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AN ALTERNATE ROUTE IN THE SYNTHESIS OF MORPHINE

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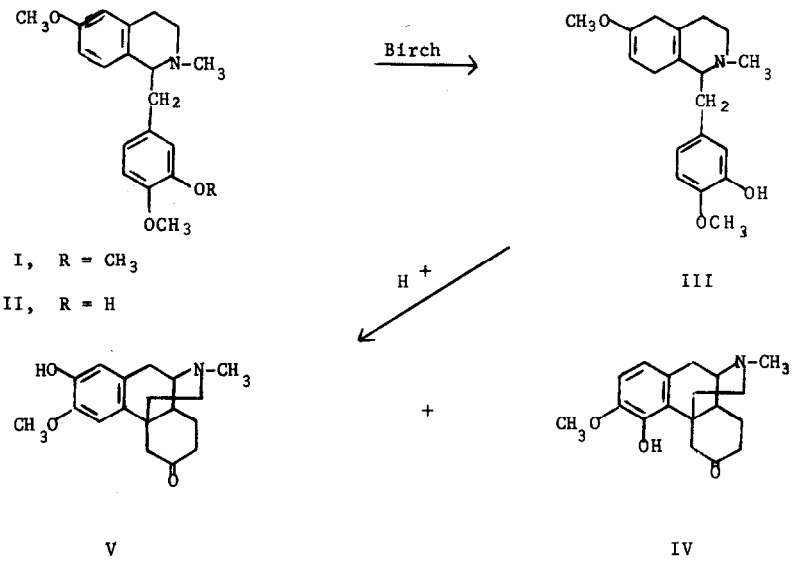
Although three syntheses of morhpine[1,2,3] have already been described, our work on indole analogues of morphinans[4] suggested a synthesis which we thought merited investigation. The benzyltetrahydroisoquinoline I, m.p. 72-73°, is readily available from m-methoxyphenethyl amine and 3,4-dimethylphenylacetic acid via amide formation, Bischler-Napieralski cyclization, reduction and methylation. This scheme is carried out experimentally by essentially the same technique as used for the preparation of the benzyl ether of II by Grewe[5].

The Birch reduction of I with sodium and t-butanol in liquid ammonia results in cleavage of the 3-methoxy group of the benzyl function[6] and reduction of the isoquinoline moiety to give III, m.p. 117.5-118.5°. Since Grewe had not described the free base of III we converted our material to a picrate, m.p. 162-163° (Lit[5] m.p. 162°).

Treatment of III with refluxing 10% hydrochloric acid brings about hydrolysis of the enol ether, conjugation of the double bond and cyclization to (±) dihydrothebainone (IV), m.p. 179.5-180.5°, in 3% yield and its positional isomer V, m.p. 202-203°, in 37% yield. Our sample of (±) dihydrothebainone was shown to have a chloroform solution infrared spectrum identical to that of an authentic sample[7] of dihydrothebainone. Since the conversion of IV to morphine has already been accomplished[1,2], this work represents a total synthesis which is considerably shorter than the preparative schemes of Gates and Tschudi[1] and Elad and Ginsburg[2].



I, R = CH_3

II, R = H

III

V

IV

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