Opium Alkaloids III. Isolation of α-Allocryptopine

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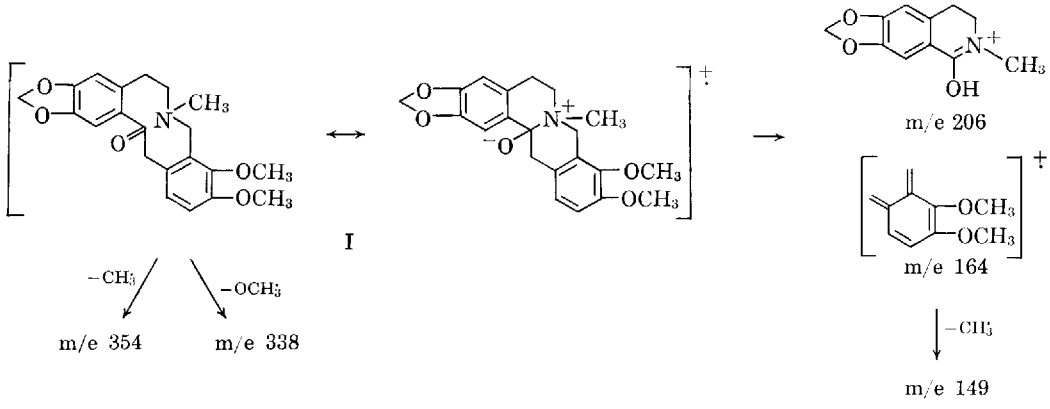
Allocryptopine has been isolated from opium in approximately 0.01 per cent yield as the α-form. The alkaloid has been identified by NMR and mass spectrometry and by comparison of its infrared spectrum with that of its allotropic modification, β-allocryptopine. The biosynthetic pathway leading to allocryptopine is discussed briefly.

RECENT STUDIES of the alkaloid composition of opium have revealed several new alkaloids, some of which have served to confirm modern theories on the biosynthetic pathways in the opium poppy (1–6). This report describes the isolation of allocryptopine which belongs to the protopine group of alkaloids.

Allocryptopine is present in many plants, especially in members of the *Papaveraceae*, and is generally found in concentrations of less than 0.1% (7). A notable exception is *Argemone squarrosa*, from which it has been isolated in quantities of approximately 1% (8). The alkaloid occurs in two allotropic modifications referred to as the α- and the β-forms with different crystal structures and melting points.

with low R_f value (between morphine and codeine) was scraped off and eluted with warm methanol. The alkaloid was purified by repeated crystallization of the picrate, m.p. 208°.[1] The base was liberated by passing through a column of neutral alumina and washing with chloroform. After evaporation of the solvent, the residue was crystallized from heptane, m.p. 160°.

Identification of α-Allocryptopine.—The NMR spectrum[2] in deuterochloroform revealed four aromatic protons in the region 3.0–3.4 τ, a methylenedioxy group at 4.08 τ, two *O*-methyl groups at 6.16 and 6.22 τ, and a *N*-methyl group at 8.15 τ. The high field absorption band of the *N*-methyl group is similar to that of protopine (10) and is probably caused by the shielding effect of the carbonyl group.



Major Fragments in Mass Spectrometry of Allocryptopine
Scheme I

EXPERIMENTAL

Isolation.—The mother liquor from the purification of morphine was extracted as described in a previous communication (2). The chloroform extract obtained at pH 1–1.5 (HCl), containing the weakly basic alkaloids, was separated into phenolic and nonphenolic bases with ether at pH 13, and the nonphenolic fraction subjected to preparative thin-layer chromatography (9). An alkaloid band

Mass spectrometry[3] gave a molecular ion with mass 369. Major fragments appeared in the mass spectrum at m/e 149, 164, 206, 338, and 354, corresponding to the expected cleavage of allocryptopine (I) as illustrated in Scheme I.

The I.R. spectrum[4] of the alkaloid base in chloroform solution was identical with that of authentic allocryptopine. The melting point agreed with that reported for α-allocryptopine (7). The β-form melts at 170° (7, 8). A mixed melting point with authentic β-allocryptopine gave a depression to 166°. When the melt was allowed to cool and crystallize, it melted at 170°. This is consistent with the observation of Soine and Willette (8). The amounts of

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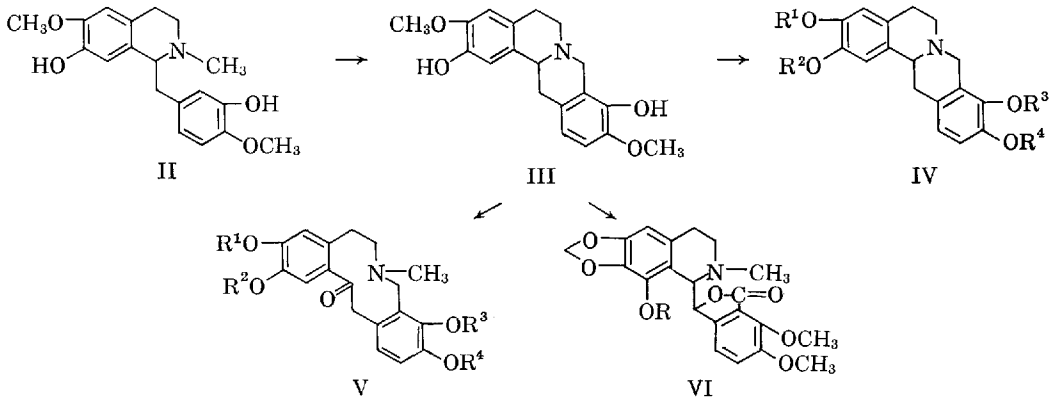
[1] All melting points were determined with a Kofler micro-melting point apparatus.
[2] The instrument used was a Varian A-60 nuclear magnetic resonance spectrometer.
[3] Associated Electrical Industries, MS9.
[4] Unicam SP-200 infrared spectrophotometer.



Scheme II

α-allocryptopine in opium appears to be of the order of 0.01%.

Anal.[5]—Calcd. for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79. Found: C, 68.24; H, 6.03; N, 3.99.

DISCUSSION

Reticuline (II) has been shown to be a precursor for protopine in several plant species (11, 12), and there is evidence that this biotransformation proceeds by way of scoulerine (III) (12), which has recently been isolated from opium (6). Scoulerine, like reticuline, represents an important branching point in the biosynthesis of opium alkaloids from which a number of tetrahydroprotoberberine (IV), protopine (V), and phthalideisoquinoline alkaloids (VI) may be derived (Scheme II). A thorough search may well reveal other members of these alkaloid groups in the opium poppy than those which have been reported so far.

[5] The analyses were carried out by the Microanalytical Laboratory, Department of Chemistry, University of California, Berkeley.

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Communications

Nonspecificity of Published Assays for Chloramphenicol Solutions

Sir:

The authors have found that the accepted spectrophotometric method (1) for chloramphenicol-containing pharmaceuticals does not yield valid results when applied to a partially degraded aqueous solution of chloramphenicol. The Code of Federal Regulations designates as acceptable various analytical methods for the antibiotic in pharmaceuticals. The procedures for two microbiological methods and one spectrophotometric method are outlined in the code (1). In addition, Higuchi, Marcus, and Bias have developed a different microbiological method and have compared this with a chromatographic method for chloramphenicol (2).

Samples of an aqueous solution of chloramphenicol containing stabilizing agents were stored at 4°, 22°, and 32° for approximately 16 months. Table I shows the chloramphenicol content of