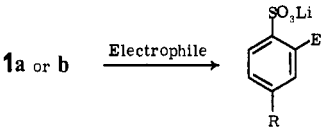
Table I. Reaction of 1a and 1b with Electrophiles

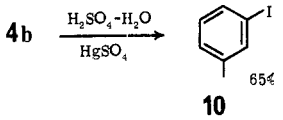


2a, 6a (R = H)
2-7b (R = CH_3)

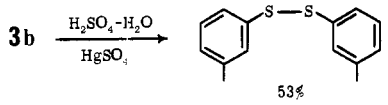
electrophile	product	E	% conversion
PhSSPh	2a	SPh	*a*
PhSSPh	2b	SPh	83
S_8	3b	S-S-*o*-$(SO_3Li)C_6H_3$-*m*-CH_3	85
I_2	4b	I	80
Br_2	5b	Br	40
p-$CH_3C_6H_4S(O)OEt$	6a	$S(O)C_6H_4$-*p*-CH_3	55
p-$CH_3C_6H_4S(O)O$-menthyl ($[\alpha]^{21}_D$ −202°)	6b	$S(O)C_6H_4$-*p*-CH_3 ($[\alpha]^{27}_D$ −103°)	67
acetone	7b	$C(CH_3)_2OH$	33

[a] The absence of a convenient NMR probe for 2a made it impractical to determine the percent conversion. The crude product was used in the preparation of 9 (see text).

difficult to obtain, is a well-known synthetic stratagem.[19] Our method allows easy access to such materials as meta-substituted toluenes through an easy desulfonation procedure. For instance, when ortho-iodo derivative **4b** (1 g) is boiled for 2 days with 100 mL of aqueous H_2SO_4 (50%) and $HgSO_4$ (10% based on moles of sulfonate)[20] in an apparatus (available from Aldrich Chemical Company) which allows continuous steam distillation with continuous extraction of products into CH_2Cl_2, *m*-iodotoluene (**10**)[21] is obtained in 65% isolated yield.[22] By the same process 3,3′-dimethyldiphenyl disulfide (**11**)[23] is obtained (53%)[22] from the desulfonation of **3b**.



10



11

The ortho lithiation of aromatic sulfonic acids makes it possible to introduce electrophilic substituents ortho to a sulfonate group. Acid hydrolysis of the sulfonic acid group provides a way to replace it by hydrogen, thus providing overall a new directing group which can be removed after it performs its directing function in a multistep synthesis of a substituted aromatic compound. Further work is currently being done to explore the full synthetic potential of this method.

(19) E. E. Gilbert, "Sulfonation and Related Reactions", Interscience, New York, 1965, Chapter 8, and references therein.
(20) For the use of $HgSO_4$ as a desulfonation catalyst, see G. Travagli, *Gazz. Chim. Ital.*, 81, 668 (1951).
(21) ^1H NMR for **10** ($CDCl_3$, 90 MHz): δ 7.72 (m, 2), 7.21 (m, 2), 2.40 (s, 3, CH_3). Mass spectrum: 218 (M^+·, 96%), 91 (M^+· − I, 100%).
(22) Since the starting material for the desulfonation is always a mixture of desired sulfonate, starting sulfonate, and LiCl, yields were calculated from the actual amount of desired sulfonate present, which was determined by NMR peak ratios in D_2O with acetone as an internal standard.
(23) Column chromatography on silica gel with hexane gave the pure disulfide. ^1H NMR for **11** ($CDCl_3$, 90 MHz): δ 7.20 (m, 4), 2.32 (s, 3, CH_3). Mass spectrum: 246 (M^+·, 100%), 123 (M^+· − $CH_3C_6H_4S$, 28%). Anal. Calcd for $C_{14}H_{14}S_2$: C, H, S.

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Garret D. Figuly, J. C. Martin*
Roger Adams Laboratory, University of Illinois
Urbana, Illinois 61801
Received May 27, 1980

Novel Synthesis of (±)-Velbanamine and (±)-Isovelbanamine

Summary: Reaction of the allyl lactams **6** (3α-H and 3β-H) with iodine in aqueous THF produced the iodo lactones **8** (3α-H and 3β-H), which were converted into (±)-velbanamine (**1**) and (±)-isovelbanamine (**2**), respectively.

Sir: We have developed[1] a new route for the synthesis of the nine-membered indole alkaloids related to the cleavamine-type alkaloids,[2] employing the thio-Claisen rearrangement[3] as a key step. However, its application has been limited to a saturated system. The syntheses of cleavamine[4] itself and its hydrated congeners, velbanamine[5-10] (**1**) and isovelbanamine[8-10] (**2**), which are potentially important for the syntheses of their parent alkaloids, oncolytic agents vinblastine[6] and vincristine,[6] and the *pandaca* alkaloids pandoline[11,12] and isopandoline[11,12] have not been accomplished. We now report here a synthesis of (±)-velbanamine (**1**) and (±)-isovelbanamine (**2**), which both are synthetic precursors[9] of cleavamine, from

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(3) Takano, S.; Yoshida, E.; Hirama, M.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1976**, 776.
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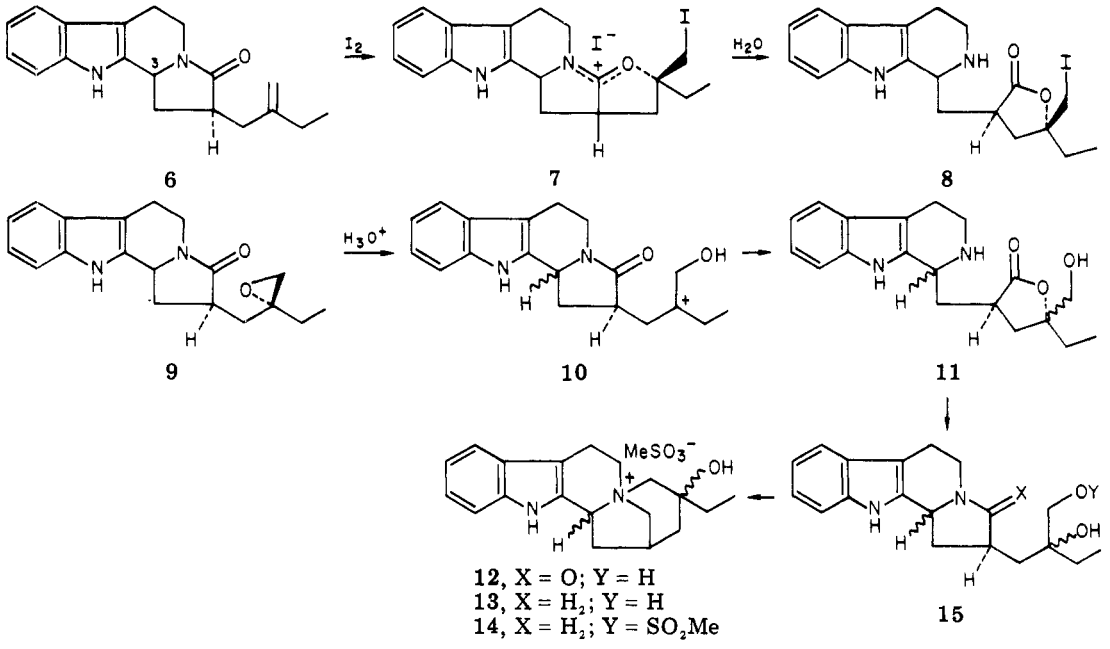
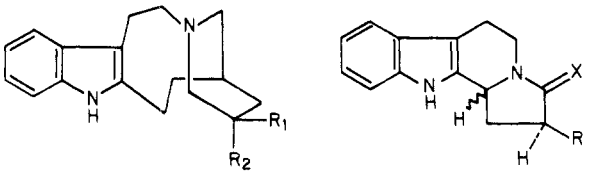
0022-3263/80/1945-3729$01.00/0

Scheme I



the known thiolactams[1] **4** (3α-H and 3β-H), respectively.



1, R_1 = Et; R_2 = OH
2, R_1 = OH; R_2 = Et

3, R = H; X = S
4, R = $CH_2C(Et)=CH_2$; X = S
5, R = $CH_2C(Et)=CH_2$; X = SMe^+I^-

Alkylation of **4** (3α-H and 3β-H), prepared from **3** and 2-ethylallyl bromide via the thio-Claisen rearrangement,[1] with methyl iodide gave the corresponding sulfonium iodides **5** (3α-H and 3β-H) which on hydrolysis[13] with aqueous sodium hydroxide (5% in MeOH, room temperature, 2 h) afforded the corresponding lactams[14] **6**. 3α-H isomer (93%): mp 174–175 °C; IR ($CHCl_3$) max 3250, 1660 cm^{-1}; NMR ($CDCl_3$) δ 1.02 (3 H, t, J = 7 Hz). 3β-H isomer (92%): mp 165.5–167 °C; IR ($CHCl_3$) max 3150, 1660 cm^{-1}; NMR ($CDCl_3$) δ 1.05 (3 H, t, J = 7 Hz). On exposure to iodine in aqueous tetrahydrofuran[15] (50%), each isomer of **6** gave the corresponding iodo lactones **8** selectively (Scheme I). 3α-H isomer (98%): amorphous foam; IR ($CHCl_3$) max 3250, 1750 cm^{-1}; NMR ($CDCl_3$) δ 0.82 (3 H, br t), 3.77 (2 H, t, J = 6 Hz), 4.33 (1 H, m), 5.63 (1 H, m). 3β-H isomer (98%): amorphous foam; IR ($CHCl_3$) max 3275, 1760 cm^{-1}; NMR ($CDCl_3$) δ 0.90 (3 H, t, J = 7 Hz), 3.92 (3 H, br s), 4.8 (1 H, m). The highly stereoselective outcome in the halolactonization may result from participation of the lactam carbonyl group, forming a rigid onium ion intermediate such as **7**. Treatment of each isomer of **8** with aqueous potassium hydroxide (room temperature, 5 h) yielded the epoxy lactams **9**, each as a single isomer. 3α-H isomer (96%): mp 206–208 °C; IR (Nujol) max 3280, 1650 cm^{-1}; NMR ($CDCl_3$) δ 0.90 (3 H, t, J = 7 Hz), 4.4–5.1 (2 H, m). 3β-H isomer (94%): mp 171–173 °C; IR (Nujol) max 3240, 1660 cm^{-1}; NMR ($CDCl_3$) δ 0.93 (3 H, t, J = 7 Hz), 4.6 (1 H, m), 5.0 (1 H, br t). When each of the isomeric epoxides **9** was exposed to dilute sulfuric acid (0.5 N, room temperature, 2 h), each generated the amino lactone **11**, IR ($CHCl_3$) max 1740 cm^{-1}, as an unseparable mixture of stereoisomers, presumably through carbonium ion intermediate **10**, and the crude product was converted into the lactam diol **12**, respectively, each as an unseparable mixture of stereoisomers, by refluxing in methanol (1 h). 3α-H isomer (92.4% overall yield): IR ($CHCl_3$) max 1640 cm^{-1}. 3β-H isomer (73.4% overall yield): IR ($CHCl_3$) max 1640 cm^{-1}. Reduction of each stereoisomeric mixture of the lactam **12** with lithium aluminum hydride (THF, reflux, 4 h) furnished the amino diols **13**, each as an unseparable mixture: 3α-H isomer (59%) and 3β-H isomer (41%). Selective mesylation of the primary alcohol of each mixture of **13** (1.2 equiv of methanesulfonyl chloride, pyridine, 0 °C, 1.5 h), followed by intramolecular quaternization of the resulting mesylate **14** ($CHCl_3$, reflux, 24 h), yielded the pentacyclic quaternary salt **15** which, on dissolving-metal reduction[16] (Na, liquid NH_3, EtOH), provided (±)-velbanamine[17] (**1**, 14% from **13** (3α-H) and 16.5% from **13** (3β-H)), gum (lit. mp 143–146,[9,18] 125–130 °C[17,18]), and (±)-isovelbanamine[17] (**2**, 8% from **13** (3α-H) and 9% from **13** (3β-H)), mp 117–119 °C (lit. mp 190–194,[9,18] 175–178 °C[17,18]).

Since both **1** and **2** have been converted into cleavamine, the present work constitutes a formal synthesis.[9]

Acknowledgment. We are greatly indebted to Dr. M. Narisada, the Research Laboratory, Shionogi & Co., for providing spectra (IR and mass) of (±)-velbanamine and (±)-isovelbanamine. We also thank the Ministry of Education, Japan, for supporting this work.

Seiichi Takano,* Michiyasu Hirama
Kunio Ogasawara
Pharmaceutical Institute
Tohoku University
Aobayama, Sendai 980, Japan
Received May 5, 1980

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(18) Optically active sample.