modate more solubilizate (5), since the hydrophilic portions of the three nonionic agents are the same, and the micellar size is a function of the size of the lipophilic group (18). Polysorbate 80, as an oleate ester, is unique in the group. Its low solubilizing capacity may be related to its unsaturated lipophilic group (the oleate) which exists in the *cis* configuration and may have the steric effect of a much shorter alkyl chain.

The solubilization of camphor by the two ionic agents and polysorbate 80 is shown in Fig. 3. The surfactant concentrations were expressed on a logarithmic molar scale to allow comparison of the general surfactant types. The molar concentration of polysorbate 80 solutions was calculated from the theoretical molecular weight (1310) assuming 20 ethylene oxide units per molecule. Over the concentration range studied the solubilizing capacity of the nonionic agent (the least efficient of those used) was greater than for either ionic agent when the comparison was made on a molar basis. This observation agrees with prediction (5).

REFERENCES

(1) Guttman, D. E., *et al.*, *J. Pharm. Sci.*, **50**, 305(1961).
(2) Applewhite, R. W., *et al.*, *J. Am. Pharm. Assoc. Pract. Pharm. Ed.*, **15**, 164(1954).
(3) Allawala, N. A., and Riegelman, S., *J. Am. Pharm. Assoc., Sci. Ed.*, **42**, 396(1953).
(4) Nakagawa, T., *J. Pharm. Soc. Japan*, **73**, 469, 732, 1106(1953); **74**, 858, 1116(1954); **75**, 997, 1141(1955); **76**, 1113(1956).
(5) Klevens, H. B., *Chem. Rev.*, **47**, 1(1950).
(6) Moore, C. D., and Bell, M., *Pharm. J.*, **1959**, 171.
(7) Harris, J. C., *J. Am. Oil Chemists Soc.*, **35**, 428(1958).
(8) McBain, M. E. L., and Hutchinson, E., "Solubilization and Related Phenomena," Academic Press Inc., New York, N. Y., 1955.
(9) Goodhart, F. A., and Martin, A. N., *J. Pharm. Sci.*, **51**, 50(1962).
(10) Mitchell, A. G., and Wan, L. S. C., *ibid.*, **53**, 1469 (1964).
(11) McBain, J. W., and Green, A. A., *J. Am. Chem. Soc.*, **68**, 1731(1946).
(12) Rosen, M. J., and Goldsmith, H. A., "Systematic Analysis of Surface-Active Agents," Interscience Publishers, Inc., New York, N. Y., 1960, p. 23.
(13) Cella, J. A., *et al.*, *J. Am. Chem. Soc.*, **74**, 2061(1954).
(14) Kushner, L. M., and Parker, R. A., *J. Phys. Chem.*, **61**, 822(1957).
(15) Weibull, B. W., *Proc. Intern. Congr. Surface Activity, 3rd, Cologne, C*, **1960**, 121.
(16) Nakagawa, T., "Colloidal Surfactants," Academic Press Inc., New York, N. Y., 1963, pp. 163–169.
(17) Becher, P., *J. Phys. Chem.*, **66**, 374(1962).
(18) Shick, M. J., *et al.*, *ibid.*, **66**, 1326(1962).

Opium Alkaloids II. Isolation and Characterization of Codamine

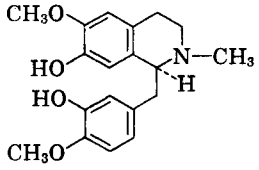
By E. BROCHMANN-HANSSEN, B. NIELSEN, and G. E. UTZINGER

A minor phenolic alkaloid has been isolated from opium and characterized as (+)-codamine. Some of its physical and chemical properties are described. The alkaloid is of interest as a possible biogenetic intermediate between (+)-reticuline and (+)-laudanosine.

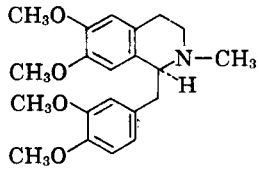
In 1870, Hesse (1, 2) isolated a phenolic alkaloid from the opium mother liquors and named it codamine. He estimated that it constituted about 0.0033% of Turkish opium. Its structure was determined in 1926 by Späth and Epstein (3) on a sample from Hesse's collection. Racemic codamine has been synthesized by several investigators using different methods (4–6). However, all attempts to resolve this compound have been unsuccessful. Very little is known about the physical and chemical properties of naturally occurring codamine, and there is no evidence that it has ever been prepared since the work of Hesse almost 100 years ago. This alkaloid is of interest because of its structural relationship to (+)-reticuline (I) (7) and (+)-laudanosine (II), both of which are present in opium. In the course of studies of the minor phenolic opium alkaloids, the authors have isolated a base which has been characterized as (+)-codamine (III).

EXPERIMENTAL

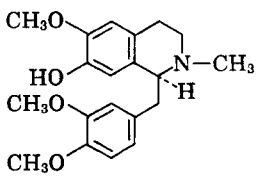
Isolation.—The mother liquor from the purification of morphine[1] was extracted as described in previous communications (8, 9). After removal of reticuline, the chloroform extract containing laudanine and other monophenolic and nonphenolic bases was subjected to preparative thin-layer chro-



(+)-Reticuline (I)



(+)-Laudanosine (II)



(+)-Codamine (III)

Received May 27, 1965, from the Department of Pharmaceutical Chemistry, School of Pharmacy, University of California, San Francisco.
Accepted for publication July 23, 1965.
This investigation was supported by research grant MH 03487 from the National Institutes of Health, U. S. Public Health Service, Bethesda, Md.
[1] The authors are indebted to Mallinckrodt Chemical Works for supplying this material.

TABLE I.—CHROMATOGRAPHIC DATA FOR CODAMINE AND RELATED OPIUM ALKALOIDS

Alkaloid	GLC Rel. Retention Times		TLC R_f Values	
	Se-30, 2.8%	XE-60, 2%	$CH_3OH:CHCl_3$ (1:9)	$C_2H_5OH:C_6H_6$ (2:8)
Laudanosine	1.00	1.00	0.53	0.36
Laudanine	1.10	1.48	0.36	0.26
Codamine	0.95	1.42	0.40	0.33
Reticuline	1.18	2.00	0.24	0.18
Column temp.	206°	217°		
Laudanosine, time in min.	13.7	5.0		

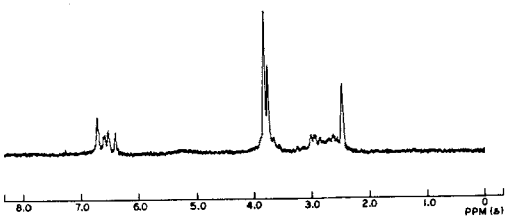


Fig. 1.—NMR spectrum of codamine.

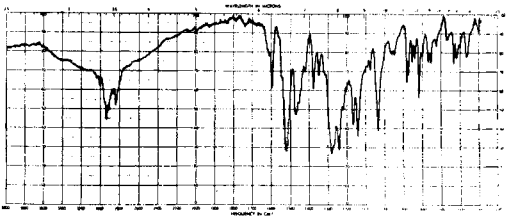


Fig. 2.—I.R. spectrum of codamine.

matography. The plates were 20 × 20 cm. in size and coated with a 1.5-mm. layer of Silica Gel H. The alkaloid solution (in methanol and chloroform) was applied as a streak and developed twice with methanol–chloroform (1:9). The alkaloid bands were located by means of ultraviolet light and by spraying with potassium iodoplatinate reagent along one edge of the plate and with Gibb's reagent along the other. The bands were scraped off with a razor blade and eluted with warm methanol.

Characterization.—Laudanine, laudanidine, laudanosine, protopine, and cryptopine were isolated from the thin-layer chromatograms and identified on the basis of melting points and chromatographic characteristics (10). One fraction contained an appreciable quantity of an alkaloid which could not be identified in this way because no standard was available for comparison. It was soluble in ether, chloroform, and benzene, had phenolic character, but gave no color reaction with Gibb's reagent. The alkaloid base could be extracted from a strongly alkaline solution with chloroform, but not with ether. It was purified by crystallization from heptane. Methylation of the alkaloid with dimethylsulfate and alkali gave (+)-laudanosine, m.p. 89°, $[\alpha]_D^{24.5}$ = +105.4° (c = 0.60 in 95% ethanol), classifying the isolated base as a benzyltetrahydroisoquinoline derivative. The NMR spectrum, when compared with those of related alkaloids (9), indicated the presence of methoxyl groups in positions 6, 3′, and 4′, thereby assigning the phenolic hydroxyl group to position 7. This was confirmed by synthesis of (±)-codamine (6), whose NMR spectrum was the same as that of the alkaloid isolated from the opium mother liquor. The I.R. spectra of the two compounds were also identical, thus proving conclusively that the natural alkaloid was indeed codamine having the structure illustrated in III.

Properties.—The melting point of the purified codamine base was 126.6° (micro m.p., K.), $[\alpha]_D^{23.5}$ = +75.5° (c = 0.5 in 95% ethanol). Hesse (1) has described color reactions for codamine with ferric chloride and with nitric and sulfuric acid. None of these reactions are very conclusive or specific, since the same or similar reactions are given by other phenolic alkaloids, *e.g.*, morphine and reticuline. When only a very small amount of codamine is available, it is most easily identified by chromatographic methods. The chromatographic retention characteristics of codamine and a few related alkaloids are given in Table I. The NMR and I.R. spectra of codamine are illustrated in Figs. 1 and 2.

REFERENCES

(1) Hesse, O., *Ann.*, **153**, 47(1870).
(2) Hesse, O., *Ber.*, **4**, 693(1871).
(3) Späth, E., and Epstein, H., *ibid.*, **59**, 2791(1926).
(4) Burger, A., Dissertation, University of Vienna, Vienna, Austria, 1927.
(5) Späth, E., and Epstein, H., *Ber.*, **61**, 334(1928).
(6) Billek, G., *Mh. Chem.*, **87**, 106(1956).
(7) Brochmann-Hanssen, E., and Nielsen, B., *Tetrahedron Letters*, to be published.
(8) Brochmann-Hanssen, E., and Furuya, T., *J. Pharm. Sci.*, **53**, 575(1964).
(9) Brochmann-Hanssen, E., and Furuya, T., *Planta Med.*, **12**, 328(1964).
(10) Brochmann-Hanssen, E., and Furuya, T., *J. Pharm. Sci.*, **53**, 1549(1964).