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Total Synthesis of the Alkaloid, (±)-Hasubanonine[1]

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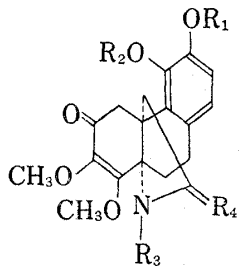
(±)-Hasubanonine was synthesized through 16-oxo-hasubanonine (**63**) as a relay substance starting from the keto-lactam (**41**). The keto-lactam (**41**) was derived to the keto-O-acetyl-phenol A (**49**) which was oxidized to the axial-acetoxy-ketone (**50**). Bromination of (**50**) followed by the rearrangement reaction with sodium acetate gave the enol-acetate (**51**) which was converted to the bromo-enolmethyl-ether (**56**) *via* the diosphenol (**54**) and the bromo-diketone (**55**). The compound (**56**) was derived to the β-diketone (**57**) which was methylated to give (±)-16-oxo-hasubanonine (**59**) and (±)-aknadilactam (**61**). On the other hand, hasubanonine was oxidized to 16-oxo-hasubanonine (**63**) which was put back to hasubanonine by lithium aluminum hydride reduction followed by manganese dioxide oxidation.

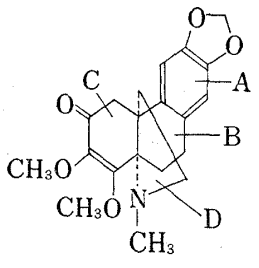
Hasubanonine was first isolated from *Stephania japonica* Miers by Kondo, *et al.*[3] and its structure was completely elucidated by Tomita, *et al.*[4] The skeletal structure of hasubanonine is different from morphinan in forming a five membered heterocyclic ring by a linkage of the ethanamine nitrogen with C_{14}, and its absolute configuration is antipodal to that of morphinan.[5] This unique skeletal structure was designated as hasubanan, and the alkaloids possessing this skeleton are then called hasubanan alkaloids. Recent investigations have indicated that the sixteen congeners have been isolated from various *Stephania* species (Menispermaceae), and the structures of these alkaloids have been established.[6] Hasubanan alkaloids are classified into three types, the cepharamine, hasubanonine, and metaphanine type, on the basis of the oxidation stage at the B and C ring and so far as we know, the six alkaloids belonging to the hasubanonine type (**1**—**6** in Chart 1) have been reported and hasubanonine is a representative of this type alkaloids.

In previous papers, we reported synthesis of hasubanan skeleton[7] and synthesis of (±)-cepharamine.[7] Later, we have reported a complete synthesis of (±)-hasubanonine in a preliminary communication[1] and we wish to give here a full detail of synthesis of this alkaloid and (±)-aknadilactam (**61**).

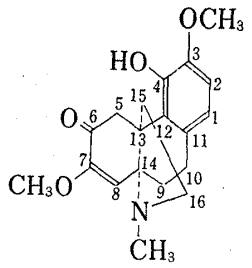
1) A preliminary communication of this work appeared in *Tetrahedron Letters*, 1970, 4811.
2) Location: *Yoshida-shimoadachi-cho, Sakyo-ku, Kyoto.*
3) H. Kondo, M. Satomi, and T. Odera, *Itsuu Kenkyusho Nempo*, **2**, 35 (1951).
4) M. Tomita, T. Ibuka, Y. Inubushi, Y. Watanabe, and M. Matsui, *Chem. Pharm. Bull.* (Tokyo), **13**, 538 (1965); D.H.R. Barton, G.W. Kirby, and A. Wiechers, *J. Chem. Soc. (C)*, **1966**, 2313.
5) M. Tomita, T. Ibuka, Y. Inubushi, Y. Watanabe, and M. Matsui, *Tetrahedron Letters*, **1964**, 2937; S. Okuda, K. Tsuda, and S. Yamaguchi, *J. Org. Chem.*, 27, 4121 (1962); *idem*, *Chem. Pharm. Bull.* (Tokyo), **13**, 1092 (1965).
6) C.W. Thornber, *Phytochem.*, **9**, 157 (1970), and references cited therein; B.K. Moza, B. Bhaduri, P.K. Basu, J. Kunitomo, Y. Okamoto, E. Yuge, Y. Nagai, and T. Ibuka, *Tetrahedron*, **26**, 427 (1970); S.M. Kupchan, M.I. Suffness, R.J. McClure, and G.A. Sim, *J. Am. Chem. Soc.*, **92**, 5756 (1970); S.M. Kupchan and M.I. Suffness, *Tetrahedron Letters*, **1970**, 4975; A.R. Battersby, S. Ruchirawart, J. Staunton, and C.W. Thornber, unpublished work; T.N. Il'inskaya, I.I. Fadeeva, M.E. Perel'son, and O.N. Tolkachev, *Khim. Prir. Soedin.*, **1971**, 7 (2), 180 (*Russ.*) [*Chem. Abstr.*, **75**, 36408*b* (1971)]; I.I. Fadeeva, T.N. Il'inskaya, M.E. Perel'son, and A.D. Kuzoukov, *Khim. Prir. Soedin.*, **1971**, 7 (6), 784 (*Russ.*) [*Chem. Abstr.*, **76**, 141108*x* (1972)]; S.M. Kupchan, A.J. Liepa and T. Fujita, *J. Org. Chem.*, **38**, 151 (1973).
7) M. Tomita, M. Kitano, and T. Ibuka, *Tetrahedron Letters*, **1968**, 3391; Y. Inubushi, T. Ibuka, and M. Kitano, *Tetrahedron Letters*, **1969**, 1611; *idem*, *Chem. Pharm. Bull.* (Tokyo), **19**, 1820 (1971).



compound	R_1	R_2	R_3	R_4
hasubanonine (1)	CH_3	CH_3	CH_3	H_2
homostephanoline (2)	H	CH_3	CH_3	H_2
aknadinine (3)	CH_3	H	CH_3	H_2
aknadilactam (4)	CH_3	H	CH_3	O
aknadicine (5)	CH_3	H	H	H_2



delavanine (6)



cepharamine (7)

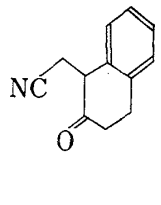
Chart 1

On the design of the synthetic scheme of hasubanonine (**1**), the keto-lactam (**41**) which was a key intermediate of cepharamine synthesis, was chosen for the starting material of the present synthesis. When surveyed the structure of cepharamine (**7**) and hasubanonine (**1**), it will be noted that hasubanonine possesses an additional oxygen function at C_8 compared with cepharamine. For hasubanonine synthesis, it is therefore essential that two additional oxygen functions must be introduced into the C_6 and C_8 position of the keto-lactam (**41**) with intention of elaborating the -CO-C(OMe)=C(OMe)- system. Prior to the synthesis of hasubanonine itself, a preliminary experiment was made to synthesize the compound (**40**), which possesses the same substitution pattern at C ring as that of hasubanonine, using 2-tetralone as a starting material. One of the reasons for adopting this model experiment is that the starting material for synthesis of the keto-lactam (**41**), 7,8-dimethoxy-2-tetralone derivative, is known to be unstable on standing and synthesis of this 2-tetralone derivative is somewhat troublesome. After the manner of this model experiment, synthesis of hasubanonine was carried out using the keto-lactam (**41**) as the starting material.

Synthesis of the Model Compound (40)

The synthetic route of the keto-lactam (**9**) from 2-tetralone *via* the keto-nitrile (**8**) has been established by the authors.[7] In order to find a suitable route for the preparation of the compound (**35**) or (**40**) possessing the same substitution pattern at C ring as that of hasubanonine, various oxidation reactions available for introduction of an oxygen function into the C_8 position of the keto-lactam (**9**) were first examined. Air oxidation of the keto-lactam (**9**) under the presence of potassium *tert*-butoxide gave the carboxylic acid (**10**) which seemed to result from an oxidation product, an α-diketone, through a benzylic acid rearrangement. The structure (**10**) for this product permits interpretation of the following transformation which this compound has been observed to undergo: methylation of this compound with diazomethane gives the methyl ester (**11**) which on reduction with $LiAlH_4$ affords the diol (**12**) and this diol is converted to the five membered ketone (**13**) by oxidation with periodate. The assumption that air oxidation took place at C_8 position of the keto-lactam (**9**) to result in an α-diketone, was supported by the following observations. Thus, oxidation of the axial-acetoxy-ketone (**23**: *vide infra*) under the presence of ferric chloride[8] provided the carboxylic acid (**10**) but no benzylic acid rearrangement under the reaction condition described above, was observed in the diketone (**17**: *vide infra*). This result suggests in turn that on oxidation, enolization of the C_7 ketone function may occur between C_7 and C_8. On the basis of this assumption, enolacetylation of the keto-lactam (**9**) followed by epoxidation and thermal rearrangement may give the desired α-acetoxy-ketone (**23**) or (**24**). The keto-lactam (**9**)

8) *cf.* Y. Hwarg and M. Matsui, *Agr. Biol. Chem.* (Tokyo), 32, 81 (1968).



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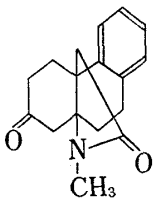

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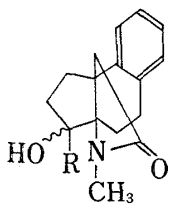
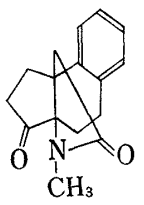


10 : R=CO_2H
11 : R=CO_2CH_3
12 : R=CH_2OH



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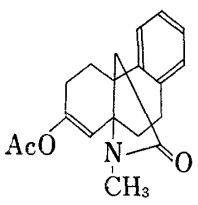

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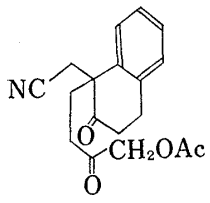

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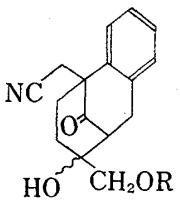
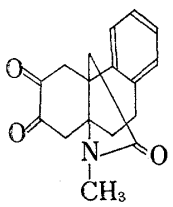


16a : R=Ac
16b : R=Ac
16c : R=H



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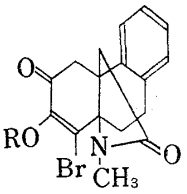
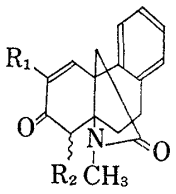


18 : R=H
22 : R=CH_3



19 : R_1=R_2=Br
20 : R_1=Br, R_2=H
21 : R_1=OCH_3, R_2=Br

Chart 2

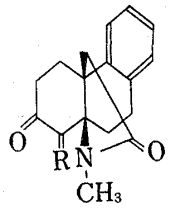
was therefore derived to the enol-acetate (**14**) by treatment with acetic anhydride-perchloric acid[9] and epoxidation of the compound (**14**) by the Johnson's method[10] was tried. However, all trials for epoxidation under various reaction conditions were unfruitful.

Next, the reaction which permits to construct the basic skeleton having two oxygen functions at C_7 and C_8, was explored. The Robinson's annelation reaction of the keto-nitrile (**8**) with acetoxymethyl vinyl ketone[11] gave a mixture of the compound (**15**) and the compounds (**16a, b, c**) which arose from the Michael addition followed by the aldol condensation, in good yield. All trials for recyclization of the compounds (**16a, b, c**) to the axial-acetoxy-ketone (**23**) and/or the equatorial-acetoxy-ketone (**24**) were, however, failed. Then, the Bordwell's diketone synthesis[12] was applied to the keto-lactam (**9**). Thus, the keto-lactam (**9**) was treated with three molar equivalents of bromine in acetic acid and the resulting bromo compounds, without purification, were heated with sodium acetate in acetic acid to result in three kinds of rearrangement products (**17**, **18**, and **19**) in 5, 20, and 20% yield, respectively. Among these, the diketone (**17**) seemed to be produced by the reaction of the keto-lactam (**9**) with two molar equivalents of bromine followed by rearrangement reaction and was derived quantitatively to the bromo-diketone (**18**) by bromination. The structure assignment of the dibromo-ketone (**19**) was based on the fact that treatment of the dibromo-ketone (**19**) with chromous chloride gave the mono-bromide (**20**) which on catalytic hydrogenation yielded the keto-lactam (**9**). The bromo-diketone (**18**) was regioselectively methylated with boron trifluoride etherate-methanol to give the bromo-enolmethyl-ether A (**21**), the nuclear magnetic resonance (NMR) spectrum of which revealed a signal due to an olefinic proton as a singlet at 4.04 τ. On the other hand, when methylated with diazomethane, the bromo-diketone (**18**) afforded selectively the bromo-enolmethyl-ether B (**22**) whose NMR spectrum showed no olefinic proton signal. The oxidation stage at C ring of this compound (**22**) is the same as that of hasubanonine and if it makes possible to substitute the bromine atom with an oxygen

9) B.E. Edwards and P.N. Rao, *J. Org. Chem.*, **31**, 324 (1966).
10) K.L. Williamson and W.S. Johnson, *J. Org. Chem.*, **26**, 4563 (1961).
11) N. Lozač, *Bull. Soc. Chim. France*, **11**, 514 (1944); I.N. Nazarov and S.G. Matsoyan, *Zh. Obshch. Khim.*, **27**, 2629 (1957).
12) *cf.* G. Bordwell and K.M. Wellman, *J. Org. Chem.*, **31**, 351 (1966); *idem*, *ibid.*, **28**, 1347 (1963).

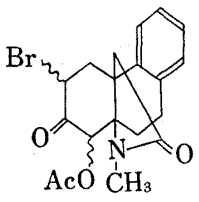
function, the compound (**35**) possessing the same substitution pattern as that of hasubanonine will be obtained. Contrary to our expectation, all trials for this substitution reaction were unsuccessful.

Oxidation of the keto-lactam (**9**) with lead tetraacetate under the presence of boron trifluoride etherate as a catalyst[13] followed by chromatographic separation gave two kinds of oxidation products, the axial-acetoxy-ketone (**23**) and the equatorial-acetoxy-ketone (**24**). A ratio of **23**/**24** and the total yield of these acetoxy-ketones (*ca.* 20—60%) varied by change of reaction condition. In these compounds, the conformation of the acetoxy group was deduced by the NMR spectral examination; a chemical shift of a signal of a proton geminal to an acetoxy group (C_8-H (**23**), 4.26 τ; C_8-H (**24**), 4.50 τ); chromatographic behavior, and the change of the ratio of **23**/**24** for variety of reaction conditions.[14] When treated with acetic acid under the presence of a trace of hydrogen bromide, the axial-acetoxy-ketone (**23**) epimerized to the equatorial-acetoxy-ketone (**24**) in 70% yield.[10]



23 : R=⟨OAc, H⟩

24 : R=⟨H, OAc⟩



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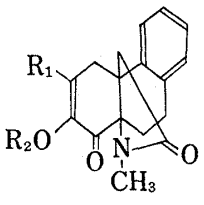
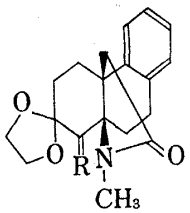


26 : R_1=Br, R_2=H
27 : R_1=Br, R_2=Ac
28 : R_1=H, R_2=Ac
29 : R_1=R_2=H
33 : R_1=Br, R_2=CH_3
38 : R_1=H, R_2=CH_3

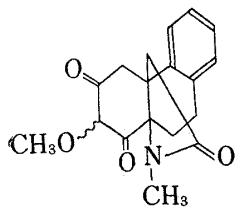


30a : R=⟨OAc, H⟩

30b : R=⟨H, OAc⟩

31 : R=⟨OH, H⟩

32 : R=O



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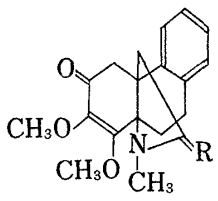
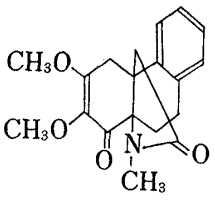


35 : R=O
40 : R=H_2



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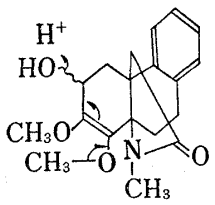

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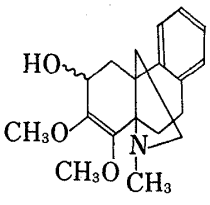

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Chart 3

The next synthetic step is introduction of one more oxygen function into the C_6 position of the acetoxy-ketones (**23**) or (**24**). Bromination of the axial-acetoxy-ketone (**23**) in acetic acid with pyridine hydrobromide perbromide complex[15] furnished a mixture of monobromides (**25**) in good yield. Oxidation of this mixture with DMSO-$NaHCO_3$[16] provided only poorly characterized materials in which a triketone seemed to be contained in some extent. Treatment of the axial-acetoxy-ketone (**23**) with two molar equivalents of bromine followed by heating with sodium acetate gave three kinds of rearrangement compounds (**26**), (**27**), and

13) H.B. Henbest, D.N. Lones, and G.P. Slater, *J. Chem. Soc.*, **1961**, 4472.
14) The stereochemistry of the acetoxy group at C_8 will be fully stated in the next paper which will appear in this Bulletin in the very near future (Total Synthesis of (±)-Metaphanine). All compounds in this paper are racemic and some of them are shown by stereostructures antipodal to those of natural alkaloid and its derivatives.
15) C. Djerassi and C.R. Scholz, *J. Am. Chem. Soc.*, **70**, 417 (1948).
16) H.R. Nace and R.N. Iacona, *J. Org. Chem.*, **29**, 3498 (1964).

(**28**) in 10, 45, and 7%, respectively, and the same treatment of the equatorial-acetoxy-ketone (**24**) afforded the bromo-diketone (**26**) alone in rather poor yield. Since the bromo-diketone (**26**) seemed to be a suitable compound for the subsequent synthesis, the synthetic route for getting this compound was examined in further detail. The bromo-diketone (**26**) was prepared quantitatively from the bromo-enol-acetate (**27**) by hydrolysis and from the diosphenol (**29**), which is obtained from the enol-acetate (**28**) by hydrolysis, by bromination, respectively. The enol-acetate (**28**) was in turn derived from a mixture of monobromides (**25**) through the rearrangement reaction with sodium acetate in 90% yield. The bromo-diketone (**26**) was also obtained through the following alternative route. Thus, the ketal-ketone (**32**) was derived from the axial-acetoxy-ketone (**23**) *via* the axial-acetoxy-ketal (**30a**) and the hydroxy-ketal (**31**), and deketalization of the ketal-ketone (**32**) followed by bromination gave the bromo-diketone (**26**) in good yield.

Methylation of the bromo-diketone (**26**) with diazomethane afforded the bromo-enolmethyl-ether (**33**) which on treatment with potassium hydroxide-methanol gave the β-diketone (**34**) in good yield together with a small amount of the compound (**36**) (*vide infra*). The β-diketone (**34**) was treated with diazomethane to give the methylated products which revealed two spots adjacent to each other on a thin-layer chromatography (TLC) plate. Careful silica gel chromatography gave the enolmethyl-ether A (**35**), mp 201° and the enolmethyl-ether B (**36**), mp 187° in a ratio of *ca.* 3/2. The structures of these compounds were deduced by the following observations. Thus, sodium borohydride reduction of the enolmethyl-ether A (**35**) gave a mixture of epimeric alcohols (**37**) and on treatment with hydrogen bromide, the epimeric alcohols were transformed to the compound (**38**) which was identical with the methylated product of the diosphenol (**29**) with diazomethane. The compound having mp 201° is therefore shown by the formula (**35**) and consequently, its structure isomer having mp 187° is represented by the formula (**36**). The NMR and infrared (IR) spectral data of the enolmethyl-ether A (**35**), B (**36**), and the related compounds are shown in Table I. It is noteworthy that the signal due to a methoxy group situated in β to the carbonyl function in the (**36**) type compounds appears at higher field than that of the (**35**) type compound.

Table I. The Characteristic NMR Signals and IR Absorption bands of **35**, **36**, **63**, **40**, **1**, and **60**

Compound	mp	NMR (τ) N-Me	O-Me	IR (cm^{-1}) conj. C=O, conj. C=C (*lactam C=O)
35	201°	7.02	6.33(C-7), 5.90(C-8)	1683*, 1612
36	187°	6.96	6.34(C-7), 5.97(C-6)	1679*, 1610
63	161°	7.03	6.33(C-7), 5.90(C-8)	1677*, 1615
40	110°	7.45	6.36(C-7), 5.91(C-8)	1665, 1601
1	116°	7.48	6.36(C-7), 5.92(C-8)	1664, 1600
60	178—180°	6.99	6.36(C-7), 6.02(C-6)	1680*, 1617

Lithium aluminum hydride reduction of the enolmethyl-ether A (**35**) followed by manganese dioxide oxidation furnished the desired compound (**40**). On the basis of these results obtained from the model experiments, synthesis of (±)-hasubanonine was undertaken.

Synthesis of (±)-Hasubanonine

Synthesis of the keto-lactam (**41**) from 7,8-dimethoxy-2-tetralone through five steps has been reported in a previous paper.[7] Synthesis of (±)-hasubanonine from the compound (**41**) has now been completed as follows.

Oxidation of the keto-lactam (**41**) with lead tetraacetate under the presence of boron trifluoride etherate as a catalyst gave three kinds of the acetoxy-ketones (**42**), (**43**), and (**44**). The total yield of these compounds was 50—70% and the relative ratio of these acetoxy-

ketones depended on both reaction condition and amount of lead tetraacetate. Among these, the NMR spectra of the compounds (**43**) and (**44**) showed only one aromatic proton signal as a singlet at 3.38 τ and 3.41 τ, respectively. This observation suggests introduction of one acetoxy group on the benzene ring but on the position of this acetoxy group, no further investigation was undertaken. Although various reaction conditions were examined, the acetoxy-ketone (**42**) was not obtained selectively in high yield. Then, the same oxidation reaction was applied to the O-acetyl-phenol A (**49**) since the electron density of the benzene ring of this compound is lower than that of the keto-lactam (**41**). The O-acetyl-phenol A (**49**) was derived from the keto-lactam (**41**) by the following reactions. It has been known that Wolff-Kishner reduction of morphinan[17a] and hasubanan[17b] alkaloids causes demethylation of a methoxy group at C_4 to give phenolic compounds. The same treatment of the ketal derivative of the keto-lactam (**41**) provided not only the phenol A (**45**) as a main product but a small amount of the phenol B (**46**) possessing a phenolic hydroxy group at C_3. The latter compound was sparlingly soluble in solvents and was characterized as the O-acetyl-phenol B (**47**) and the keto-O-acetyl-phenol B (**48**). The phenol B (**46**) was regarded as a convenient starting material for homostephanoline (**2**) synthesis. Acetylation of the phenol A (**45**) followed by deketalization gave the keto-O-acetyl-phenol A (**49**) which was oxidized with lead tetra-acetate-boron trifluoride etherate to furnish the desired axial-acetoxy-ketone (**50**) in *ca.* 65% yield. The axial conformation of the acetoxy group at C_8 of the compound (**50**) was assigned as follows. The chemical shift of a signal of a proton geminal to an acetoxy group at C_8 of the axial-acetoxy-ketone (**50**) was almost the same as that of the model compound (**23**) in which the conformation of the acetoxy group at C_8 was established as being axial. Furthermore, the long range interproton coupling (J=1.5 Hz) between the C_6-H and C_8-H (4σ-bond coupling according to the W rule[18]) was observed in the ethylene ketal derivative of the axial-acetoxy-ketone (**50**).

In analogy with the model experiment, treatment of the axial-acetoxy-ketone (**50**) with two molar equivalents of bromine followed by heating with sodium acetate provided the enol-acetate (**51**) which seemed to be formed from the resulting monobromide by being subject to the rearrangement reaction, as a main product (yield; *ca.* 70%) together with the bromo-enol-acetate (**52**) (yield; *ca.* 5%). Then, the intermediate of this transformation, the bromo-acetoxy-ketone (**53**), was prepared from the acetoxy-ketone (**50**) by treatment with pyridine hydrobromide perbromide[15] in 65% yield. That the conformation of the bromine substituent of this compound is equatorial was deduced by the coupling constant of the C_6-proton signal (q., J=5 Hz, δ_{AB}=8 Hz) in the NMR spectrum. The bromo-acetoxy-ketone, (**53**) was subject to the rearrangement reaction with sodium acetate in acetic acid to provide the enol-acetate (**51**) in 75% yield.

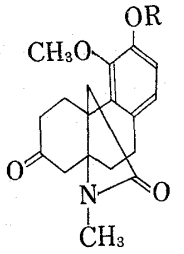
The next step is introduction of a bromine atom to the C_6 position of the enol-acetate (**51**) and such transformation requires partial hydrolysis of one of two acetoxy groups of the enol-acetate (**51**), thus hydrolysis of the C_7 acetoxy group alone. When refluxed with 2% hydrochloric acid in acetone, the enol-acetate (**51**) gave quantitatively the diosphenol (**54**) which was brominated to afford quantitatively the bromo-diketone (**55**) and this was then converted to the bromo-enolmethyl-ether (**56**) by methylation with diazomethane. Then, substitution of the bromine atom by a hydroxy group was tried in analogy with the model experiment. In this case, the substitution reaction under the presence of bases, however, gave only uncharacterized materials. The undesirable result may be due to air oxidation of a phenolic compound which results from hydrolysis of the acetoxy group with bases. Then,

17) *a*) H. Gate and G. Tschudri, *J. Am. Chem. Soc.*, **78**, 1380 (1956); *b*) M. Tomita, T. Ibuka, Y. Inubushi, and K. Takeda, *Tetrahedron Letters*, **1964**, 3605.

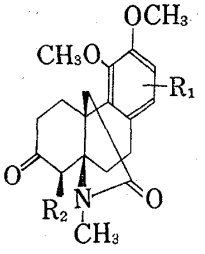
18) A. Rassat, C.W. Jefford, J.M. Lehn, and B. Waegell, *Tetrahedron Letters*, **1964**, 233; N.S. Bhacca and D.H. Williams, "Application of NMR Spectroscopy in Organic Chemistry", Holden-Day, Inc., San Francisco, **1964**, pp. 115—121.

the substitution reaction under the presence of an acid according to the Hesse's procedure[19] was carried out. Thus, heating of the bromo-enolmethyl-ether (**56**) with 5% sulfuric acid-1,2-dimethoxyethane in a sealed tube provided the desired β-diketone (**57**) in *ca.* 30% yield. In this reaction, although the formation of a phenolic compound by hydrolysis was observed, the enolmethyl ether group remained unaltered under this reaction condition.

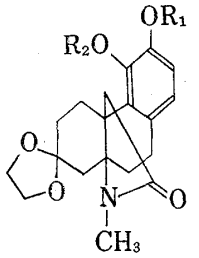
Methylation of the β-diketone (**57**) with diazomethane followed by the column chromatography gave a mixture of (±)-16-oxo-hasubanonine (**59**) and its structural isomer (**60**) in a



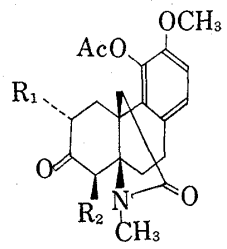
41 : R=CH_3
48 : R=Ac



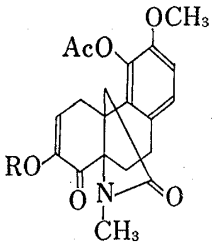
42 : R_1=H, R_2=OAc
43 : R_1=R_2=OAc
44 : R_1=OAc, R_2=H



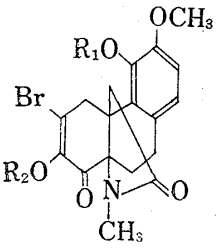
45 : R_1=CH_3, R_2=H
46 : R_1=H, R_2=CH_3
47 : R_1=Ac, R_2=CH_3



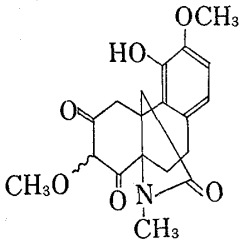
49 : R_1=R_2=H
50 : R_1=H, R_2=OAc
53 : R_1=Br, R_2=OAc



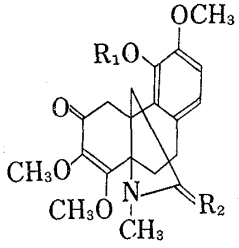
51 : R=Ac
54 : R=H



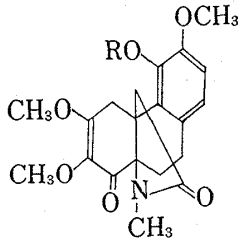
52 : R_1=R_2=Ac
55 : R_1=Ac, R_2=H
56 : R_1=Ac, R_2=CH_3
58 : R_1=H, R_2=CH_3



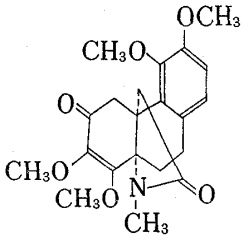
57



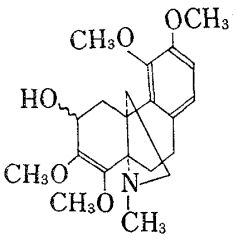
dl-16-oxo-hasubanonine (**59**) : R_1=CH_3, R_2=O
dl-aknadilactam (**61**) : R_1=H, R_2=O
dl-hasubanonine (**65**) : R_1=CH_3, R_2=H_2



60 : R=CH_3
62 : R=H



16-oxo-hasubanonine (**63**)



64

Chart 4

19) G. Hesse and E. Bücking, *Ann.*, **563**, 31 (1949); *idem*, *ibid.*, **592**, 120 (1955); G. Hesse, G. Krehbiel, and F. Rämisch, *ibid.*, **592**, 137 (1955).

ratio of 1/1. By careful fractional recrystallizations, (±)-16-oxo-hasubanonine (**59**), mp 177° and its structural isomer (**60**), mp 179—180°, were separated, respectively, in a pure state. Further elution of the column afforded a mixture of (±)-aknadilactam ((±)-16-oxo-aknadinine; **61**) and its structural isomer (**62**) in a ratio of 1/1. The less polar (±)-aknadilactam (**61**) was obtained as a pure state by repeated silica gel column chromatography. The IR, NMR, and mass spectra of this compound (**61**) were completely identical with those of natural alkaloid. Because of its labile nature, the compound (**62**) was not isolated in a pure state.

The compound (**59**) was identified in terms of IR, NMR, mass spectra and TLC behavior with a sample of 16-oxo-hasubanonine (**63**), mp 161°, which was derived from natural hasubanonine by permanganate oxidation. Since 16-oxo-hasubanonine was converted to hasubanonine by lithium aluminum hydride reduction followed by manganese dioxide oxidation, the present synthesis amounts to total synthesis of (±)-hasubanonine.

Experimental

All melting points were measured on a Yanagimoto Melting Point Apparatus and were uncorrected. Unless otherwise stated, IR spectra were measured for solutions in chloroform with a Hitachi EPI-S Spectrometer. Measurements of NMR spectra were made for deuteriochloroform solutions on a Varian A-60 Spectrometer with tetramethylsilane as an internal standard and chemical shifts were given in τ values. Mass spectra were taken on a Hitachi Mass Spectrometer Model RMU-6D. TLC was carried out on Alumina (Aluminiumoxid G nach Stahl) or silica gel (Kieselgel G nach Stahl) using acetone–chloroform (1: 4) or (1: 1) as a developing solvent. Column chromatography was performed with Mallinckrodt silicic acid, 100 mesh or Brockmann basic alumina, activity II—III, unless otherwise stated.

The Five Membered Ketone (13)——To a stirred solution of 300 mg of the keto-lactam (**9**) in 20 ml of dry *tert*-butanol was added 820 mg of sublimed potassium *tert*-butoxide and the reaction mixture was stirred for 200 hr at room temperature, acidified with aqueous 5% HCl, concentrated under reduced pressure, diluted with water, and extracted with a mixture of ether–chloroform (3: 1). After washing with water and drying over $MgSO_4$, the solvent was evaporated to leave a crystalline solid which was recrystallized from ethanol–acetone to give 204 mg of the carboxylic acid (**10**) as colorless prisms, mp 264°. IR ν_{max}^{Nujol} cm^{-1}: 3420, 2200—2700, 1704, and 1640. Mass Spectrum *m/e*: 301 (M^+), 199 and 198. *Anal.* Calcd. for $C_{17}H_{19}O_4N$: C, 67.76; H, 6.36; N, 4.65. Found: C, 68.03; H, 6.39; N, 4.91.

To a solution of 100 mg of the carboxylic acid (**10**) in 5 ml of methanol was added a solution of diazomethane in ether with ice cooling and the reaction mixture was allowed to stand overnight at room temperature. After decomposition of excess diazomethane with 3% acetic acid, the solvent was evaporated. The residue was made alkaline with 5% NH_4OH and extracted with chloroform. The chloroform extract was washed with water, dried over $MgSO_4$ and evaporated to leave a crystalline solid. Recrystallization from chloroform–ether gave 90 mg of the methyl ester (**11**) as colorless prisms, mp 200°. IR ν_{max} cm^{-1}: 3490, 1720 and 1675. NMR τ: 7.35 (3H, s., N–Me) and 6.19 (3H, s., O–Me). *Anal.* Calcd. for $C_{18}H_{21}O_4N$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.72; H. 6.72; N, 4.17.

To a stirred solution of 80 mg of the methyl ester (**11**) in 5 ml of dry tetrahydrofuran and 20 ml of dry ether was added 50 mg of $LiAlH_4$ at −5° and the reaction mixture was stirred for 30 min at the same temperature. After excess reagent was decomposed with water, the mixture was concentrated. The residue was acidified with 5% HCl and extracted with chloroform. The chloroform extract was washed with water, dried over $MgSO_4$ and evaporated to yield 40 mg of colorless oil which on trituration with acetone solidified. Recrystallization from acetone gave 20 mg of the diol (**12**) as colorless prisms, mp 181°. IR ν_{max} cm^{-1}: 1668. Mass Spectrum *m/e*: 287 (M^+), 199 and 198. A mixture of 11 mg of the diol (**12**), 0.5 ml of dioxane, 2 ml of water and 8 mg of HIO_4 was allowed to stand at room temperature for 20 hr. The reaction mixture was made alkaline with 5% Na_2CO_3 and extracted with chloroform. The chloroform extract was washed with water, dried over $MgSO_4$ and evaporated to give 8 mg of the five membered ketone (**13**) as a colorless oil, bp 100° (2×10^{-4} mmHg). IR ν_{max} cm^{-1}: 1739 and 1680. NMR τ 7.12 (3H, s., N–CH_3). *Anal.* Calcd. for $C_{16}H_{17}O_2N$: C, 75.27; H, 6.71; N, 5.49. Found: C, 74.62; H, 6.99; N, 5.60. Mass Spectrum *m/e*: 255 (M^+) and 199.

Oxidation of the Axial-acetoxy-ketone 23: *vide infra* with Ferric Chloride——To a solution of 73 mg of the axial-acetoxy-ketone (**23**) in 5 ml of 50% acetic acid was added 300 mg of $FeCl_3\cdot6H_2O$ and the mixture was heated for 3 hr at 100° with stirring. After being concentrated under reduced pressure, the mixture was diluted with water and extracted with chloroform. The chloroform extract was washed with water and dried over $MgSO_4$. After removal of the solvent, the residue in chloroform was chromatographed on silica gel column. Elution with chloroform gave 30 mg of unchanged starting material (**23**). Further elution with chloroform–methanol (50: 1) gave 10 mg of the carboxylic acid (**10**) as colorless prisms, mp 264°.

The sample of this was identified with a sample of the compound (**10**) described above by mixed melting point determination and IR spectral (Nujol) comparison.

The Enol-acetate (14)——A mixture of 50 mg of the keto-lactam (**9**) and 10 ml of a solution of Ac_2O–$HClO_4$–EtOAc (the reagent B[9]) was heated on a water bath for 1 hr. After cooling, the reaction mixture was washed with a saturated solution of $NaHCO_3$, water and dried over $MgSO_4$. Removal of the organic solvent under reduced pressure left 80 mg of brown oily residue which was chromatographed over silica gel column in chloroform. Elution with the same solvent gave 45 mg of crystalline solid which was recrystallized from ether to give 30 mg of the enol-acetate (**14**), mp 133° as colorless prisms. IR ν_{max} cm^{-1}: 1752 and 1677. NMR τ: 7.90 (3H, s., OAc), 7.16 (3H, s., N–CH_3) and 4.61 (1H, s., olefinic H). *Anal.* Calcd. for $C_{19}H_{21}O_3N$: C, 73.29; H, 6.80. Found: C, 73.06; H, 6.82.

Treatment of the Keto-nitrile (8) with Acetoxymethyl Vinyl Ketone——a) To a solution of 920 mg of the keto-nitrile (**8**) in 15 ml of dry benzene were added 960 mg of acetoxymethyl vinyl ketone and 10 drops of triethylamine, and the mixture was kept on standing in a refrigerator for 20 hr. Removal of the solvent under reduced pressure at room temperature afforded a slightly yellow oil which was chromatographed over silica gel column in chloroform and elution of the column with the same solvent gave 920 mg of the compound (**15**) which was recrystallized from ether to yield colorless silky needles, mp 91°. IR ν_{max} cm^{-1}: 2270, 1730 and 1715. NMR τ: 7.90 (3H, s., OAc) and 5.51 (2H, $-CH_2OAc$). *Anal.* Calcd. for $C_{18}H_{19}O_4N$: C, 68.99; H, 6.11; N, 4.47. Found: C, 69.02; H, 6.16; N, 4.60. Further elution of the column with the same solvent left 45 mg of the compound (**16b**) as an oil. IR ν_{max} cm^{-1}: 3400—3550, 2290, 1737 (sh.) and 1722. NMR τ: 7.86 (3H, s., OAc), 7.15 (1H, OH), and 7.04 (2H). Elution of the column with a mixture of chloroform–methanol (10: 1) afforded 20 mg of the compound (**16c**), mp 192°. IR ν_{max} cm^{-1}: 3430, 2220, and 1722. *Anal.* Calcd. for $C_{16}H_{17}O_3N$: C, 70.83; H, 6.32. Found: C, 70.76; H, 6.38. A mixture of 20 mg of the compound (**16c**), 1 ml of acetic anhydride and 1 ml of pyridine was allowed to stand overnight at room temperature. Working up as usual gave 22 mg of colorless oil, a sample of which was identified with a sample of the compound (**16b**) described above by comparison of NMR and IR spectra and TLC behavior.

b) To a solution of 920 mg of the keto-nitrile (**8**) and 960 mg of acetoxymethyl vinyl ketone in 20 ml of dry benzene was added 10 mg of sublimed potassium *tert*-butoxide, and the reaction mixture was allowed to stand at room temperature for 100 hr. To the reaction mixture was added 50 ml of a mixture of ether–chloroform (3: 1) and the organic solution was washed with 5% HCl and water, dried over $MgSO_4$ and evaporated to leave the residue as a slightly yellow oil which was chromatographed over silica gel column in chloroform. From the earlier eluate, 400 mg of the starting material was recovered. Further elution with the same solvent provided 400 mg of the compound (**15**), a sample of which was identical with a sample of the compound (**15**) obtained through the procedure a) described above.

Cyclization Reaction of the Compound (15)——a) A mixture of 280 mg of the compound (**15**), 20 ml of dry *tert*-butanol and 135 mg of sublimed potassium *tert*-butoxide was kept on standing in an ice box for 2 days. The mixture was acidified with 5% HCl, concentrated under reduced pressure, and extracted with chloroform. The chloroform extract was washed with water, dried and evaporated to give 270 mg of colorless oil. This oil in chloroform was chromatographed on silica gel column and elution with the same solvent furnished 130 mg of the compound (**16a**), mp 178°, as colorless prisms. IR ν_{max} cm^{-1}: 3425—3550, 2250, and 1727. NMR τ: 7.86 (3H, s., OAc), 7.32 (1H, OH) and 7.01 (2H, broad s.). *Anal.* Calcd. for $C_{18}H_{19}O_4N$: C, 68.99; H, 6.11; N, 4.47. Found: C, 68.88; H, 6.34; N, 4.41.

b) To a solution of 300 mg of the compound (**15**) and 124 mg of benzoic acid in 20 ml of dry toluene was added 75 mg of triethylamine, and the reaction mixture was refluxed for 20 hr.[20] The mixture was concentrated under reduced pressure and extracted with a mixture of chloroform–ether (1: 4). The extract was successively washed with 5% NaOH, water, 3% HCl and water, and dried over $MgSO_4$. Evaporation of the solvent left 210 mg of yellow oil which crystallized on trituration with ether–acetone. Recrystallization from acetone afforded 150 mg of the compound (**16a**) as colorless prisms, a sample of which was identical with a sample of (**16a**) obtained from the procedure a) described above.

c) A mixture of 140 mg of the compound (**15**), 10 ml of dry benzene and 10 mg of *p*-toluene sulfonic acid was refluxed for 20 hr. After being concentrated under reduced pressure, the mixture was mixed with water and extracted with a mixture of chloroform–ether (1: 3). The extract was washed with 2% NaOH, water, and dried over $MgSO_4$. Evaporation of the solvent left 140 mg of yellow oil which was chromatographed over silica gel column in chloroform. Elution of the column with the same solvent gave 30 mg of colorless oil which was assumed to be the dehydrated product of the compound (**16a**) from IR and NMR spectral data but no further investigation was undertaken. Continued elution with the same solvent afforded 20 mg of the compound (**16a**) as colorless prisms, a sample of which was identical with a sample of the compound (**16a**) obtained from the procedure a) described above.

d) A mixture of 140 mg of the compound (**15**), 10 ml of dry benzene and 0.3 ml of BF_3·etherate was allowed to stand at room temperature for 2 days.[21] The reaction mixture was made alkaline with dil. NH_4-

20) von P. Wieland, H. Überwasser, G. Anner, and K. Miescher, *Helv. Chim. Acta*, **36**, 376 (1953).
21) E.J. Corey and S. Nozoe, *J. Am. Chem. Soc.*, **87**, 5728 (1965).

OH and extracted with a mixture of ether–chloroform (3: 1). The extract was washed with water, dried over $MgSO_4$ and evaporated to give a brown oil. This oil was chromatographed on silica gel column and trituration of the eluate with acetone gave crystals. Recrystallization from acetone furnished 40 mg of the compound (**16a**) as colorless prisms, a sample of which was identical with a sample of (**16a**) obtained from the procedure a) described above.

The Diketone (17), the Bromo-diketone (18), and the Dibromo-ketone (19)——To a solution of 3.0 g of the keto-lactam (**9**) in 100 ml of acetic acid was added dropwise with stirring a solution of 5.40 g of bromine and 0.3 ml of 48% HBr in 50 ml of acetic acid, and the reaction mixture was stirred for 72 hr at room temperature. The red color of the reaction mixture was almost faded during this period. Removal of the solvent under reduced pressure left the crude bromo-ketones which without purification were dissolved in 100 ml of acetic acid. To this acetic acid solution was added 20 g of freshly fused sodium acetate and the mixture was heated at 120° on an oil bath for 7 hr. The solvent was removed under reduced pressure and the residue was diluted with water and extracted with chloroform. The extract was washed with water and evaporated to yield a slightly yellow oil. This oil was chromatographed on silica gel column and elution of the column with chloroform gave a crystalline solid in the earlier eluate. Recrystallization from benzene gave 900 mg of the dibromo-ketone (**19**) as a benzene adduct, colorless prisms, mp 204°. IR ν_{max} cm^{-1}: 1702, 1691, and 1609. NMR τ: 7.14 (3H, s., N–Me), 5.28 (1H, s., C_8–H) and 2.52 (1H, s., olefinic H). Mass Spectrum *m/e*: 425 (M^+). *Anal.* Calcd. for $C_{17}H_{15}O_2NBr_2 \cdot C_6H_6$: C, 54.90; H, 4.21; N, 2.78; Br, 31.77. Found: C, 54.83; H, 4.16; N, 2.87; Br, 33.68. Continued elution afforded a crystalline solid which was recrystallized from a mixture of acetone–benzene (1: 1) to yield 820 mg of the bromo-diketone (**18**) as colorless prisms, mp 216°. IR ν_{max} cm^{-1}: 3450, 1687 and 1652. NMR τ: 7.30 (3H, s., N–Me) and 6.88 (2H, q., $J=3$ Hz, $\delta_{AB}=17$ Hz, C_5–H). Mass Spectrum *m/e*: 362 (M^+). *Anal.* Calcd. for $C_{17}H_{16}O_3NBr$: C, 56.21; H, 4.44; N, 3.86; Br; 22.00. Found: C, 56.82; H, 4.70; N, 3.79; Br, 22.35. Further elution of the column with chloroform containing methanol in 1% proportion gave 120 mg of the diketone (**17**) which was identical with an authentic sample[7] in terms of mixed melting point determination, IR spectrum and TLC behavior.

Bromination of the Diketone (17)——To a solution of 107 mg of the diketone (**17**) in 10 ml of acetic acid was added a solution of 67 mg of bromine and 0.1 ml of 48% HBr in 1 ml of acetic acid and the mixture was stirred for 2.5 hr at room temperature. Removal of the solvent under reduced pressure left the crude bromide which was dissolved in chloroform and then extracted with 10% NaOH. The alkaline aqueous layer was made acidic with 10% HCl and extracted with chloroform. The extract was washed with water, dried over $MgSO_4$ and evaporated to give a crystalline solid. Recrystallization from a mixture of acetone–benzene (1: 1) gave 125 mg of the bromo-diketone (**18**) as colorless prisms, whose IR spectrum and TLC behavior were identical with those of an authentic sample.

The Keto-lactam (9) from the Dibromo-ketone (19)——A mixture of 450 mg of the dibromo-ketone (**19**), 15 ml of acetone freed from gaseous oxygen and 500 mg of chromous chloride was stirred for 24 hr at room temperature under nitrogen atmosphere. The solvent was removed under reduced pressure and the residue was extracted with chloroform. The extract was washed with water, dried over $MgSO_4$ and evaporated to afford 250 mg of colorless oil. Trituration of the oil with ether afforded a crystalline solid which was recrystallized from a mixture of hexane–ether to yield 180 mg of the monobromide (**20**), mp 213°. IR ν_{max} cm^{-1}: 1690 and 1610. NMR τ: 7.19 (3H, s., N–Me) and 2.55 (1H, s., olefinic H). *Anal.* Calcd. for $C_{17}H_{16}O_2NBr$: C, 58.98; H, 4.66; N, 4.05; Br, 23.08. Found: C, 58.82; H, 4.61; N, 3.99; Br, 23.35. A mixture of 115 mg of the monobromide (**20**), 0.5 ml of 1% $PdCl_2$ solution and 10 ml of methanol was shaken for 2 hr under hydrogen at an atmospheric pressure. The mixture was concentrated under reduced pressure, extracted with chloroform, and the extract was washed with water and dried over $MgSO_4$. Removal of the solvent left 100 mg of colorless oil which was triturated with ether to give a crystalline solid. Recrystallization from ether–acetone mixture furnished 70 mg of the keto-lactam (**9**), a sample of which was identical with an authentic sample in all respects.

The Bromo-enolmethyl-ether A (21) and the Bromo-enolmethyl-ether B (22) [Methylation of the Bromo-diketone (18)]——a) A mixture of 102 mg of the bromo-diketone (**18**), 10 ml of anhydrous methanol and 0.3 ml of BF_3·etherate was allowed to stand at room temperature for 40 hr. At the end of this period, the starting material was still recognized by TLC examination and hence the mixture was further refluxed for 23 hr, until no starting material had been detected by TLC. The mixture was evaporated to dryness to afford a slightly yellow oil. The oil was purified by chromatography on alumina column to give a crystalline solid. Recrystallization from acetone yielded 46 mg of the bromo-enolmethyl-ether A (**21**) as colorless prisms, mp 238°. IR ν_{max} cm^{-1}: 1690 and 1631. NMR τ: 7.12 (3H, s., N–CH_3), 6.33 (3H, s., O–Me), 5.35 (1H, s., C_8–H) and 4.04 (1H, s., olefinic H). Mass Spectrum *m/e*: 375 (M^+) and 377 (M^++2). *Anal.* Calcd. for $C_{18}H_{18}O_3NBr$: C, 57.43; H, 4.82; N, 3.72. Found: C, 57.48; H, 4.89; N, 3.74.

b) To a solution of 61 mg of the bromo-diketone (**18**) in 15 ml of methanol was added a solution of diazomethane in ether under ice cooling until a yellow color of the reaction mixture had been maintained, and the mixture was then allowed to stand at room temperature for 25 hr. Excess diazomethane was decomposed with 5% acetic acid and the solvent was removed under reduced pressure. The residue was mixed with 10 ml of water and extracted with chloroform. The extract was washed with water, dried

over $MgSO_4$ and evaporated. The residual oil in ether was chromatographed on alumina and elution of the column with the same solvent gave a crystalline solid. Recrystallization from acetone afforded 60 mg of the bromo-enolmethyl-ether B (22) as colorless prisms, mp 178°. IR ν_{max} cm^{-1}: 1685 and 1598. NMR τ: 6.89 (3H, s., N–Me) and 6.20 (3H, s., O–Me). *Anal.* Calcd. for $C_{18}H_{18}O_3NBr$: C, 57.43; H, 4.82; N, 3.72. Found: C, 57.53; H, 4.70; N, 3.77.

The Axial-acetoxy-ketonl (23) and the Equatorial-acetoxy-ketone (24); (Oxidation of the Keto-lactam (9) with Lead Tetraacetate)——a) To a stirred solution of 540 mg of the keto-lactam (9) and 1.5 ml of BF_3–etherate in 40 ml of dry benzene was added 1.06 g of lead tetraacetate and the reaction mixture was heated for 3 hr at 50—55° with stirring. After cooling, 40 ml of a mixture of ether–chloroform (3 : 1) was added to the reaction mixture and the organic solution was washed with water, dil. NH_4OH and water, dried over $MgSO_4$ and evaporated to dryness under reduced pressure to leave 600 mg of a crystalline solid. Recrystallization from a mixture of acetone–ether gave 290 mg of the axial-acetoxy-ketone (23) as colorless prisms. The mother liquor from recrystallizations was combined and chromatographed on silica gel column. Recrystallization of the eluate gave another crop of the axial-acetoxy-ketone (23: 73 mg). The total yield of the compound (23) was 56% from the keto-lactam. The physical data of (23) were as follows. mp 199—200°, IR ν_{max} cm^{-1}: 1745, 1738, and 1682. NMR τ: 7.73 (3H, s., OAc), 7.16 (3H, s., N–Me) and 4.26 (1H, s., C_8–H). Mass Spectrum *m/e*: 327 (M^+), 284, 267, 199, 198, 115 and 43. *Anal.* Calcd. for $C_{19}H_{21}O_4N$: C, 69.70; H, 6.47; N, 4.28. Found: C, 70.00; H, 6.60; N, 4.24.

b) To a solution of 540 mg of the keto-lactam (9) and 0.3 ml of BF_3·etherate in 40 ml of benzene was added 1.40 g of lead tetraacetate and the reaction mixture was stirred for 48 hr at room temperature and then heated for 48 hr at 60° with stirring. The solution was worked up as stated above to afford 570 mg of the crude product as a yellow oil which was chromatographed on a silica gel column in chloroform. Elution with the same solvent afforded 110 mg of the axial-acetoxy-ketone (23) in the earlier eluate. Continued elution of the column with the same solvent gave a crystalline solid which was recrystallized from acetone to afford 35 mg of the equatorial-acetoxy-ketone (24) as colorless prisms, mp 211—212°. IR ν_{max} cm^{-1}: 1751, 1736, and 1686. NMR τ: 7.74 (3H, s., OAc), 7.15 (3H, s., N–Me), and 4.50 (1H, s., C_8–H). Mass Spectrum *m/e*: 327 (M^+), 284, 267, 199, 198, 115 and 43. *Anal.* Calcd. for $C_{19}H_{21}O_4N$: C, 69.70; H, 6.47; N, 4.28. Found: C, 69.42; H, 6.56; N, 4.48. From the following eluate, 20 mg of the starting material was recovered.

c) To a solution of 540 mg of the keto-lactam (9) and 0.8 ml of BF_3·etherate in 42 ml of dry benzene and 8 ml of acetic acid was added 1.60 g of lead tetraacetate with stirring and the reaction mixture was stirred for 27 hr at room temperature and then heated at 55° with stirring for 3 hr. The reaction mixture was worked up in the same manner as that described above to yeild 140 mg of the axial-acetoxy-ketone (23). The mother liquor from recrystallizations of (23) was evaporated and the residue in chloroform was chromatographed on a silica gel column. Elution with the same solvent gave 120 mg of (23) as a pure crystalline solid. Continued elution of the column with the same solvent afforded 55 mg of the equatorial-acetoxy-ketone (24) as colorless prisms. From the following eluate, 22 mg of the starting material was recovered.

Epimerization of the Axial-acetoxy-ketone (23) to the Equatorial-acetoxy-ketone (24) with Hydrogen Bromide——A solution of 50 mg of the axial-acetoxy-ketone (23) and a trace of 48% hydrogen bromide in 5 ml of acetic acid was allowed to stand at room temperature overnight. The solvent was removed under reduced pressure and the residual oil was mixed with water and extracted with chloroform. The extract was washed with water, dried over $MgSO_4$ and evaporated to leave 50 mg of slightly yellow oil which was chromatographed over silica gel column in chloroform. From the earlier eluate, 13 mg of the axial-acetoxy-ketone (23) was recovered. Further elution of the column with the same solvent afforded 32 mg of the equatorial-acetoxy-ketone (24) which was identical with an authentic sample in terms of mixed mp, IR spectrum and TLC behavior.

Ketalization of the Axial-acetoxy-ketone (23)——A mixture of 78 mg of the axial-acetoxy-ketone (23), 10 mg of *p*-toluenesulfonic acid, 1 ml of ethylene glycol and 10 ml of dry benzene was refluxed for 20 hr while water was separated with a Dean-Stark type apparatus. The mixture was concentrated under reduced pressure, made alkaline with dil. NH_4OH and extracted with methylene chloride. The extract was washed with water, dried over $MgSO_4$ and evaporated to give a crystalline solid. Recrystallization from ether afforded 70 mg of the axial-acetoxy-ketal (**30a**) as colorless needles, mp 190°. IR ν_{max} cm^{-1}: 1735 and 1680. NMR τ: 7.92 (3H, s., OAc), 7.34 (3H, s., N–Me) and 5.02 (1H, d., J=1.5 Hz, C_8–H). *Anal.* Calcd. for $C_{21}H_{25}O_5N$: C, 67.90; H, 6.78; N, 3.77. Found: C, 67.68; H, 6.84; N, 3.70.

Ketalization of the Equatorial-acetoxy-ketone (24)——A mixture of 74 mg of the equatorial-acetoxy-ketone (24), 10 mg of *p*-toluenesulfonic acid, 1 ml of ethylene glycol and 20 ml of dry benzene was refluxed for 20 hr while water was separated with a Dean-Stark type apparatus. The mixture was worked up as stated above to yield 98 mg of colorless oil. This oil solidified on standing and recrystallization from a mixture of acetone–ether afforded 50 mg of the equatorial-acetoxy-ketal (**30b**) as colorless prisms, mp 230—232°. IR ν_{max} cm^{-1}: 1744 and 1680. NMR τ: 7.87 (3H, s., OAc), 7.28 (3H, s., N–Me) and 4.73 (1H, s., C_8–H). *Anal.* Calcd. for $C_{21}H_{25}O_5N$: C, 67.90; H, 6.78; N, 3.77. Found: C, 67.61; H, 6.52; N, 3.73.

Bromination of the Axial-acetoxy-ketone (23) with Pyridine Hydrobromide Perbromide Complex——To a stirred solution of 1.90 g of the axial-acetoxy-ketone (**23**) in 1 ml of acetic anhydride and 40 ml of acetic acid was added 2.20 g of freshly prepared pyridine hydrobromide perbromide complex[15] and the mixture was stirred for 2 hr at 55—60°. Removal of the solvent under reduced pressure afforded a yellow oil which was mixed with water and then extracted with methylene chloride. The methylene chloride extract was washed with water, dil. NH_4OH and dried over $MgSO_4$. The solvent was evaporated to leave a slightly yellow oil which was triturated with a cold acetone–ether mixture to afford a crystalline solid, mp 178—182°. Judging from its NMR spectrum, the compound having mp 178—182° assumed to be a mixture of stereoisomers, the monobromides (**25**), due to the asymmetric centers at C_6 and/or C_8 position but no further separation was undertaken.

The Enol-acetate (28) from a Mixture of Monobromides (25)——A solution of 515 mg of a mixture of monobromides (**25**) in 80 ml of acetic acid was heated with 2.0 g of freshly fused sodium acetate at 95—100° on an oil bath for 2 hr and the mixture was concentrated to dryness. The residual brown oil was mixed with 100 ml of water and extracted with chloroform. The extract was washed with water, and dried over $MgSO_4$. Evaporation of the solvent and chromatography of the residue over a silica gel column in chloroform gave 398 mg of the enol-acetate (**28**) as a colorless oil which was identified with an authentic sample of the compound (**28**) obtained through the well-established synthetic route (*vide infra*).

The Bromo-diketone (26), the Bomo-enol-acetate (27), and the Enol-acetate (28)——To a solution of 1.052 g of the axial-acetoxy-ketone (**23**) in 230 ml of acetic acid was added dropwise a solution of 1.03 g of bromine and 0.5 ml of 48% hydrogen bromide in 6 ml of acetic acid with stirring at room temperature. An additional 100 ml of acetic acid was added to the solution and the reaction mixture was further stirred for 100 hr at room temperature. After a red yellow color of the mixture had almost faded, the solvent and excess reagent were evaporated under reduced pressure and 200 ml of acetic acid was added to the residue. To this solution was added 3.5 g of freshly fused sodium acetate and the mixture was heated on an oil bath at 100° for 1.3 hr. The solvent was removed under reduced pressure and 200 ml of water was added to the residue. The mixture was extracted with chloroform and the extract was washed with water, dried over $MgSO_4$ and evaporated to afford a slightly yellow oil which was chromatographed over a silica gel column in chloroform. Elution of the column with the same solvent gave 505 mg of the bromo-enol-acetate (**27**) as colorless prisms (from acetone), mp 220°. IR ν_{max} cm^{-1}: 1771, 1679 and 1643. NMR τ: 7.72 (3H, s., OAc) and 6.96 (3H, s., N–Me). *Anal.* Calcd. for $C_{19}H_{18}O_4NBr$: C, 56.44; H, 4.49; N, 3.47. Found: C, 56.16; H, 4.61; N, 3.62. Continued elution of the column gave the crude bromo-diketone (**26**) which was recrystallized from acetone to afford 115 mg of the compound (**26**) as colorless prisms, mp 202°. IR ν_{max} cm^{-1}: 3425, 1685 and 1643. *Anal.* Calcd. for $C_{17}H_{16}O_3NBr$: C, 56.21; H, 4.44; N, 3.86. Found: C, 56.11; H, 4.64; N, 4.04. Further elution of the column with the same solvent yielded 70 mg of the enol-acetate (**28**) as a colorless oil. IR ν_{max} cm^{-1}: 1762 and 1685. NMR τ: 7.76 (3H, s., OAc); 6.97 (3H, s., N–Me) and 3.44 (1H, q., $J=4$ Hz, $\delta_{AB}=1$ Hz, olefinic H). Mass Spectrum m/e: 325 (M^+).

The Bromo-diketone (26) from the Equatorial-acetoxy-ketone (24) or the Bromo-enol-acetate (27)——a) Bromination and rearrangement reaction using 650 mg of the equatorial-acetoxy-ketone (**24**) was accomplished by the same way as that mentioned above. The reaction mixture was worked up as usual and 150 mg of the bromo-diketone (**26**) was obtained. A sample of this compound was identified with an authentic sample in terms of mixed mp, IR and NMR spectra and TLC behavior.

b) A solution of 400 mg of the bromo-enol-acetate (**27**) in 20 ml of methanol and 20 ml of 3% sulfuric acid was refluxed for 5 hr on a water bath. Usual work up afforded 505 mg of colorless oil, which solidified on standing. Recrystallization from a mixture of ether–acetone gave 304 mg of the bromo-diketone (**26**) as colorless prisms, mp 202°. A sample was identical with an authentic sample.

The Diosphenol (29)——A solution of 100 mg of the enol-acetate (**28**) in 10 ml of methanol and 10 ml of 3% sulfuric acid was refluxed for 4 hr on a water bath. Usual work up afforded 85 mg of the diosphenol (**29**) as crystals. Recrystallization from acetone yielded 80 mg of the pure diosphenol (**29**) as colorless prisms, mp 216—217°. IR ν_{max} cm^{-1}: 3470, 1685 and 1653. *Anal.* Calcd. for $C_{17}H_{17}O_3N$: C, 72.06; H, 6.05; N, 4.94. Found: C, 72.13; H, 6.00; N, 5.02.

The Bromo-diketone (26) from the Diosphenol (29)——A mixture of 76 mg of the diosphenol (**29**), 0.1 ml of 48% hydrogen bromide, 52 mg of bromine and 10 ml of acetic acid was stirred for 10 hr at room temperature. Removal of the solvent under reduced pressure left the crude product which was mixed with water and extracted with chloroform. The chloroform extract was washed with water, dried over $MgSO_4$ and evaporated to afford a crystalline solid. Recrystallization from acetone gave 87 mg of the bromo-diketone (**26**). A sample was identical with an authentic sample.

The Hydroxy-ketal (31)——A mixture of 910 mg of the axial-acetoxy-ketal (**30a**), 50 ml of methanol, 5 g of potassium hydroxide, and 50 ml of water was refluxed for 3 hr, cooled, then poured into ice-water and extracted with chloroform. The extract was dried over $MgSO_4$ and removal of the solvent left a crystalline solid. Recrystallization from methanol gave 742 mg of the hydroxy-ketal (**31**) as colorless prisms, mp 279—280°. IR ν_{max} cm^{-1}: 3550 and 1677. *Anal.* Calcd. for $C_{19}H_{23}O_4N$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.09; H, 7.07; N, 4.36.

The Ketal-ketone (32)——a) A solution of 2.275 g of the hydroxy-ketal (**31**) in 180 ml of methylene chloride was stirred with 10.80 g of Collin's bispyridinechromium (VI) oxide reagent[22] for 6 hr at 40°. Then, the reaction mixture was allowed to stand at room temperature for 40 hr and filtered through a glass filter. The filtrate was washed with water, 1% citric acid solution, water and concentrated to dryness. The residual brown oil (3.5 g) was chromatographed over a silica gel column in chloroform. The earlier eluate gave crystals which were recrystallized from a mixture of acetone–ether (1: 1) to afford 1.388 g of the ketal-ketone (**32**) as colorless prisms, mp 139°. IR ν_{max} cm^{-1}: 1725 and 1680. NMR τ: 7.03 (3H, s., N–Me), 5.95 (4H, ethylene ketal). *Anal.* Calcd. for $C_{19}H_{21}O_4N$: C, 69.70; H, 6.47; N, 4.28. Found: C, 69.63; H, 6.43; N, 4.29. From the following eluate, 310 mg of the starting material was recovered.

b) A mixture of 1.89 g of the hydroxy-ketal (**31**), 5 ml of acetic acid and 300 ml of acetone was strirred with 4 ml of the Jones reagent[23] at room temperature. After 30 min, a small amount of methanol was added and the mixture was concentrated under reduced pressure. The residue was mixed with water and extracted with ether. The ether extract was washed with 5% NH_4OH, water and evaporated to give 1.388 g of the ketal-ketone (**32**). A sample of this material was identified with an authentic sample.

The Diosphenol (29) from the Ketal-ketone (32)——A solution of 500 mg of the ketal-ketone (**32**) in 5 ml of acetone and 35 ml of conc. hydrochloric acid was heated at 50—60° for 3 hr with stirring and poured into ice-water and extracted with chloroform. The extract was treated as usual and recrystallization of the product from a mixture of acetone–ether (2: 1) gave 265 mg of the diosphenol (**29**), a sample of which was identical with an authentic sample.

The Bromo-enolmethyl-ether (33)——To a solution of 200 mg of the bromo-ketone (**26**) in 20 ml of methanol was added a solution of excess diazomethane in methanol–ether, and the mixture was worked up as usual to give 195 mg of crystalline solid. Recrystallization from a mixture of acetone–ether afforded 183 mg of the bromo-enolmethyl-ether (**33**) as colorless prisms, mp 153—154°. IR ν_{max} cm^{-1}: 1680 and 1624. NMR τ: 6.98 (3H, s., N–Me) and 6.23 (3H, s., O–Me). *Anal.* Calcd. for $C_{18}H_{18}O_3NBr$: C, 57.46; H, 4.82; N, 3.73. Found: C, 57.74; H, 4.64; N, 3.76.

The β-Diketone (34)——To a stirred solution of 210 mg of the bromo-enolmethyl-ether (**33**) in 15 ml of methanol was added dropwise a solution of 224 mg of potassium hydroxide in 10 ml of methanol and 2 ml of water. The reaction mixture was stirred for 6 hr at room temperature under nitrogen atmosphere and poured into an ice-cooled mixture of 10% HCl and $CHCl_3$. The mixture was stirred for 30 min and extracted with chloroform. Evaporation of the solvent and recrystallization of the residue from methanol afforded 130 mg of the β-diketone (**34**) as colorless flakes, mp 243—244°. IR ν_{max} cm^{-1}: 3450, 1683, and 1629. NMR τ: 6.94 (3H, s., N–Me) and 6.25 (3H, s., O–Me). *Anal.* Calcd. for $C_{18}H_{19}O_4N$: C, 68.99; H, 6.11; N, 4.47. Found: C, 68.97; H, 6.38; H, 4.39. The mother liquor from recrystallizations of the β-diketone (**34**) was evaporated and the residue was chromatographed over a silica gel column in chloroform. Elution with the same solvent gave 15 mg of a crystalline solid, a sample of which was identical with an authentic sample of the compound (**36**; *vide infra*). Continued elution of the column with a mixture of chloroform–methanol (50: 1) gave another crop of the β-diketone (20 mg).

The Enolmethyl-ether A (35) and the Enolmethyl-ether B (36)——To a solution of 150 mg of the β-diketone (**34**) in 15 ml of methanol was added a solution of an excess diazomethane in a mixture of ether–methanol and the mixture was allowed to stand for 2 hr at room temperature. Usual work up of the reaction mixture gave 174 mg of an oil which was chromatographed over a silica gel column in chloroform. Elution with the same solvent afforded 32 mg of the enolmethyl-ether A (**35**) in the earlier eluate. A pure sample of this material was obtained by recrystallization from a mixture of acetone–ether, colorless prisms, mp 201°. IR ν_{max} cm^{-1}: 1683 and 1612. NMR τ: 7.02 (3H, s., N–Me), 6.33 and 5.90 (each 3H, s., OMe). *Anal.* Calcd. for $C_{19}H_{21}O_4N$: C, 69.70; H, 6.47; N, 4.28. Found: C, 69.45; H, 6.41; N, 4.25. Successive elution of the column with the same solvent gave 20 mg of the enolmethyl-ether B (**36**). Recrystallization from a mixture of acetone–ether gave colorless prisms, mp 187°. IR ν_{max} cm^{-1}: 1679 and 1610. NMR τ: 6.96 (3H, s., N–Me), 6.34 and 5.97 (each 3H, s., OMe). *Anal.* Calcd. for $C_{19}H_{21}O_4N$: C, 69.70; H, 6.47. Found: 69.44; H, 6.69. The mother liquor from recrystallizations was combined and evaporated. Rechromatography of the residue in chloroform gave another crops of the enolmethyl-ether A (8 mg) and B (7mg), respectively.

Borohydride Reduction of the Enolmethyl-ether A (35), Followed by Acid Treatment: The Compound (38)——To an ice-cooled solution of 35 mg of the enolmethyl-ether A (**35**) in 7 ml of methanol and 1 ml of water was added portionwise 50 mg of sodium borohydride with stirring, and stirring was continued for 2 hr at room temperature. The solvent was evaporated under reduced pressure to yield a crude oil of epimeric mixture of the compounds (**37**) which without purification was dissolved in 10 ml of acetone containing 1 ml of 48% hydrogen bromide. The mixture was refluxed for 1.8 hr on a water bath and then poured into ice-water and extracted with chloroform. The chloroform extract was washed with dil. NH_4OH, water and evaporated to dryness. The residual oil was chromatographed over an alumina column and

22) J.C. Collins, W.W. Hess, and F.J. Frank, *Tetrahedron Letters*, **1968**, 3363.
23) K. Bowden, I.M. Heilbron, E.R. Jones, and B.C.L. Weedon, *J. Chem. Soc.*, **1946**, 39.

elution with benzene gave 20 mg of the compound (**38**) as a colorless oil. IR ν_{max} cm^{-1}: 1685 and 1644. NMR τ: 6.97 (3H, s., N–Me), 6.33 (3H, s., O–Me) and 4.15 (1H, q., $J=4$ Hz, $\delta_{AB}=2$ Hz, olefinic H). Mass Spectrum *m/e*: 297 (M^+). A sample of this oil was identical with a sample of the compound (**38**) obtained from the diosphenol (**29**) by methylation with diazomethane.

The Compound (40)——To a solution of 250 mg of the enolmethyl-ether A (**35**) in 10 ml of dry tetrahydrofuran and 40 ml of dry ether was added 250 mg of lithium aluminum hydride and the mixture was refluxed with stirring for 20 hr. Excess reagent was decomposed with wet ether and the precipitate was filtered off and washed with ether. The organic solution and washings were combined and extracted with 3% aqueous acetic acid solution. The aqueous acidic solution was made alkaline with NH_4OH and extracted with ether. The ether extract was washed with water, dried over $MgSO_4$ and evaporated to leave 215 mg of yellow oil which was dissolved in 25 ml of chloroform. To this solution, 215 mg of manganese dioxide was added and the mixture was stirred for 3 hr at room temperature. Excess reagent was filtered off and the residue was thoroughly washed with ether. The filtrate and washings were combined, evaporated and the residue was dissolved in ether. The ether solution was extracted with 3% aqueous acetic acid solution and then the aqueous solution was made alkaline with NH_4OH, and extracted with ether. The extract was evaporated to leave a slightly yellow oil (106 mg) which was chromatographed over an alumina column in benzene. Elution of the column with the same solvent gave a crystalline solid which was recrystallized from ether to give 21 mg of the compound (**40**) as colorless prisms, mp 110°. IR ν_{max} cm^{-1}: 1665 and 1601. NMR τ: 7.45 (3H, s., N–Me), 6.36 and 5.91 (each 3H, s., OMe). Mass Spectrum *m/e*: 313 (M^+).

Oxidation of the Keto-lactam (41) with Lead Tetraacetate——a) To a solution of 2.0 g of the keto-lactam (**41**) and 4.7 ml of boron trifluoride ether complex in 250 ml of dry benzene was added portionwise 3.91 g of lead tetraacetate with stirring and the mixture was further stirred at 50—60° for 1.5 hr. To this reaction mixture were added 50 ml of chloroform and 100 ml of water and the mixture was washed with dil. NH_4OH and evaporated to leave 2.91 g of a yellow oil. This oil was chromatographed over a silica gel column in chloroform. The column was eluted with the same solvent to leave a crystalline solid. Recrystallization from a mixture of acetone–ether afforded 150 mg of the acetoxy-ketone (**42**) as colorless prisms, mp 204°. IR ν_{max} cm^{-1}: 1749, 1738 and 1682. NMR τ: 7.72 (3H, s., OAc), 7.18 (3H, s., N–Me), 6.13 and 6.10 (each 3H, s., OMe), 4.18 (1H, s., C_8–H), 3.16 (2H, s., aromatic H). *Anal.* Calcd. for $C_{21}H_{25}O_6N$: C, 65.10; H, 6.50; N, 3.62. Found: C, 65.29; H, 6.62; N, 3.40. Continued elution of the column with the same solvent left 370 mg of a crystalline solid which was recrystallized from a mixture of acetone–ether to provide the acetoxy-ketone (**43**) as colorless prisms, mp 220°. IR ν_{max} cm^{-1}: 1753, 1743, 1739 and 1684. NMR τ: 7.73 and 7.68 (each 3H, s., OAc), 7.19 (3H, s., N–Me), 6.20 and 6.07 (each 3H, s., OMe), 4.20 (1H, s., C_8–H) and 3.38 (1H, s., aromatic H). *Anal.* Calcd. for $C_{23}H_{27}O_8N$: C, 62.01; H, 6.11; N, 3.14. Found: C, 62.25; H, 6.12; N, 3.18. Further elution of the column with a mixture of chloroform–methanol (50: 1) gave 83 mg of the keto-lactam (**41**). Repeated chromatography of the mother liquor from recrystallizations afforded 43 mg of the acetoxy-ketone (**42**) and 121 mg of the acetoxy-ketone (**43**), respectively.

b) A mixture of 200 mg of the keto-lactam (**41**), 0.5 ml of boron trifluoride etherate, 270 mg of lead tetraacetate and 30 ml of dry benzene was heated at 40—47° for 2 hr with stirring. The mixture was worked up in the same manner as that described in the procedure a) to afford 37 mg of the acetoxy-ketone (**42**), 15 mg of the acetoxy-ketone (**43**), 69 mg of the acetoxy-ketone (**44**), and 12 mg of the starting material, respectively. The spectral data of the compound (**44**) were as follows. IR ν_{max} cm^{-1}: 1754, 1718, and 1678. NMR τ: 7.68 (3H, s., OAc), 7.22 (3H, s., N–Me), 6.21 and 6.07 (each 3H, s., O–Me), and 3.41 (1H, s., aromatic H). For analysis, the compound (**44**) was derived to a crystalline phenolic compound. A mixture of 40 mg of the acetoxy-ketone (**44**), 5 ml of methanol, and 5 ml of 5% sulfuric acid was refluxed for 3 hr. Usual work up gave a crystalline phenolic compound which was recrystallized from chloroform to leave 19 mg of the phenolic compound (**44**; R_1=OH) as colorless prisms, 207—208°. IR ν_{max} cm^{-1}: 3500, 1718 and 1677. *Anal.* Calcd. for $C_{19}H_{23}O_5N \cdot CHCl_3$: C, 51.69; H, 5.20; N, 3.01; Cl, 22.89. Found: C, 51.54; H, 5.12; N, 3.01; Cl, 23.18. Mass Spectrum *m/e*: 345 (M^+).

The Phenol A (45) and the Phenol B (46)——A solution of 2.22 g of the ketal derivative of the keto-lactam (**41**), 20 g of potassium hydroxide and 20 ml of 80% hydrazine hydrate in 120 ml of ethylene glycol was heated at 150° on an oil bath for 30 min and then at 180° for 20 hr. After cooling, the reaction mixture was poured into water and made alkaline with ammonium chloride and extracted with chloroform. The extract was washed with water, dried over $MgSO_4$ and evaporated. On trituration with a mixture of acetone–ether, the residue crystallized and recrystallization from a mixture of acetone–ether provided 1.60 g of the phenol A (**45**) as slightly yellow flakes, mp 220—225°, a sample of which was identified with an authentic sample.[7] The mother liquor from recrystallizations was evaporated and the residue in chloroform was chromatographed on a silica gel column. Elution of the column with the same solvent gave 100 mg of the phenol A (**45**) in the earlier eluate and further elution with chloroform containing MeOH in 1% portion afforded 245 mg of the phenol B (**46**) as slightly yellow flakes, mp 235°. IR ν_{max} cm^{-1}: 3520, 3050—3400 and 1668. *Anal.* Calcd. for $C_{20}H_{25}O_5N \cdot 1/2H_2O$: C, 65.16; H, 7.11; N, 3.81. Found: C, 65.08; H, 7.31; N, 3.63.

The O-Acetyl-phenol B (47)——The phenol B (**46**: 100 mg) was acetylated with acetic anhydride (0.5 ml) and pyridine (1 ml) and usual work up gave 101 mg of the O-acetyl-phenol B (**47**) as colorless prisms from ether), mp 147—148°. IR ν_{max} cm^{-1}: 1759 and 1674. NMR τ: 7.69 (3H, s., OAc), 7.22 (3H, s., N–Me), 6.15 (3H, s., O–Me), 6.09 (4H, s., ethylene ketal H), and 3.16 (2H, q., J=9 Hz, δ_{AB}=1 Hz, aromatic H). *Anal.* Calcd. for $C_{22}H_{27}O_6N$: C, 65.82; H, 6.78. Found: C, 65.73; H, 6.85.

The Keto-O-acetyl-phenol B (48)——To a solution of 50 mg of the O-acetyl-phenol B (**47**) in 8 ml of acetone was added 8 ml of 1% hydrochloric acid solution and the mixture was refluxed for 1.5 hr on a water bath. The organic solvent was removed under reduced pressure and the residue was extracted with chloroform. The extract was washed with water, dried over $MgSO_4$ and evaporated to give 45 mg of a crude crystalline solid. Recrystallization from acetone–ether afforded 40 mg of the keto-O-acetoxy-phenol B (**48**) as colorless prisms, mp 201—202°. IR ν_{max} cm^{-1}: 1760, 1720, and 1679. NMR τ: 7.66 (3H, s., OAc), 7.20 (3H, s., N–Me), 6.12 (3H, s., O–Me) and 3.10 (2H, q., J=9 Hz, δ_{AB}=1 Hz, aromatic H). *Anal.* Calcd. for $C_{20}H_{23}O_5N$: C, 67.21; H, 6.49. Found: C, 67.24; H, 6.58.

Oxidation of the Keto-O-acetyl-phenol A (49) with Lead Tetraacetate: The Axial-acetoxy-ketone (50)——To a mixture of 2.10 mg of the keto-O-acetyl-phenol A (**49**),[7] 5 ml of boron trifluoride etherate and 350 ml of dry benzene was added 3.50 g of lead tetraacetate and the reaction mixture was heated at 55° with stirring. After 2 hr, 150 ml of water, 50 ml of chloroform and 200 ml of ether were added to the mixture and the organic layer was washed with dil. NH_4OH, water, and dried over $MgSO_4$. Evaporation of the solvent and recrystallization of the residue from acetone–ether afforded 1.56 g of the axial-acetoxyketone (**50**) as colorless prisms, mp 235°. IR ν_{max} cm^{-1}: 1750, 1740, and 1685. NMR τ: 7.72 and 7.66 (each 3H, s., OAc), 7.20 (3H, s., N–Me), 6.19 (3H, s., O–Me), 4.19 (1H, s., C_8–H), 3.07 (2H, q., J=9 Hz, δ_{AB}=4 Hz, aromatic H). *Anal.* Calcd. for $C_{22}H_{25}O_7N$: C, 63.60; H, 6.07; N, 3.37. Found: C, 63.31; H, 6.36; N, 3.15.

The Enol-acetate (51) and the Bromo-enol-acetate (52)——To a stirred solution of 1.11 g of the axial-acetoxy-ketone (**50**) in 0.5 ml of 48% hydrogen bromide and 300 ml of acetic acid was added dropwise a solution of 898 mg of bromine (2.05 eq.) in 23 ml of acetic acid, and the mixture was stirred at room temperature. After one week, the solvent and excess bromine were removed under reduced pressure to give a crude oil which without purification, was dissolved in 240 ml of acetic acid. To this solution was added 4.0 g of sodium acetate and the mixture was heated on an oil bath at 95—100° for 2 hr. Removal of the solvent left a crude oil which was extracted with chloroform and the extract was washed with water, dried over $MgSO_4$ and evaporated. The residue in chloroform was chromatographed on a silica gel column and elution with the same solvent gave 70 mg of the bromo-enol-acetate (**52**) which was recrystallized from acetone–ether to give colorless prisms, mp 176—177°. IR ν_{max} cm^{-1}: 1770, 1687 and 1644. NMR τ: 7.72 and 7.63 (each 3H, s., OAc), 7.01 (3H, s., N–Me) and 6.20 (3H, s., O–Me). *Anal.* Calcd. for $C_{22}H_{22}O_7NBr$: C, 53.66; H, 4.51; N, 2.85; Br, 16.23. Found: C, 53.84; H, 4.46; N, 2.85; Br, 16.65. Continued elution of the column with the same solvent gave 700 mg of the enol-acetate which was recrystallized from ether to afford 305 mg of the pure enol-acetate (**51**) as colorless prisms, mp 207—208°. IR ν_{max} cm^{-1}: 1760 and 1687. NMR τ: 7.78 and 7.66 (each 3H, s., OAc), 7.01 (3H, s., N–Me), 6.22 (3H, s., O–Me) and 3.51 (1H, t., J=5 Hz, C_6–H). *Anal.* Calcd. for $C_{22}H_{23}O_7N$: C, 63.91; H, 5.61; N, 3.39. Found: C, 63.75; H, 5.61; N, 3.30.

The Enol-acetate (51) from the Bromo-acetoxy-ketone (53)——To a solution of 373 mg of the bromo-acetoxy-ketone (**53**) in 100 ml of acetic acid was added 1.70 g of freshly fused sodium acetate and the mixture was heated on an oil bath at 95—100°. After 2 hr, the solvent was evaporated under reduced pressure. The residual oil was mixed with water and extracted with chloroform. The extract was washed with water, dried over $MgSO_4$ and evaporated to leave 497 mg of an oil which crystallized on trituration with ether. Recrystallization from ether gave 209 mg of the enol-acetate (**51**), a sample of which was identical with an authentic sample in terms of mixed melting point determination, IR spectrum, and TLC behavior.

The Bromo-acetoxy-ketone (53)——To a solution of 380 mg of the axial-acetoxy-ketone (**50**) in 40 ml of acetic acid was added 390 mg of pyridine hydrobromide perbromide complex and the mixture was stirred for 4.5 hr at 62—65°. Removal of the solvent under reduced pressure left a yellow oil which was mixed with water and extracted with chloroform. The extract was washed with water, dried over $MgSO_4$ and evaporated to afford a crystalline solid (350 mg). Recrystallization from acetone–ether gave 314 mg of the bromo-acetoxy-ketone (**53**) as colorless prisms, mp 230—235°. IR ν_{max} cm^{-1}: 1758, 1750 and 1689. NMR τ: 7.70 and 7.61 (each 3H, s., OAc), 7.18 (3H, s., N–Me), 6.18 (3H, s., O–Me), 4.07 (1H, s., C_8–H), 5.47 (1H, q., J=5 Hz, δ_{AB}=8 Hz, C_6–H) and 3.04 (2H, q., J=9 Hz, δ_{AB}=3 Hz, aromatic H). *Anal.* Calcd. for $C_{22}H_{24}O_7NBr \cdot 1/2H_2O$: C, 52.49; H, 5.01; N, 2.78. Found: C, 52.49; H, 4.88; N, 2.66.

The Diosphenol (54)——A solution of 200 mg of the enol-acetate (**51**) in 25 ml of acetone was refluxed with 2% aqueous hydrochloric acid for 9 hr on a water bath. The cooled mixture was mixed with water and extracted with chloroform. The extract was washed with water, dried over $MgSO_4$. Evaporation of the solvent and recrystallization of the residue from acetone–ether afforded 149 mg of the diosphenol (**54**) as colorless prisms, mp 221—223°. IR ν_{max} cm^{-1}: 3450, 1760, 1685, and 1654. NMR τ: 7.67 (3H, s., OAc), 6.96 (3H, s., N–Me), 6.23 (3H, s., O–Me), 3.93 (1H, t., J=5 Hz, olefinic H) and 3.85 (1H, s., OH). *Anal.* Calcd. for $C_{20}H_{21}O_6N$: C, 64.68; H, 5.70; N, 3.77. Found: C, 64.72; H, 5.86; N, 3.56.

The Bromo-diketone (55)——To a solution of 150 mg of the diosphenol (**54**) in 26 ml of acetic acid and 5 drops of 48% hydrogen bromide was added 68 mg of bromine with stirring at room temperature. After

2 hr, the solvent was removed under reduced pressure and the residue was extracted with chloroform. The chloroform extract was washed with water, dried over $MgSO_4$ and concentrated to give 279 mg of a slightly yellow oil which solidified on trituration with acetone. Recrystallization from acetone afforded 154 mg of the bromo-diketone (**55**) as colorless prisms, mp 250—252°. IR ν_{max} cm^{-1}: 3420, 1760, 1685 and 1643. *Anal.* Calcd. for $C_{20}H_{20}O_6NBr$: C, 53.34; H, 4.48; N, 3.11. Found: C, 53.06; H, 4.32; N, 2.84.

The Bromo-enolmethyl-ether (56)——To a solution of 100 mg of the bromo-diketone (**55**) in 25 ml of methanol was added a solution of excess diazomethane in ether–methanol and the mixture was worked up as usual. The residual oil was purified by alumina chromatography to furnish 100 mg of the bromo-enolmethyl-ether (**56**) as colorless prisms, mp 192° (recrystallized from a mixture of acetone–ether), mp 192°. IR ν_{max} cm^{-1}: 1760, 1684 and 1629. NMR τ: 7.63 (3H, s., OAc), 7.02 (3H, s., N–Me), 6.24 and 6.20 (each 3H, s., O–Me). *Anal.* Calcd. for $C_{21}H_{22}O_6NBr$: C, 54.32; H, 4.78; N, 3.02. Found: C, 54.59; H, 4.88; N, 2.87.

The β-Diketone (57) and the Compound (58)——A mixture of 62 mg of the bromo-enolmethyl-ether (**56**), 4 ml of 1,2-dimethoxyethane and 10 ml of 5% aqueous sulfuric acid solution was heated in a sealed tube at 150—155°. After 18 hr, the solvent was evaporated under reduced pressure and the residual oil was extracted with chloroform. The extract was washed with water, dried over $MgSO_4$. The solvent was evaporated and the residue in chloroform was chromatographed on a silica gel column. Elution of the column with chloroform gave 10 mg of the compound (**58**) in the earlier eluate, which was recrystallized from acetone–ether to provide crystals having mp 213—214°. IR ν_{max} cm^{-1}: 3490, 1680 and 1626. NMR τ: 6.97 (3H, s., N–Me), 6.22 and 6.14 (each 3H, s., O–Me) and 3.52 (1H, s., OH). *Anal.* Calcd. for $C_{19}H_{20}O_5NBr$: C, 54.03; H, 4.78; N, 3.32. Found: C, 54.15; H, 5.01; N, 3.43. Further elution of the column with chloroform–methanol (50: 1) gave 13 mg of the crude product as a slightly yellow oil which crystallized on trituration with ether–methanol and recrystallization from ether–methanol afforded 9 mg of the β-diketone (**57**) as colorless flakes, mp 264—267°. IR ν_{max} cm^{-1}: 3480, 3450, 1675, and 1621. Mass Spectrum *m/e*: 359 (M^+). *Anal.* Calcd. for $C_{19}H_{21}O_6N \cdot 1/3H_2O$: C, 62.47; H, 6.02; N, 3.84. Found: C, 62.43; H, 5.94; N, 3.64. Both the β-diketone (**57**) and the compound (**58**) were positive to the Gibbs test.

(±)-16-Oxo-hasubanonine (59) and (±)-Aknadilactam (61)——To a solution of 96 mg of the β-diketone (**57**) in 30 ml of methanol was added a solution of excess diazomethane in ether, and the mixture was allowed to stand at room temperature for 2 hr and worked up as usual to give 181 mg of colorless oil. The oil was chromatographed over a silica gel column in chloroform and elution with the same solvent afforded 67 mg of colorless oil from the earlier eluate. Judging from its NMR spectrum, this material was a mixture of (±)-16-oxo-hasubanonine (**59**) and its structural isomer (**60**) approximately in a 1/1 ratio. Fractional recrystallization from acetone–ether gave 24 mg of (±)-16-oxo-hasubanonine (**59**) and 12 mg of its structural isomer (**60**) as colorless prisms, respectively. The synthetic (±)-16-oxo-hasubanonine (**59**) was completely identical with a sample of 16-oxo-hasubanonine (**63**) derived from natural hasubanonine by comparison of their IR, NMR, Mass spectra and TLC behavior. The physical data of (±)-16-oxo-hasubanonine and its structural isomer (**60**) were as follows. (±)-16-Oxo-hasubanonine (**59**): mp 177°, IR ν_{max} cm^{-1}: 1677 and 1615. NMR τ: 7.03 (3H, s., N–Me), 6.33, 6.19, 6.08 and 5.90 (each 3H, s., O–Me) and 3.23 (2H, s., aromatic H). Mass Spectrum *m/e*: 387 (M^+). The compound (**60**): mp 179—180°, IR ν_{max} cm^{-1}: 1680 and 1617. NMR τ: 6.99 (3H, s., N–Me), 6.36, 6.15, 6.05 and 6.02 (each 3H, s., O–Me) and 3.19 (2H, s., aromatic H). Mass Spectrum *m/e*: 387 (M^+). Continued elution of the column with the same solvent gave 40 mg of colorless oil which was assumed to be a mixture of (±)-aknadilactam (**61**) and its structural isomer (**62**) in a 1/1 ratio by the NMR spectral examination. Chromatography over a silica gel column (Merck Kieselgel unter 0.08 mm) in chloroform was repeated three times and 8 mg of (±)-aknadilactam (**61**) was obtained as a pure colorless oil which was proved to be identical with a sample of natural aknadilactam (**4**) in terms of their IR, NMR, and Mass spectra. (±)-Aknadilactam (**61**), an oil, IR ν_{max} cm^{-1}: 3500, 1680, and 1612. NMR τ: 7.04 (3H, s., N–Me), 6.31, 6.16, and 5.89 (each 3H, s., O–Me), 3.27 (1H, d., J=8.5 Hz, aromatic H) and 3.46 (1H, d., J=8.5 Hz, aromatic H). Mass Spectrum *m/e*: 373 (M^+).

16-Oxo-hasubanonine (63) from Hasubanonine——To an ice-cooled solution of 3.0 g of hasubanonine (**1**), 2.0 g of magnesium sulfate in 300 ml of acetone (distilled under the presence of potassium permanganate) and 6 ml of water was added dropwise 100 ml of 2% aqueous potassium permanganate solution, and the mixture was stirred for 2 hr at room temperature. Excess reagent was decomposed with sodium bisulfate-dil. sulfuric acid solution and the solvent was evaporated under reduced pressure at room temperature. The residue was extracted with chloroform and the extract was washed with dil. HCl, dil. NaOH, and water, dried over $MgSO_4$ and evaporated to afford a crystalline solid. Recrystallization from benzene–ether (1: 4) gave 802 mg of 16-oxo-hasubanonine as colorless pillars, mp 161°. IR ν_{max} cm^{-1}: 1677 and 1615. NMR τ: 7.03 (3H, s., N–Me), 6.33, 6.19, 6.08, and 5.90 (each 3H, s., O–Me) and 3.23 (2H, s., aromatic H). *Anal.* Calcd. for $C_{21}H_{25}O_6N$: C, 65.10; H, 6.50; N, 3.62. Found: C, 65.05; H, 6.36; N, 3.63. Mass Spectrum *m/e*: 387 (M^+). The aqueous washings were combined and made alkaline with aqueous sodium hydroxide and extracted with ether. Evaporation of the solvent and chromatography of the residue over alumina in benzene gave 1.32 g of unchanged hasubanonine (**1**).

Hasubanonine (1) from 16-Oxo-hasubanonine (63)——To a solution of 500 mg of 16-oxo-hasubanonine (**63**) in 3 ml of dry tetrahydrofuran and 50 ml of dry ether was added 700 mg of lithium aluminum hydride,

and the mixture was refluxed for 13 hr with stirring. After cooling, excess hydride was decomposed with a few drops of water under ice-cooling and the precipitate was filtered off and washed with ether. The filtrate and washings were combined and extracted with 3% acetic acid. The aqueous acidic solution was made alkaline with 3% NH_4OH and extracted with ether. The extract was washed with water, dried over $MgSO_4$ and evaporated to leave a yellow oil. The oil in benzene–ether was chromatographed on alumina and elution of the column with the same solvent gave 425 mg of a mixture of epimeric alcohols (**64**). To a solution of these alcohols, without separation, in 70 ml of chloroform was added 5.2 g of manganese dioxide and the mixture was stirred for 3 hr at room temperature. The reaction mixture was filtered and the precipitate was washed with chloroform. The filtrate and washings were combined, concentrated to afford an oil which was mixed with ether and extracted with 5% aqueous hydrochloric acid. The aqueous extract was made alkaline with 28% NH_4OH and extracted with ether. The ether extract was washed with water, dried, and evaporated. The residue in benzene was chromatographed on an alumina column and elution of the column with the same solvent gave 130 mg of a crystalline solid. Several recrystallizations from methanol gave 70 mg of hasubanonine (**1**), mp 114—115°, a sample of which was completely identical with an authentic sample of hasubanonine by comparison of TLC behavior, IR spectrum and mixed melting point determination.

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