in 8 drops of methanol was heated to boiling and 1 ml of ethyl acetate was added. After standing in the refrigerator for 1 day, this gave 25 mg of crystals: mp 135-137°. This was recrystallized four times to give 0.5 mg of constant mp 136-138° (no depression in melting point when admixed with the cinchonidine salt prepared from senecic acid: mp 136-138°). The infrared (KBr) spectra of the two samples were identical. The synthetic cinchonidine salt was dissolved in dilute hydrochloric acid and extracted with ether. Evaporation of the extract and crystallization from ether-petroleum ether gave crystals, mp 146-148°, and no depression resulted when admixed with senecic acid. The infrared (KBr) spectra of the synthetic sample and senecic acid were identical in every respect.

Acknowledgment.—The authors gratefully acknowledge support of this work by a grant from the Robert A. Welch Foundation. We are indebted to Dr. C. C. J. Culvenor, C.S.I.R.O., Melbourne, Australia, for a sample of senecione.

![Diagram](image-url)
with ethyl acetate afforded an oil, which was separated.

Benzene was found to be identical with bufotenine in all

The minor bases obtained from the ether-methyl

alcohol eluates were characterized by paper chromatog-

raphy as: S,N-dimethyltryptamine,7 and \( N,N\)-dimethyltrypt-

amine oxide.7

The mixture of bases obtained upon washing the

alumina column with methyl alcohol was eventually separated into pure components by rechromatography on cellulose powder and on Brockmann alumina. The less polar compounds eluted out of the cellulose column through the formation of their picrates and fractional crystallization of these derivatives from acetone. Gramine picrate obtained from the acetone mother liquor was recrystallized from ethyl alcohol and the crystalline material, mp 138-143°, was identical with the \( N,N\)-dimethyltryptamine oxide prepared from the corresponding base by treatment with hydrogen peroxide and gave identical results.

The major bases obtained from the ether-methyl

alcohol eluates were separated by chromatography as \( \text{5-methoxy-} N,N\)-dimethyltryptamine,4 bufotenine,7

\( N,N\)-dimethyltryptamine,7 and \( N,N\)-dimethyltrypt-

amine oxide.7

The occurrence of several tertiary amine oxides in a single plant species is of considerable biogenetic interest because the amine oxides are probably the key intermediates in certain alkaloid biosyntheses.8

Of the series of nine tryptamines having the general formula II, all except 5-methoxytryptamine are known
to occur in nature. These observations together with the present isolation of two tertiary amine oxides, gramine, and four other secondary and tertiary bases from a single natural source are consistent with the pathway of tryptophan metabolism shown in Scheme II.

It is pertinent to mention in this connection the recent paper by Ferris and Gerwe. They have shown that the following are the stages in the iron-catalyzed demethylation of trimethylamine oxide. Stages 2 and 3 are shown in formula (1).

\[
\begin{align*}
\text{(CH}_3\text{)}_3\text{N}^+ + \text{Fe}^{\text{II}} & \rightarrow \text{(CH}_3\text{)}_3\text{N}^+ + \text{Fe}^{\text{III}} + \text{H}_2\text{O} \\
\text{(CH}_3\text{)}_2\text{N}^+ + \text{Fe}^{\text{II}} + \text{H}^+ & \rightarrow \text{(CH}_3\text{)}_2\text{N}^+ + \text{Fe}^{\text{III}} \\
\text{(CH}_3\text{)}_2\text{NHCH}_2^+ + \text{CH}_3\text{NOH} & \rightarrow \text{(CH}_3\text{)}_2\text{NHCH}_2^+ + \text{(CH}_3\text{)}_2\text{N}^+ \\
\end{align*}
\]

\[(4)\]

4 are consistent with the formation of both tertiary and secondary amines (the latter is presumably formed via the carbinol amine base) from tertiary amine oxides and has been further tested in the present study with other amine oxides. When treated with aqueous ferrous sulfate at ordinary temperatures, N,N-dimethyltryptamine oxide was rearranged to give a mixture of formaldehyde, N-methyltryptamine, and indole-3-acetaldehyde. This determination lends further credence to the metabolic sequence of tryptophan envisaged in the above scheme.

The significance of the foregoing results lies further in the mode of formation of certain complex alkaloid patterns. Our recent paper may be cited in this connection. While suggesting a hypothetical biogenetic route common to all indole bases, we contend that entities (IV to VI), formed from III, via the corresponding N-oxide, are presumably the branch points enroute to different indole structure patterns. The present and previous laboratory analogies amply support this scheme and advocate it as a working hypothesis for further biochemical testing. (See Scheme III.)

**Experimental Section**

All melting points were uncorrected and determined in open capillary. Infra-red spectra were taken in a Perkin-Elmer double-beam spectrophotometer and ultraviolet spectra were recorded in a Beckman DU spectrophotometer. Microanalyses were performed by Dr. Alfred Bernhardt, Mikroanalytisches Laboratorium im Max-Planck-Institut fur Kohlenforschung, Mulheim (Ruhr). Isolation of the Alkaloids.—Dried and finely ground whole plant (4 kg) of *D. pulchellum* was treated with benzene under reflux in a Soxhlet apparatus for 8 hr. The benzene extract was kept aside for further examination for alkaloids and neutral components. The defatted plant material was extracted with alcohol (95%) containing acetic acid (2%) in a percolator at room temperature for 4 weeks. The alcoholic solution was concentrated under reduced pressure to give a viscous brown slurry (170 g) which was poured into aqueous acetic acid (2%, 200 ml) with stirring and the mixture kept overnight at ordinary temperature. Suspended impurities were filtered off and the filtrate shaken with chloroform (three 500-ml portions) which removed 1.7 g of the material. The pH of the aqueous solution was brought to 9 with ammonia and the liberated bases were extracted with chloroform. The chloroform solution was washed with water and dried (CaCl₂); solvent was removed under reduced pressure giving a thick slurry (ca. 15 g).

**Chromatographic Resolution of the Bases on Alumina.**—The total basic extractable was dissolved in methanol (10 ml) and chromatographed on Brockmann alumina (35 × 4 cm). The results are presented in Table I. Elution was carried out with 100-ml portions of petroleum ether (bp 40–40°C), petroleum ether–benzene (90:10, 80:20, 50:50), benzene, benzene–ether (85:5, 90:10, 80:20, 50:50, 20:80); and methanol; 40-ml fractions were collected. The course of separation was followed by paper chromatography (ascending type) using isopropl alcohol–ammonia–water (9:1:1) as the solvent system and 0.5% solution of p-dimethylaminobenzaldehyde in 1 N hydrochloric acid as the spraying reagent.

**Table I**

<table>
<thead>
<tr>
<th>Fraction</th>
<th>Residue, g</th>
<th>Rt values and color developed</th>
</tr>
</thead>
<tbody>
<tr>
<td>2–3</td>
<td>4.62</td>
<td>0.97 blue</td>
</tr>
<tr>
<td>6–8</td>
<td>3.00</td>
<td>0.96 blue, 0.92 red</td>
</tr>
<tr>
<td>9–11</td>
<td>0.74</td>
<td>0.97 blue, 0.916 blue</td>
</tr>
<tr>
<td>20–25</td>
<td>0.016</td>
<td>0.92 blue, 0.82 red</td>
</tr>
<tr>
<td>27–33</td>
<td>0.472</td>
<td>Four spots: 0.92 blue, 0.86 blue, 0.62 red</td>
</tr>
<tr>
<td>37–40</td>
<td>0.322</td>
<td>0.86 blue, 0.56 red</td>
</tr>
</tbody>
</table>

**5-Methoxy-N,N-dimethyltryptamine.**—Fractions 2–11 were combined and concentrated under reduced pressure. The residue (8.36 g) upon crystallization from ether–light petroleum ether (1:1) gave colorless plates: mp 69°C (lit. mp 69°C). Infrared, \( \text{CHN} \), 293 (NH), 3.55 (NMe), 6.19 (aromatic OMe); ultraviolet, \( \text{max} \), 224, 277, and 296 nm (log e 4.46, 3.84, and 3.76, respectively).

**Anal.** Caled for \( \mathrm{C_{12}H_{11}NO} \): C, 71.55; H, 8.25; 1-OMe, 14.22; \( \text{H}^{+} \), 0.46. Found: C, 70.47; H, 8.29; 1-OMe, 14.22; \( \text{H}^{+} \), 0.46.

The base gave a methiodide which crystallized from acetone-methyl alcohol (9:1): mp 181–182°C.

**Anal.** Caled for \( \mathrm{C_{12}H_{11}NO} \): C, 46.66; H, 5.83; N, 7.77; I, 35.25. Found: C, 46.55; H, 5.88; N, 7.65; I, 35.35.

The base picrate was crystallized from methyl alcohol in orange-yellow needles, mp 172°C.

**Anal.** Caled for \( \mathrm{C_{12}H_{11}NO} \cdot \mathrm{C_{2}H_{5}OH} \): N, 15.66. Found: N, 15.60.

**5-Methoxy-N,N-dimethyltryptamine.**—Fractions 27–33 were combined, the solvent was removed under reduced pressure, and the crude mixture of bases obtained was divided into few small portions. To one of these portions in dry ether, hydrogen chloride gas was passed, and the crude hydrochloride which separated was crystallized from methyl alcohol in needles: mp 167°C (lit. mp 165–166°C). Ultraviolet, \( \text{max} \), 223, 237, and 292 μm.

**Anal.** Caled for \( \mathrm{C_{12}H_{11}NO} \cdot \mathrm{C_{2}H_{5}OH} \): N, 15.66. Found: N, 15.98.

**Boufotine, N,N-Dimethyltryptamine, and N,N-Dimethyltryptamine Oxide.**—A sample from fractions 27–33 was subjected to paper chromatography on Whatman No. 1 paper and an isopropyl alcohol–ammonia–water (9:1:1) system was used for development. The entire width of the paper was utilized. Three zones were cut at Rt values (0.91, 0.52, 0.63) determined with marker strips. Each zone was eluted with ethyl alcohol. The three solutions obtained this way were used for final paper chromatographic determinations. Tentative identification of these bases was substantiated by chromatography with authentic samples.

The Rt values of the seven alkaloids isolated so far were de-
TABLE II
PAPER CHROMATOGRAPHIC DATA OF D. pulchellum ALKALOIDS

<table>
<thead>
<tr>
<th>Compd</th>
</tr>
</thead>
<tbody>
<tr>
<td>$N,N$-Dimethyltryptamine</td>
</tr>
<tr>
<td>$N,N$-Dimethyltryptamine oxide</td>
</tr>
<tr>
<td>Gramine</td>
</tr>
<tr>
<td>Bufotetine</td>
</tr>
<tr>
<td>5-Methoxy-$N$-methyltryptamine</td>
</tr>
<tr>
<td>5-Methoxy-$N,N$-dimethyltryptamine</td>
</tr>
<tr>
<td>5-Methoxy-$N,N$-dimethyltryptamine oxide</td>
</tr>
</tbody>
</table>


dimethyltryptamine oxide) on the thin layer chromatogram using alumina as the adsorbent and chloroform–methyl alcohol (90:10) as the developer. The red picrate was recrystallized from ethyl alcohol in needles, mp 158°.

Anal. C$_{15}$H$_{22}$N$_{2}$O$_{3}$; C$_{15}$H$_{24}$N$_{2}$O requires: C, 49.24; H, 4.53; N, 15.33. Found: C, 49.24; H, 4.32; N, 15.08.

Demethylation of 5-Methoxy-$N,N$-dimethyltryptamine.—5-Methoxy-$N,N$-dimethyltryptamine (200 mg) was dissolved in dry benzene (20 ml) to which anhydrous aluminum chloride (1.1 g) was added. The mixture was refluxed on a water bath for 6 hr and cooled in ice; aluminum chloride was decomposed with water. The benzene layer was washed with water and dried (Na$_2$SO$_4$); solvent was removed under reduced pressure. The residue, a brown gum (177 mg), $R_f 0.84$ (IPA), gave a picrate which was crystallized from methanol in yellow needles, mp 177–178°, identical in all respects with bufotinopicrate.

Preparation of 5-Methoxy-$N,N$-dimethyltryptamine Oxide.—A solution of 5-methoxy-$N,N$-dimethyltryptamine (500 mg) in ethyl alcohol (2 ml) was treated with a solution (3 ml) of 50% hydrogen peroxide in ethyl alcohol (2 ml in 5 ml). The mixture was kept at room temperature for 2 hr, then diluted with ether when flocculent solid separated. The hygroscopic amine oxide ($R_f 0.80$; BAW) yielded a red picrate from ethyl alcohol: mp 158–159°.

Anal. Calcd for C$_{15}$H$_{22}$N$_{2}$O$_{3}$: C, 49.54; H, 4.33; N, 15.73. Found: C, 49.54; H, 4.27; N, 15.73. 

Rearrangement$^a$ of 5-Methoxy-$N,N$-dimethyltryptamine Oxide with Ferrous Sulfates.—A solution of the alcohol (94 mg) in aqueous acetic acid (5 ml) and ferrrous sulfate heptahydrate (195 mg) in water (10 ml) was kept for 40 min over a steam bath (60–65°) after which the mixture was cooled in ice.

Detection of Formaldehyde.—To an aliquot of the above solution an aqueous solution of dinitrophenylhydrazine (0.5%, 50 ml) was added; the mixture was vigorously shaken and kept at room temperature overnight. The formaldehyde dinitrophenyldrazide which precipitated was filtered, washed with water, and dried in vacuo: mp 157–158°.

The melting point of the picrate of this compound and the corresponding picrates were separated by fractional crystallization from methyl alcohol in which the picrate of the latter compound was more soluble.

Rearrangement of N,N-Dimethyltryptamine Oxide$^b$ with Ferrous Sulfates.—The preceding experiment was repeated with N,N-dimethyltryptamine oxide (140 mg) and ferrous sulfate (212 mg); the aldehyde compounds formed were found to be a mixture of formaldehyde and indole-3-acetaldehyde.$^c$

The more polar components were obtained by washing the alumina column with ether–methyl alcohol (90:10) and identified as 5-methoxy-N,N-dimethyltryptamine and 5-methoxy-N,N-dimethyltryptamine oxide ($R_f 0.86$, 0.97; IPA). The corresponding picrates were separated by fractional crystallization from methyl alcohol in which the picrate of the latter compound was more soluble.

$^{a}$ Rearrangement of this type was first investigated by Hornig et al.; cf. ref 7.

$^{b}$ The ultraviolet absorption maxima and minima are comparable with those of 10-methoxy-3,4,6-tetrahydro-3-carboline.

$^{c}$ The latter was identified as the 3,4-dihydro-3-carbonifer uniform derivative. The DNP reagent was prepared by dissolving 2,4-DNP (2 g) in aqueous hydrochloric acid (2 N, 500 ml). The ferrous sulfate rearranged solution was shaken vigorously with the above DNP reagent and kept for 4 hr at room temperature; the mix-


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(14) Rearrangement of this type was first investigated by Hornig et al.; cf. ref 7.

(15) The ultraviolet absorption maxima and minima are comparable with those of 10-methoxy-3,4,6-tetrahydro-3-carboline; see ref 14.

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(95: 5) 10 (80: 20)

11-15 Brown oil (142 mg) $R_f 0.69$, 0.85, BAW

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11-15 Brown oil (142 mg) $R_f 0.69$, 0.85, BAW
Intramolecular Hydrogen Bonding in cis-2-Phenylmercaptoindanol

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Received November 19, 1965

The cis- and trans-2-phenylmercaptoindanols exhibit some interesting differences in their physical and chemical properties which can be attributed to the existence of an intramolecular hydrogen bond in the cis isomer.

Experimental Section

Determination of Infrared Spectra.—The infrared spectra of the cis- and trans-2-phenylmercaptoindanols, \( \text{mp} \) 71.5 and 101°, respectively, were determined in a variable-path cell by means of a Perkin-Elmer Model 237 spectrophotometer. Carbon tetrachloride was employed as solvent and the concentrations were varied between 0.00625 and 100 \( M \). The temperature range of the measurements was 25 ± 2°. The absorbances of the "free" \( \text{OH} \) stretching frequency were measured at 3600 cm\(^{-1}\) in the case of both isomers. As will be shown below, the "free" \( \text{OH} \) band is actually believed to be a "5-bonded" \( \text{OH} \) association. Absorbances of the "sulfide-bound" \( \text{OH} \) were determined at 3470 cm\(^{-1}\) in the case of the rather simple band of the cis compound, and at 3510 cm\(^{-1}\) for the trans isomer. The results of these measurements are listed in Table I. The infrared spectra of the two isomers were also examined at a single concentration of 0.005 \( M \) in carbon tetrachloride using a 1-cm cell and a Perkin-Elmer Model 521 spectrophotometer, and the bands, together with those of the corresponding sulfoxides and sulfones, are listed in Table II.

Determination of Ultraviolet Spectra.—The ultraviolet spectra were determined by means of a Zeiss PMQ II spectrophotometer using 1-cm cells, and spectrophotometry cyclohexane and purified 95\% ethanol as solvents. The spectra exhibited one strong band at 253–258 \( m\mu \), and peaks of a weaker and partially hidden band at 272 \( m\mu \). These results are summarized in Table III.

Spontaneous Decomposition of cis-2-Phenylmercaptoindanol.

On several occasions it was noted that a sample of cis-2-phenylmercaptoindanol, purified satisfactorily by crystallization from ethanol or hexane, decomposed upon standing with the production of a strong thiphenol-like odor. In order to ascertain the nature of this decomposition a 0.202-g sample of pure compound was kept for 2 months in a closed container. At the end of this period the crystals became oily and there was noted a strong thiophenol-like odor. The mixture was carefully chromatographed on a silica gel column using chloroform as eluent. The eluted material consisted of at least two components, approximately 180 mg of unchanged starting material, and approximately 90 mg of a material, the infrared spectrum of which showed an absence of the hydroxyl function and strong absorption at 1700 cm\(^{-1}\) characteristic of a ketone. The material also showed other bands at 1605 and 1585 cm\(^{-1}\) characteristic of the 1-indanone spectrum. The material gave a 2,4-dinitrophenydrazone of mp 265–268° which did not depress the melting point of an

Acknowledgement.—The junior author (B. M.) is grateful to East India Pharmaceutical Works Ltd., Calcutta, for financial assistance during the tenure of this work.

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