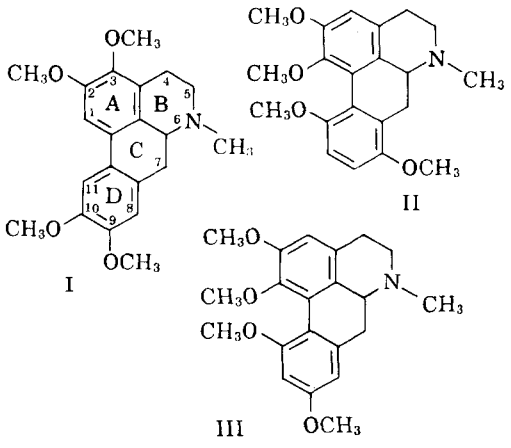
Observations on the Structure of Argemonine

Sir:

Our interest in certain of the *Argemone* alkaloids (1–3) recently led us to postulate three tentative aporphine structures for argemonine (4). All of these structures adopted a 2:3 placement for two of the methoxyl groups with the other two vicinally placed in the 8:9, 9:10, or 10:11 positions. The 9:10 position was favored, largely on the basis of negative oxidative evidence that had failed to indicate the presence of isolable *o*-hemipinic acid (3,4-dimethoxyphthalic acid) in the oxidation residues with only *m*-hemipinic acid (4,5-dimethoxyphthalic acid) being observed. Thus, structure I was suggested as being the most reasonable structure for argemonine with the evidence in hand at that time. Since then, Shamma (5) has postulated two additional structural possibilities (II and III) in an attempt to reconcile our low ultraviolet extinction coefficients for argemonine and its related alkaloids. His reasoning was that 1:11 methoxyl interaction would accentuate the known twist of the biphenyl moiety in the aporphine nucleus, thereby reducing coplanarity with resultant reduction in absorption. On this basis, he found it necessary to adopt a *non-vicinal* arrangement of methoxyls in ring *D* to implement his arguments. His reasoning for a 1:2 placement of the ring *A* methoxyls was based on the observation (6) that all known naturally-occurring aporphine alkaloids have the 1:2 arrangement. Our recent oxidative experiments have shown that Shamma's assumptions are unfounded.



We have ethylated the monophenol, norargemonine[1], with diazoethane and oxidized the resultant ethylnorargemonine without further purification, other than removal of unreacted norargemonine, with manganese dioxide in dilute sulfuric acid by the same procedure as we had previously oxidized argemonine (4). The neutral fraction from this oxidation yielded a small amount of N-methyl-*m*-hemipinimide, m.p. 261–262°, identified by mixed melting point with authentic material prepared by the usual method from authentic *m*-hemipinic acid. The acidic fraction from the above oxidation, on being treated with ethylamine and subsequently heated to 180° and sublimed, yielded N-ethyl-4-ethoxy-5-methoxyphthalimide, m.p. 202–203°. The identity of this product was established by mixed melting point determination and comparison of X-ray powder diffraction patterns, ultraviolet, and infrared spectra with the authentic compound prepared by permanganate oxidation of boldine that had been completely ethylated with diazoethane, followed by the usual treatment to obtain the desired phthalimide derivative. The above findings, assuming an aporphine ring system, show that the phenolic group in norargemonine is on ring *D* rather than on ring *A* and, therefore, indicate that the placement of the methoxyl groups in ring *D* of argemonine is *vicinal* and must be the same as that found in glaucine, namely 9:10. Ring *A* obviously could bear the methoxyls in the 1:2 or 2:3 positions because the necessary *o*-decarboxylation to yield N-methyl-*m*-hemipinimide does not indicate the placement unequivocally but could have arisen from either arrangement. The 1:2 placement, however, could not be entertained as a possible structure because this is the arrangement in glaucine, an isomer of argemonine, which is not identical with the latter alkaloid. Thus, structure I is the only remaining possibility for argemonine.

We previously had referred (4) to the recent elucidation of the structure of crebanine (9) in which a biogenetically unacceptable 8:9 placement of vicinal methoxyls was found in ring *D* and a normal 1:2 placement in ring *A*. If our structural arguments are valid, argemonine, on the other hand, represents a biogenetically acceptable 9:10 placement in ring *D* but an abnor-

[1] Manske and Ashford (7) have suggested that norargemonine "could be partly racemic isocorypalmine." Our own experience in methylating it to argemonine and the similar findings of Boit and Flentje (8) indicate that the above statement is without basis and that norargemonine can be considered a homogeneous entity related to argemonine as a monophenol to its methyl ether.

mal 2:3 placement in ring A. To our knowledge, this would be the first example of such an aporphine alkaloid and, together with the crebanine structure, illustrates the necessity for extreme caution when applying biogenetic principles to solving structural problems in the aporphine group.

We are carrying out presently the synthesis of argemonine to further implement our structural assignment. This work will be the subject of a future communication.

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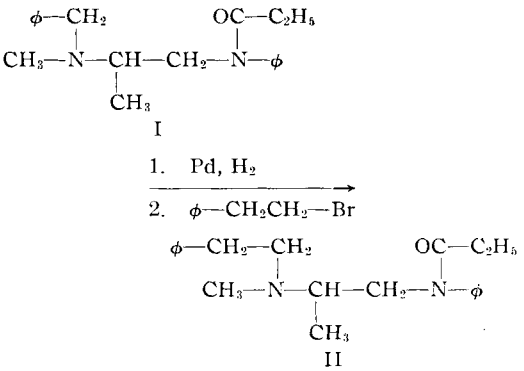
The Absolute Antipodal Activity of Analgesics in the Basic Anilide Series

Sir:

The influence of absolute configuration on the activity of potent analgesics possessing one asymmetric center has been demonstrated by Beckett and co-workers (1). These experiments have shown that most of the analgesic activity resides in the enantiomorph possessing the D-configuration. A hypothesis was advanced which attempted to define an analgesic receptor surface on the basis of three points of contact. This implies that the orientation of the methyl group on the asymmetric carbon of the methadones and thiambutenes is held in a favorable position only in those compounds having the D-configuration. In an effort directed at testing this hypothesis we have determined the absolute configuration of diampromid (II) (2), a member of a new class of analgesics of the basic anilide type.

The D-(−)-N-methyl-N-benzyl compound (I) (3), which has been related to D-alanine, was catalytically hydrogenolyzed with palladium on carbon according to the procedure of Wright, Brabander, and Hardy (2). The resulting debenzylated intermediate was then phenethylated with phenethyl bromide to give D-(−)-diampromid (II), $[\alpha]_D^{28°}$ −26.4° (c 5% in ethanol), b.p. 159–163° (0.1 mm.). The infrared spectrum is identical with that of racemic II (2). Wright, Brabander, and Hardy (4) have independently prepared (+) and (−)-diampromid. Their physical constants are in close agreement with our data.



The (+) and (−) enantiomers of compound I and of diampromid (II) were tested (5) subcutaneously on rats by a modification of the rat-tail heat response method. The L-(+)-isomers of I and II possess analgesic activity comparable to that of morphine, whereas the D-(−)-isomers are substantially less active. These pharmacological results are quite unexpected since it has been demonstrated that the more active enantiomorphs of methadone-type and thiambutene-type analgesics have the D-configuration (1). The potent analgesic action and addictive properties of I and II suggest that they are acting by a mechanism similar to that of methadone and other potent analgesics in spite of the fact that the more active enantiomorphs