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A TOTAL SYNTHESIS OF dl-VELBANAMINE

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Velbanamine (1a) constitutes the tetracyclic indole moiety of the dimeric alkaloids, vinblastine (2a) and vincristine (2b) (1), and was obtained during structure elucidation studies (1a, 2) on the latter alkaloids. The reported syntheses of 1a, a potential intermediate for the preparation of the oncolytic alkaloids (2a) and (2b), utilized conversion of the Iboga alkaloid skeleton into the cleavamine ring system by a retro-aldol reaction (3) or a 1,4-fragmentative solvolysis (4). We now present a total synthesis of dl-velbanamine in which an indole of the simple Iboga structure, easily prepared by a method established previously in our laboratory (5), was converted into the cleavamine type indole by an oxidative fragmentation.

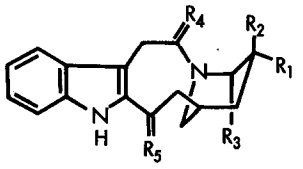
With the idea that the fragmentation as depicted in the figures (3a) or (3b) would give the keto enamine (4a) and that the enamino group might be utilized for the introduction of the functional group at C-4, oxidative fragmentation of the hydroxyl amine (5a) was investigated first. The keto amide (6) (5a) was treated with perchloric acid in acetic acid at 25° to give the hydroxyl lactam (5b), mp 296-300° (d), in 78% yield, aluminum hydride reduction (5c) of which at -18 to 0° afforded the desired hydroxyl amine (5a), mp 187-188°, in 77% yield. Oxidation of 5a with an excess of lead tetraacetate in pentane-benzene at 0° proceeded rapidly to produce an α-acyl indole, mp 220.5-221°, to which the rearranged structure (7a) was assigned from the spectral data: ir ($CDCl_3$) 1763 cm^{-1}; nmr ($CDCl_3$) 3.25τ (d, J 5.2 Hz, 4a-H); m/e 384, 253 (8a). Oxidation in methanol at 0 to 5° also furnished the rearranged acetal (7b), mp 216-219°; nmr ($CDCl_3$) 5.84 τ (d, J 6.3 Hz, 4a-H); m/e 328, 253 (8a). In both cases, the desired fragmentation did in fact occur but it was accompanied by subsequent rapid oxidation of the resulting enamine (4a) followed by rearrangement.

The difficulty was eliminated by using the hydroxyl lactam (5b) as the starting material. Thus, oxidation with lead tetraacetate in methanol-tetrahydrofuran at 0° produced the methoxy ketolactam (1b), mp 133-135/167-167.5°, in 44% yield: nmr ($CDCl_3$) τ 4.36 (t, J 2.5 Hz, 5-H), 6.67 (s, OCH_3); m/e 312, and the acetoxy

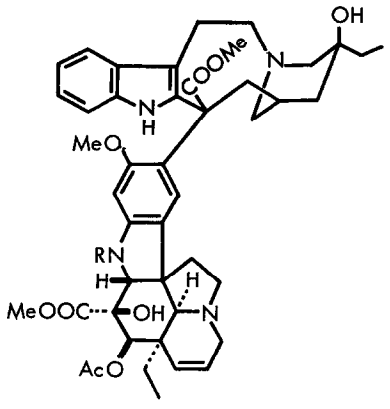
indolenine (9), mp 224.5-225°, in 11% yield; ir (KBr) 1764 cm^{-1}; m/e 340, 280. The skeleton of 1b was confirmed based on the mass spectrum of the product (1c) obtained on reduction with aluminum hydride (5c) at -60°, which showed the base peak at m/e 110 attributable to 10a analogous to that for 10b observed in the mass spectrum of velbanamine (1a) (1a). Fusion of 1b with a catalytic amount of p-toluenesulfonic acid or potassium hydrogen sulfate at 165-175° under reduced pressure yielded the keto enamide (4b), mp 252.5-253° (d), in 70% yield; nmr (d_6-DMSO) τ 3.14 (d of ms, J 8 Hz, 5-H), 4.74 (br. Wh/2 16 Hz, 4-H); m/e 280, accompanied by a small amount of a methyl ester, mp 238-239° (d), the structure of which was tentatively assigned as described in 11 based on mechanistic considerations and its spectral data: ir (KBr) 1735, 1604 cm^{-1}; nmr (d_6-DMSO) 6.40 τ (s, OCH_3); m/e 312, 311.

Several attempts to introduce an oxygen atom at the C-4 position were carried out. Lead tetraacetate oxidation of 4b in dioxane at 42° afforded the desired diacetoxy ketolactam (1d), mp above 285° (browning); ir (KBr) 1746 cm^{-1}; nmr (d_6-DMSO) τ 2.99 (d, J 4.2 Hz, 5-H), 5.11 (br, Wh/2 19 Hz, 4-H), and the rearranged isomer (7c), mp 245-247° (d): ir (KBr) 1764 cm^{-1}; nmr (d_6-DMSO) 3.19 τ (d, J 4.2 Hz, 4a-H), in yields of 30 and 9% , respectively. The structures of the skeletons of both diacetoxy ketolactams (1d) and (7c) were determined on the basis of the electron impact fragmentations of the corresponding diol amines (1e) and (7d) obtained on aluminum hydride reduction (5c) at -50°, in which the formation of the ions (10c) and (8b), respectively, was deduced, thereby confirming the structures. Reduction of 1d with lithium aluminum hydride (6) in boiling dioxane gave the amorphous amino alcohol (1f) in 16% yield: m/e 270, 126 (10c) [(the acetate (1g), mp 170-171°: nmr ($CDCl_3$) 5.05 τ (septuplet, J 5 Hz, 4-H)], the isomeric amino alcohol (7e), mp 156-159°; in 23% yield: m/e 270, 239 (8c), and the vinyl amine (12), mp 122-124° ; in 9% yield: ir ($CHCl_3$) 1640, 994, 915 cm^{-1}; nmr ($CDCl_3$) multiplets centered at τ 4.24, 4.92, 5.11 (vinyl protons); m/e 252, 251, 209 (13). The last compound was identified with one of products (7), (1h) and (12), of reduction with lithium aluminum hydride of the ketolactam (1i), mp 224.5-225°, prepared by hydrogenation of 4b. Unsatisfactory results were obtained on attempted hydroboration of 4b with diborane or disiamylborane followed by alkaline hydrogen peroxide oxidation; the resulting basic product, consisting mainly of the diol amines, on further drastic reduction with lithium aluminum hydride gave a yield of 1f only comparable with that described above.

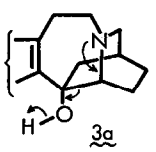
Oxidation of 4b with osmium tetroxide (4) and subsequent treatment with hydrogen sulfide produced the desired glycol (1j), mp 195.5-197° (d), as the sole isolable product in a yield of 55%.. On reduction with



	R_1	R_2	R_3	R_4	R_5
1a,	Et	OH	H	H_2	H_2
1b,	H	H	OMe	O	O
1c,	H	H	H	H_2	H, OH
1d,	OAc	H	OAc	O	O
1e,	OH	H	H	H_2	H, OH
1f,	OH	H	H	H_2	H_2
1g,	OAc	H	H	H_2	H_2
1h,	H	H	H	H_2	H_2
1i,	H	H	H	O	O
1j,	OH	H	OH	O	O
1k,	=O		H	H_2	H_2
1l,	OH	Et	H	H_2	H_2

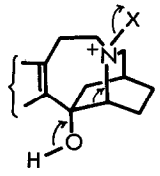


2a, R = CH_3
2b, R = CHO

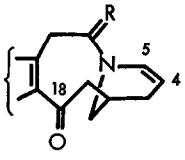


3a

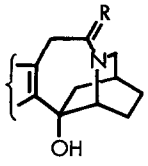
or



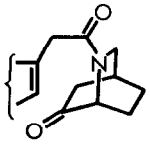
3b



4a, R = H_2
4b, R = O



5a, R = H_2
5b, R = O



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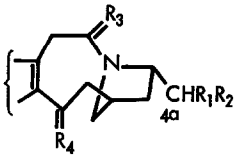
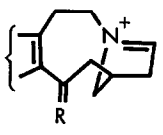
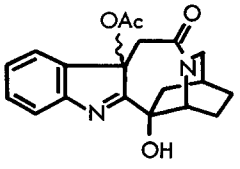


	R_1	R_2	R_3	R_4
7a,	OAc	OAc	H_2	=O
7b,	OMe	OMe	H_2	=O
7c,	OAc	OAc	=O	=O
7d,	OH	H	H_2	H, OH
7e,	OH	H	H_2	H_2



	R	m/e
8a,	O	253
8b,	H, OH	255
8c,	H_2	239



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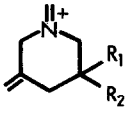
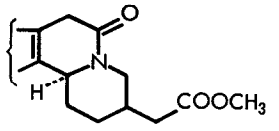


	R_1	R_2	m/e
10a,	H,	H	110
10b,	Et,	OH	154
10c,	H	OH	120
10d,	=O		124



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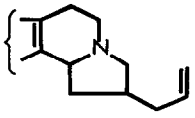

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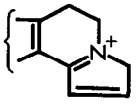
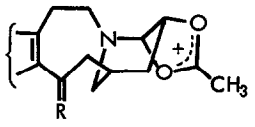
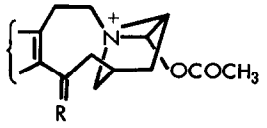


13, m/e 209



14a, R = O
14b, R = H, OH



15a, R = O
15b, R = H, OH

lithium aluminum hydride in refluxing dioxane 1j afforded 1f and 12 in 29 and 13% yield, respectively. Absence of the rearranged amino alcohol (7e) in the products was confirmed, suggesting the important role of the acetoxy group at C-4 in the rearrangements observed in the lead tetraacetate oxidation of the enamine (4a) and in the drastic hydride reduction of the diacetoxy ketolactam (1d). As plausible intermediates, 14a and 14b are suggested for these reactions, respectively, and the rearrangement would proceed through the formation of the corresponding aziridinium compounds (15a) and (15b), respectively. Oppenauer oxidation in a sealed tube with argon, using aluminum tri-tertiary butoxide and cyclohexanone, gave mainly the amino ketone (1k): ir ($CHCl_3$) 1717 cm^{-1}; m/e 268, 124 (10d). An attempt to purify the product by layer chromatography reduced the yield substantially and therefore the crude material was used for the next reaction. Treatment with ethylmagnesium bromide twice proceeded unexpectedly to give a mixture of almost equal amounts of the ethylhydrins. The more mobile material obtained in a yield of 5% based on 1j: ir (CCl_4) OH, 3394, 3291 cm^{-1}; was proved to be dl-velbanamine (1a) by comparison of its tlc behavior and its ir and mass spectra with those of an authentic sample of natural velbanamine (8). The less mobile ethylhydrin obtained in 4% yield: ir (CCl_4) OH, 3605 cm^{-1}, was proved to be dl-isovelbanamine (1l) by comparison with optically active isovelbanamine (4,8). The optically active velbanamine was separated as its salt of dl-p-tolyl-l-tartrate, mp 143-144° (3b).

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7) Reduction of 18-oxo-quebrachamine lactam with lithium aluminum hydride in boiling dioxane has been reported to yield 1,18-dehydroquebrachamine and quebrachamine. However, there are some ambiguities in the structure of the former compound. See: F. E. Ziegler, J. A. Klock, and P. A. Zoretic, J. Am. Chem. Soc. 91, 2342 (1969).

8) The authors are very grateful to Prof. G. Buchi of M. I. T. and Dr. N. Neuss of Eli Lilly Co., for the supply of the sample of natural velbanamine and also to Prof. J. P. Kutney, University of Columbia, for the supply of the sample of isovelbanamine.