A NEW SYNTHETIC ROUTE TO INDOLOQUINOLIZIDINE ALKALOIDS†

Tozo Fujii,* Shigeyuki Yoshifuji, and Harue Ito

Faculty of Pharmaceutical Sciences, Kanazawa University

Takara-machi, Kanazawa 920, Japan

Syntheses of 1-[2-(3-indolyl)ethyl]-2-piperidone (Va) and ethyl dl-trans-1-[2-(3-indolyl)ethyl]-5-ethyl-2-oxo-4-piperidineacetate (Vb) from the lactams Ia,b have been accomplished in acceptable overall yields through the lactim ethers IIa,b, the lactam ketones IIIa,b, and the lactam alcohols IVa,b, concluding formally the total syntheses of 1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine (VIa), dl-dihydrocorynantheine (VId), and related alkaloids (VIc,e).

Of primary importance to the entire problem of our recent alkaloid synthesis in the dl-emetine,[1,2] dl-ankorine,[2] dl-alangicine,[3] and related areas was the question of introduction of an adequate phenethyl carbon skeleton onto the nitrogen of ethyl dl-trans-5-ethyl-2-oxo-4-piperidineacetate (Ib), which was readily prepared[4] and characterized fully[5] in our laboratory. We found a general synthetic route to N-(2-arylethyl)lactams from 5-, 6-, and 7-membered lactams through conversion into lactim ethers followed by N-alkylation with a phenacyl bromide, re-

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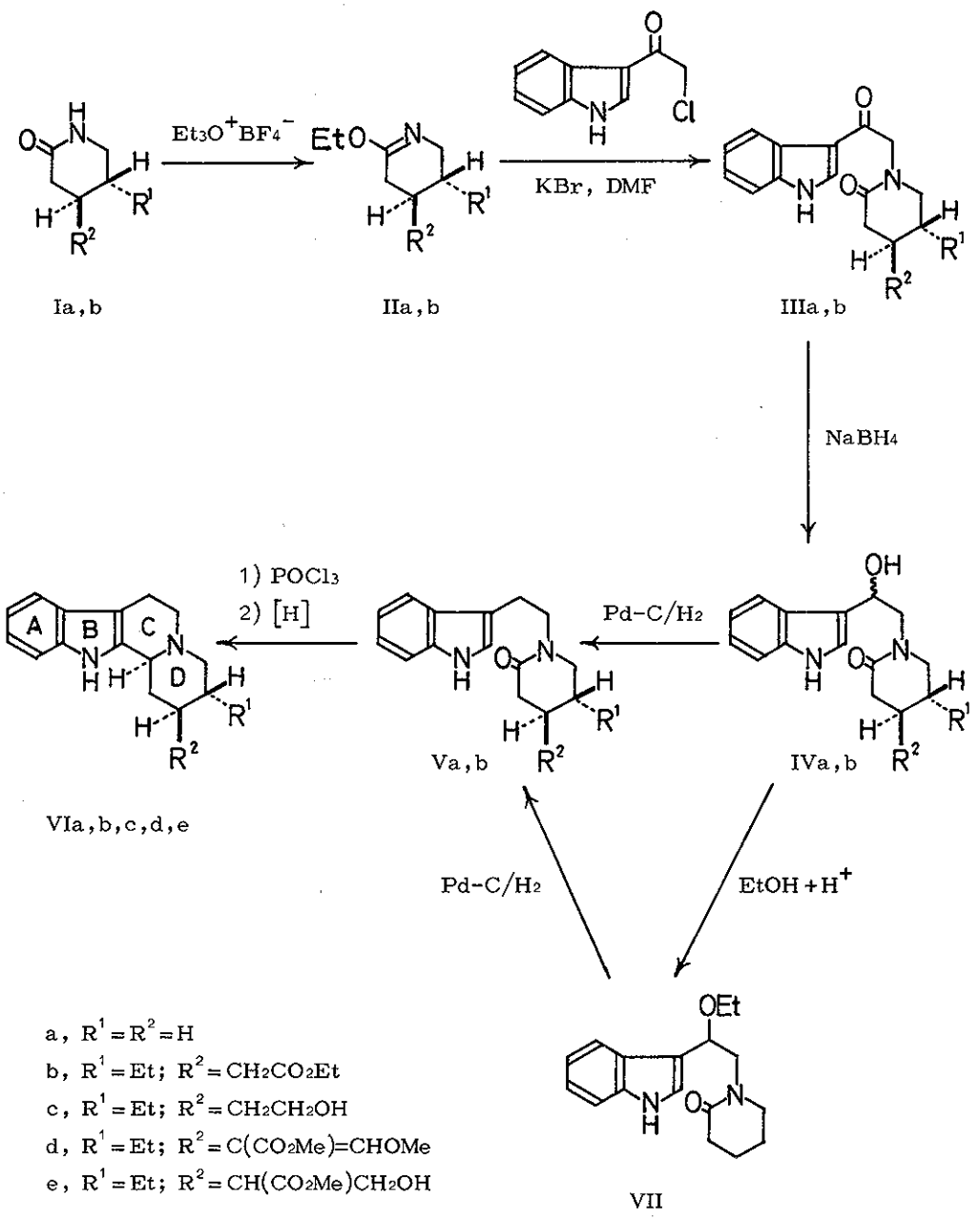
†Dedicated to Professor R. B. Woodward on the occasion of his sixtieth birthday.



a, $R^1 = R^2 = H$

b, $R^1 = Et$; $R^2 = CH_2CO_2Et$

c, $R^1 = Et$; $R^2 = CH_2CH_2OH$

d, $R^1 = Et$; $R^2 = C(CO_2Me)=CHOMe$

e, $R^1 = Et$; $R^2 = CH(CO_2Me)CH_2OH$

duction of the carbonyl group, and hydrogenolysis of the resulting benzylic hydroxyl group.[6] When brought into practice, this "lactim ether method"[6] worked satisfactorily in the integral part of the above alkaloid syntheses. Now we report the results of our synthetic studies in the indoloquinolizidine alkaloid area, which have enlarged the scope of the "lactim ether method" operations.

Treatment of the O-ethyllactim IIa, prepared in 84% yield from the lactam Ia according to the literature,[7] with 3-chloroacetylindole[8] in N,N-dimethylformamide (DMF) at 60° in the presence of KBr for 24 hr gave the lactam ketone IIIa (mp 240–241°)[9] in 71% yield. Reduction of IIIa with $NaBH_4$ (80% aq. EtOH, room temp., 20 hr) produced the lactam alcohol IVa (96% yield; mp 178–179°), which was then hydrogenolyzed [Pd-C/H_2, EtOH, 70% aq. $HClO_4$ (0.01 molar equiv.), 1 atm, room temp., 50 min] to the lactam Va (96% yield; mp 155–156°), identical with an authentic sample.[10] The hydroxyl group of IVa at the benzylic position was found to be considerably reactive: on treatment with EtOH in the presence of a catalytic amount of HCl at room temp. for 1 hr, the lactam alcohol IVa produced the ethoxy derivative VII (mp 138–139°) in 94% yield. Catalytic hydrogenolysis of VII to the lactam Va (94% yield) was smoothly effected under reaction conditions similar to those used in the conversion of IVa into Va, but only less satisfactory when carried out in the absence of $HClO_4$.

Dehydrocyclization of the lactam Va ($POCl_3$, boiling benzene, 75 min)[10] and reduction of the resulting quaternary salt ($NaBH_4$, MeOH, room temp., 1 hr)[10] furnished the tetracyclic base VIa (95% overall yield from Va; mp 152.5–153°), which was identified (by mixed melting-point test and comparison of ir, nmr, and mass spectra and chromatographic behavior) with an authentic sample.[10] The tetracycle VIa is the simplest of the indoloquinolizidine alkaloids and its l-isomer has been isolated[11] in partially racemic form from Dracontomelum mangiferum Bl. Although more than a score of synthetic routes to this parent framework (VIa)

have been reported,[10,12] our route described above may be of value, not only in preparing the alkaloid material (VIa) in an acceptable overall yield, but also in the design and execution of total syntheses of analogous alkaloids carrying substituents in ring A and/or ring D.

In order to assess the applicability of the "lactim ether method" to synthesis of more complex indoloquinolizidine alkaloids, we next tried to synthesize dl-dihydrocorynantheine (VId) and related alkaloids from the lactam ester Ib. Treatment of the lactim ether IIb, obtained quantitatively from Ib[4,5] by a method given in the literature,[13] with 3-chloroacetylindole[8] in DMF at 60° in the presence of KBr for 32 hr furnished the lactam ketone IIIb (70% yield; mp 135–136°), which was reduced ($NaBH_4$, EtOH, room temp., 3 hr) to afford a diastereoisomeric mixture of the lactam alcohol IVb (70% yield; mp 122–123°). Catalytic hydrogenolysis of the diastereoisomeric mixture [Pd-C/H_2, EtOH, 70% aq. $HClO_4$ (0.01 molar equiv.), 1 atm, room temp., 60 min] gave the lactam ester dl-Vb (74% yield; mp 107–108°), identical (by mixed melting-point test and comparison of ir spectrum and chromatographic behavior) with an authentic sample[14] kindly provided by Professor van Tamelen.

The lactam ester dl-Vb has been shown to lead to dl-dihydrocorynantheine (dl-VId)[14,15] and dl-dihydrocorynantheol (dl-VIc)[16] through the tetracyclic amino-ester dl-VIb,[14] and d-dihydrocorynantheine (d-VId) has been converted into l-dihydrositsirikine (l-VIe).[17] Accordingly, the above results (Ib → IIb → IIIb → IVb → Vb) imply that an alternative synthesis of each of these alkaloids has now been completed formally.

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REFERENCES

1 T. Fujii and S. Yoshifuji, Abstracts of Papers, 40th Meeting of Hokuriku Branch, Pharmaceutical Society of Japan, Kanazawa, Japan, June 21, 1975, p. 3.

2 T. Fujii, S. Yoshifuji, and K. Yamada, Tetrahedron Letters, 1975, 1527.

3 T. Fujii, K. Yamada, S. Yoshifuji, S. C. Pakrashi, and E. Ali, Tetrahedron Letters, 1976, 2553.

4 T. Fujii, Chem. Pharm. Bull. (Tokyo), 1958, 6, 591.

5 T. Fujii, S. Yoshifuji, and M. Tai, Chem. Pharm. Bull. (Tokyo), 1975, 23, 2094, and references cited.

6 T. Fujii, S. Yoshifuji, and K. Yamada, Chem. Ind. (London), 1975, 177.

7 T. Oishi, M. Nagai, T. Onuma, H. Moriyama, K. Tsutae, M. Ochiai, and Y. Ban, Chem. Pharm. Bull. (Tokyo), 1969, 17, 2306.

8 (a) J. Bergman, J. Heterocyclic Chem., 1970, 7, 1071; (b) J. Bergman, J.-E. Bäckvall, and J.-O. Lindström, Tetrahedron, 1973, 29, 971.

9 The assigned structures were supported by satisfactory elemental analyses and/or ir, nmr, and mass spectral evidence.

10 M. Nakagawa, M. Kiuchi, M. Obi, M. Tonozuka, K. Kobayashi, T. Hino, and Y. Ban, Chem. Pharm. Bull. (Tokyo), 1975, 23, 304.

11 S. R. Johns, J. A. Lamberton, and J. L. Occolowitz, Austral. J. Chem., 1966, 19, 1951.

12 (a) ref. 10 in ref. 10; (b) S. Yamada and T. Kunieda, Chem. Pharm. Bull. (Tokyo), 1967, 15, 499; (c) C. A. Scherer, C. A. Dorschel, J. M. Cook, and P. W. Le Quesne, J. Org. Chem., 1972, 37, 1083; (d) H.-P. Husson, L. Chev-

olot, Y. Langlois, C. Thal, and P. Potier, J. Chem. Soc., Chem. Commun., 1972, 930; (e) E. E. van Tamelen, J. Webber, G. P. Schiemenz, and W. Barker, Bioorg. Chem., 1976, 5, 283.

13 M. Uskoković, C. Reese, H. L. Lee, G. Grethe, and J. Gutzwiller, J. Am. Chem. Soc., 1971, 93, 5902.

14 (a) E. E. van Tamelen and J. B. Hester, Jr., J. Am. Chem. Soc., 1959, 81, 3805; (b) E. E. van Tamelen and J. B. Hester, Jr., J. Am. Chem. Soc., 1969, 91, 7342.

15 J. A. Weisbach, J. L. Kirkpatrick, K. R. Williams, E. L. Anderson, N. C Yim, and B. Douglas, Tetrahedron Letters, 1965, 3457.

16 C. Szántay and M. Bárczai-Beke, Chem. Ber., 1969, 102, 3963.

17 J. P. Kutney and R. T. Brown, Tetrahedron, 1966, 22, 321.

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