Tetrahedron Letters No 39, pp 3849 - 3850, 1973 Pergamon Press Printed in Great Britain

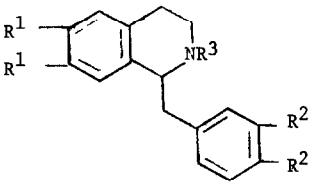
AN IMPROVED SYNTHESIS OF PAVINANES

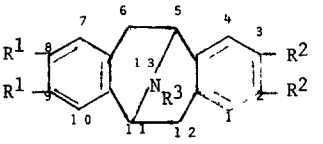
David A. Walsh[†] and Robert E Lyle

Department of Chemistry, University of New Hampshire
Durham, New Hampshire 03824

(Received in USA 7 May 1973, received in UK for publication 17 August 1973)

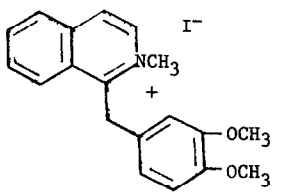
Schopf[1] observed that 1,2-dihydro-N-methylpapaverine (1a) yielded N-methylpavine (2a) under acidic conditions, confirming his proposed structure for pavine Many subsequent studies of this reaction have shown that in the presence of acids 1,2-dihydroisoquinolines may undergo disproportionation, polymerization, and/or rearrangement to 3-benzyl-3,4-dihydroisoquinolinium compounds, which then undergo disproportionation [2] Because of these competing reactions, cyclizations of 1-benzyl-1,2-dihydroisoquinolines using the classical reaction conditions are highly unpredictable giving yields ranging from 1-75%[3-6] usually at the lower end of the range



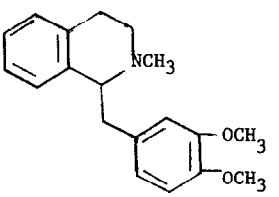


1a $R^1=R^2=OCH_3$, $R^3=CH_3$
b $R^1=H$; $R^2=OCH_3$, $R^3=CH_3$
c $R^1=H$, $R^2=OCH_3$, $R^3=C_6H_5CH_2$
d $R^1=H$, $R^2=OCH_3$, $R^3=pNO_2C_6H_4CH_2$
e $R^1=H$; $R^2=OCH_3$, $R^3=2,6\text{-}Cl_2C_6H_3CH_2$

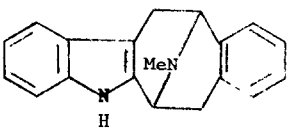
2a $R^1=R^2=OCH_3$; $R^3=CH_3$
b $R^1=H$, $R^2=OCH_3$, $R^3=CH_3$
c $R^1=H$, $R^2=OCH_3$, $R^3=C_6H_5CH_2$
d $R^1=H$, $R^2=OCH_3$, $R^3=p\text{-}NO_2C_6H_4CH_2$
e $R^1=H$, $R^2=OCH_3$, $R^3=2,6\text{-}Cl_2C_6H_3CH_2$



3



4



5

[†]National Defense Education Act Title IV Fellow, 1972 University of New Hampshire Dissertatio Year Fellow, 1973

In attempting to prepare a series of substituted pavines in this Laboratory these anomolies were confirmed. For example, the treatment of the methiodide* of 1-(3,4-dimethoxybenzyl)-isoquinoline (3)[7] with sodium borohydride in pyridine[8] gave the dihydroisoquinoline 1b which on treatment with acid underwent disproportionation to give the tetrahydroisoquinoline (4) * The structure 4 was confirmed by comparison with the reaction product of 3 with sodium borohydride in ethanol

This type of disproportionation reaction has been shown to be a bimolecular process[2], and the rearrangement of 1-benzyl-1,2-dihydroisoquinolines to the 3-benzyl derivative has recently been shown to be bimolecular also [9] The cyclization of the 1-benzyl-1,2-dihydroisoquinoline to pavine must be unimolecular and thus the reaction pathway favored by high dilution

*To test this hypothesis 1 0 g (3 5 mmol) of 2b in 50 ml of chloroform was added dropwise over a period of 3 hrs to a stirred mixture of 100 ml of chloroform and 50 ml of 70% aqueous perchloric acid under a nitrogen atmosphere Stirring was continued at room temperature for 65-72 hrs The layers were separated, and 600 ml of water was added to the aqueous layer After standing overnight 0.81 g (60% from 3) of 2b** perchlorate, mp 272-274°d (picrate, mp241-243°d, base, mp 107-109°C) was isolated A 100 MHz nmr spectrum of 2b shows signals consistent with the spectral data of other unsymmetrical pavinane derivatives[6], nmr ($CDCl_3$) δ 7 26-7 00 (m, 4H), 6 67 (s, 1H), 6 49 (s, 1H), 4 13 (d, 1H), 4 07 (d, 1H), 3 87 (s, 3H), 3 79 (s, 3H), 3 69-3 32 (m, 2H), 2 92-2 47 (m, 2H), 2 56 (s, 3H)*

This method also gave 50% of 2c**, mp 120°d, 95% 2d**, mp 158-160°d, 58% 2e**, mp 169°d and quantitative yield of 5[6], mp (CH_3I, 255-258°d).

ACKNOWLEDGEMENTS The authors wish to express appreciation to the donors of the Petroleum Research Fund to the American Chemical Society for partial support of the project by grant PRF-3441-A1,4.

References

1 C. Schopf, *Experientia*, 5, 201 (1949)

2. S. F. Dyke in "Advances in Heterocyclic Chemistry", A R Katritzky and A J Boulton, Eds. Academic Press, New York, 1972, Vol 14, p 279.

3 A R Battersby and R. Binks, *J Chem Soc.*, 2888 (1955)

4. M. Sainsbury, D. W. Brown, S. F Dyke, R G Kinsman and B J Moon, *Tetrahedron*, 24, 6695 (1968)

5 C. Chen and T O. Soine, *J Pharm. Sci* , 61, 55 (1972)

6 H. Zinnes, F R. Zuleski and J Shavel, Jr., *J Org. Chem* , 33, 3605 (1968)

7 B C Uff and J R. Kershaw, *J Chem Soc.*, 666 (1969)

8 D. H R Barton, R H Hesse and G W Kirby, *J. Chem Soc* , 6379 (1965).

9 J. Knabe, R Dorr, S. F. Dyke and R. G Kinsman, *Tetrahedron Lett* , 5373 (1972)

*All new compounds gave spectral and microanalytical data consistent with the assigned structures.

**Analytical data and spectra were correct for these compounds isolated as the perchlorate