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CONSTITUTION OF THREE NEW ALKALOIDS, AKNADININE (4-DEMETHYLHASUBANONINE), AKNADICINE (4-DEMETHYLNORHASUBANONINE), AND AKNADILACTAM (4-DEMETHYL-16-OXOHASUBANONINE)*

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Abstract—The constitution of three new alkaloids, aknadinine (4-demethylhasubanonine) (**4**) from *Stephania hernandifolia* and *S. Sasakii*, aknadicine (4-demethylnorhasubanonine) (**6**) from *S. hernandifolia*, and aknadilactam (4-demethyl-16-oxohasubanonine) (**13**) from *S. Sasakii* is discussed.

THE Menispermaceous herb, *Stephania hernandifolia* (WILLD.) WALP., has been found to contain a number of alkaloids.[1-7] Previously, Moza *et al.* reported the isolation of three new alkaloids, aknadine, aknadinine and aknadicine from its rhizomes collected around Calcutta.[8] An investigation of basic constituents of *Stephania Sasakii Hayata* of Formosa by Tomita *et al.*[9] and Kunitomo *et al.* revealed the presence of aknadinine,[10] aknadilactam and steporphine[11] along with a number of other alkaloids.

In a recent report[12] structures **4** and **6** were proposed by X-ray crystallographic analysis of aknadinine (4-demethylhasubanonine) brosylate for the alkaloid aknadinine and aknadicine(4-demethylnorhasubanonine), respectively. This has prompted us to publish in detail the independent findings,[13] leading to the assignment of the same structures for aknadinine and aknadicine, respectively.

Aknadinine (4-demethylhasubanonine, **4**) is an amorphous phenolic base, which sublimes at 120–130°/0·2 mmHg to fine flakes, m.p. 70°, $C_{20}H_{25}O_5N$, $[\alpha]_D$ −283° (EtOH). It shows a molecular ion peak at *m/e* 359 in its mass spectrum confirming the molecular formula to be $C_{20}H_{25}O_5N$ (M.W. 359·41) and UV absorption max at 266 mμ (log $E^{1\%}_{1cm}$ 2·46) which shifts to longer wave-length by addition of alkali solution. The nature of the OH group, revealed by the 2,6-dichloroquinone-4-chlorimide (Gibbs' reagent) test, is phenolic with an unsubstituted *para* position. The

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spectral data (Exp.) indicates the presence of the empirical formula $C_{20}H_{25}O_5N{=}C_{12}H_{10}.(OH).(OMe)_3.(-CH_2-CO-C{=}C\langle)$. (N—Me) in aknadinine.

Methylation of **4** with Rodionov reagent[14] in boiling toluene, methyl iodide and sodium methoxide, or diazomethane afforded hasubanonine (**1**),[15] m.p. 116°, $[\alpha]_D$ −218°, characterized by direct comparison of IR spectra, NMR spectra, and mixed m.p. determination with an authentic sample. The mass spectrum of aknadinine shows a characteristic fragment ion peak at *m/e* 231[16] which can be formulated as **12a** or **12b**, but aknadinine being isomeric with homostephanoline (**2**) and phenolic in nature, suggests the structure for this fragment ion to be **12a**. Based on these structure **4** could be assigned to aknadinine.

The final proof of aknadinine constitution came from chemical degradation by a route parallel to that used for hasubanonine (**1**)[15] and O-ethylhomostephanoline (**3**)[17] to afford 3,4-dimethoxy-N-methylhasubanan (**9**) and 3-ethoxy-4-methoxy-N-methylhasubanan (**10**), respectively. Reduction of **4** with sodium borohydride provided [by analogy with the reduction of hasubanonine (**1**), O-ethylhomostephanoline (**3**), and cepharamine[18]] two epimeric alcohols. Without separation, the alcohol mixture was treated to afford a conjugated CO compound **8**. Clemmemsen reduction of **8**, followed by catalytic hydrogenation afforded 3-methoxy-4-hydroxy-N-methylhasubanan (**11**), characterized by direct comparison of IR spectra ($CHCl_3$) and TLC behaviour with an antipodal authentic deoxodihydroindolinothebainone.[15] On the basis of above result, the structure of aknadinine was unambiguously assigned to the formula **4** including the stereochemistry of the ethanamine side chain.

Aknadicine (4-demethylnorhasubanonine, **6**), m.p. 156°, $[\alpha]_D$ −200° (EtOH), $C_{19}H_{23}O_5N$, shows a molecular ion peak at *m/e* 345 confirming the $C_{19}H_{23}O_5N$ formula, and shows a UV max at 266 mμ (log $E^{1\%}_{1cm}$ 2·45).

All the spectral data (Exp.) suggests that aknadicine belongs to the "hasubanan" type of alkaloids and that it is related to aknadinine because it is positive towards Gibbs reagent indicating that the phenolic OH group is at C-4 with unsubstituted *para* position. In agreement with this observation, it was methylated to O-methylaknadicine (**7**) as an amorphous solid, which was characterized as its hydrobromide, m.p. 222·5°, $[\alpha]_D$ −105° (MeOH), analyzed for $C_{20}H_{25}O_5N.HBr$. Interestingly, methylation of aknadicine (**6**) with formaldehyde and formic acid by the Eschweiler–Clarke method gave rise to the phenolic derivative N-methylaknadicine, obtained in crystalline form as its hydrobromide, m.p. 215°, $[\alpha]_D$ −155° (MeOH), which was found to be identical with the authentic hydromobride of aknadinine (**4**) by mixed m.p., UV spectra and TLC.

However, when reacted with methyl iodide and sodium methoxide aknadicine gave the O,N-dimethyl derivative, hasubanonine (**1**), which was found to be identical in all respects with that prepared from aknadinine. All the evidence conclusively demonstrated the N-nor-aknadinine structure (**6**) for the new base aknadicine.

Aknadilactam (4-demethyl-16-oxohasubanonine, **13**) is a phenolic alkaloid, obtained as an amorphous solid, which could not be induced to crystallize and its homogenity was shown by a single spot on TLC. The IR spectrum of the base clearly demonstrated the presence of an OH group (3500 cm^{-1}), a 5-membered lactam and conj CO group (overlapped at 1680 cm^{-1}), and an enolic double bond (1612 cm^{-1}).

Positive reaction towards Gibbs reagent and a shift of UV max (267 mμ) to longer wave-length by addition of sodium hydroxide solution suggested that the OH group is phenolic. As shown in Table 1, comparison of the NMR signals for the OMe groups and the NMe group of aknadilactam with those of aknadinine (**4**) and aknadicine (**6**) indicated that the aknadilactam is 16-oxo-aknadinine.

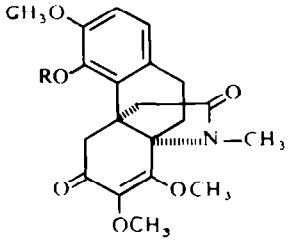
TABLE 1. NMR METHOXYL AND N-METHYL RESONANCES OF AKNADININE, AKNADICINE, AKNADILACTAM, HASUBANONINE, AND HOMOSTEPHANOLINE[a]

	C-3-OMe	C-4-OMe	C-7-OMe	C-8-OMe	N-Me
Aknadinine (**4**)	6·15		6·37	5·93	7·46
Aknadicine (**6**)	6·17		6·31	5·89	
Aknadilactam (**13**)	6·16		6·31	5·89	7·04
Hasubanonine (**1**)[15]	6·20	6·06	6·36	5·92	7·48
Homostephanoline (**2**)[15]		6·14	6·40	5·92	7·47

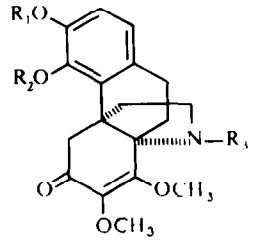
All values are in τ for $CDCl_3$ solutions using TMS as an internal standard.

Attempts have been made to correlate aknadinine (**4**) with aknadilactam (**13**). Thus, acetylation of **4** with Ac_2O-pyridine gives rise to O-acetylaknadinine (**15**), whose IR spectrum shows acetate band at 1768 cm^{-1}. Oxidation of **15** to acetyl-aknadilactam (**14**), followed by hydrolysis afforded aknadilactam (**13**), characterized by comparison of IR spectra ($CHCl_3$), TLC, NMR spectra and specific rotations with those of natural aknadilactam. Thus, the constitution of aknadilactam was represented by the formula **13**.

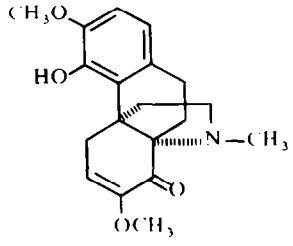
Aknadinine, aknadicine and aknadilactam are three more additions to the recently established and rarely occuring "hasubanan" tyoe alkaloids.[18–20]



13 R = H
14 R = Ac



	R_1	R_2	R_3
1	CH_3	CH_3	CH_3
2	H	CH_3	CH_3
3	C_2H_5	CH_3	CH_3
4	CH_3	H	CH_3
5	CH_3	C_2H_5	CH_3
6	CH_3	H	H
7	CH_3	CH_3	H
15	CH_3	Ac	CH_3



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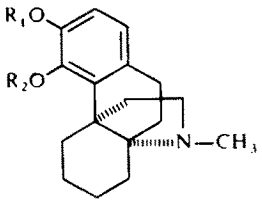
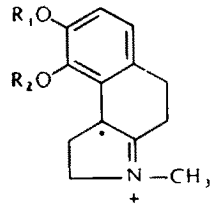


	R_1	R_2
9	CH_3	CH_3
10	C_2H_5	CH_3
11	CH_3	H



	R_1	R_2
12a	CH_3	H
12b	H	CH_3

EXPERIMENTAL

All m.ps were uncorrected. TLC were performed on Kieselgel G nach Stahl developed by $CHCl_3$–acetone (1:1) or aluminium oxide G (Stahl) developed by $CHCl_3$ or $CHCl_3$–acetone (1:1). The low-resolution mass spectra were recorded on Hitachi Mass Spectrometer Model RMU-6D equipped with a direct inlet system at an ionization potential of 80 eV, an ion acceleration voltage of 1·8 KV and an evaporating temp of 180–200°. All NMR spectra were taken on a Varian Associates Recording Spectrometer (A-60) at 60 Mc in $CDCl_3$ using TMS as an internal standard and chemical shifts were reported in τ values. Abbreviation used for the multiplicity of the signals: s, singlet; d, doublet; t, triplet; q, quartet, and m, multiplet.

Aknadinine (*4-demethylhasubanonine*) (**4**)

Free base. Colourless amorphous solid and sublimed at 120–130°/0·2 mmHg as fine flakes, m.p. 70°, $[\alpha]_D^{29}$ −283° (*c* = 0·1, EtOH); UV λ_{max}^{EtOH}: 266 mμ (log $E_{1cm}^{1\%}$ 2·46); λ_{min}^{EtOH}: 245 mμ (log $E_{1cm}^{1\%}$ 2·21); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550 (OH), 1660 (conj. ketone), 1600 (enolic double bond); NMR ($CDCl_3$) τ: 7·46 (3H, NCH_3); 5·93 (3H, OCH_3), 6·15 (3H, OCH_3), 6·37 (3H, OCH_3); two aromatic protons; 3·32 (1H, d, *J* = 8·5 c/s), 3·42 (1H, d, *J* = 8·5 c/s). (Found: C, 66·80; H, 6·95; N, 3·85. $C_{20}H_{25}O_5N$ requires: C, 66·83; H, 7·01; N, 3·90%). *Aknadinine styphnate*: recrystallized from EtOH-MeOH mixture as yellow needles, m.p. 207° (dec). (Found: C, 51·42, 51·40; H, 4·83, 4·63; N, 9·13, 9·15. $C_{20}H_{25}O_5N.C_6H_3O_8N_3$ requires: C, 51·65; H, 4·67; N, 9·29%). *Aknadinine hydrobromide*: recrystallized from MeOH.EtOH mixture as colourless needles, m.p. 210–215°, $[\alpha]_D^{26}$ −155° (*c* = 0·2, MeOH). (Found: C, 54·28, 54·65, H, 6·07, 5·94; N, 3·01, 3·18; Br, 18·09. $C_{20}H_{25}O_5N.HBr$ requires: C, 54·44; H, 5·95; N, 3·18; Br, 18·15%).

O-Methylation of aknadinine (**4**)

(a) *Rodionov method.* Aknadinine (**4**) (20 mg) was dissolved in anhyd. toluene (6 ml), and then Rodionov reagent[13] (0·7 ml of MeOH solution) was added. The mixture was heated at 100° to remove MeOH, and then refluxed at 130° for 8 hr with stirring. After dimethylaniline was removed by steam distillation, the crude product was extracted with Et_2O. The Et_2O extract was washed, dried over $MgSO_4$, and evaporated. The residue was chromatographed on an alumina column from benzene, and recrystallization from acetone giving pure **1** as colourless prisms, m.p. 114°, $[\alpha]_D^{15}$ −212° (*c* = 1·0, $CHCl_3$). (Found: C, 67·53; H, 7·42; N, 3·50. $C_{21}H_{27}O_5N$ requires: C, 67·54; H, 7·29; N, 3·75%). On admixture of the O-methylated product with an authentic sample of **1**[15] no depression of m.p. was observed and the IR spectra ($CHCl_3$) of two compounds were superimposable.

(b) *Methyl iodide and sodium methoxide method.* Aknadinine **4** (1 g) was added to a cooled (0°) soln of Na (1·8 g) in MeOH (50 ml). The mixture was treated with MeI (7 ml), refluxed for 4 hr and then kept at room temp for 16 hr. The solvent was subsequently removed *under vacuo* and the residue dissolved in H_2O (60 ml) which was completely extracted with Et_2O. The Et_2O extract was washed with 10% NaOH aq and then with H_2O, dried over Na_2SO_4 and evaporated to dryness. The residue was crystallized from MeOH as needles, m.p. 116·5°, $[\alpha]_D^{25}$ −218° (*c* = 0·12, MeOH). (Found: C, 67·33; H, 7·22; N, 4·00. $C_{21}H_{27}O_5N$ requires: C, 67·54; H, 7·29; N, 3·75%). The mixed m.p., optical rotation, PPC and TLC, and IR comparisons of O-methylaknadinine with those of authentic **1**[15] were identical. The base was also characterized as its hydrobromide: m.p. 205°, $[\alpha]_D^{26}$ −211° (*c* = 0·13, MeOH). (Found: C, 55·44; H, 6·31; N, 3·15. $C_{21}H_{27}O_5N.HBr$ requires: C, 55·51; H, 6·21; N, 3·09%).

(c) *Diazomethane method.* Aknadinine **4**; (0·1 g) in MeOH (5 ml) was treated with a saturated solution of diazomethane in Et_2O and kept at room temp for 48 hr. The solvent was evaporated and the residue purified by passing through a column of silica gel in benzene. The desired product was eluted with EtOH-benzene (1:99) and crystallized from MeOH gave needles, m.p. 115°, $[\alpha]_D^{27}$ −218° (*c* = 0·11, MeOH). These were found to be identical with those obtained in (b) by paper and TLC and spectroscopic comparisons.

O-Ethylaknadinine (**5**). Aknadinine (**4**; 1 g) was added to a cooled (0°) soln of Na (1·8 g) in EtOH (90 ml). The mixture was treated with EtI (9 ml), refluxed for 4 hr and kept at room temp for 16 hr. The residue obtained, after the removal of the solvent *under vacuo*, was dissolved in H_2O (60 ml) and extracted completely with Et_2O. The Et_2O extract was washed with 10% NaOH aq and then with H_2O, dried over Na_2SO_4 and evaporated to dryness. The residue was difficult to crystallize and was characterized as its hydrobromide, m.p. 196·5°, $[\alpha]_D^{26}$ −135° (*c* = 0·31, MeOH). (Found: C, 56·57; H, 6·47; N, 2·97. $C_{22}H_{29}O_5N.HBr$ requires: C, 56·41; H, 6·45; N, 2·99%).

Conjugated carbonyl compound (**8**)

To a solon of **4** (44 mg) in 10% aqueous MeOH (5 ml) was added $NaBH_4$ (70 mg), and the mixture was stirred at room temp for 4·5 hr, and then the excess reagent was decomposed with slight excess of AcOH. The solvent was evaporated under reduced press to dryness, made alkaline with 10% NaOH aq and extracted with Et_2O. The Et_2O solon, washed and dried over $MgSO_4$, was evaporated to give 41 mg of oily dihydroaknadinine which was purified over alumina column (1·5 × 0·3 cm) from benzene. On TLC it showed two spots which were positive towards Gibbs reagent. The above mixture (40 mg) was dissolved in acetone (2 ml) and then 0·5 ml of 10% HBr was added. The solon was heated at 60° for 2·5 hr, made alkaline with 5% NH_4OH and extracted with Et_2O. The organic layer was washed, dried over $MgSO_4$, and evaporated to leave a yellow oily conj. carbonyl compound (**8**). On trituration with n-hexane–Et_2O it gave crystals, which were recrystallized from n-hexane–Et_2O to afford yellow needles, m.p. 136–137°; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500 (OH), 1650 (conj. ketone), 1617 (enolic double bond); NMR ($CDCl_3$) τ: 7·46 (3H, N-CH_3), 6·12, 6·24 (each 3H, OCH_3), 4·29 (1H, olefinic proton, q, *Ja* = 4·5 c/s, *Jb* = 6 c/s). (Found: C, 69·30; H, 7·16. $C_{19}H_{23}O_4N$ requires: C, 69·28; H, 7·04%).

3-Methoxy-4-hydroxy-N-methylhasubanan (**11**)

Compound **8** (90 mg) was dissolved in conc HCl (1 ml), and amalgamated Zn prepared from 400 mg Zn and 100 mg $HgCl_2$ added in portions. The mixture was heated at 70° for 4 hr, during which time 4 ml of conc HCl was added in portions. After standing overnight, inorganic ppts was removed by filtration, and soln was made alkaline with NH_4OH aq, and extracted with Et_2O. The Et_2O soln was washed, dried over $MgSO_4$, and evaporated to leave oily substance, which was successively hydrogenated over PtO_2 (10 mg) in 10% AcOH (8 ml) for 4 hr at atm press. The catalyst was filtered off, made alkaline with dil NH_4OH aq and extracted with Et_2O. The Et_2O extract was washed, dried over $MgSO_4$ and evaporated to leave crude product of **11**. Purification by column chromatography over alumina from benzene afforded pure **11**, characterized by direct comparison of IR spectra ($CHCl_3$) and TLC behaviour with an antipodal authentic sample.[15]

Aknadicine (*4-methylnorhasubanonine*) (**6**)

Aknadicine was recrystallized from MeOH as colourless plates, m.p. 156°, $[\alpha]_D^{27}$ −200° (*c* = 0·55, EtOH); UV λ_{max}^{EtOH}: 266 mμ (log $E_{1\,cm}^{1\%}$ 2·45); λ_{min}^{EtOH}: 245 mμ (log $E_{1\,cm}^{1\%}$ 2·24); λ_{max}^{EtOH} 240 mμ (log $E_{1\,cm}^{1\%}$ 2·28); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450 (hydroxyl), 3300 (secondary amino group), 1664 (conj. ketone), 1612 (enolic double bond); NMR ($CDCl_3$) τ: 3·32 (1H, d, *J* = 8·5 c/s, aromatic proton), 3·43 (1H, d, *J* = 8·5 c/s, aromatic proton); 5·89 (3H, OCH_3), 6·17 (3H, OCH_3), 6·31 (3H, OCH_3); 6·37 (1H, d, *J* = 16·5 c/s, one proton of an active methylene), 7·50 (1H, d, *J* = 16·5 c/s, a proton of an active methylene); Mass spectrum: M 345. (Found: C, 66·28; H, 6·81; N, 3·78. $C_{19}H_{23}O_3N$ requires: C, 66·09; H, 6·67; N, 4·06%).

O-*Methylaknadicine* (**7**)

Methylation of **6** *with diazomethane.* To a soln of **6** (0·2 g) in MeOH, diazomethane in Et_2O was added, and kept at room temp for 45 hr. Usual working up left a semi-solid mass which was purified by passing through a silica gel column in benzene. EtOH-benzene (1:99) eluted the desired product, which was oily but could be obtained crystalline as the hydrobromide, m.p. 222·5°, $[\alpha]_D^{26}$ − 105° (*c* = 0·12, MeOH); UV λ_{max}^{EtOH} 265 mμ, λ_{min}^{EtOH} 243 mμ. (Found: C, 54·34; H, 6·12; N, 3·12. $C_{20}H_{25}O_5N.HBr$ requires: C, 54·56; H, 5·96; N, 3·18%).

N-*Methylaknadicine* (**4**)

Methylation of **6** *by Eschweiler–Clarke method.* Aknaidicine **6** (0·1 g) was refluxed for 4 hr with 83% formic acid (0·5 ml) and 37% formaldehyde (0·6 ml) on a water bath. The mixture was cooled and diluted with H_2O (10 ml) and extracted with Et_2O. The aqueous soln was made alkaline with dil NH_4OH aq and then extracted exhaustively with pure Et_2O. The ethereal extract gave a semisolid residue which was isolated as hydrobromide, m.p. 215°, $[\alpha]_D^{26}$ −155° (c = 0·11, MeOH). (Found: C, 54·38; H, 5·83; N, 3·28. $C_{20}H_{25}O_5N.HBr$ requires: C, 54·56; H, 5·96; N, 3·18%). The N-methylated aknadicine hydrobromide was found to be identical with the hydrobromide of **4** by mixture m.p., UV, PPC and TLC.

Hasubanonine (**1**)

Methylation of **6** *with methyl iodide and sodium hydride.* To a cooled (0°) soln of Na (0·4 g) in MeOH (10 ml), aknadicine (0·1 g) and MeI (1·6 ml) were added and the mixture refluxed for 4 hr. The solvent was removed *in vacuo* and the residue was treated with H_2O (10 ml) and extracted exhaustively with Et_2O. The ethereal extract was washed with 10% NaOH aq and then with H_2O and dried over Na_2SO_4. This, on evaporation gave a semisolid residue which was crystallized as a hydrobromide, m.p. 205°, $[\alpha]_D^{25}$ −220·5° (c = 0·11, MeOH) identical with **1** prepared from aknadinine.

Aknadilactam

4-*Demethyl*-16-*oxohasubanonine* (**13**). This was a phenolic, amorphous solid, which could not be induced to crystallize and its homogeneity was shown by a single spot on TLC; UV λ_{max}^{EtOH}: 267 mμ (log $E_{1cm}^{1\%}$ 3·98), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500 (hydroxyl), 1680 (5-membered lactam and conj. ketone), 1612 (enolic double bond); NMR ($CDCl_3$) τ: 7·04 (3H, N-CH_3), 5·89 (3H, OCH_3), 6·16 (3H, OCH_3), 6·31 (3H, OCH_3), two aromatic protons; 3·27 (1H, d, J = 8·5 c/s), 3·46 (1H, d, J = 8·5 c/s).

Synthesis of aknadilactam (**13**) *from aknadinine* (**4**)

Aknadinine **4** (300 mg) was treated with Ac_2O (2 ml) and pyridine (0·5 ml) at room temp for 2 days. The excess Ac_2O and pyridine were removed under reduced press and the residue was dissolved in H_2O (10 ml), made alkaline with 10% NH_4OH aq, and extracted with Et_2O. The Et_2O extract was washed, dried over $MgSO_4$, and evaporated to leave 280 mg of an oily **15**, which showed a single spot on TLC; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1768 (acetyl group).

A mixture of **15** (120 mg), $MgSO_4$ (120 mg), acetone (10 ml) and H_2O (20 ml) was treated with $KMnO_4$ (190 mg) in acetone (15 ml) and H_2O (20 ml) at room temp with stirring for 5 hr. The inorganic ppts were removed by filtration, and the solvent was evaporated to dryness under reduced press. The residue was acidified with dil HCl, and extracted with CH_2Cl_2. The extract was washed, dried over $MgSO_4$, and evaporated to leave a yellow oily crude **14** (95 mg), which was successively purified by silica gel column chromatography (6·5 × 0·5 cm) from $CHCl_3$ to afford a pure **14** (25 mg); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1714 (acetyl group), 1684 (conj. ketone and 5-membered lactam).

A mixture of **14** (25 mg), MeOH (2 ml), H_2O (0·5 ml), and $NaHCO_3$ (30 mg) was stirred at room temp for 40 min, and then H_2O (10 ml) was added, and extracted with CH_2Cl_2. The extract was washed, dried over K_2CO_3, and evaporated to afford a yellow oily substance, which was chromatographed over silica gel column (0·8 × 4·5 cm) from $CHCl_3$. Elution with $CHCl_3$ gave a pure **13** (15 mg), $[\alpha]_D^{20}$ −189·1° (c = 0·64, $CHCl_3$), which was characterized by direct comparison of TLC, IR ($CHCl_3$), and NMR spectra, and specific rotations with those of natural aknadilactam (**13**).

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