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INTRAMOLECULAR [4+2] CYCLOADDITION OF AN INDOLENINE[1,2]

Josef Hájíček and Jan Trojánek

Research Institute for Pharmacy and Biochemistry,
19404 Prague 9, Czechoslovakia

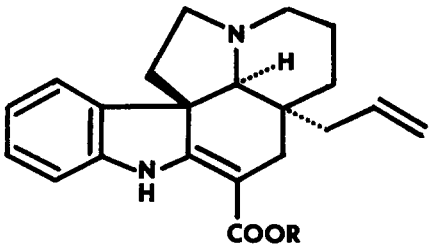
Summary: Attempted transformation of readily accessible 18-methylenevincadifformine (I) to indolenine VI in acidic medium afforded unexpectedly the intramolecular [4+2] cycloadduct VIII in almost quantitative yield

Aspidospermane alkaloids, especially those possessing the 1,2 or 2,16 unsaturation, are suitable starting materials for the syntheses of several types of indole alkaloids. Among them, 18-methylenevincadifformine (I) seemed to be a versatile synthetic intermediate, the allyl grouping having been already utilised in aspidospermane alkaloids chemistry[3,4]. In order to achieve this objective, the Kuehne´s excellent stereospecific approach[5] was successfully adopted.

Thus, alkylation of cyclohexylimine of 4-pentenal[6] (II) with chlorobromopropane in the presence of LDA[7] followed by acid hydrolysis at pH 3 for 15 h (RT) gave 2-allyl-5-chloropentanal (III) [78 %; bp 63 °C/80 Pa; ^{1}H-NMR ($CDCl_3$) δ 9.62 (1H, d, J=1 Hz), 5.70 (1H), 5.10 (1H), 3.55 (2H); IR ($CHCl_3$) 2820, 2700, 1715, 1636 cm^{-1}]. This aldehyde was reacted with methyl 1-methyl-1,2,3,4-tetrahydropyrido[3,4-b]indole-1-carboxylate (IV)[5,8] to give, after heating in toluene under reflux for 115 h followed by 15 h refluxing in the presence of DBU, the desired 18-methylenevincadifformine (I) [50,5 %; mp 108-110,5 °C (acetonitrile); ^{1}H-NMR ($CDCl_3$) δ 8.90 (1H, bs), 7.20-6.60 (4H, complex), 5.50 (1H, com- 4.82 (1H, bd, J=10 Hz), 4.63 (1H, bd, J=16 Hz), 3.71 (3H, s); IR ($CHCl_3$) 3340, 1670, 1600 cm^{-1}; UV (MeOH) nm (log ε) 331 (4,078), 300 (3,954), 227 (4,033)].

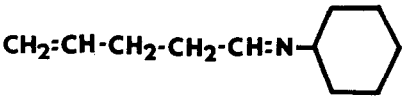
Aspidospermane alkaloids possessing a β-anilinoacrylate moiety can be easily converted to the corresponding indolenines by hydrolysis and decarboxylation[9]. However, when the base I was subjected to alkaline hydrolysis, and the acid VII thus obtained (quant. yield) was refluxed in 3 % aqueous hydrochloric acid for 25 minutes, the only product isolated in almost quantitative yield was identified as the dieneimine VIII [94,5 %; mp 142-146 °C (ether); ^{1}H-NMR ($CDCl_3$) δ 6.67-6.13 (4H, complex), 3.08-0.76 (20H, complex); IR ($CHCl_3$) 2939, 2867, 2781, 1635, 1556 cm^{-1}; UV nm (log ε): (MeOH-H_2O 1:1) 319 (3,571), 259min (2,130), (MeOH-0,1 N HCl 1:1) 351 (3,616), 295min (2,838), 260 (3,318)].

The primary process involved in mass spectrometry of imine VIII is very pro-

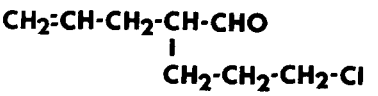


I : R = Me

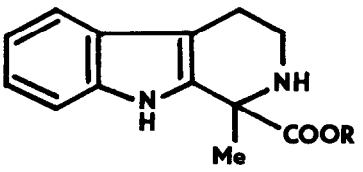
VII : R = H



II

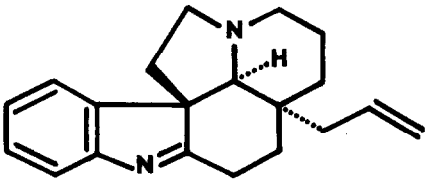


III



IV : R = Me

V : R = Et



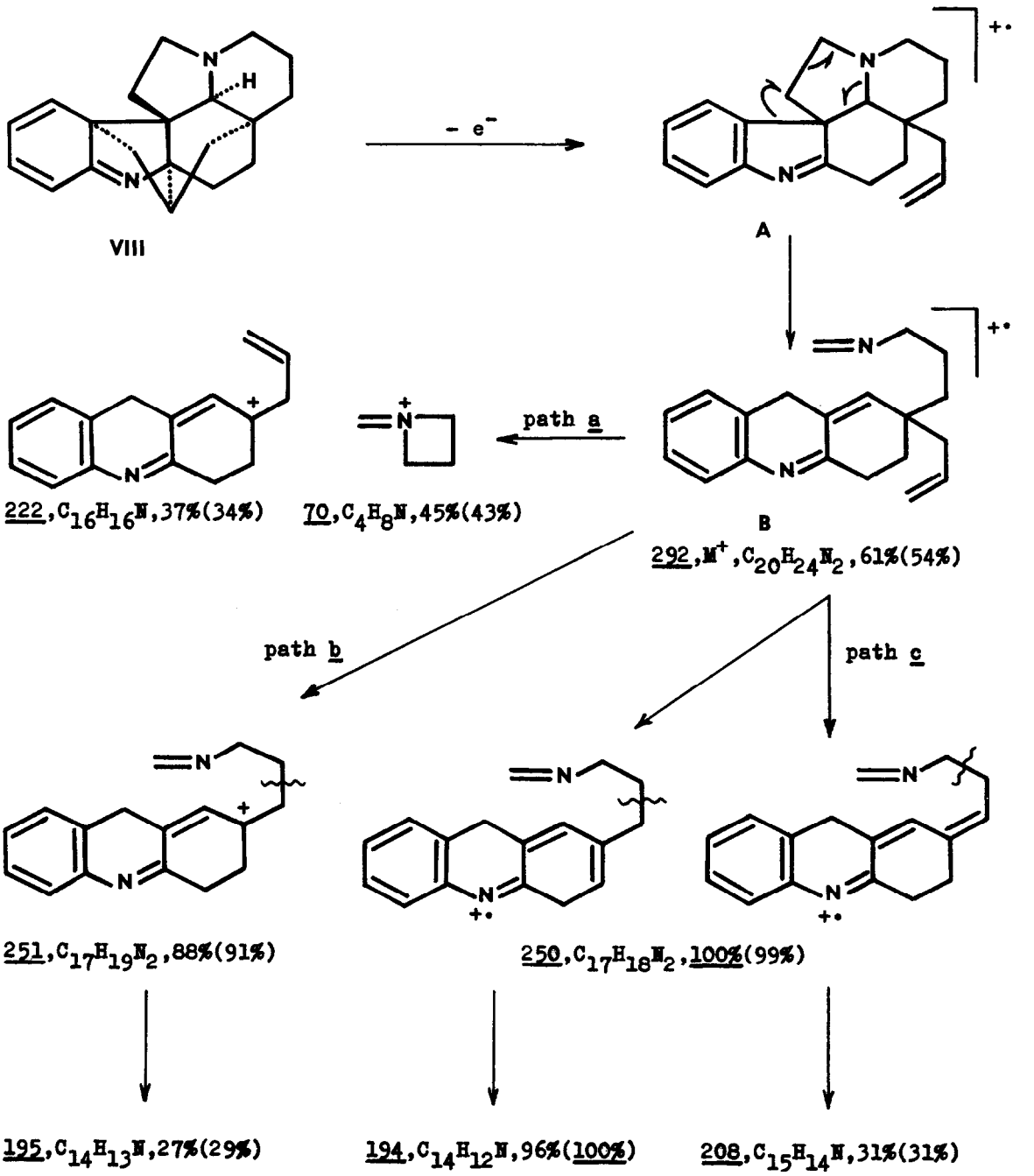
VI

bably a retro-Diels-Alder opening[10] (scheme 1). Therefore, the mass spectral fragmentation pattern should parallel that of 1,2-dehydroaspidospermidine and its congeners[11], as evidenced by strong peak at m/z 70 (C_4H_8N, 45 %). However, substantial differences in number of intense peaks are observed, which may be attributed to the presence of allyl side chain. The structure B may be fragmented in several ways. Apart from characteristic $[M - C_4H_8N]^+$ fragment (path a), the loss of allyl grouping (path b) or of elements of propene by cyclic mechanism (path c; ions of m/z 250, base peak) becomes important in this case.

On the other hand, the oily 18-methylene-1,2-dehydroaspidospermidine[10] (VI) is exclusively formed when the decarboxylation of acid VII is carried out in boiling benzene (96 %), even in the presence of p-toluenesulphonic acid. The dieneimine VIII is produced in trace amounts only even by decarboxylation in acetic acid at 100 °C. A remarkable effect of strong acids on the rate of the cycloaddition reaction is illustrated by the fact that the indolenine VI is quantitatively transformed into the cycloadduct VIII by 15 minutes refluxing in 1-3 % aqueous hydrochloric acid.

To our knowledge, this is the first case of intramolecular [4+2] cycloaddition reaction of indolenines. Inspection of molecular models clearly shows that the double bond of the allyl group is ideally oriented with respect to

SCHEME 1


VIII
- e⁻
A
path a
path b
path c
222, C16H16N, 37%(34%)
70, C4H8N, 45%(43%)
B
292, M+, C20H24N2, 61%(54%)
251, C17H19N2, 88%(91%)
250, C17H18N2, 100%(99%)
195, C14H13N, 27%(29%)
194, C14H12N, 96%(100%)
208, C15H14N, 31%(31%)

the plane of the indolenine moiety.

Experiments are now in progress as to the scope and utility of this reaction.

REFERENCES and NOTES

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3) Saxton J.E., Smith A.J., Lawton G.: Tetrahedron Lett. 1975, 4161; Lawton G., Saxton J.E., Smith A.J.: Tetrahedron 33, 1641 (1977)

4) Hájíček J.: PhD. Thesis, Prague 1980; Hájíček J., Trojánek J.: Paper presented at the Meeting on Bioorganic Chemistry, May 2-4, 1979, Liblice, Czechoslovakia

5) Kuehne M.E., Huebner J.A., Matsko T.H.: J. Org. Chem. 44, 2477 (1979)

6) Prepared by condensation of 4-pentenal with cyclohexylamine in 74,5 % yield; bp 87-88,5 °C/1,1 kPa

7) Kuehne M.E., Matsko T.H., Bohnert J.C., Kirkemo C.L.: J. Org. Chem. 44, 1063 (1979)

8) Prepared in 82 % yield by base catalyzed transesterification (NaOMe-MeOH, 1 h reflux) of the ethyl ester V, which in turn was obtained by condensation of tryptamine hydrochloride with ethyl pyruvate in refluxing ethanol; 82,5 %; mp 114-115 °C

9) Zsadon B., Otta K.: Acta Chim. Acad. Sci Hung. 69, 87 (1971) and references cited therein

10) The mass spectrum is almost identical with that of indolenine VI; for relative intensities of VI see scheme 1, in parentheses

11) Biemann K., Spitteller G.: J. Amer. Chem. Soc. 84, 4578 (1962)

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