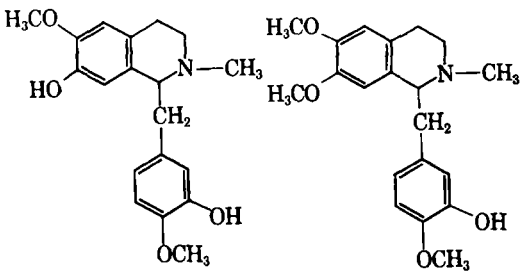
New Opium Alkaloid

Sir:

Recent chromatographic studies have shown that opium may contain several alkaloids which have not been previously described (1, 2). Some of these are phenolic in nature and are of particular interest because of possible interference in the quantitative determination of morphine and because of the role they may play in the biogenetic pathways of the various opium alkaloids. One such phenolic alkaloid has now been isolated from crude opium and from the mother liquor produced during purification of morphine.[1] It was separated from morphine by extraction with chloroform in the presence of dichloroacetic acid (3). Further purification was achieved by extracting a strongly alkaline solution (about pH 13) with chloroform. This removed laudanine, laudanidine, and other monophenolic alkaloids, leaving the unknown compound in the aqueous phase. After adjustment of pH to about 8.5, the new alkaloid was extracted with chloroform and purified by crystallization from a mixture of ether and petroleum ether. Its purity was demonstrated by thin-layer and gas chromatography. Column acetylation (4) resulted in displacement of the gas chromatographic peak and eliminated tailing, indicating esterification of a phenol. This was confirmed by methylation with diazomethane which produced (±)-laudanosine, thus identifying the alkaloid as a benzyltetrahydroisoquinoline derivative. It became evident from its N.M.R. spectrum that the new compound must contain two phenolic hydroxyl groups and two methoxy groups. The positions of these groups were located by comparing the N.M.R. spectrum with those of laudanidine, pseudolaudanine, armepavine, and laudanosine. The stereochemistry of the new alkaloid was established by its relationship to (±)-laudanosine, thus making it possible to assign it the structure in formula I. The dextrorotatory isomer of this alkaloid was isolated from *Cocculus laurifolius* (*Menispermaceae*) by Kusuda (5), who named it coclanoline. Later Gopinath, *et al.* (6), found this isomer in *Anona reticulata* (*Anonaceae*) and called it reticuline. (±)-Reticuline [(±)-coclanoline] has been synthesized (7, 8), but has not previously been isolated from a natural source.

Consideration of the structure of (±)-reticuline indicates that it is very unlikely that racemization would occur during the isolation pro-



(±) Reticuline (I) Laudanidine (II)

cedure. This has been confirmed by Späth and Burger (9), who were unable to affect racemization of levorotatory laudanidine (II), a closely related alkaloid. They, therefore, concluded that laudanidine and laudanine [(±)-laudanidine], both of which have been isolated from opium, exist as separate, genuine alkaloids. Since laudanine is (±)-7-methylreticuline, it is reasonable to assume that the two alkaloids are closely related biogenetically. It is interesting to note that both have been postulated as biogenetic precursors for the morphine group of alkaloids (10–13). Recently, Battersby, *et al.* (14), and Barton, *et al.* (15), using radioactively labeled reticuline, have shown that this alkaloid is very efficiently converted to morphine in the opium poppy.

Details of the methods for isolation and characterization of (±)-reticuline will be published at a later date.

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