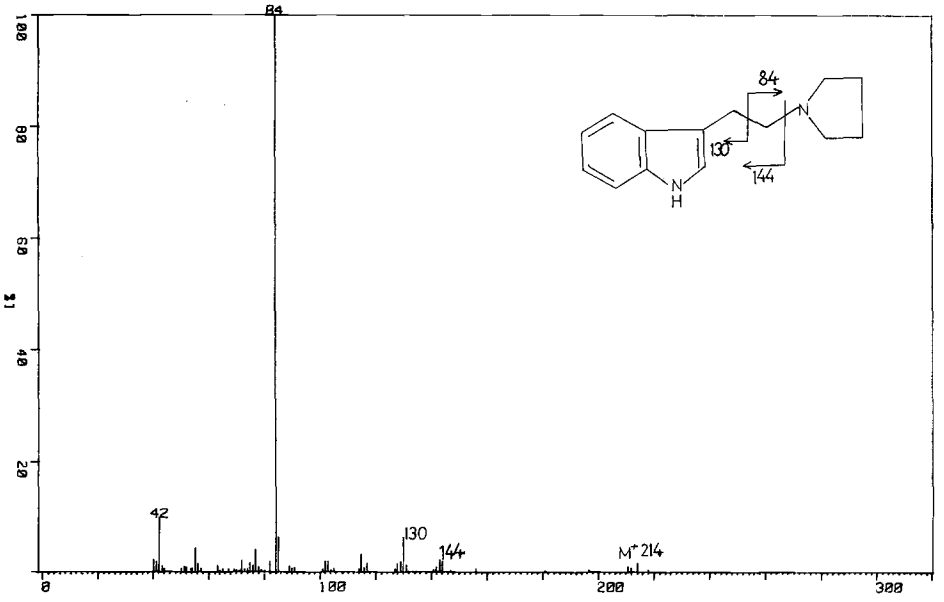



FIG. 8—*Mass spectrum of Substance IV.*

tively. Ions at *m/e* 84 (base peak) and 42 were observed. These have been reported for *N*-substituted pyrrolidines [*20*], the 84 ion arising from $\beta$ cleavage to the pyrrolidine nitrogen while the 42 ion is attributed to a $C_2H_4N^+$ species. The chemical ionization spectrum of Substance IV confirmed that the weak 214 ion is in fact the molecular ion since an intense $(MH)^+$ ion at *m/e* 215 was observed.

The infrared spectrum of Substance IV (Fig. 9) shows a marked similarity to that of diethyl tryptamine, the slight differences in the 1000 to 1260 $cm^{-1}$ region of the spectrum can be assigned to the pyrrolidine ring.

The proton magnetic resonance spectrum of Substance IV (Fig. 10) gives a broad signal for the single indolyl imino hydrogen at 8.30 ppm and a complex set of multiplets for the five aromatic protons at 6.95 to 7.80 ppm [*6*]. The $A_2B_2$ four-proton pattern centered at 2.90

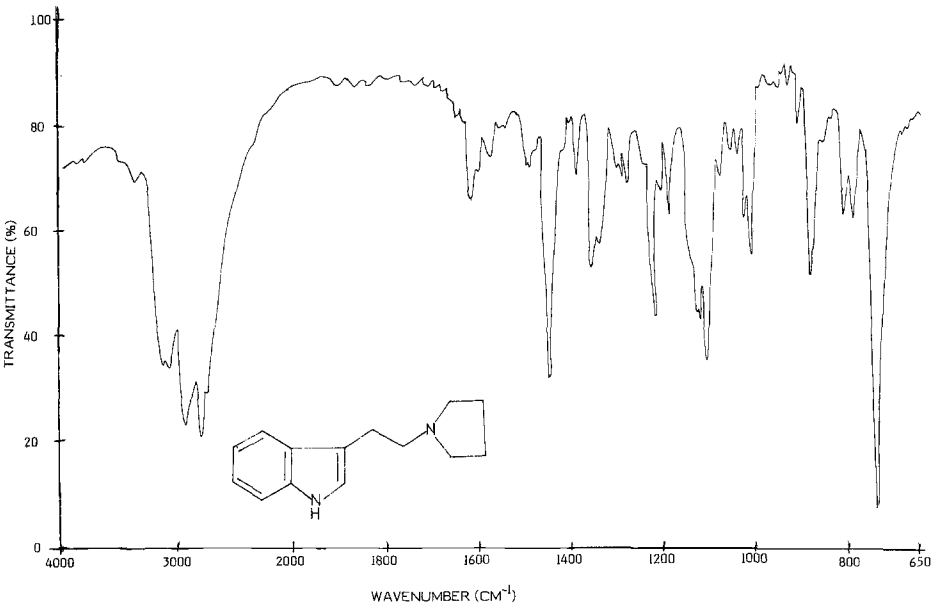



FIG. 9—*Infrared spectrum of Substance IV.*

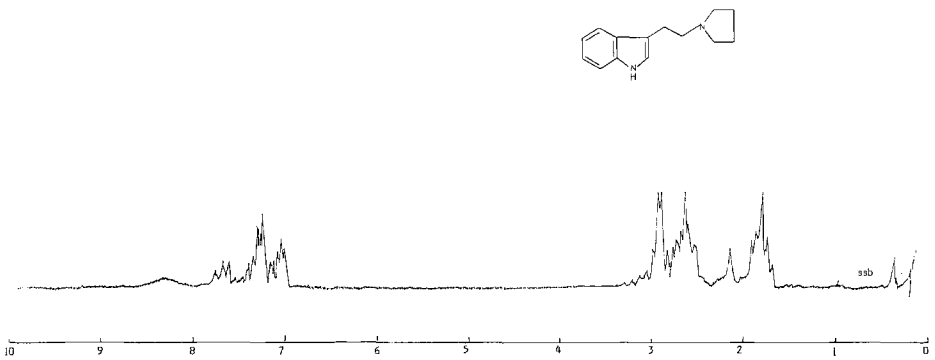



FIG. 10—*Proton magnetic resonance spectrum of Substance IV (ssb = spinning side band from tetramethylsilane signal).*

ppm arises from the methylene protons of the indolyl side chain. The four-proton multiplet at 2.63 ppm can be assigned to the four methylenic protons of the pyrrolidine ring $\alpha$ to the heteroatom. The remaining four protons of the pyrrolidine ring exhibit a signal centered at 1.80 ppm.

### N-*[1-Hydroxy-2-(3-indolyl)ethyl]pyrrolidine (III)*

The mass spectrum of Substance III (Fig. 11) has a base peak at *m/e* 212, which corresponds to the loss of water from the molecule; an identical ion in the chemical ionization mode indicates that this is a fragment ion and not the molecular or pseudo-molecular ion. The ion at *m/e* 130 indicates that the hydroxy group is on the "1" position; this is supported by the absence of an ion at *m/e* 84.

Comparison of the infrared spectrum of Substance III (Fig. 9) with that of Substance IV (Fig. 12) shows that the former has two additional absorption bands at 3300 $cm^{-1}$ and 1060 $cm^{-1}$. These bands are consistent with the presence of a hydroxyl function.

The proton magnetic resonance spectrum of Substance III (Fig. 13) shows a broad single proton absorption at 8.20 ppm for the imino proton and two multiplets for the five aromatic protons centered at 7.73 and 7.25 ppm. A complex single proton absorption consisting of an overlapping doublet of doublets centered at 5.10 ppm can be assigned to the methine hydrogen. This complex splitting pattern arises from the nonequivalence of the methylene protons of the indolyl side chain. The six-proton multiplet at 3.45 to 2.40 ppm is due to the indolyl side chain methylenic hydrogens together with those of the pyrrolidine ring $\alpha$ to the heteroatom. The four remaining pyrrolidine protons give rise to the multiplet centered at 1.78 ppm.

### *1-(*N,N-*Diethylamino)-2-(3-indolyl)-ethan-1-ol (VI)*

The mass spectrum of Substance VI (Fig. 14) exhibits a base peak at *m/e* 214 that, as in the case of Substance III, represents the loss of water from the molecule. The chemical

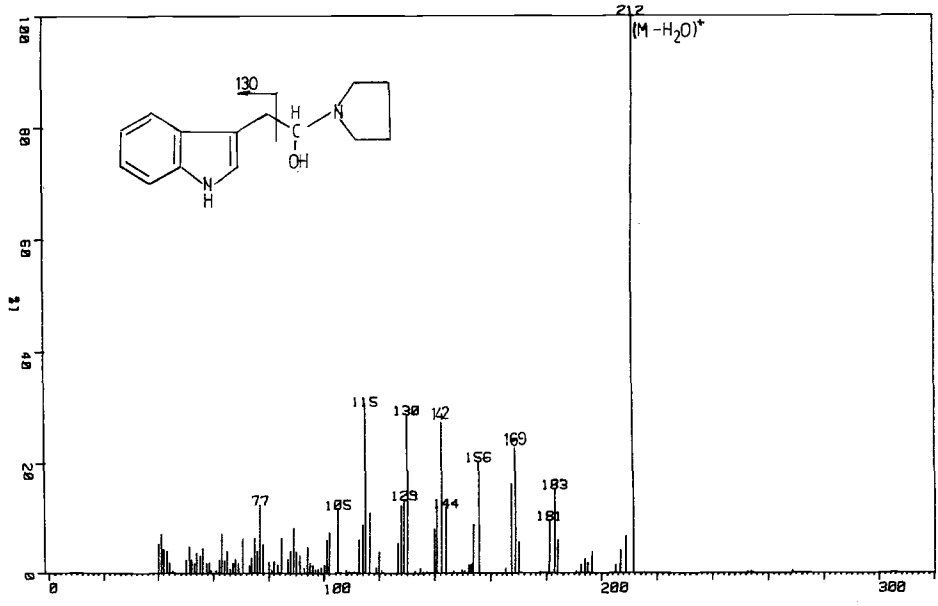



FIG. 11—*Mass spectrum of Substance III.*

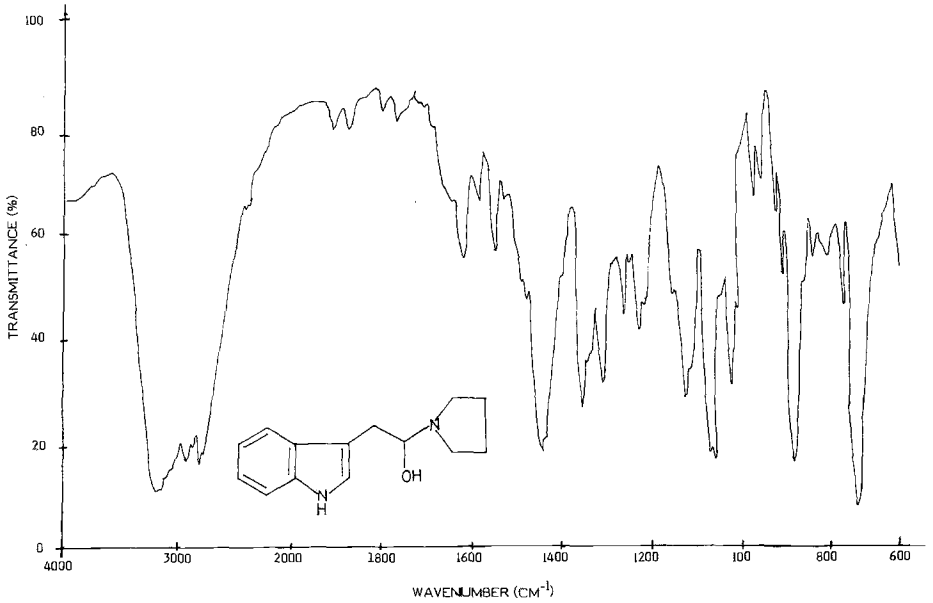



FIG. 12—*Infrared spectrum of Substance III.*

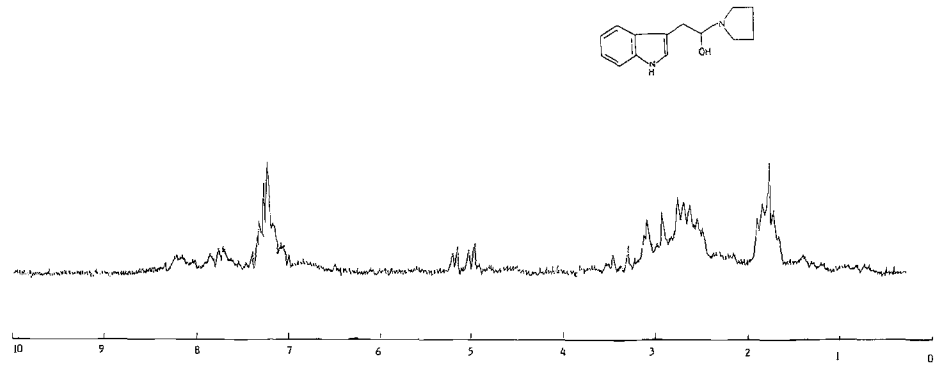



FIG. 13—*Proton magnetic resonance spectrum of Substance III.*

ionization spectrum again showed the 214 ion as the base peak. The low intensity of the *m/e* 86 ion compared with that of the *m/e* 130 ion indicates that the "1-hydroxy" assignment is reasonable. The 199 ion corresponds to loss of a methyl group from the 214 ion—that is, $\beta$ cleavage to the amino nitrogen.

The infrared spectrum of Substance VI (Fig. 15) when compared with that of diethyl tryptamine shows that the former has two additional absorption bands at 3300 $cm^{-1}$ and 1050 $cm^{-1}$. These bands indicate the presence of a hydroxyl group.

The proton magnetic resonance spectrum of Substance VI (Fig. 16) was similar to that of Substance III, again displaying the broad single imino proton signal at 8.10 ppm and two complex multiplets at 7.80 and 7.28 ppm for the five aromatic protons. The methine proton appears as a triplet centered at 5.05 ppm. A six-proton multiplet at 2.70 ppm can be at-

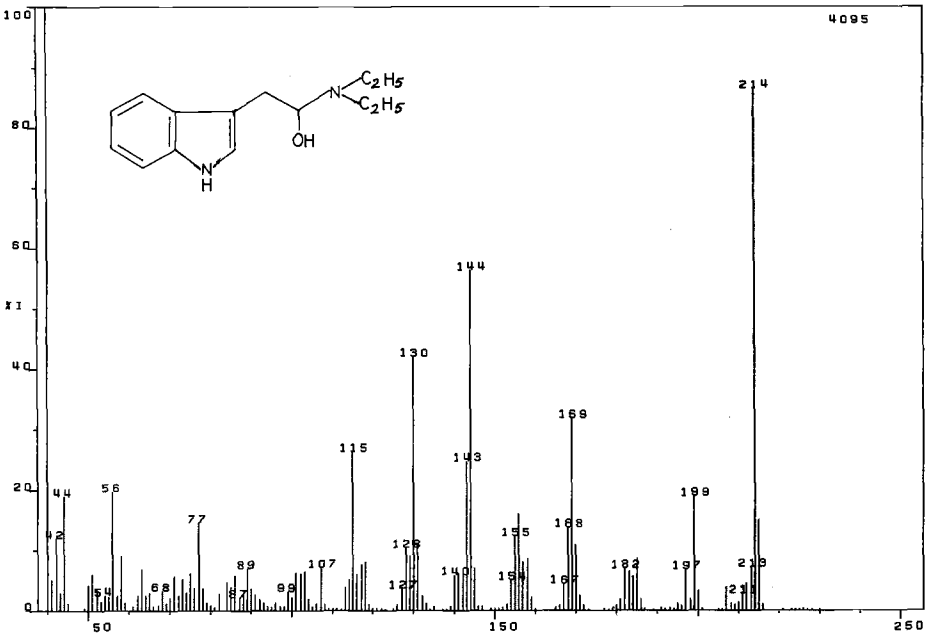



FIG. 14—*Mass spectrum of Substance VI.*

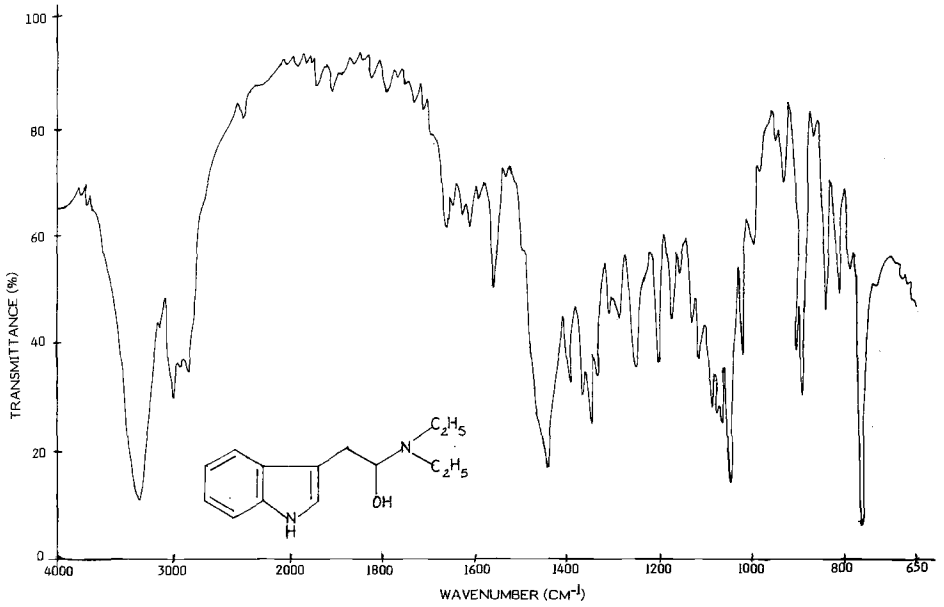



FIG. 15—*Infrared spectrum of Substance VI.*

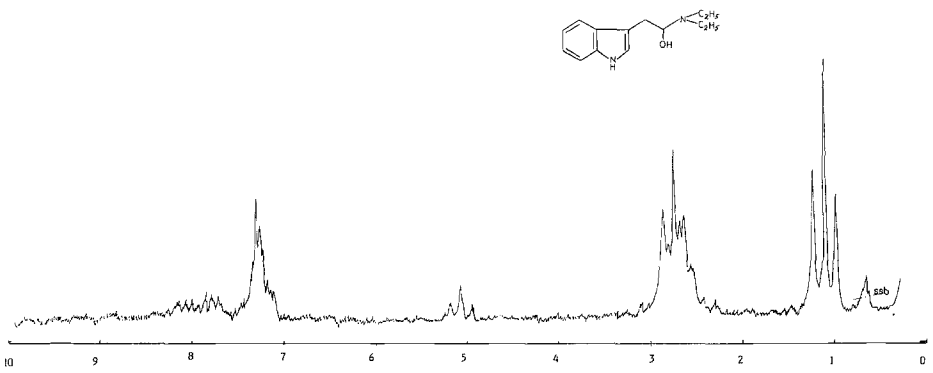



FIG. 16—*Proton magnetic resonance spectrum of Substance VI (ssb = spinning side band from tetramethylsilane signal).*

tributed to the methylene protons, and the six-proton triplet at 1.10 ppm is due to the two methyl groups.

### *2-(3-Indolyl)-ethan-1-ol (VIII)*

Any small quantity of Substance I that hydrolyses to the acid and is then carried through to the lithium aluminum hydride reduction stage will result in Substance VIII. This product has been seen before by Ruebsamen and Mueler [*21*]; although it was only present in minute amounts we were able to obtain its mass spectrum (Fig. 17). This impurity, however, is less specific in determining the synthetic route since Substance VIII is used as a precursor in the synthesis of tryptamines in the method of Vitali and Mossini [*22*].

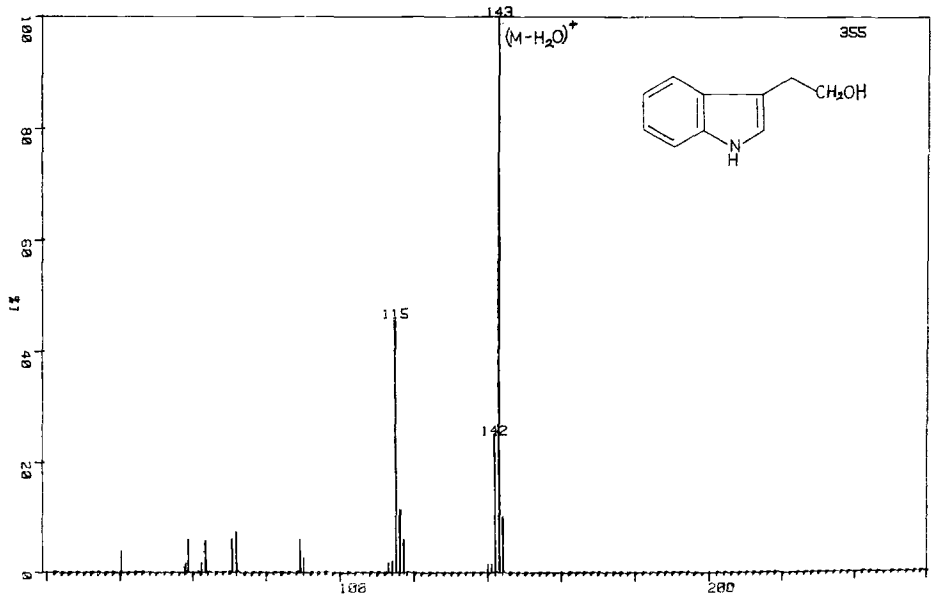



FIG. 17—*Mass spectrum of Substance VIII.*

The thin-layer chromatographic behavior of the reduction products for both reactions was similar in that the tryptamines (Substances IV and VII) gave blue spots on being sprayed with Van Urk reagent ($R_f$ approximately 0.55) and the hydroxy compounds (Substances III and VI) gave pink spots ($R_f$ approximately 0.35).

Consideration of the electronic and steric factors together with the likely transition states involved during the lithium aluminum hydride reduction would indicate that the 1-hydroxy isomer will predominate. However, if the 2-hydroxy isomer does occur in small amounts the products analyzed by GC/MS would be the same in each case. Water elimination is kinetically favorable since the double bond formed is fully conjugated with the aromatic ring system. Water elimination from the 1- and 2-hydroxy isomers results in the same indolylenamine, namely 1-amino-2-(3-indolyl)-ethylene.

It is worthwhile bearing in mind that in the clandestine laboratory the facilities and reagents are often of poor quality and the chemist may have little experience of the reaction being conducted. With this in mind we conducted the syntheses described using a deficiency of lithium aluminum hydride.

If the tryptamine synthesis was performed by an inept chemist, using inactive lithium aluminum hydride in "wet" solvents, then one may isolate the types of intermediates described above together with the precursors.

*Acknowledgment*

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