

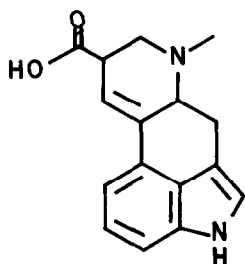
A NEW SYNTHESIS OF LYSERGIC ACID

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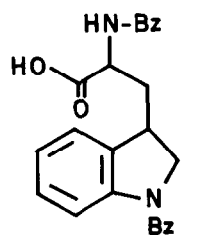
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ABSTRACT: Tryptophane has been converted to the methyl ester of lysergic acid in 10 steps.

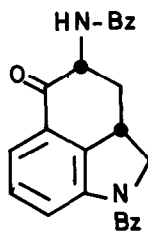
While a number of syntheses of lysergic acid have been recorded¹, all have avoided the use of the biosynthetic precursor, tryptophan. We have successfully converted this amino acid to the ergot alkaloids rugulovasine² and lysergine³ and here we evince the versatility of this strategy through a new and efficient synthesis of lysergic acid.



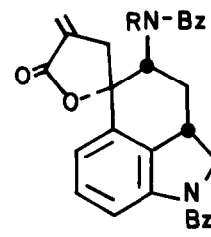
Lysergic Acid



1 Bz = Benzoyl



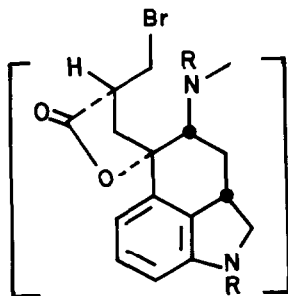
2



3a R = H

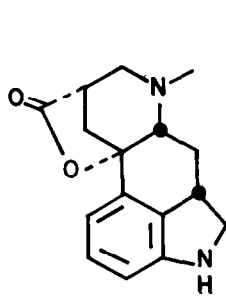
3b R = CH₃

The fully blocked amino acid derivative⁴ 1 was converted to the ketone 2 from which the lactone 3a is obtained in a single step as previously described.² Methylation (MeI, NaH/DMF) gave 3b⁵ (80%) which on treatment with HBr in CH₂Cl₂ afforded a crude addition product formulated as 4a. Without purification this substance was subjected to the deacylation sequence described by Hanesian⁶ (Et₃O⁺BF₄⁻/CH₂Cl₂; HCl/H₂O; NaHCO₃/H₂O) to give - presumably via 4b - the pentacyclic lactone⁷ 5, m.p. 220° (55% from 3b).

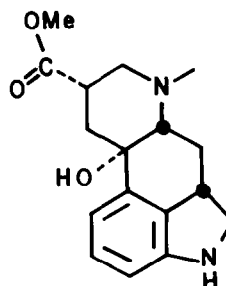


4a R = Bz

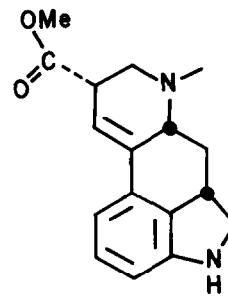
4b R = H



5



6



7

The lactone was opened ($\text{SOCl}_2/\text{MeOH}$) to give the ester 6, which, as the dihydrochloride, was dehydrated ($\text{P}_2\text{O}_5/\text{MeSO}_3\text{H}$) to the olefin 7 of isolysergic stereochemistry (95% from 5). This substance was also encountered by Ramage^{1C}, and is partly converted to the lysergic stereochemistry by warming in MeOH. Oxidation (MnO_2) gave a mixture of the methyl esters of isolysergic and lysergic acids, the latter being spectroscopically identical with a sample prepared by esterification of the naturally occurring substance.⁸

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5. All new substances were characterized by IR, Mass spectra and 300 MHz ^1H NMR spectroscopy.
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