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MODEL STUDIES IN THE VINOXINE SERIES

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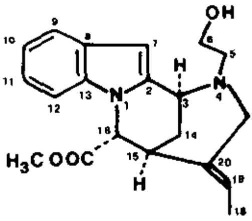
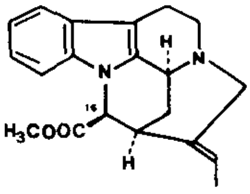
Abstract- The synthesis of 1a, fundamental tetracyclic framework of vinoxine, and its 16-methoxycarbonyl substituted analogue 1b by mercuric acetate oxidation of appropriate 1-(4-pyridylmethyl)indoles is described.

Vinoxine,[1] a minor alkaloid isolated from *Vinca minor* L., has an unusual structure lacking the characteristic tryptamine unit present in the greater part of indole alkaloids and having a bridged 2,7-diazabicyclo[3.3.1]nonane moiety as pleiocarpamine.[2] In contrast to pentacyclic structures related to the latter alkaloid,[3] no synthesis for vinoxine or for simplified analogues has been described.

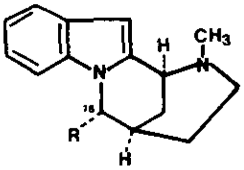
We report here the synthesis of 1a and 1b, which can be considered, respectively, as the fundamental tetracyclic framework of vinoxine and a more complex structural analogue possessing the 16-methoxycarbonyl[4] substituent of the natural product.



VINOXINE



PLEIOCARPAMINE



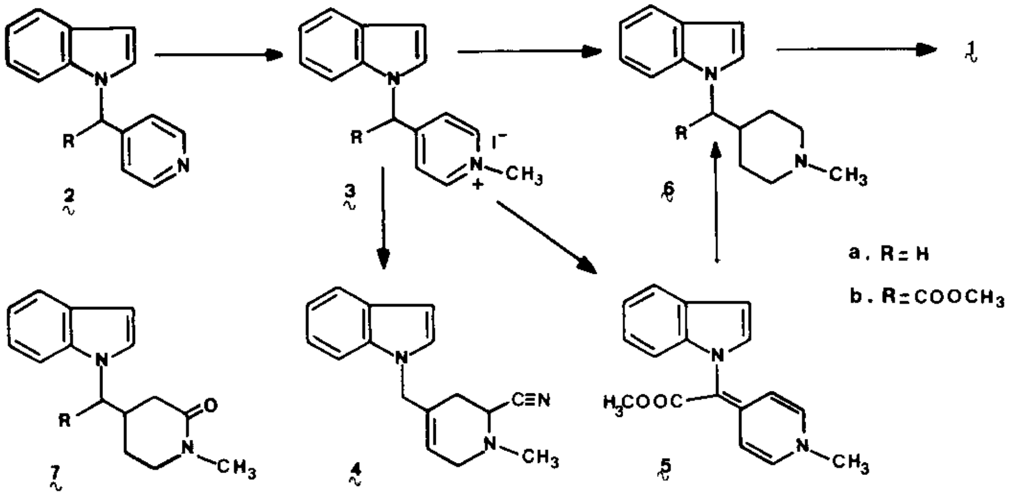
1a. R=H
1b. R=COOCH$_3$

Our synthetic approach implies formation of the C$_2$-C$_3$ bond[4] in the last synthetic step through intramolecular cyclization between the indole nucleus and an iminium salt generated by mercuric acetate oxidation of a suitable piperidine 6. Thus, condensation between indole and 4-chloromethylpyridine hydrochloride[5] (KOH, DMSO, 4 h, rt, 92%) afforded pyridylmethylindole 2a[6] which, by reaction with methyl iodide (90%) and further catalytic hydrogenation (PtO$_2$, 89%) of the resulting pyridinium salt **3a**, led to the piperidine **6a**.

Attempts to obtain **2b** by N-alkylation of indole with methyl α-bromo-4-pyridineacetate[7] failed. However, **2b** was obtained in 72% yield by carboxylation of **2a** (n-BuLi, THF, 1 h, -30°C, CO_2 gas, rt) and subsequent esterification (2.5 N MeOH/HCl, 17 h, rt). When n-BuLi was used as a base and dimethyl carbonate as acylating agent, **2b** was only obtained in 30-40% yield, similar to those reported in related cases.[8] Quaternization of **2b** (CH_3I, 12 h, rt) gave an unstable pyridinium salt **3b** which was converted into the vinylogous urethane **5** (60% yield from **2b**) on basic treatment (5% aqueous $NaHCO_3$). Catalytic hydrogenation (PtO_2) of **5** gave (93%) piperidine **6b**.

Finally, oxidative cyclization of piperidines **6a** and **6b** by means of mercuric acetate (5 eq.) in aqueous solution (1 h, reflux) in the presence of EDTA.2Na (5 eq.) afforded, after sodium borohydride treatment, the desired tetracyclic compounds **1a**[9,10] (40%) and **1b**[11] (10%), respectively. In both cases, the corresponding starting piperidine **6** and lactam **7** were isolated as by-products, the latter coming from nucleophilic attack of water to the initially formed iminium salt and further oxidation of the resulting carbinolamine.

Another approach to the iminium salt required for cyclization to **1a** based on the behavior of α-aminonitriles under acid conditions[12] was unsuccessful. Thus, 2-cyanotetrahydropyridine **4**, obtained by reductive cyanation[13] ($NaBH_4$, NaCN, H_2O, Et_2O, 60%) of **3a**, could not be reduced to the required 2-cyanopiperidine because of the easy hydrogenolysis of the cyano group.



The relative configuration of the methoxycarbonyl group in **1b**, coincident with that of vinoxine, was inferred from the chemical shift (δ4.81) of the C_{16}-H proton in the nmr spectrum. This chemical shift is similar to the one observed in vinoxine[1] (δ4.84) and in 16-epipleiocarpamine[2] (δ4.74) but different from the one reported for pleiocarpamine[2] (δ5.26).

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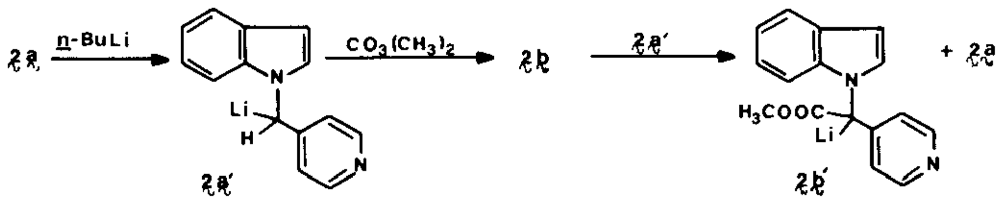
3. (a) D. D. O'Rell, F. G. H. Lee, and V. Boekelheide, *J. Am. Chem. Soc.*, 1972, **94**, 3205; (b) S. Sakai and N. Shinma, *Chem. Pharm. Bull.*, 1974, **22**, 3013; (c) S. Sakai and N. Shinma, *Heterocycles*, 1976, **4**, 985; (d) S. Sakai and N. Shinma, *Yakugaku Zasshi*, 1978, **98**, 950; (e) M. J. Caverley, J. B. Banks, and J. Harley-Mason, *Tetrahedron Lett.*, 1981, **22**, 1635.
4. The biogenetic numbering is used throughout this paper. J. Le Men and W. I. Taylor, *Experientia*, 1965, **21**, 508.
5. H. S. Mosher and J. E. Tessieri, *J. Am. Chem. Soc.*, 1951, **73**, 4925.
6. All new compounds gave ir, nmr and elemental analyses consistent with the proposed structures except **2b** which was characterized by ir and nmr alone.
7. This compound was obtained by bromination of methyl 4-pyridineacetate by the procedure described for the 2-substituted isomer: O. E. Edwards, M. Chaput, F. H. Clarke, and T. Singh, *Can. J. Chem.*, 1957, **32**, 785.
8. It is well known that acylations on disubstituted carbanions proceed only to the extent of 50% reaction since the acylated product (**2b** in our case) undergoes further ionization by the original carbanion **2a**' to give the corresponding conjugate acid and a stabilized carbanion (**2b**').



See: (a) E. M. Kaiser, L. E. Solter, R. A. Schwarz, R. D. Beard, and C. R. Hauser, *J. Am. Chem. Soc.*, 1971, **93**, 4237; (b) C. R. Hauser, F. W. Swamer, and J. T. Adams, *Organic Reactions*, 1954, **8**, 113.

9. Nmr ($CDCl_3$): δ 2.30 (s, 3H, NCH_3), 3.90 (br, 1H, C_3-H), 4.10 (d, J=4 Hz, 2H, C_{16}-H), 6.10 (s, 1H, C_7-H).

10. **1a** was also obtained in low yield (<10%) by the modified Polonovski reaction from the N-oxide corresponding to piperidine **6a**. A. Ahond, A. Cavé, C. Kan-Fan, and P. Potier, *Bull. Soc. Chim. France*, 1970, 2707.

11. Nmr ($CDCl_3$): δ2.20 (s, 3H, NCH_3), 3.55 (s, 3H, OCH_3), 3.90 (br, 1H, C_3-H), 4.81 (s, 1H, C_{16}-H), 6.21 (s, 1H, C_7-H).

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