Tetrahedron Letters No. 46, pp 4159 - 4162, 1976. Pergamon Press. Printed in Great Britain.

MODEL FOR THE SYNTHESIS OF CANCENTRINE

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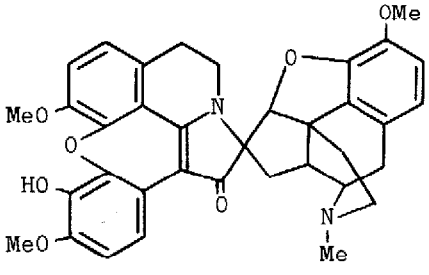
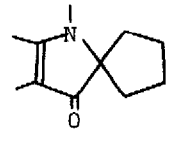
(Received in Japan 30 August 1976; received in UK for publication 1 October 1976)

Cancentrine[1](I) was isolated from Dicentra canadensis (Goldie) Wald in 1932. The complex structure was not solved until 1970 when it was shown to be a cularine morphine dimer. We were interested in the synthesis of the spiro moiety (II) and *wish to report our results.*

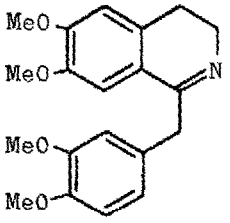


(I)

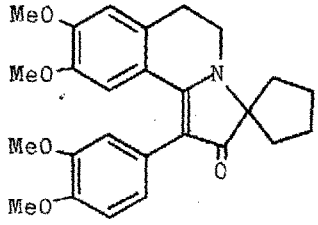


(II)

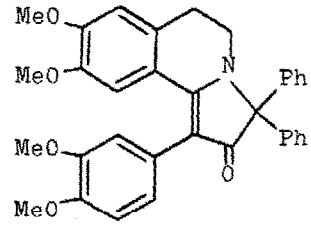
Treatment of 3,4-dihydropapaverine (III) or the corresponding hydrochloride with 1,2-cyclohexanedione and triton B (prepared in situ from benzyltrimethylammonium chloride and 50% aqueous sodium hydroxide solution) in pyridine under reflux for 5 hrs. resulted in a smooth conversion of compound (III) to the spiro compound (IV) in 62% yield. Compound (IV) had the following physical data, mp: 156-157, ir: 1680 cm^{-1}, nmr: (δ $CDCl_3$) 1.98 (br.s, 4x$CH_2$$CH_2$), 2.94 (t, J = 6Hz, benzylic CH_2), 3.79 (t, J = 6Hz, CH_2N), 3.38 (s, OCH_3), 3.85 (s, 2xOCH_3), 3.90 (s, OCH_3), 6.59 (s, C-8 ArH), 6.71 (s, C-5 ArH), 6.87 (d, J = 1.5Hz, C-2 ArH) 6.95 (d, J = 1.5Hz, C-6 ArH), 6.96 (s, C-5 ArH), ms: m/e 435 (M^+)



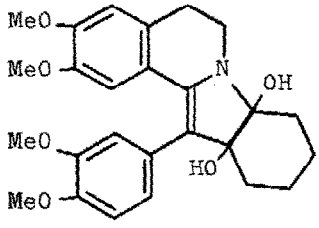
(III)



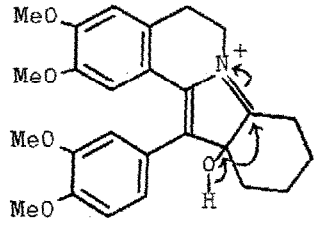
(IV)



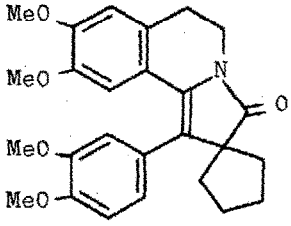
(V)



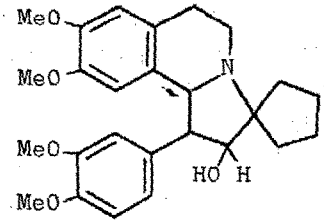
(VI)



(VII)



(VIII)



(IX)

It was found that this type of rearrangement[2] is general for other diketones, for example, replacement of 1,2-cyclohexanedione with benzil in the above reaction, compound (V) was isolated in 56% yield.

We have studied the above reaction with various bases and solvents. Triton B in pyridine was found to be most effective. We suggest that the reaction proceeds as follows.

Abstraction of a proton from α position to imine gave the corresponding carbanion which then reacted with a carbonyl group followed by isomerization and reaction of amino group with another carbonyl group (or in the reversed order) would produce intermediate (VI). Elimination of hydroxide ion facilitated by a lone pair electrons on nitrogen would yield intermediate (VII) which could then rearrange to product. Significantly, the biosynthesis[4] of cancentrine was proposed to occur by the same type of rearrangement with the ring contraction in the morphinan moiety. The involvement of intermediate (VII) explained the formation of only one product. Conceivably, rearrangement in the opposite direction from (VI) would produce compound (VIII).

Catalytic hydrogenation (PtO_2) in ethyl acetate of the product obtained from the reaction of imine (III) with 1,2-cyclohexanedione gave compound (IX) as an unstable oil, ir: 3550 cm^{-1}, nmr: δ 5.19 (d, J = 6Hz, -CH-OH). This further confirms the structure of the spiro compound as (IV).

Compounds (IV) and (V) show high field chemical shifts for one aromatic proton and one methoxyl group in the NMR spectra[5]. For example, in compound (IV) one aromatic proton appears at δ 6.59 and one methoxyl group at δ 3.38, we assign these chemical shifts to C-8 aromatic proton and methoxyl group attached to C-7. The high field chemical shift is due to the anisotropy effect exerted by aromatic ring C. The proximity of rings A and C is due to the cis arrangement around carbon-carbon double bond, thus hydrogenated product (IX) gave lower field chemical shift for methoxyl group[6].

Our studies demonstrate how cularine and morphinan moieties can be joined together in vitro and further support the feasibility of the proposed mechanism for the spiro linkage formation in the biosynthesis of cancentrine.

Acknowledgement: We are grateful to Dr. J. A. Weisbach and Mr. J. E. Zarembo of Smith-Klein and French Laboratories for mass spectra.

References and Footnotes

1. For a review, see (a) M. Shamma,'The Isoquinoline Alkaloids', Academic Press, New York, 1972, Ch. 7, p. 165. (b) R. Rodrigo,'The Alkaloids', R. H. F. Manske ed. Academic Press, New York, 1973, vol. 14, p. 407.

2. This type of rearrangement was also found in other related systems, see (a) G. E. Means and R. E. Feeney, 'Chemical Modification of Proteins' Holden Day Inc. 1971, Ch. 10, p. 194 (b) T. Sasaki, S. Eguchi and S. Hattori, Synthesis 718 (1975) and references cited therein.

3. Compound (V) had the following physical data, mp: 201-203, ir: 1690 cm^{-1}, nmr: 3.03 (t, J = 6Hz, benzylic $C\underline{H}_2$), 3.37, 3.51, 3.93, 4.01 (s, 4x$OC\underline{H}_3$), 4.11 (t, J = 6Hz, $C\underline{H}_2N$), 6.28 (s, C-8 Ar$\underline{H}$), 6.83 (m, 4xAr$\underline{H}$), 7.41 (br. s, 10 Ar$\underline{H}$), ms: m/e 533 (M^+ 100%).

4. R. Rodrigo, R. H. F. Manske, D. B. MacLean, L. Baczynskyj and J. K. Saunders, Can. J. Chem. 50, 853 (1972).

5. For a discussion of the NMR spectra of 1-benzylisoquinoline derivatives, see ref. 1 (a) p. 81 and references cited therein.

6. The highest chemical shift for methoxyl group was observed at 3.65.