Tetrahedron Letters No.24, pp. 1619-1622, 1964. Pergamon Press Ltd.
Printed in Great Britain.

# BIOSYNTHESIS OF HYOSCYAMINE : PROOF THAT ORNITHINE-2-$C^{14}$ YIELDS TROPINE LABELLED AT C-1

Edward Leete[a]

Department of Chemistry, University of Minnesota, Minneapolis.

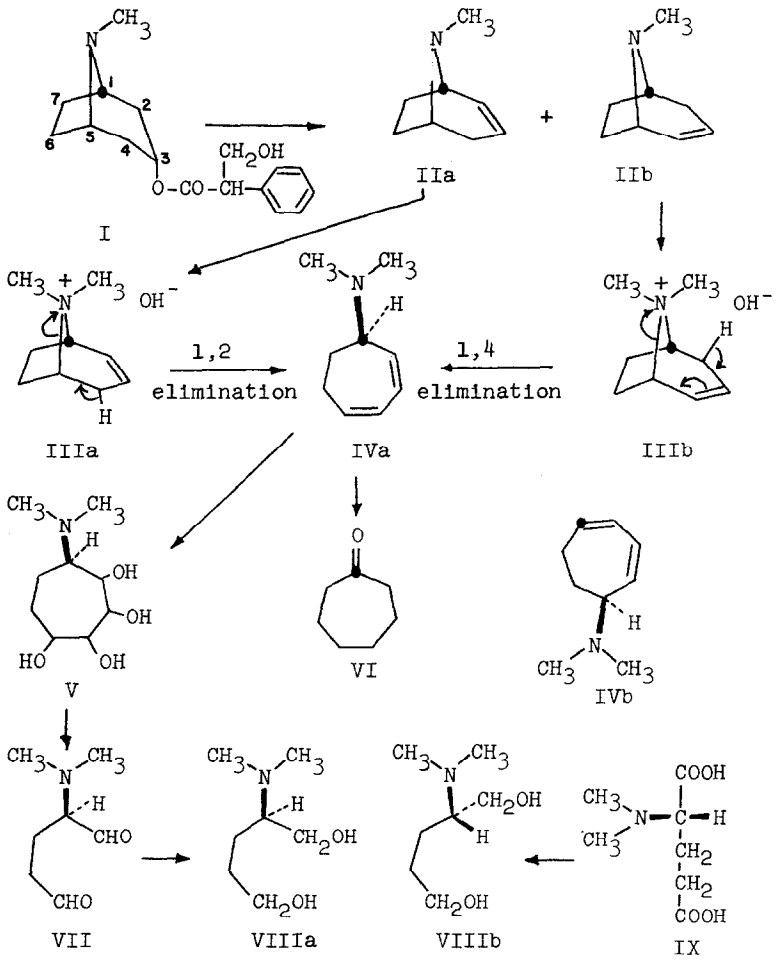
(Received 3 April 1964; in revised form 13 April 1964)

I have previously shown that the administration of DL-ornithine-2-$C^{14}$ to Datura stramonium plants leads to the formation of hyoscyamine (I) which is labelled on only one of the bridgehead carbons (C-1 or C-5) of the tropine moiety of this ester alkaloid (1). I have now determined the absolute configuration of (+)-1-dimethylamino-2,4-cyclo-heptadiene (α-methyltropidine) (IVa), thus establishing that all the activity in the tropine was at C-1.

In the previously described degradation, hyoscyamine was pyrolysed yielding a mixture of the enantiomorphic tropidines IIa and IIb, which were converted to their methiodides without separation (1,2). A Hofmann elimination on these methiodides yielded the α-methyltropidines IVa and IVb. Isomer IVa results from a 1,2 elimination on the methohydroxide IIIa , or a 1,4 elimination on the methohydroxide IIIb. Similarly the α-methyltropidine IVb arises from a 1,4 elimination on IIIa or a 1,2 elimination on IIIb.

---

[a]Alfred P. Sloan Fellow, 1962-1965.




At this stage the racemic α-methyltropidine was resolved with dibenzoyl-D-tartaric acid. It was actually the salt of the (+)-α-methyltropidine which crystallized from a mixture of ethanol and ethyl acetate. Subsequent steps in the degradation

involved the conversion of this isomer to cycloheptanone (VI), which had all its radioactivity located on the carbonyl carbon.

The (+)-α-methyltropidine was shown to have the (R)-configuration at C-1 by the following degradation. Two equivalents of osmium tetroxide were added to a solution of the α-methyltropidine in ether. After two days the resultant osmate ester was decomposed with sodium sulfite yielding 1-dimethylamino-2,3,4,5-tetrahydroxycycloheptane (V). This compound was dissolved in dilute acetic acid and oxidized with sodium metaperiodate. After 15 minutes barium chloride was added to precipitate iodate and periodate. The filtered solution was made faintly alkaline with sodium carbonate and then sodium borohydride added to reduce the dialdehyde VII to 2-dimethylamino-1,5-pentadiol (VIIIa). This compound was isolated from the aqueous solution as follows. Oxalic acid was added to decompose the excess borohydride and then the solution was made basic with barium hydroxide. Barium oxalate was filtered off and the residue obtained on evaporation of the filtrate was distilled (120°, 0.01 mm.) yielding the aminodiol as a colorless oil, having an infrared spectrum identical with an authentic specimen prepared from N,N-dimethylglutamic acid. The product from two separate degradations of (+)-α-methyltropidine had rotations : $[\alpha]_D^{25}$ = - 4.2 and - 3.4° (in ethanol). N,N-Dimethyl-L-glutamic acid (IX) (3) was converted to its diethyl ester which was reduced with lithium aluminum hydride in ether using the procedure of Karrer and Portmann (4) affording (+)-(S)-2-dimethylamino-1,5-pentadiol (VIIIb) having a

rotation : $[\alpha]_D^{25}$ = + 5.2° (in ethanol), (Calcd for $C_7H_{17}NO_2$ : C, 57.11; H, 11.64; N, 9.52. Found : C, 57.63; H, 11.56; N, 9.55.). Since the aminodiol obtained from (+)-α-methyltropidine had an opposite rotation the absolute configuration of these two compounds at their asymmetric centers must be (R) as depicted in formulas VIIIa and IVa . The somewhat lower specific rotation observed for the product obtained from (+)-α-methyltropidine may be due to partial racemization occurring during the reduction of the dialdehyde VII in slightly basic solution.

This investigation was supported by a research grant MH-02662, from the National Institutes of Health, U.S. Public Health Service.

REFERENCES

1. E. Leete, J. Amer. Chem. Soc., 84, 55 (1962).

2. A. A. Bothner-By, R. S. Schutz, R. F. Dawson and M. L. Solt, J. Amer. Chem. Soc., 84, 52 (1962).

3. S. Kanao, J. Pharm. Soc. Japan, 66, 5 (1946).

4. P. Karrer and P. Portmann, Helv. Chim. Acta, 31, 2088 (1948).