Tetrahedron Letters No 18, pp. 1271-1274, 1965 Pergamon Press Ltd
Printed in Great Britain.

(+)-RETICULINE -- A NEW OPIUM ALKALOID

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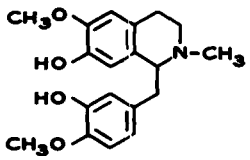
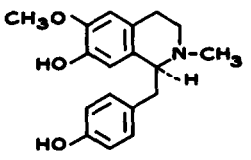
(Received 1 March 1965)

In 1957 Barton and Cohen (1) suggested that the hydrophenanthrene alkaloids of opium might be synthesized in Papaver somniferum by way of an intermediate diphenolic benzyltetrahydroisoquinoline (I). Feeding experiments with the radioactively labeled compound (2-4) and short-term exposure to $^{14}CO_2$ (5) have confirmed the correctness of this hypothesis. The dextrorotatory isomer of I was first isolated from Anona reticulata and named reticuline (6). It was shown recently that opium contains an appreciable amount of (±)-reticuline (7,8). Since only the (-)-isomer has the correct steric configuration to serve as a direct precursor for the morphine alkaloids, a question arises as to the fate of (+)-reticuline. It seemed reasonable to expect that one of the enantiomorphs should predominate in the plant. We have now demonstrated that the reticuline fraction of opium consists of approximately 60% of the (+)-isomer and 40% of the (-)-isomer.

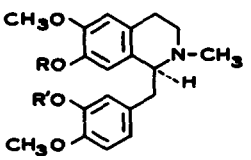
Reticuline was extracted from opium as described previously (8) and purified by preparative thin-layer chromatography. The purified alkaloid gave the characteristic NMR (8) and IR spectra (9) of reticuline and produced single gas chromatographic peaks with three stationary liquids of greatly different polarity. The alkaloid base was dextrorotatory, $[\alpha]_D^{25}$ = +21.4° (c = 1.16 in 95% ethanol). Optical rotatory dispersion measurements showed it to have the same absolute configuration as (+)-N-methylcoclaurine (II), (+)-laudanidine (III, R = CH_3, R' = H) and (+)-laudanosine (III),



(I)



(II)



(III)

R = R' = CH_3) (10).

N-Methylcoclaurine had previously been isolated from Cocculus laurifolius and mistakenly characterized as I (11,12). It would be difficult to detect a relatively small amount of (+)-N-methylcoclaurine in (±)-reticuline by NMR and IR spectroscopy. However, the alkaloids were readily separated by gas chromatography on a polyester column.

Codamine, another phenolic dextrorotatory opium alkaloid belonging to the benzyltetrahydroisoquinoline group (III, R = H, R' = CH_3) was synthesized (13) and found to be easily differentiated from reticuline by NMR spectroscopy and by gas and thin-layer chromatography.

Methylation of the purified reticuline fraction with dimethyl sulfate gave a 97% yield of laudanosine, identified by IR and NMR spectroscopy and by gas and thin-layer chromatography (14), $[\alpha]_D^{25}$ = +21.6° (c = 1.2 in 95% ethanol). It was separated by repeated crystallization from ether-petroleum ether into (+)-laudanosine, m.p. 89.5°, $[\alpha]_D^{25}$ = +105.3° (c = 0.55 in 95% ethanol) and (±)-laudanosine, m.p. 114°. These values are in good agreement with those reported in the literature (15,16). It, therefore, follows that the methylated reticuline fraction consisted of about 60% (+)-laudanosine and about 40% (-)-laudanosine. Based on this ratio, a quantitative determination of reticuline in a sample of opium gave the following results: 0.22% (±)-reticuline and 0.06% (+)-reticuline corresponding to 0.17% and 0.11% of the (+)- and (-)-isomers, respectively.

Thus, it appears that reticuline is one of the six or seven principal alkaloids of opium, and in view of the intensive work which has been carried out in the field of opium chemistry for more than 150 years, it is indeed surprising that this alkaloid has for so long escaped detection.

Acknowledgments. The authors are grateful to Dr. M. Tomita who kindly provided samples of (+)-N-methylcoclaurine and (+)-laudanidine, and to Dr. A. R. Battersby and Dr. J. C. Craig for permission to read their manuscripts (4,10) prior to publication.

This investigation was supported by a research grant MH-03487 from the National Institutes of Health, U.S. Public Health Service, Bethesda, Maryland.

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