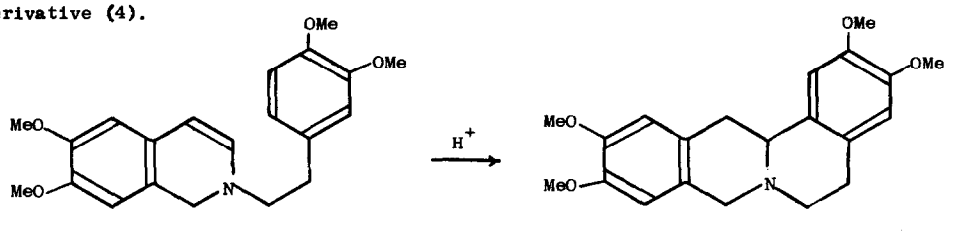
Tetrahedron Letters No.21, pp. 2609-2612, 1968. Pergamon Press. Printed in Great Britain.

THE ACTION OF ACIDS ON SOME SUBSTITUTED ACETALDEHYDE DIMETHYLAMINOACETALS

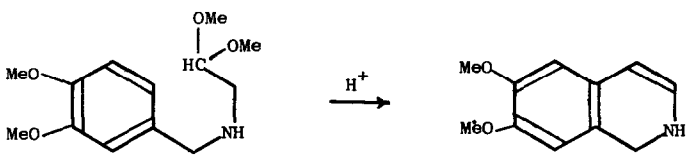
D.W. Brown, S.F. Dyke, G. Hardy and M. Sainsbury
School of Chemistry,
Bath University of Technology,
Ashley Down,
Bristol 7,
England.

(Received in UK 16 January 1968; accepted for publication 26 February 1968)

It has been shown[1,2,3] that N-β-arylethyl-1,2-dihydroisoquinolines, such as (1), can be cyclised by acids to berbine derivatives, for example (2), and it is also known[4,5] that the aminoacetaldehyde dialkylacetal (3) can be cyclised by acids to the 1,2-dihydroisoquinoline derivative (4).



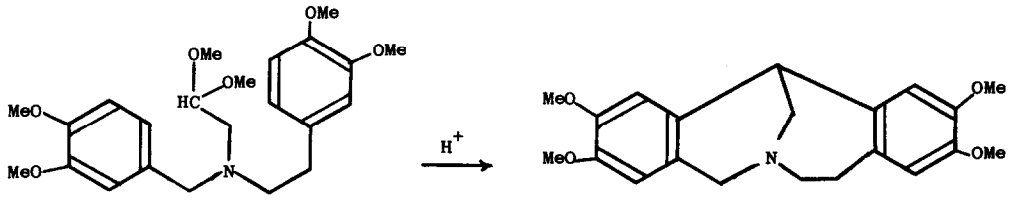
(1) (2)



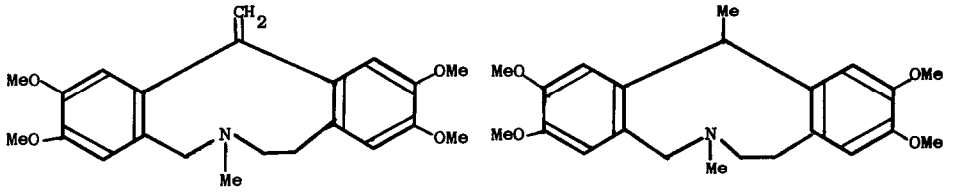
(3) (4)

It occurred to us that a double cyclisation of an appropriately substituted amino-acetaldehyde dimethylacetal such (5) may lead, in a single step, to the berbine skeleton (2). When (5) was treated with conc. HCl for five days at room temperature a base hydrochloride $C_{21}H_{25}NO_4.HCl$ was isolated[6] in 76% yield; its NMR spectrum indicated the presence of only FOUR aromatic protons so that a double cyclisation had indeed occurred. However, it was quickly found that the product differed from a sample of the hydrochloride of (2). The most likely alternative structure (6) is supported by the fact that Hofmann degradation yields a

methine base (7) whose spectral properties indicate the presence of an exocyclic methylene group. Catalytic hydrogenation of (7) proceeded with the uptake of 1 mole gas to give (8)

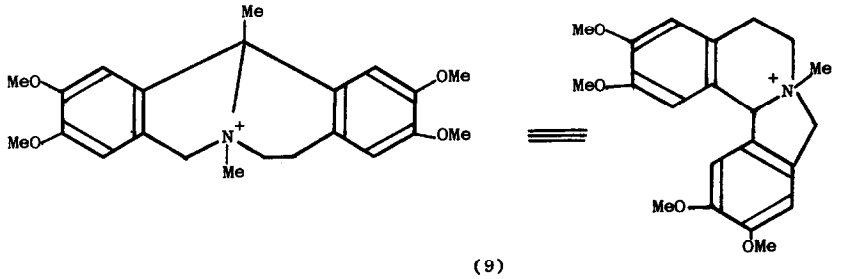


(5) (6)



(7) (8)

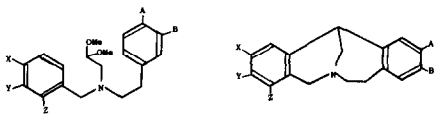
whose NMR spectrum (taken at 60 Mg/S in $CDCl_3$ solution with internal TMS as reference) contains a three proton doublet centred at 1.7 ppm (J = 6.5 C/S). When the methine (7) was treated with acetic acid, transannular addition to the double bond occurred to yield a quaternary salt (9) whose spectral characteristics are fully consistent with this structure.



(9)

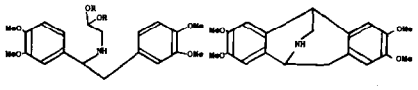
A variety of conditions of acid treatment were studied in an effort to cyclise (5) to the berbine derivative (2), but in each case the product was (6); indeed with phosphoric acid at room temperature for two days, the yield of (6) was raised to 90%. Several differently substituted aminoacetaldehyde dimethylacetals were studied, and in each case structures analogous to (6) were formed. These results are summarised in the TABLE.

TABLE



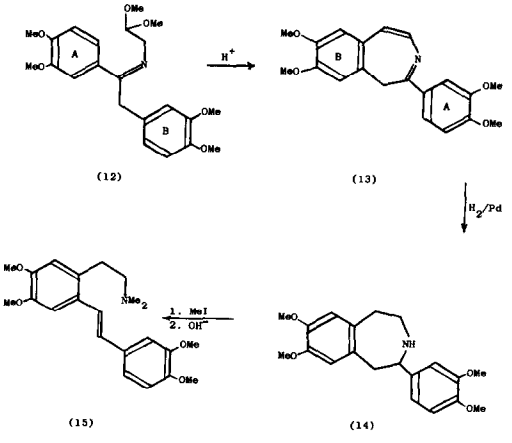
X	Y	Z	A	B	Yield
H	OMe	OMe	OMe	OMe	83
OMe	OMe	H	OMe	OMe	76
H	OMe	OMe	O	$-CH_2-O$	76
OMe	OH	H	OMe	OMe	50
OMe	OMe	H	H	H	0

An analogy for this double cyclisation is provided by the ring-closure of the aminoacetal (10) to the compound (11), termed ISOPAVINE.

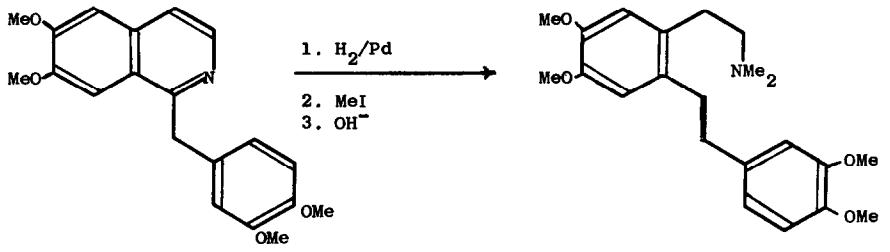


(10) (11)

In 1903 Fritsch[8] reported that when the aminoacetal (12) was treated with conc. H_2SO_4 a base was obtained in 15% yield, and this reaction was re-examined by Guthrie et. al[9] who proposed a structure for this product. However Guthrie's structure was questioned by Battersby and Yoewell[7] who proposed a structure based upon isopavine (11). We have now found that the product described by Fritsch and by Guthrie et. al. can be obtained in 37% yield from (12) by using conc. HCl in place of the conc. H_2SO_4 and that its NMR spectrum can be completely interpreted in terms of structure (13). This deduction was confirmed by the reduction of (13) to a tetrahydro derivative (14) and its degradation to the methine (15), which was shown to be identical with the product obtained from papaverine (16) by reduction and Hofmann degradation.



(12) (13) (15) (14)



(16) (15)

References

1 A.R. Battersby, R.Binks and P.S. Uzzell, Chem. and Ind., 1955, 1039. A.R. Battersby D.J. Le Count, S. Garratt and R.I. Thrift, Tetrahedron, 1961, 14, 46

2 J.W. Huffman and E.G. Millar, J. Org. Chem., 1960, 25, 90

3 D.W. Brown and S.F. Dyke, Tetrahedron, 1966, 22, 2429

4 J.M. Bobbitt, K.L. Khanna and J.M. Kiely, Chem. and Ind., 1964, 1950; J.M. Bobbitt, J.M. Kiely, K.L. Khanna and R. Ebermann, J. Org. Chem., 1965, 30, 2247. J.M. Bobbitt, D.N. Roy, A. Marchand and C.W. Allen, J. Org. Chem., 1967, 32, 2225.

5 S.F. Dyke and M. Sainsbury, Tetrahedron,1967, 23, 3161; S.F. Dyke, M. Sainsbury and B.J. Moon, Tetrahedron, 1968, in the press.

6 Satisfactory analyses were obtained for all compounds reported.

7 A.R. Battersby and D.A. Yeowell, J. Chem. Soc., 1958, 1988

8 P. Fritsch, Annalen, 1903, 329, 37.

9 D.A. Guthrie, A.W. Frank and C.B. Purves, Can. J. Chem., 1955, 33, 729.