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THE CONVERSION OF LYSERGIC ACID TO THE CLAVINE ALKALOIDS, PENNICLAVINE AND ELYMOCLAVINE, AND TO DESCARBOXYLYSERGIC ACID[1,5]

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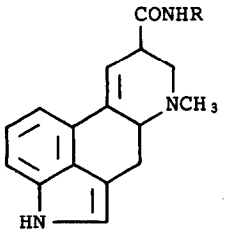
Ergot alkaloids occur generally in two structural groups: (a) those that are amides (1) of lysergic acid and (b) those of the simpler clavine class (2).[1,2] In the later series, the lysergic acid carboxyl appears in reduced form (2, R' and R" = H or OH), and in most a double bond occurs in either the 8,9 or 9,10



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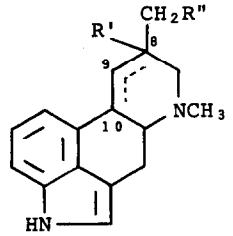

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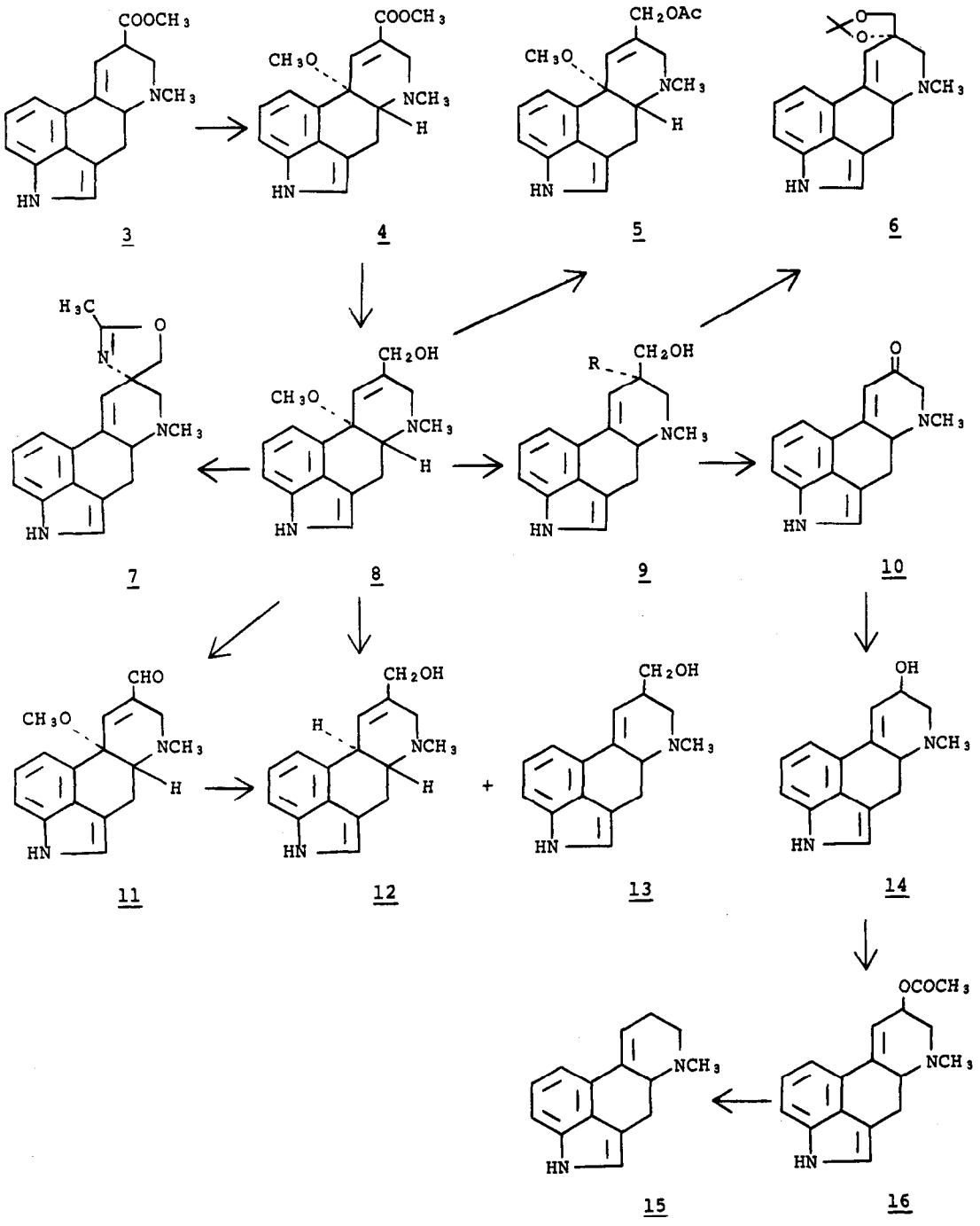
position. We record here efficient routes from lysergic acid to the clavine alkaloids penniclavine[3] (9, R = OH) and elymoclavine[4] (12) and to descarboxylysergic acid[7] (15). Compounds of this class are known to be effective inhibitors of the pituitary hormone prolactin and may be useful, therefore, in the therapy of prolactin-dependent conditions.[5]

Italian workers[6] have shown that when the methyl ester 3 of lysergic acid reacts with mercuric acetate in methanol, followed by sodium borohydride, the product is the 10-methoxy ester 4. Hydride reduction of the ester function of 4 with $NaAlH_2(OCH_2CH_2OCH_3)_2$ afforded in our hands the methoxy carbinol 8, which was characterized as the acetate derivative 5. Simple treatment of the carbinol 8 with 2% aqueous tartaric acid gave penniclavine[3] (9, R = OH) in good yield. Penniclavine was converted to an acetonide 6 in the usual fashion and to the unsaturated ketone 10 by periodate oxidation.[3] The racemic form of the ketone


COOCH3
NCH3
HN
3
CH3O
H
4
CH2OAc
5
O
6
H3C
N
7
CH2OH
8
R
9
10
CHO
11
12
13
OH
14
OCOCH3
15
16

10 was previously obtained here by total synthesis.[7] When the carbinol 8 was treated with 1N HCl, a mixture of penniclavine (9, R = OH) and its methyl ether (9, R = OCH_3), in a ratio of 3:1, was obtained. (The formation of 9, R = OCH_3, in this case, is apparently a case of "internal return".[8]) Acid catalyzed solvolysis of 8 with rearrangement was quite general.[9] With BF_3-MeOH, 8 gave 9, R = OCH_3, and with $HClO_4$-EtOH 9, R = OEt, was formed. Glacial acetic acid led to the penniclavine ester 9, R = OAc, and methylmercaptan-BF_3 afforded the thioether 9, R = SCH_3. Of interest also was the transformation of 8 in a modified Ritter reaction[10] to the spiro oxazoline 7 with CH_3CN-BF_3. Finally, oxidation of 8 with MnO_2 or with DCC-DMSO-TFA[11] gave the unsaturated methoxy aldehyde 11. Reduction of 11 with zinc and acetic acid led to elymoclavine (12) in good yield. An alternate route to 12 was achieved by $LiAlH_4$-$AlCl_3$ reduction of 8; however, in this case lysergol (13) was formed along with the desired 12.[12] Identities of synthetic penniclavine (9, R = OH) and elymoclavine (12) were proved by comparison of uv, ir, ms, and nmr spectra and tlc behavior with those of natural samples.

Since we have reported a total synthesis of lysergic acid,[13] the present conversions constitute total syntheses for two additional clavine alkaloids.[14]

With the conjugated ketone 10 readily available from penniclavine (9, R = OH), we used it in a three-stage conversion to d-descarboxylysergic acid (15) (previously known only as the racemate[7]). 10 was reduced by $NaBH_4$ to the allylic alcohol 14, the acetate ester 16 of which on electrochemical reduction[7] afforded 15 in good yield.

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