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Total Synthesis of *dl*-Cepharamine[1]

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The synthesis of *dl*-cepharamine (**4**) which is a member of hasubanan alkaloids, was accomplished after the model experiments started from 2-tetralone (**5**) were examined.

The keto-lactam (**30**) was synthesized from 7,8-dimethoxy-2-tetralone (**7**) *via* the keto-ester (**27**) or the keto-nitrile (**53**). Ketalization of the compound (**30**), followed by treatment under the Wolff–Kishner reaction condition caused by demethylation of a methoxyl group at C_4 to result in the phenolic compound (**63**). Acetylation of the compound (**63**), followed by deketalization gave the keto-acetate (**65**). The diketone (**67**) was synthesized by bromination of the compound (**65**) with two equivalents of bromine, followed by heating with anhydrous sodium acetate in acetic acid. The target molecule, *dl*-cepharamine (**4**), was synthesized from the diketone (**67**) by successive treatments with BF_3·ether–MeOH (monoenolmethylation), $LiAlH_4$ reduction and oxidation with DMSO-phosphoric acid-DCC.

The number of hasubanan alkaloids isolated from *Stephania* species of Menispermaceae goes on increasing and so far as we know, the nine congeners have been reported.[3]

Hasubanonine,[4] metaphanine,[5] prometaphanine[6] and homostephanoline[7] isolated from *Stephania japonica* MIERS and cepharamine (**1**)[8] isolated from *Stephania cepharantha* HAYATA are common in possessing the hasubanan skeleton (**2**) which is different from morphinan (**3**) in forming a five membered heterocyclic ring by a linkage of the ethanamine nitrogen with C_{14}. Later, this unique structure was supported by X-ray crystallography.[9]

The hasubanan alkaloids are of interest in connection with their pharmacological activity since these alkaloids are regarded as the derivatives of prafadol[10] which is used as a potent analgesic. On the other hand, the synthesis of hasubanan (**2**)(1,2,3,4,9,10-hexahydro-10a(*S*), 4a(*R*)-(iminoethano)-phenanthrene) and its derivatives, has not been yet established. A series of investigations were undertaken to our interest in the synthetic problems posed by these alkaloids and to examine the pharmacological activity of the hasubanan derivatives. This paper describes a full detail of the synthesis of *dl*-cepharamine (**4**) which has the relatively simple structure among the hasubanan alkaloids.

1) This paper forms Part CCLX of the series "Studies on the Alkaloids of Menispermaceous Plants." Part CCLIX: M. Tomita, Y. Okamoto, T. Kikuchi, K. Osaki, M. Nishikawa, K. Kamiya, Y. Sasaki, K. Matoba, and K. Goto, *Chem. Pharm. Bull.* (Tokyo), **19** 770 (1971). Preliminary communication of this work appeared in *Tetrahedron Letters*, **1969**, 1611.
2) Location: *Yoshida-shimoadachi-cho, Sakyo-ku, Kyoto.*
3) C.W. Thornber, *Phytochem.*, **9**, 157 (1970), and references cited therein; B.K. Moza, B. Bhaduri, D.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).
4) M. Tomita, T. Ibuka, Y. Inubushi, Y. Watanabe, and M. Matsui, *Tetrahedron Letters*, **1964**, 2937; *idem*, *Chem. Pharm. Bull.* (Tokyo), **13**, 538 (1965).
5) M. Tomita, T. Ibuka, Y. Inubushi, and K. Takeda, *Tetrahedron Letters*, **1964**, 3605.
6) M. Tomita, T. Ibuka, and Y. Inubushi, *Tetrahedron Letters*, **1964**, 3617.
7) Y. Watanabe, M. Matsui, and K. Ido, *Yakugaku Zasshi*, **85**, 584 (1965); T. Ibuka and M. Kitano, *Chem. Pharm. Bull.* (Tokyo), **15**, 1939 (1967).
8) M. Tomita and M. Kozuka, *Tetrahedron Letters*, **1966**, 6229.
9) S.M. Kupchan, M.I. Suffness, D.N.J. White, A.T. Mepail, and G.A. Sim, *J. Org. Chem.*, **33**, 4529 (1968).
10) R.E. Bowman, *Chem. Ind.* (London), **1969**, 1077.

On the synthesis of *dl*-cepharamine, 7,8-dimethoxy-2-tetralone (**7**) seemed to be a suitable starting material but this compound was somewhat troublesome to synthesize and found to be susceptible to air oxidation. Therefore, the model experiments started from 2-tetralone (**5**) were first examined and parallel to these experiments, the synthesis of *dl*-cepharamine was then accomplished using the compound (**7**) as a starting material.

Synthesis of Hasubanan Skeleton and Related Compounds

Condensation of pyrrolidine enamine[11] of 2-tetralone (**5**) with ethyl bromoacetate gave the keto-ester (**6**) in a 80% yield. Robinson annelation reaction[12] of **6** with N,N-diethylaminobutanone methiodide under the presence of potassium ethoxide catalyst resulted simultaneously in the construction of a new ring and the lactone ring closure to give the keto-lactone (**8**) in a reasonable yield. Ketalization of **8** with excess ethylene glycol under the presence of *p*-toluene sulfonic acid catalyst gave quantitatively the ketal-lactone (**9**). In order to transform **9** to the ketal-amine (**25**) or keto-amine (**26**) *via* the diol (**10**), the compound (**9**) was reduced with $LiAlH_4$ to the diol (**10**). An attempt to substitute only the primary hydroxyl group in **10** with a methylamino group was made by utilizing a difference in reactivity between the primary and tertiary hydroxyl group. Thus, monotosylation or monochlorination of **10** with tosyl chloride or thionyl chloride was tried but these reactions afforded merely the furano derivative (**12**). Next, introduction of an acetyl group, which is considered as a milder leaving group than the tosyl group, to the compound (**10**), followed by deketalization with 80% aqueous acetic acid was examined. The resulting compounds, however, were the keto-acetate (**13**) and the α,β-unsaturated ketone (**14**). All trials for ketalization of the latter under the various reaction conditions and for introduction of a methylamino group at the β-position of the α,β-unsaturated ketone function under the Michael reaction condition were unsuccessful.

The synthesis of the hasubanan skeleton from the keto-amide (**15**) was then examined. Condensation of pyrrolidine enamine of 2-tetralone with N,N-dimethyl bromoacetamide gave an oily keto-amide (**15**) which showed one spot on thin-layer chromatography (TLC), and ketalization of **15** produced the ketalamide (**16**) as crystals. $LiAlH_4$ reduction of **16** to von Braun cyanogen bromide reaction afforded the N-cyano compound (**18**). Deketalization the ketal-amine (**17**), followed by of the ketal-amide (**16**), the ketal-amine (**17**) and the N-cyano compound (**18**) under various reaction conditions was unsuccessful and in the case of the compound (**16**), the unsaturated- lactone (**19**) which is not the objective, was obtained. In order to effect β-aminoethylation at 1 position of 2-tetralone, alkylation of 2-tetralonepyrrolidine enamine with the alkylating reagents such as N-benzyloxycarbonyl-N-methyl-β-bromoethylamine, N-ethoxycarbonyl-N-methyl-β-bromoethylamine and N-formyl-N-methyl-β-chloroethylamine was tried but all these experiments were unfruitful.

Transformation of the keto-lactone (**8**) and the ketal-lactone (**9**) to the corresponding lactams was examined. Thus, reaction of **8** with ammonia or methylamine did not provide the expected compound and the substrate tended to resinify by these experiments. This propensity may be due to the β-oxy-ketone system in the molecule. When heated a solution of **9** in anhydrous dioxane previously saturated with methylamine at 200° in a sealed tube, the starting material was recovered, and under the forcing condition at 250°, the compound (**9**) decomposed to give only poorly characterized materials. Then, a solution of **9** in a mixed solvent of dioxane–water (10:1) saturated with methylamine, to which methylamine hydrochloride was added, was heated at 215° in a sealed tube. In this case, the desired lactam (**20**) and the ketal-amide (**23**) which is considered as an intermediate from **9** to **20**, were obtained. The presence of methylamine hydrochloride is essential for this reaction and the

11) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovics, and T. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963).
12) J.W. Cornforth and R. Robinson, *J. Chem. Soc.*, **1949**, 1855.

dioxane/water ratio is also an important factor. Deketalization of **23** under the usual condition did not afford the desired keto-lactam (**20**) but gave the keto-lactone (**8**). This is presumably the result that the lactone ring formation by an angular hydroxyl group occurs in preference to deketalization. When chosen the reaction condition employed in the transformation of **9** to **20**, the compound (**20**) was obtained from **23** in a 20% yield. From these results, this reaction seems to be related to the equilibrium involving **9** and **23** as shown in Fig. 1.

Huang-Minlon reduction of **20**, followed by $LiAlH_4$ reduction gave *dl*-N-methylhasubanan (**24**). *dl*-N-Methylhasubanan was also obtained by an alternative route. Thus, ketalization of **20** gave the ketal-lactam (**21**) which was reduced with $LiAlH_4$ to afford the ketal-amine

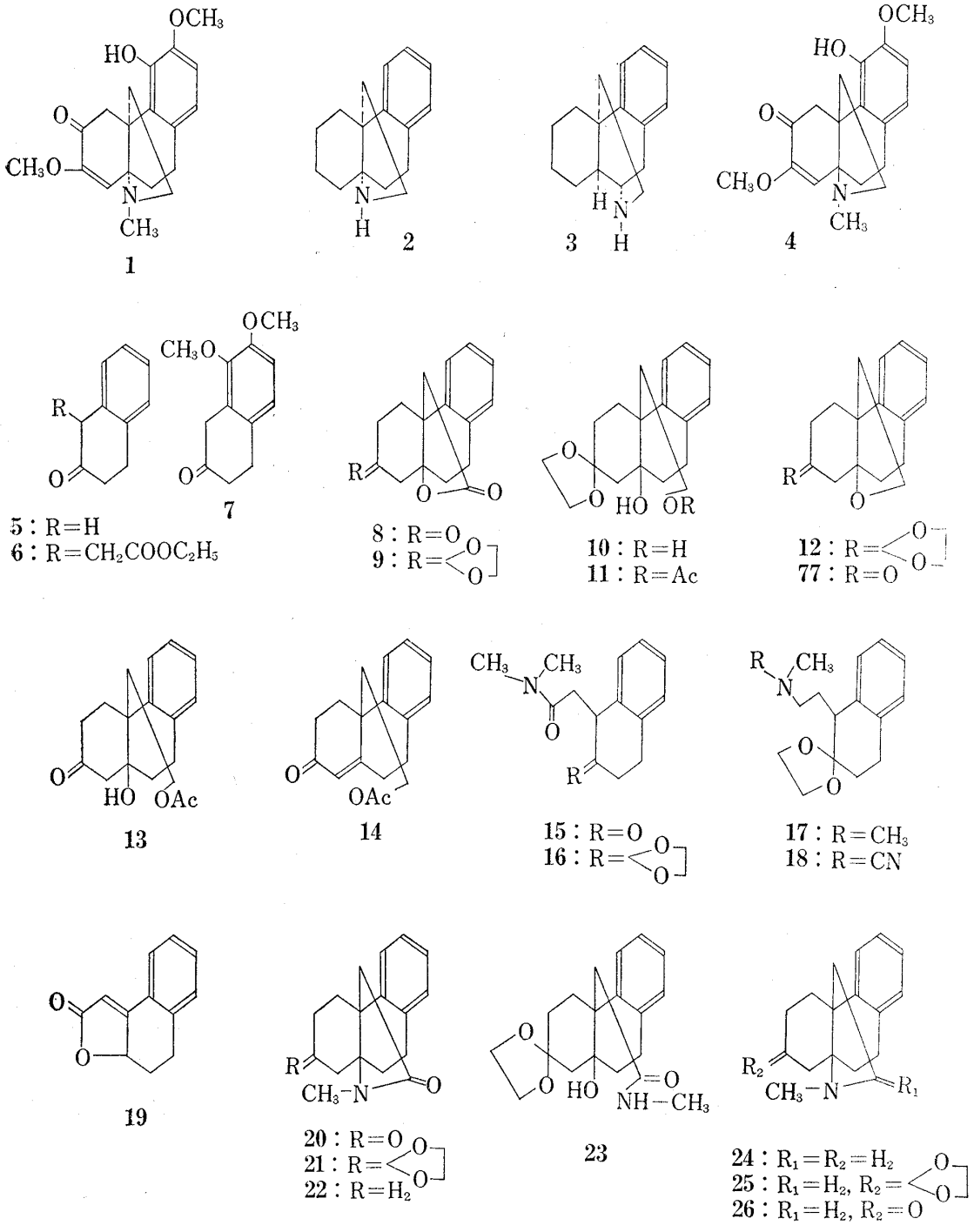

Chart 1

(**25**), and deketalization of the latter provided the keto-amine (**26**)[13] which was reduced by Huang–Minlon reduction to give *dl*-N-methylhasubanan (**24**). *dl*-N-Methylhasubanan thus obtained is an oil and a sample of its perchlorate, mp 229° was analyzed to $C_{17}H_{23}N \cdot HClO_4$ and in the mass spectrum, the characteristic base peak at *m/e* 185 for the hasubanan derivative[14] was observed. Thus, the *dl*-N-Methylhasubanan structure of the synthetic sample was confirmed.

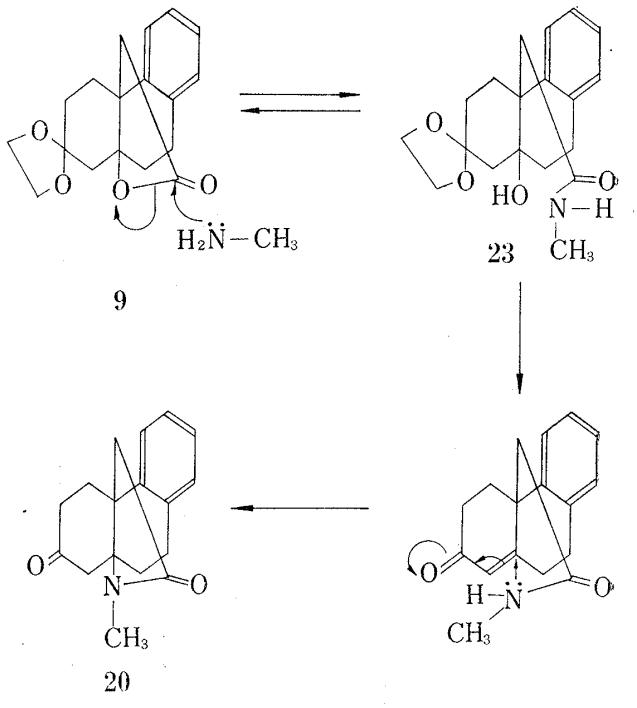

Fig. 1

Parallel to the model experiments, the compound (**30**) was derived from 7,8-dimethoxy-2-tetralone (**7**)[15] *via* the keto-ester (**27**) and the ketal-lactone (**29**). Thus, the keto-lactam (**30**) and the phenolic compound (**31**) which was formed by demethylation of a methoxyl group at C_4 position and gave a positive Gibbs test, were obtained from **29** in 40% and 1% yield, respectively. Huang–Minlon reduction of the keto-lactam (**30**) afforded the lactam (**32**) which was reduced with $LiAlH_4$ to give *dl*-3,4-dimethoxy-N-methylhasubanan (**33**). This compound was identified with an authentic sample (**34**) which had been derived from hasubanonine and metaphanine, by comparison of infrared (IR), nuclear magnectic resonance (NMR) and mass spectra and TLC behavior.

Through the synthetic route described above, the keto-lactam (**30**) which is an important intermediate for the *dl*-cepharamine synthesis, could be synthesized in fairly good yield. This route, however, is still less satisfactory because the yield of **30** from the ketal-lactone (**29**) unsettled and the reaction in a sealed tube is inadequate for the synthesis of a relatively large amount of **30**. We, therefore, examined an alternative route.

Reaction of 2-tetralonepyrrolidine enamine with iodoacetonitrile[16] or chloroacetonitrile in acetonitrile gave the keto-nitrile (**35**) in good yield. When used benzene or dioxane as a solvent, the yield of **35** was rather low and the starting material was recovered in fairly large quantities. Treatment of **35** with methyl vinyl ketone under the presence of triethylamine and silicagel chromatography of the product gave mainly the diketo-nitrile (**37**)[17] in a 70% yield, together with the compound (**36**)[18] which is the air oxidation product of the starting material (**35**), and the C-methyl compounds (**38**)[19] and (**39**)[19] which are the cyclization products of the compound (**37**). Cyclization of **37** under the presence of potassium *tert*-butoxide catalyst in benzene at room temperature provided the keto-lactam (**40**) and the unsaturated

13) D.A. Evans, *Tetrahedron Letters*, **1969**, 1537. This compound was synthesized through a different synthetic route from ours by Evans. Mass and NMR spectral data of this compound and the melting point of the hydrochloride reported in the literature, however, are different from those of our sample.
14) M. Tomita, A. Kato, and T. Ibuka, *Tetrahedron Letters*, **1965**, 1019.
15) M.D. Soffer, R.A. Stewart, J.C. Cavagnol, H.G. Gellerson, and E.A. Bowler, *J. Am. Chem. Soc.*, **72**, 3704 (1950).
16) R. Scholl, *Chem. Ber.*, **29**, 2417 (1896).
17) *cf.* R.B. Turner, D.E. Nettleton, Jr., and R. Ferebee, *J. Am. Chem. Soc.*, **78**, 5923 (1956).
18) *cf.* W.E. Bachmann, G.I. Fujimoto, and L.B. Wick, *J. Am. Chem. Soc.*, **72**, 1955 (1950).
19) *cf. a)* W.S. Johnson, J.J. Korst, R.A. Clement, and J. Dutta, *J. Am. Chem. Soc.*, **82**, 614 (1960); *b)* T. Matsumoto and A. Suzuki, *Bull. Chem. Soc. Japan*, **34**, 274 (1961).

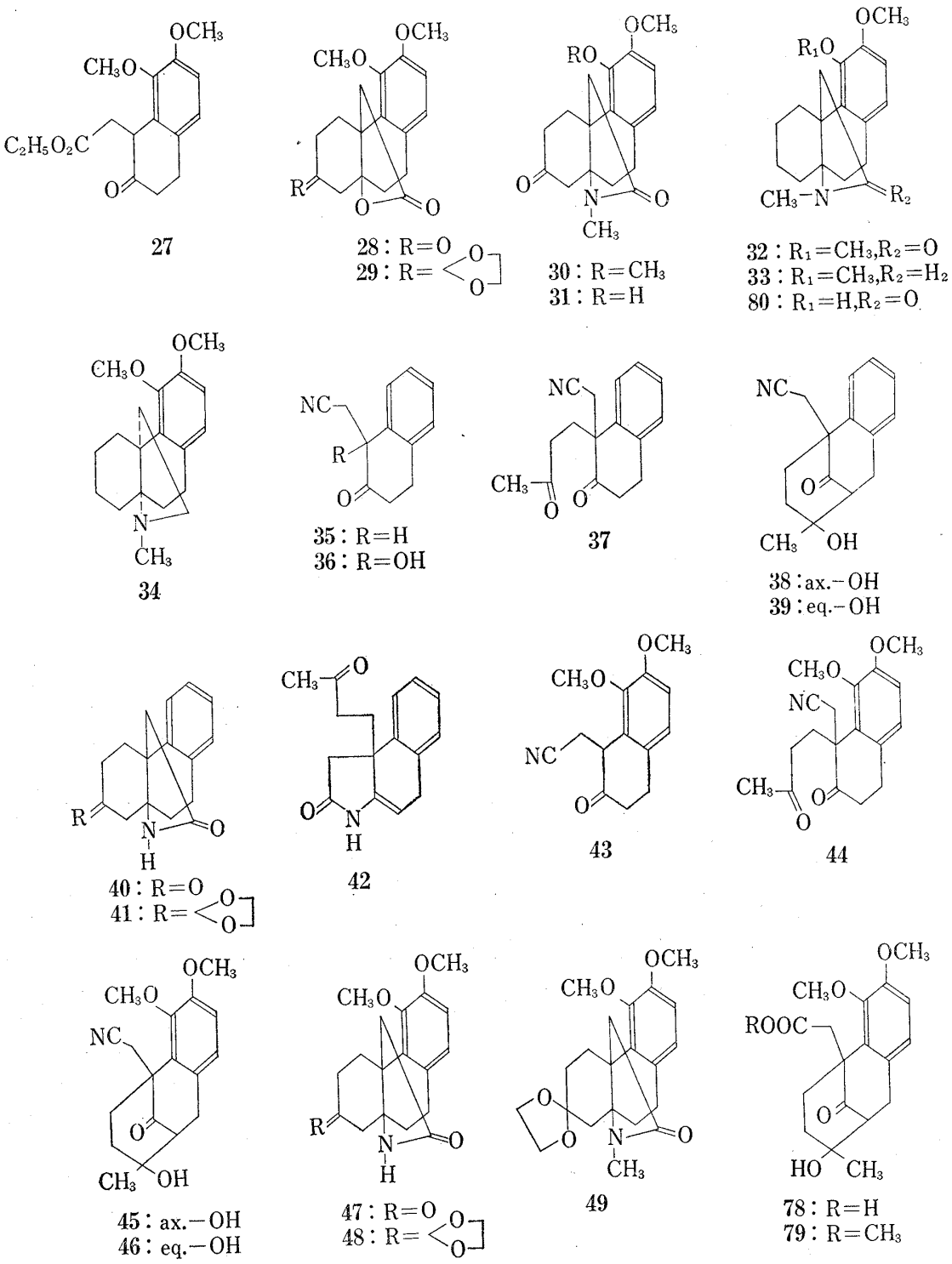

Chart 2

lactam (**42**) in 37 and 30% yield, respectively. Then, transformation of **42** to **40** was tried. Treatment of **42** with bases recovered only the starting material, while the compound (**42**) could be readily converted to the keto-lactam (**40**) when treated with an acid catalyst such as *p*-toluene sulfonic acid or phosphoric acid *etc.* in a similar manner as employed in the synthesis of the erythrina-alkaloid by Mondon, *et al.*[20]

20) A. Mondon, *Tetrahedron*, **19**, 911 (1963); A. Mondon and H.U. Menz, *ibid.*, **20**, 1729 (1964); A. Mondon and K.F. Hansen, *Tetrahedron Letters*, **1960**, 5.

These results described above can be rationalized by assuming the reaction mechanisms as shown in Fig. 2. Thus, under the presence of base catalyst, the compound (**37**) gives the keto-lactam (**40**) *via* (a) route and the unsaturated lactam (**42**) *via* (b) route which under the presence of an acid catalyst, is transformed to the compound (**40**).

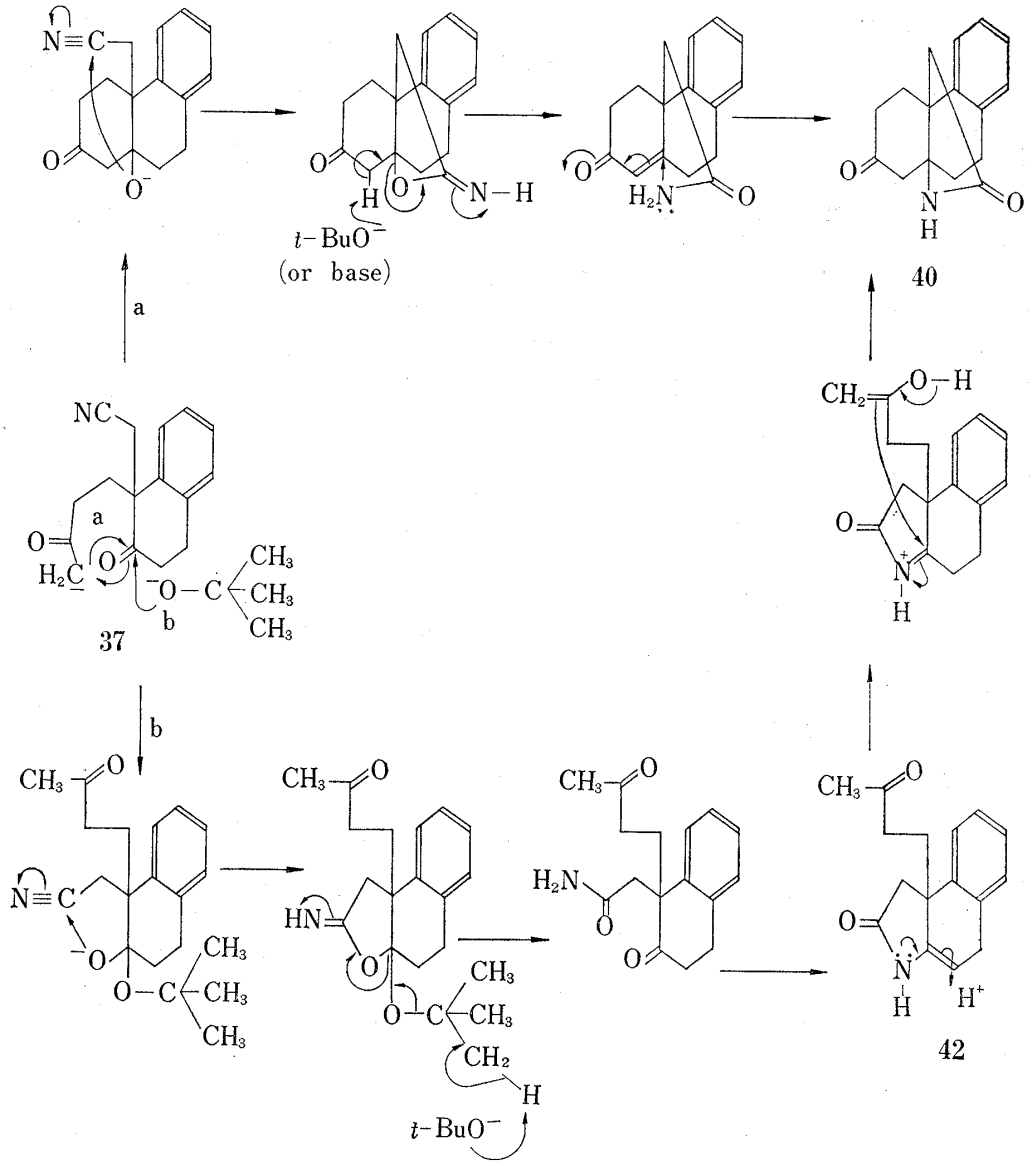

Fig. 2

The C-methyl compounds (**38**) and (**39**) could be also converted to the keto-lactam (**40**) by refluxing a solution of each compound in ethanol with sodium ethoxide in 40 and 50% yield, respectively. On the other hand, treatment of the keto-nitrile (**35**) in methanol with methyl vinyl ketone under the presence of sodium methoxide catalyst for several hours at room temperature, followed by refluxing the solution for *ca.* 1 hour, gave the compound (**40**) at one operation in a 80% yield. This procedure was the most excellent one among the model experiments examined for obtaining the compound (**40**). The compound (**40**) was derived to the ketal-lactam (**41**) and the latter was subjected to N-methylation to give the N-methyl-ketal-lactam (**21**) which was proved to be identical with an authentic sample previously synthesized.

In a similar manner, condensation of 7,8-dimethoxy-2-tetralone-pyrrolidine enamine with iodoacetonitrile gave the keto-nitrile (**43**). This compound was unreactive to methyl

vinyl ketone under the presence of triethylamine catalyst but reacted with the same reagent under the presence of potassium tert.-butoxide catalyst to provide the compound (**44**) in a 39% yield and the C-methyl compound (**45**) and (**46**) in a 19% yield as mixed crystals consisted of these two compounds, respectively. The C-methyl compounds were also obtained by refluxing a solution of the keto-nitrile (**43**) and methyl vinyl ketone in methanol under the presence of sodium hydroxide catalyst in a 75% yield, and the separation of the two components of the product was effected by silicagel column chromatography. By refluxing a solution of these compounds (**45**) and (**46**), without separation, in ethanol under the presence of sodium ethoxide catalyst, these could be converted readily to the keto-lactam (**47**). Taking into account these experimental results, the keto-lactam (**47**) was obtained from the keto-nitrile (**43**) at one operation. Thus, the keto-nitrile (**43**) was allowed to react with methyl vinyl ketone under the presence of sodium hydroxide and then, without isolation of the products, the reaction mixture to which sodium ethoxide was added, was refluxed to give the desired keto-lactam (**47**) in a 50% yield. Ketalization of **47** to the ketal-lactam (**48**), followed by N-methylation with methyl iodide and sodium hydride provided the ketal-lactam (**49**) which was proved to be identical with an authentic sample derived from the keto-lactam (**30**) *via* the ketal-lactone (**29**).

Synthesis of the Model Compound (50)

The synthesis of the model compound (**50**) was examined prior to practice the synthesis of *dl*-cepharamine (**4**). The various procedures by which introduction of the oxygen function into the C_6 position of the keto-lactam (**20**) possessing a ketone group at C_7 position is feasible, are found in the literature. After several trials, it was ascertained that the method developed by Bordwell, *et al.*[21] serves our purpose. The position of a newly introduced ketone group by this method, thus C_6 or C_8, was not predicted but fortunately, the product from the compound (**20**) was the desired diketone (**51**). Thus, treatment of the compound (**20**) with two equivalents of bromine gave the dibromo compound which without purification was heated in acetic acid with freshly fused anhydrous sodium acetate at 110—120° to afford the diketone (**51**) possessing the ketone groups at C_6 and C_7, in a 24% yield and the structure of the diketone was estimated by its NMR spectrum examination, thus, from the signal pattern of the olefinic proton due to the enolic form. On the other hand, hydrolysis of the mother liquors from recrystallizations of the diketone (**51**) with diluted hydrochloric acid gave the additional diketone (**51**) in a 11% yield. This result suggests that the compound (**51**) and its enol acetate were formed simultaneously by the rearrangement reaction of the dibromo compound.

Next, direction of monoenolmethylation of the diketone (**51**) and (**52**) was examined. First, diketalization of the diketone (**51**) with butanone ethylene ketal[22] was tried but the yield was poor. The desired diketal compound (**53**) was, then, obtained in a fairly good yield by refluxing a solution of **51** in benzene with ethylene glycol under the presence of *p*-toluenesulfonic acid catalyst. That this diketal is not the 1,4,5,8-naphthodioxane derivative[23a,c] was confirmed by NMR spectral examination of the product (**53**). Thus, ethylene proton signals of **53** was quite analogous to that of the diketal (**56**)[23b] of two kinds of diketal compounds (**56**) and (**57**), which were obtained by ketalization of the diketone (**55**) derived from sinomenine. $LiAlH_4$ reduction of **53** to the amine (**54**), followed by deketalization with conc. hydrochloric acid gave the diketone (**52**) possessing an ethanamine bridge. In the NMR spectrum of this amine, a signal of an olefinic proton due to the enolic form was observed at 3.78 τ and the rather

21) F.G. Bordwell and K.M. Wellman, *J. Org. Chem.*, **31**, 351 (1966); *idem*, *ibid.*, **28**, 1347 (1963). *cf.* also M. Yanagita and A. Tahara, *J. Org. Chem.*, **18**, 792 (1953); M. Yanagita and K. Yamakawa, *ibid.*, **22**, 291 (1957).

22) H.J. Dauben, B. Löken, and H.J. Ringold, *J. Am. Chem. Soc.*, **76**, 1359 (1954).

23) *a*) E. Caspi, T.A. Wittstruck, and N. Grover, *J. Org. Chem.*, **28**, 763 (1963); *b*) Y.K. Sawa, K. Okabe, and T. Miyamoto, *Tetrahedron*, **24**, 261 (1968); *c*) B. Fuchs, *Tetrahedron Letters*, **1970**, 1747.

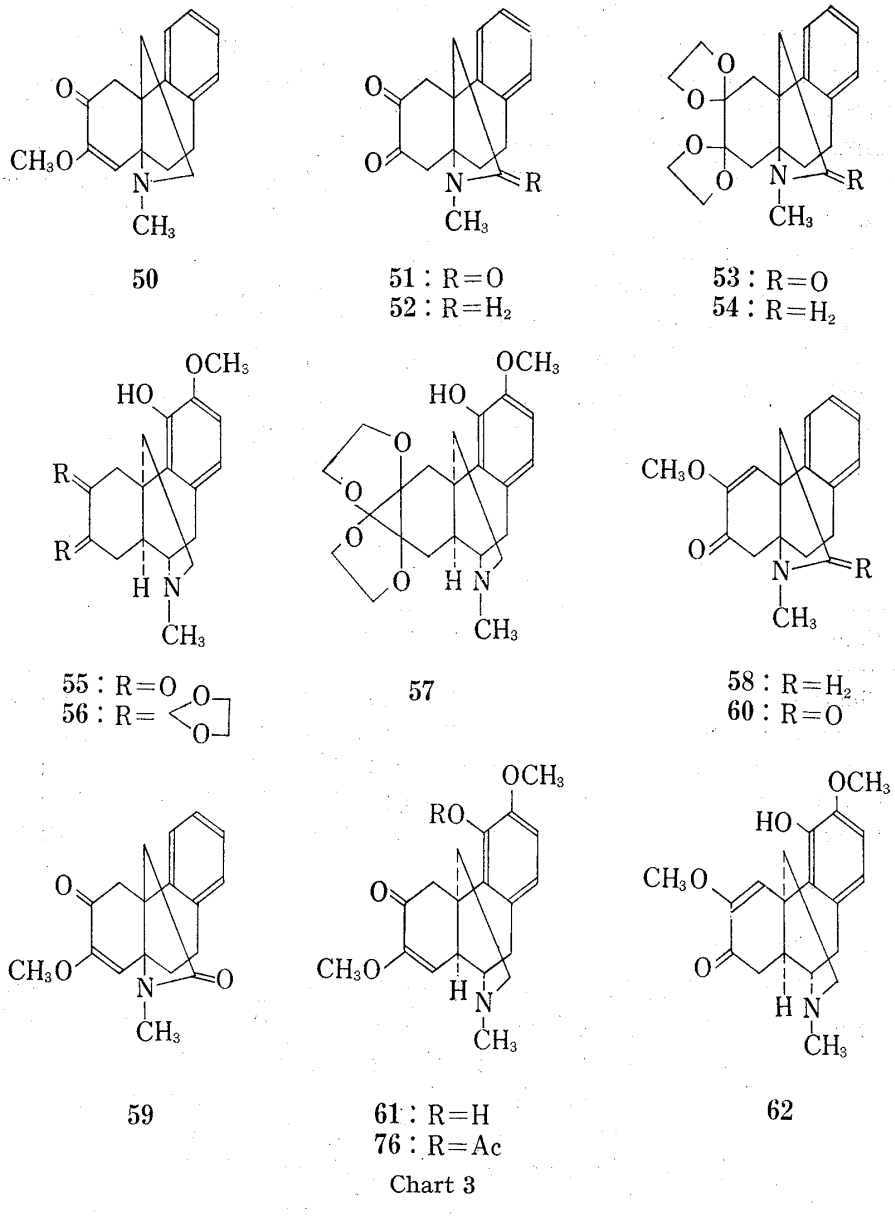

Chart 3

lower field chemical shift of this signal can be explained by assuming an anisotropy caused by an aromatic ring, suggesting that the C_6 ketone group would be enolizable. Methylation of **52** with MeOH–BF_3·ether gave the enol-methyl ether (**58**): $\nu_{max}^{CHCl_3}$ 1670 and 1631 cm^{-1}; NMR τ, 7.79 (3H, N-Me), 6.65 (3H, OMe) and 3.85 (1H, s., olefinic proton) as a sole methylated product. The structure of **58** was supported by the chemical shift of the singal due to an olefinic proton in the NMR spectrum.[24] Thus, the signal concerned in the compound (**58**) appeared at 3.85 τ, whereas the signal due to an olefinic proton at C_8 position in natural cepharamine (**1**) was observed at 4.38 τ. Consequently, the reaction sequence in which the lactam carbonyl is first reduced and the resulted amino-diketone is then enolmethylated, is inadequate for the *dl*-cepharamine synthesis since enolmethylation of the amino-diketone (**52**) proceeds in the opposite sense to the cepharamine type structure. On the other hand, methylation of the diketone (**51**) possessing the lactam structure, with MeOH–BF_3·ether[24] gave

24) In the course of the *dl*-cepharamine synthesis, the compound (**67**) was enolmethylated by this treatment. After completion of this synthesis, enolmethylation reaction was further examined and it was observed that methylation of the diketone (**51**) with diazomethane proceeded nearly in one direction to give the desired compound (**59**).

the product consisted of two compounds (**59**) and (**60**) in the 4:1 ratio which was estimated from the relative intensity of the signals due to the olefinic proton (4.49 τ/4.15 τ=4/1). All attempts to separate of the two compounds were unfruitful. Then, the mixture, without separation, was reduced with $LiAlH_4$ and oxidized with activated manganese dioxide. Finally, the desired compound (**50**): $\nu_{max}^{CHCl_3}$ 1688 and 1629 cm^{-1}; NMR τ, 7.58 (3H, N-Me), 6.35 (3H, OMe) and 4.35 (1H, s, olefinic proton), could be isolated in a homogeneous state from the reaction product. The structure of **50** was supported by comparison of NMR and IR data of this compound with those of the isomer (**58**) previously synthesized, sinomenine (**61**),[25] isosinomenine (**62**)[25] and cepharamine (**1**)[8] as shown in Table I. In particularly, the chemical shift of the signal due to the olefinic proton of **50** at 4.35 τ is almost the same as that of sinomenine (**61**: 4.35 τ) and cepharamine (**1**: 4.38 τ). From these results, it is considered possible that *dl*-cepharamine will be synthesized by the reaction sequence, that is enolmethylation of the diketone possessing the lactam carbonyl group such as the lactam-diketone (**51**) and then, reduction of the lactam carbonyl group of the product.

Table I. The Characteristic NMR Signals and IR Absorptions of **61**, **62**, **1**, **50**, and **58**

Compound	NMR (τ)	IR (cm^{-1})
Sinomenine (**61**)	4.50 (C_8-H); 6.55 (C_7-OCH_3)	1685; 1630
Isosinomenine (**62**)[25]	3.25 (C_5-H); 6.48 (C_6-OCH_3)	1685; 1623
Cepharamine (**1**)[8]	4.38 (C_8-H); 6.35 (C_7-OCH_3)	1685; 1630
Compound (**50**)	4.35 (C_8-H); 6.35 (C_7-OCH_3)	1688; 1629
Compound (**58**)	3.85 (C_5-H); 6.65 (C_6-OCH_3)	1670; 1631

Synthesis of *dl*-Cepharamine

It has been known that in 3,4-dimethoxy-N-methylmorphinan derivatives[26] and 3,4-dimethoxy-N-methylhasubanan derivatives,[5] demethylation reaction takes place selectively at C_4 under the Huang–Minlon reduction condition to give a certain amount of the phenolic derivative. Based on these facts, the ketal-lactam (**49**) was heated at 190° under this condition to provide the phenolic compound (**63**), which is positive to the Gibbs test, in a 60% yield. Acetylation of the phenol with acetic anhydride-pyridine gave the acetate (**64**) and then, partial hydrolysis of the ketal function of the acetate was brought about by dil. hydrochloric acid in acetone to afford the keto-acetate (**65**). This compound was also obtained from the phenol (**63**) by an alternative route, thus deketalization, followed by acetylation. In this case, however, acetylation reaction occured simultaneously at a phenolic group and a ketonic function to give a certain amount of the enol acetate (**66**) together with **65**. The compound **65**, therefore, was synthesized through the former route.

Bromination of **65** with two equivalents of bromine, followed by treatment with anhydrous sodium acetate in acetic acid gave in a 30% yield the crystalline product which formed the mixed crystals consisted of the diketone (**67**) and a substance of an unknown structure in the ratio 1:1. The attempted separation of two components was unsuccessful. These mixed crystals, without separation, were, then, methylated with MeOH–BF_3·ether and from the reaction product, the desired *dl*-16-oxo-cepharamine acetate (**68**) could be isolated as crystalline state in a 10% yield from the keto-acetate (**65**). Treatment of this compound with $LiAlH_4$ resulted in reduction of an acetoxyl group at C_4, a lactam carbonyl and an α,β-unsaturated ketone group to give an epimeric mixture (**69**) of *dl*-dihydrocepharamine which showed

25) K. Okabe, K. Hayashi, and Y.K. Sawa, *Chem. Pharm. Bull.* (Tokyo), **16**, 1611 (1968).
26) M. Gates and G. Tschudi, *J. Am. Chem. Soc.*, **78**, 1380 (1956).

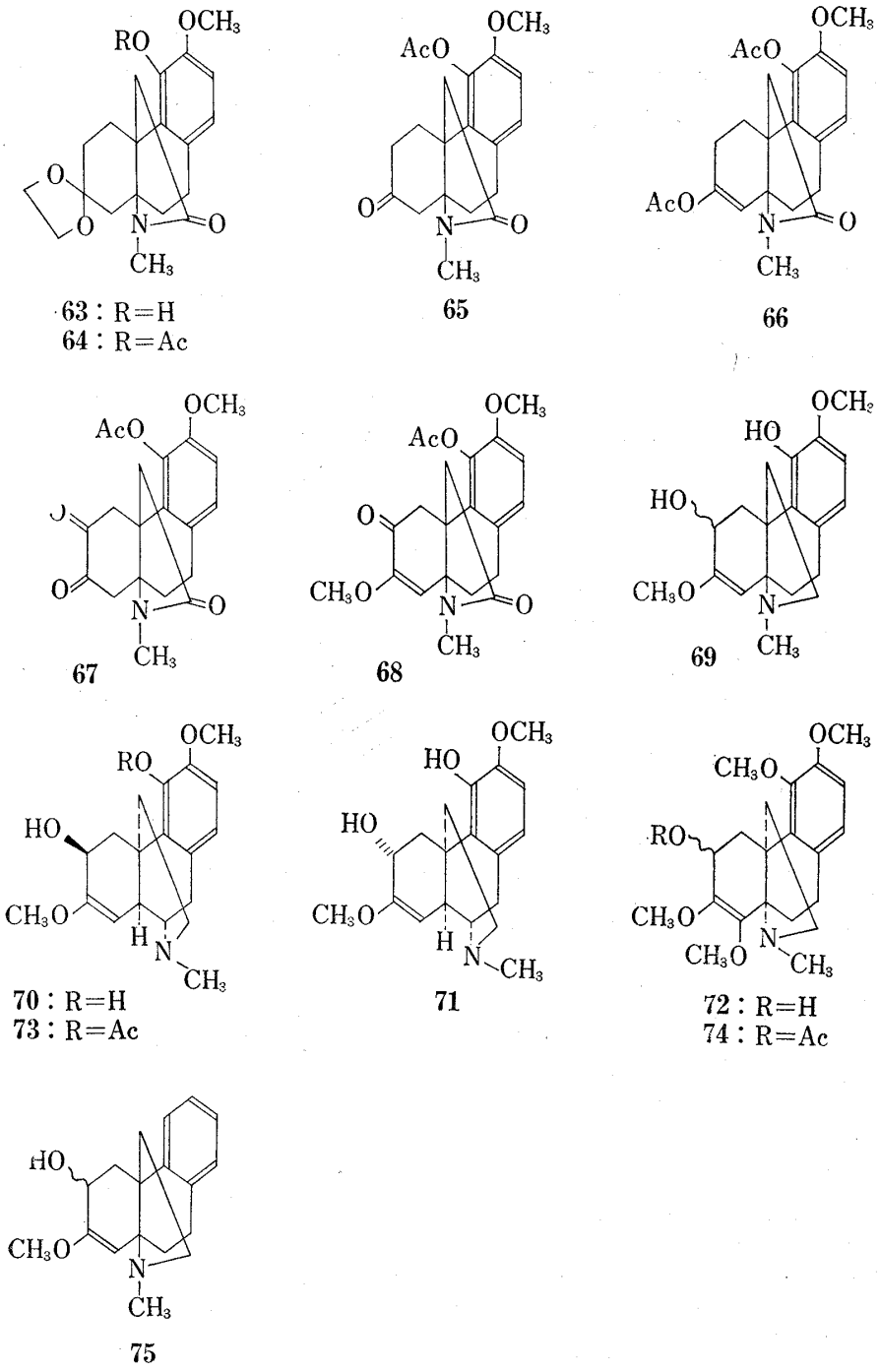

Chart 4

two distinguishable spots on TLC. Because of a small amount of **69** avairable, the mixture, without separation, was subjected to allylic oxidation. However, it seemed difficult to oxidize only an allylic alcohol function of **69** with the usual reagents avairable for oxidation of allylic alcohols such as activated manganese dioxide and silver carbonate[27] *etc.* because the compound (**69**) is phenolic. This difficulty will be overcome by using DMSO as an oxidizing reagent since the aromatic ring in **69** will not suffer under such a mild condition required to this reagent. Then, oxidation of dihydrosinomenine (**70**: β-q ax.-OH),[28] (**71**: α-q eq.-

27) H. Rapoport and H.N. Reist, *J. Am. Chem. Soc.*, **77**, 490 (1955).
28) K. Okabe, *Yakugaku Zasshi*, **82**, 1512 (1962).

OH),[28] dihydrohasubanonine (**72**: epimeric mixture),[4] and a model compound (**75**) using DMSO[29] was examined. Thus, dihydrosinomenine (**70**) was oxidized to give sinomenine acetate (**76**) in a 45% yield with DMSO-acetic anhydride and sinomenine (**61**) in a 53% yield with DMSO-phosphoric acid-DCC, respectively. On the other hand, the compound (**71**) possessing a α-q eq.-hydroxyl group gave poorly characterized materials, which showed many spots on TLC, under both reaction conditions. Oxidation of dihydrohasubanonine (**72**) with DMSO-acetic anhydride gave the acetate (**74**) only and under the reaction condition using DMSO-phosphoric acid-DCC, the compound (**72**) tended to resinify and the desired compound was not obtained. Next, oxidation of the model compound (**75**) was tried using DMSO-phosphoric acid-DCC and the desired compound (**50**) was obtained in a fairly good yield. Finally, *dl*-dihydrocepharamine (**69**) was oxidized with DMSO-phosphoric acid-DCC to give *dl*-cepharamine (**4**) as an oil, characterized as its crystalline hydrobromide, in a 30% yield. Both natural cepharamine and synthetic *dl*-cepharamine were proved to be identical in terms of their IR, NMR and mass spectra and TLC behavior.

Experimental

All melting points were measured on Yanagimoto Melting Point Apparatus and were uncorrected. IR spectra were measured on Hitachi EPI-S Spectrometer. NMR spectra were measured on Varian A-60 Spectrometer in $CDCl_3$ or pyridine-d_5 with tetramethylsilane as an internal standard and chemical shifts were given in τ values. Mass spectra were taken on Hitachi Mass Spectrometer Model RMU-6D. TLC were performed on Alumina (Aluminium Oxyd G nach Stahl) or silica gel (Kieselgel G nach Stahl) using acetone–chloroform (1:4) or chloroform as a developing solvent.

Keto-ester (6)——A solution of 20.5 g of 2-tetralone (5) and 40 g of pyrrolidine in 400 ml of dry benzene was refluxed on an oil bath for 10 hr while water, distilled off as an azeotropic mixture with benzene, was separated with a Dean–Stark type apparatus. Removal of benzene and excess pyrrolidine *in vacuo* left the crude enamine which was dissolved in 50 ml of dry dioxane. To this solution was added a solution of 23.5 g of ethyl bromoacetate in 20 ml of dry dioxane in portions with ice cooling and the reaction mixture was refluxed for 5 hr. After cooling, 30 ml of 3% HCl and 100 ml of water were added and the mixture was stirred vigorously for 10 min at room temperature. The solvent was removed *in vacuo* and the residue was extracted with ether. The ether extract was washed with water, dried over $MgSO_4$ and evaporated to give 24.5 g of the keto-ester (6) as a colorless oil, bp 155° (7 mmHg). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720 (COOEt and CO). NMR τ ($CDCl_3$): 8.79 (3H, t, J=7 cps, -O-CH_2-Me), 5.87 (2H, AB-q, J=7 cps, δ_{AB}=17 cps, -O-C$\underline{H}_2$-Me), 6.05 (1H, AB-q, J=5 cps, δ_{AB}=7 cps, Ar(CH_2)-C$\underline{H}$-CO-). *Anal.* Calcd. for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.22; H, 7.13.

Keto-lactone (8)——To 7.15 g of diethylaminobutanone was added 7.15 g of MeI with ice cooling and the mixture was allowed to stand over night in a refrigerator. The precipitated crystalline methiodide was washed with dry ether and added to a solution of 11.5 g of the keto-ester (6) in 50 ml of dry benzene. To this benzene solution was added a solution of 4 g of potassium in 60 ml of dry ethanol with ice cooling and the mixture was stirred for 2 hr and then refluxed gently for 15 min. After cooling, the mixture was acidified by adding excess 2N H_2SO_4 as quickly as possible with ice cooling and stirred for 20 min. The solvent was evaporated *in vacuo* and the residue was extracted with ether. The ether extract was washed with water, dried over $MgSO_4$ and evaporated to yield 12 g of a yellow crystalline residue. Recrystallization from benzene–ether or chloroform–ether gave the keto-lactone (8) as slightly yellow prisms, mp 167°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1773 (lactone), 1722 (CO). *Anal.* Calcd. for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 74.84; H. 6.23.

Ketal-lactone (9)——To a solution of 3.6 g of the keto-lactone (8) in 50 ml of benzene were added 10 ml of ethylene glycol and 50 mg of *p*-toluenesulfonic acid and the reaction mixture was refluxed for 20 hr, while water was separated with a Dean–Stark type apparatus. After cooling, the benzene solution was washed with 5% NaOH, water, dried over $MgSO_4$ and evaporated to dryness *in vacuo* to yield a crystalline solid. Recrystallization from ether gave 3.5 g of the ketal-lactone (9) as colorless prisms, mp 157°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1765 (lactone). NMR τ($CDCl_3$): 6.06 (4H, s, ethylene ketal). *Anal.* Calcd. for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 72.22; H, 6.43.

Diol (10)——A mixture of 200 mg of the keto-lactone (9), 5 ml of dry tetrahydrofuran, 40 ml of dry ether and 150 mg of $LiAlH_4$ was stirred for 1 hr at room temperature, and then refluxed for 2 hr with continued stirring. Excess $LiAlH_4$ was decomposed with water and the organic layer was decanted, washed

29) K.E. Pfitzer and J.G. Mofatt, *J. Am. Chem. Soc.*, **87**, 5661 (1965); *idem, ibid.*, **87**, 5670 (1965).

with water, dried over $MgSO_4$ and evaporated to yield 180 mg of a crystalline solid. Recrystallization from ether gave the diol (**10**) as colorless prisms, mp 131°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3440 (OH). *Anal.* Calcd. for $C_{18}H_{24}O_4$: C, 71.02; H, 7.95. Found: C, 71.26; H, 8.21.

Reaction of the Diol (10) with *p*-Toluenesulfonyl Chloride (Furano Derivative (12))——To a solution of 120 mg of the diol (**10**) in 2 ml of dry pyridine was added 150 mg of *p*-toluenesulfonyl chloride and the reaction mixture was allowed to stand at room temperature over night. The solvent was removed *in vacuo* and the residue was dissolved in ether. The ether solution was washed with water, dried over $MgSO_4$ and evaporated to give an oily residue, an ether solution of which passed through an alumina column. Evaporation of the solvent left the furano derivative (**12**) as an oil, bp 90° (2×10^{-4} mmHg). Yield 90 mg. NMR $\tau(CDCl_3)$: 6.09 (4H, s, ethylene ketal). Mass Spectrum *m/e*: 286 (M^+). *Anal.* Calcd. for $C_{18}H_{22}O_3$: C, 75.49; H, 7.74. Found: C, 75.99; H, 7.83.

Deketalization of the Furano Derivative (12) with 5% HCl (Keto-furan (77))——After a mixture of 12 mg of the furano derivative (**12**), 2 ml of 5% HCl and 2 ml of acetone was allowed to stand at room temperature for one week, 20 ml of water was added and the reaction mixture was extracted with ether. The ether extract was washed with water, dried over $MgSO_4$ and evaporated. Distillation of the residue gave 11 mg of the keto-furan (**77**) as a colorless oil, bp 95° (2×10^{-4} mmHg). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1715 (CO). *Anal.* Calcd. for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 79.61; H, 7.64. The IR spectrum ($CHCl_3$) and TLC behavior of the product were identical with those of an authentic sample.

Reaction of the Diol (10) with Thionyl Chloride (the Furano Derivative (12))——To a solution of 100 mg of the diol (**10**) in dry pyridine was added a solution of 0.3 ml of thionyl chloride in 2 ml of dry pyridine in portions with ice cooling, and the mixture was allowed to stand at room temperature for 2 days. Pyridine was removed *in vacuo* at room temperature and the residual liquid was poured into ice water and extracted with ether. The ether extract was washed with water, dried over $MgSO_4$ and evaporated to dryness to yield 70 mg of an oil, an ether solution of which was chromatographed over alumina column and eluted with ether. The furano derivative (**12**) obtained as a colorless oil was found to be identical with an authentic sample in terms of their IR spectra ($CHCl_3$), NMR spectra ($CDCl_3$) and TLC behaviors.

Acetylation of the Diol (10) (Acetate (11))——To a solution of 220 mg of the diol (**10**) in 3 ml of dry pyridine was added 0.5 ml of acetic anhydride. After being allowed to stand at room temperature over night, pyridine and excess acetic anhydride were removed *in vacuo*, and the residue was made alkaline with NH_4OH and extracted with ether. The ether extract was washed with water, dried over $MgSO_4$ and evaporated to give 220 mg of an oily substance, an ether solution of which was chromatographed over alumina column and elution with the same solvent gave a colorless oil. Trituration with hexane afforded a crystalline solid. Recrystallization from ether–hexane gave the acetate (**11**) as colorless prisms, mp 47°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500 (OH), 1725 (OAc). NMR τ ($CDCl_3$): 2.75—2.95 (4H, m, aromatic protons), 5.75—6.15 (4H, m, ethylene ketal), 8.06 (3H, s, OAc).

Deketalization Reaction of the Acetate (11) with 80% Acetic Acid——A solution of 220 mg of the acetate (**11**) in 1 ml of 80% acetic acid was heated at 100° for 3 hr. After cooling, 30 ml of water was added and the mixture was extracted with ether. The ether extract was washed with water, dried over $MgSO_4$ and evaporated to yield 180 mg of a slightly yellow oil. Trituration with ether gave a crystalline solid. Recrystallization from ether gave 65 mg of the keto-acetate (**13**) as colorless prisms, mp 157°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1725 (OAc), 1719 (CO), 3400—3550 (OH). NMR $\tau(CDCl_3)$: 8.06 (3H, s, OAc), 7.34 (1H, s, OH), 5.75—6.15 (2H, m, -C<u>H</u>$_2$-OAc). *Anal.* Calcd. for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 70.93; H, 7.29. The mother liquor from recrystallization of the keto-acetate (**13**) was diluted with ether and chromatographed over alumina column and elution with the same solvent gave 54 mg of α,β-unsaturated ketone (**14**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1732 (OAc), 1665 (CO), 1627 (double bond). NMR τ ($CDCl_3$): 8.10 (3H, s, OAc), 6.00 (2H, t, J=8 cps, -C<u>H</u>$_2$-OAc), 4.01 (1H, s, olefinic proton), 2.65—2.91 (2H, m. aromatic protons).

Reaction of the Acetate (11) with 5% HCl (Keto-furan (77))——To a solution of 60 mg of the acetate (**11**) in 5 ml of acetone was added 5 ml of 5% HCl and the mixture was allowed to stand at room temperature for a week. Water was added and the mixture was extracted with ether. The ether extract was washed with water, dried over $MgSO_4$ and evaporated to dryness to yield an oily residue which was chromatographed over alumina column. Elution with ether afforded the keto-furan (**77**) as a colorless oil, bp 96° (2×10^{-4} mmHg). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1715 (CO). *Anal.* Calcd. for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 79.61; H, 7.64.

Condensation of 2-Tetralone (5) with N,N-Dimethylbromoacetoamide (Compound (15))——A solution of 3.98 g of 2-tetralone (**5**) and 6 g of pyrrolidine in 30 ml of benzene was refluxed on an oil bath for 2 hr, while water was separated with a Dean–Stark type apparatus. Removal of the solvent and excess pyrrolidine *in vacuo* left the crude enamine which was dissolved in 15 ml of dry dioxane. To this solution was added a solution of 5 g of N,N-dimethylbromoacetoamide in 15 ml of dry dioxane in portions at room temperature. After refluxing on an oil bath for 12 hr, the solution was cooled to room temperature and 20 ml of water was added and the mixture was heated on a water bath for an hour. Removal of dioxane *in vacuo* left the brown residue, to which 20 ml of water was added and extracted with ether. The ether extract was washed with water, dried over $MgSO_4$ and evaporated to give the keto-amide (**15**) as a slightly brown oil. Because of its lability to alumina chromatography, this oil, without purification, was used for the next stage reaction.

Ketal-amide (16)——A mixture of 1.09 g of the keto-amide (**15**), 1 ml of ethylene glycol, 30 mg of *p*-toluenesulfonic acid and 30 ml of dry benzene was refluxed on an oil bath for 4 hr while water was separated with a Dean–Stark type apparatus. After cooling, 10 ml of water and 5 ml of 28% NH_4OH were added and the reaction mixture was extracted with ether, washed with water, dried over $MgSO_4$ and evaporated to dryness. The residue in benzene was chromatographed on alumina column and eluted with a mixture of hexane and benzene (7:3) to give 865 mg of a crystalline solid. Recrystallization from ether afforded the ketal-amide (**16**) as colorless prisms, mp 130—131°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1634 (amide). NMR $\tau(CDCl_3)$: 7.17 (3H, s, N-Me), 7.03 (3H, s, N-Me), 6.25 (1H, t, $J=6$ cps, Ar (CH_2)-C<u>H</u>-C), 5.85—6.05 (4H, m, ethylene ketal), 2.89 (4H, s, aromatic protons). *Anal.* Calcd. for $C_{16}H_{21}O_3N$: C, 69.79; H, 7.69. Found: C, 69.80; H, 7.95.

Ketal-amine (17)——To a solution of 180 mg of the ketal-amide (**16**) in 3 ml of dry tetrahydrofuran were added 25 ml of dry ether and 140 mg of $LiAlH_4$ and the reaction mixture was refluxed for 5 hr. After cooling, excess reagent was decomposed with water and the reaction mixture was extracted with ether, washed with water, dried over $MgSO_4$ and evaporated. The residual oil in ether was chromatographed over alumina column and elution with ether gave the ketal-amine (**17**) as a colorless oil, bp 130° (4×10^{-5} mmHg). NMR $\tau(CDCl_3)$: 7.75 (6H, s, N-Me×2), 5.95—6.04 (4H, m, ethylene ketal), 2.90 (4H, s, aromatic protons). *Anal.* Calcd. for $C_{16}H_{23}O_2N$: C, 73.53; H, 8.89. Found: C, 73.23; H, 9.09.

Treatment of the Ketal-amine (17) with Cyanogen Bromide (N-Cyano Compound (18))——To a solution of 57 mg of the ketal-amine (**17**) in dry benzene was added 70 mg of cyanogen bromide and the reaction mixture was stirred at room temperature for 4 hr and then allowed to stand over night. To the reaction mixture, 20 ml of ether was added and the mixture was washed with 3% acetic acid and then with water, dried over $MgSO_4$ and evaporated to dryness to give 55 mg of the N-cyano compound (**18**) as a slightly yellow oil, bp 160° (8×10^{-5} mmHg). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2230 (CN). *Anal.* Calcd. for $C_{16}H_{20}O_2N_2$: C, 70.56; H, 7.40. Found: C, 70.32; H, 7.51.

Treatment of the Ketal-amide (16) with 70% Acetic Acid (Unsaturated-lactone (19))——A solution of 93 mg of the ketal-amide (**16**) in 1 ml of 70% acetic acid was heated on a water bath for 2 hr. After cooling, water was added and the reaction mixture was extracted with ether. The ether extract was wahsed with water, dried over $MgSO_4$ and evaporated to dryness. The residual oil in ether was chromatographed on alumina column and elution with ether gave 35 mg of a crystalline solid. Recrystallization from ether afforded the unsaturated-lactone (**19**) as colorless prisms, mp 111—114°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1780 (lactone), 1629 (double bond). Mass Spectrum *m/e*: 186 (M^+). *Anal.* Calcd. for $C_{12}H_{10}O_2$: C, 77.40; H, 5.41. Found: C, 77.39; H, 5.43.

Keto-lactam (20)——(a) A mixture of 400 mg of the ketal-lactone (**9**), 12 ml of dioxane saturated with monomethylamine, 300 mg of monomethylamine hydrochloride and 1 ml of water was heated in a sealed tube at 215° for 48 hr, and the solvent was removed *in vacuo*. The residual oil was diluted with water and extracted with ether. The ether extract was washed with water, dried over $MgSO_4$ and evaporated to yield an oil, which was chromatographed over silica gel column in chloroform and elution with the same solvent gave a crystalline solid. Recrystallization from acetone–ether gave 190 mg of the keto-lactam (**20**) as colorless prisms, mp 144—146°. bp 130° (2×10^{-4} mmHg). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720 (CO), 1680 (lactam). NMR $\tau(CDCl_3)$: 7.20 (3H, s, N-Me). *Anal.* Calcd. for $C_{17}H_{19}O_2N$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.51; H, 7.38; N, 5.14.

(b) In the same manner as described above, 14 g of the ketal-lactone (**9**) was reacted with monomethylamine in 9 tubes. The reaction mixture was worked up as before except that extraction was carried out with chloroform instead of ether. The residual oil in chloroform was chromatographed over silica gel column and elution with the same solvent afforded 1.7 g of the keto-lactam (**20**) in the earlier eluate and the successive elution gave 4.1 g of the ketal-amide (**23**). The ketal-amide (**23**) was recrystallized from benzene–ether and melted at 180—182° (colorless prisms). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500, 3350 (NH and OH), 1660, 1530 (amide). NMR $\tau(CDCl_3)$: 7.46 (3H, d, $J=5$ cps, N-Me), 5.93—6.20 (4H, m, ethylene ketal), 5.47 (1H, s, OH), 4.95 (1H, s, NH), 2.65—3.05 (4H, m, aromatic protons). *Anal.* Calcd. for $C_{19}H_{25}O_4N$: C, 68.86; H, 7.60; N, 4.23. Found: C, 68.65; H, 7.60; N, 4.02.

Conversion of the Ketal-amide (23) to the Keto-lactam (20)——A mixture of 196 mg of the ketal-amide (**23**), 3 ml of dioxane saturaed with monomethylamine, 120 mg of monomethylamine hydrochloride and 0.25 ml of water was heated in a sealed tube for 43 hr at 210°. The solvent was removed *in vacuo* and water was added. The mixture was extracted with chloroform, washed with water, dried over $MgSO_4$ and evaporated. The redisual oil in chloroform was chromatographed over alumina column and elution with the same solvent gave a crystalline solid which was recrystallized from acetone–ether to give 40 mg of the keto-lactam (20) as colorless prisms, mp 144—146°. The IR spectrum and TLC behavior of the keto-lactam (**20**) were identical with those of an authentic sample and the melting point was not depressed on admixture with an authentic sample.

Lactam (22)——A mixture of 250 mg of the keto-lactam (**20**) and 2 ml of 80% hydrazine hydrate was heated at 100° for 1 hr. After cooling, 500 mg of KOH and 3 ml of diethylene glycol were added and the reaction mixture was heated again at 180° for 4 hr. After cooling, 10 ml of water was added and the reaction mixture was extracted with ether. The ether extract was washed with water, dried over $MgSO_4$ and evaporated to give 130 mg of a slightly yellow oil. Distillation under reduced pressure afforded the lactam (**22**)

as a colorless oil, bp 100° (2×10^{-4} mmHg). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1672 (lactam). *Anal.* Calcd. for $C_{17}H_{21}ON$: C, 79.92; H, 8.29; N, 5.49. Found: C, 80.16; H, 8.30; N, 5.44.

***dl*-N-Methylhasubanan (24)**——To a mixture of 90 mg of the lactam (**22**), 20 ml of dry tetrahydrofuran and 30 ml of dry ether was added 200 mg of $LiAlH_4$ and the reaction mixture was refluxed for 15 hr with stirring. After cooling, excess reagent was decomposed with water and the organic layer was decanted. Removal of the solvent gave an oily residue which was dissolved in 5% HCl and washed with ether. The aqueous layer was made alkaline with 28% NH_4OH and extracted with ether. The ether extract was washed with water, dried over $MgSO_4$ and evaporated to give 65 mg of a slightly yellow oil. The oil in benzene was chromatographed on alumina column and eluted with benzene. Evaporation of the solvent and distillation of the residue gave a colorless crystalline solid, bp 70° (2×10^{-4} mmHg). NMR τ ($CDCl_3$): 7.78 (3H, s, N-Me). Mass Spectrum *m/e*: 241 (M^+), 185 (base peak). The crystalline solid could not be purified by recrystallization owing to the high solubility to almost all solvents, so this compound was characterized as its perchlorate, mp 229°(colorless prisms) which could be recrystallized from acetone. *Anal.* Calcd. for $C_{17}H_{23}N\cdot HClO_4$: C, 59.73; H, 7.08; N, 4.10. Found: C, 59.43; H, 7.26; N, 4.00.

Ketal-lactam (21)——A mixture of 130 mg of the keto-lactam (**20**), 6 g of butanone ethylene ketal[22] and 10 mg of *p*-toluenesulfonic acid was refluxed for 25 hr. After cooling, 3 ml of aqueous 10% NaOH was added and the mixture was extracted with ether. The ether extract was washed with water, dried over $MgSO_4$ and evaporated to yield a crystalline solid. Recrystallization from benzene–ether gave 130 mg of the ketal lactam (**21**) as colorless flakes, mp 80—85°. This melting point was raised to 133—135° when the sample was allowed to stand *in vacuo*. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1675 (lactam). NMR τ ($CDCl_3$): 7.21 (3H, s, N-Me), 6.04 (4H, s, ethylene ketal). *Anal.* Calcd. for $C_{19}H_{23}O_3N$: C, 72.82; H, 7.40. Found: C, 72.92 H, 7.52.

Ketal-amine (25)——To a mixture of the ketal-amine (**21**), 20 ml of dry tetrahydrofuran and 30 ml of dry ether was added 300 mg of $LiAlH_4$ and the reaction mixture was refluxed for 25 hr with stirring. After cooling, excess reagent was decomposed with water and the organic layer was decanted and evaporated. The residue was diluted with water and extracted with ether. The ether extract was washed with water, dried over $MgSO_4$ and evaporated to dryness to give 200 mg of a slightly yellow oil. Trituration with ether gave a crystalline solid. Recrystallization from ether gave the ketal-amine (**25**) as colorless prisms, mp 107°. *Anal.* Calcd. for $C_{19}H_{25}O_2N$: C, 76.22; H, 8.42; N, 4.68. Found: C, 76.37; H, 8.35; N, 4.91.

Keto-amine (26)——A solution of 130 mg of the ketal-amine (**25**) in 4 ml of 5% HCl was heated at 100° for 2 hr. After cooling, the reaction mixture was made alkaline with Na_2CO_3 and extracted with ether. The ether extract was washed with water, dried over $MgSO_4$ and evaporated to give 100 mg of the keto-amine (**26**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1710 (CO). NMR τ($CDCl_3$): 7.76 (3H, s, N-Me). The hydrobromide was recrystallized from acetone to give colorless prisms, mp 197—200°. *Anal.* Calcd. for $C_{17}H_{21}ON\cdot HBr$: C, 60.71; H, 6.60; N, 4.17. Found: C, 60.79; H, 6.55; N, 4.18.

***dl*-N-Methylhasubanan (24)**——A mixture of 46 mg of the keto-amine (**26**) hydrobromide and 1 ml of 80% hydrazine hydrate was heated on a water bath for 2 hr. After cooling, 500 mg of KOH and 3 ml of diethylene glycol were added and the reaction mixture was heated at 190° for 3 hr. After cooling, 10 ml of water was added and the mixture was extracted with ether. The ether extract was washed with water, dried over $MgSO_4$ and evaporated to give 15 mg of *dl*-N-methylhasubanan (**24**) as a cololess oil, the perchlorate of which was recrystallized from acetone and melted at 228°. The IR spectrum (Nujol) of the perchlorate was identical with that of an authentic sample and its melting point was not depressed on admixture with an authentic sample.

Keto-ester (27)——A solution of 9.3 g of 7,8-dimethoxy-2-tetralone (**7**) and 10 ml of pyrrolidine in 100 ml of dry benzene was refluxed on an oil bath for 4 hr while water was separated with a Dean–Stark type apparatus. Removal of the solvent and excess pyrrolidine *in vacuo* left the crude enamine which was dissolved in 30 ml of dry dioxane. To this solution was added dropwise a solution of 8.29 g of ethyl bromoacetate in 10 ml of dry dioxane with ice cooling and the reaction mixture was refluxed for 12 hr. After cooling, 40 ml of water was added and the reaction mixture was stirred for 2 hr at room temperature. The solvent was removed *in vacuo* and the residue was extracted with ether. The ether extract was washed with 3% HCl, water, dried over $MgSO_4$ and evaporated. The residual dark brown oil in ether was chromatographed on acidic alumina column and eluted with ether to give a crystalline solid. Recrystallization from ether gave 6.7 g of keto-ester (**27**) as coloress prisms, mp 68—68.5°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1737 (ester), 1720 (CO). NMR τ($CDCl_3$): 8.85 (3H, t, J=7 cps, -O-CH_2-Me), 5.96 (2H, AB-q, J=7 cps, δ_{AB}=14 cps, -O-CH_2-Me), 6.14 (6H, s, -OMe×2), 3.16 (2H, s, aromatic protons). *Anal.* Calcd. for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.25; H, 6.95.

Keto-lactone (28)——To 3.18 g of diethylaminobutanone was added 3.16 g of MeI in portions with ice cooling and the mixture was kept on standing in a refrigerator over night. To the crystalline methiodide which was washed with dry ether, was added a solution of 6.5 g of the keto-ester (**27**) in 25 ml of dry benzene. Then, to this solution was added a solution of 1.3 g of potassium in 25 ml of absolute ethanol in portions with ice cooling and the reaction mixture was stirred for 2.5 hr, and then refluxed gently for 30 min. After cooling, 30 ml of 3N HCl was added to the reaction mixture as quickly as possible with ice cooling and the mixture was stirred for 15 min. Removal of the solvent *in vacuo* left a brown oil, to which water was added and extracted with ether. The ether extract was washed with water, dried over $MgSO_4$ and evaporated to

dryness to yield 8.2 g of a brown oil. Trituration with ether gave a crystalline solid. Recrystallization from ether–benzene afforded 2.25 g of the keto-lactone (**28**) as colorless prisms, mp 160—163°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1767 (lactone), 1722 (CO). NMR τ($CDCl_3$): 6.16 (3H, s, -OMe), 6.12 (3H, s, -OMe), 3.20 (2H, s, aromatic protons). Mass Spectrum *m/e*: 316 (M^+). *Anal.* Calcd. for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37. Found: C, 68.07; H, 6.38. In the extraction procedure mentioned above, the crystalline substance, which was not extracted with ether or chloroform, was collected by filtration, washed successively with water, acetone to leave 130 mg of the keto-acid (**78**) as a crystalline powder. Recrystallization was not effected because of its poor solubility. IR ν_{max}^{Nujol} cm^{-1}: 3400 (OH), 1705 (COOH), 1685 (CO). NMR τ(pyridine-d_5): 8.54 (3H, s, C-Me), 6.30 (3H, s, -OMe), 6.00 (3H, s, -OMe), 3.10 (2H, s, aromatic protons). *Anal.* Calcd. for $C_{18}H_{22}O_6$: C, 64.65; H, 6.63. Found: C, 64.76; H, 6.62.

Methyl-ester (**79**)——To a solution of 45 mg of the keto-acid (**78**) in 12 ml of methanol was added a solution of diazomethane in ether until the yellow color had not faded. Excess diazomethane was decomposed with 5% acetic acid and the solvent was removed. The residual oil in benzene was chromatographed on an acidic alumina column and eluted with benzene to give a crystalline solid. Recrystallization from ether–acetone afforded 40 mg of the methyl-ester (**79**) as colorless needles, mp 166—170°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550 (OH), 1720 (ester). NMR τ($CDCl_3$): 8.70 (3H, s, C-Me), 6.45 (3H, s, -CO-O-Me), 6.21 (3H, s, -OMe), 6.18 (3H, s, -OMe), (3.21 2H, s, aromatic protons). *Anal.* Calcd. for $C_{19}H_{24}O_6$: C, 65.50; H, 6.94. Found: C, 65.26; H, 7.00.

Ketal-lactone (**29**)——A mixture of 2.217 g of the keto-lactone (**28**), 1.5 g of ethylene glycol, 20 mg of *p*-toluenesulfonic acid and 50 ml of dry benzene was refluxed for 12 hr while water was separated with a Dean–Stark type apparatus. After cooling, 28% NH_4OH was added and the mixture was extracted with chloroform. The chloroform extract was washed with water, dried over $MgSO_4$ and evaporated to give a crystalline solid. Recrystallization from ether gave the ketal-lactone (**29**) as colorless needles, mp 194—196°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1765, 1755 (lactone). NMR τ($CDCl_3$): 6.16 (3H, s, -OMe), 6.09 (4H, s, ethylene ketal), 6.05 (3H, s, -OMe), 3.21 (2H, s, aromatic protons). *Anal.* Calcd. for $C_{20}H_{24}O_6$: C, 66.65; H, 6.71. Found: C, 66.85; H, 6.98.

Ketal-lactam (**30**) **and Phenolic Compound** (**31**)——A mixture of 0.8 g of the ketal-lactone (**29**), 1 ml of dioxane saturated with monomethylamine, 0.5 g of monomethylamine hydrochloride and 1 ml of water was heated in a sealed tube at 210° for 70 hr. Removal of the solvent gave a brown oil, to which water was added and extracted with chloroform. The chloroform extract was washed with water, dried over $MgSO_4$ and evaporated to dryness. The residual brown oil in chloroform was chromatographed over silica gel column and elution with the same solvent gave two compounds; the keto-lactam (**30**) (40%) in the earlier eluate, and and the phenolic compound (**31**) (1%) in the following eluate. The keto-lactam (**30**): mp 170—172°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1718 (CO), 1675 (lactam). NMR τ($CDCl_3$): 7.20 (3H, s, N-Me), 6.14 (3H, s, -OMe), 6.10 (3H, s, -OMe), 3.19 (2H, s, aromatic protons). *Anal.* Calcd. for $C_{19}H_{23}O_4N$: C, 69.28; H, 7.04. Found: C, 69.09; H, 7.34. The phenolic compound showed the following physical data. mp 247—250°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500 (OH), 1715 (CO), 1675 (lactam). NMR τ($CDCl_3$): 7.20 (3H, s, N-Me), 6.11 (3H, s, -OMe), 3.89 (1H, s, OH), 3.33 (2H, AB-q, J=8 cps, δ_{AB}=11 cps, aromatic protons). *Anal.* Calcd. for $C_{18}H_{21}O_4N$: C, 68.55; H, 6.71. Found: C, 68.55; H, 6.82.

Lactam (**32**) **and Phenolic-lactam** (**80**)——A mixture of 250 mg of the keto-lactam (**30**), 15 ml of diethylene glycol and 3 ml of 85% hydrazine hydrate was heated on an oil bath at 120° for 2 hr. After cooling, 1.5 g of KOH was added and the reaction mixture was again heated at 180° for 4 hr. After cooling, 30 ml of water was added and the mixture was extracted with chloroform. The chloroform extract was washed with water, dried over $MgSO_4$ and evaporated to give a yellow oil, which was chromatographed over alumina column in benzene and elution with the same solvent gave a crystalline solid. Recrystallization from acetone gave 76 mg of the lactam (**32**) as colorless plates, mp 187.5—190°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1670 (lactam). NMR τ($CDCl_3$): 7.23 (3H, s, N-Me), 6.18 (3H, s, -OMe), 6.13 (3H. s, -OMe), 3.27 (2H, s, aromatic protons). *Anal.* Calcd. for $C_{19}H_{25}O_3N$: C, 72.35; H, 7.99. Found: C, 72.49; H, 7.82. Successive elution of the column with chloroform gave a crystalline solid. Recrystallization from chloroform–ether afforded the phenolic-lactam (**80**) as colorless needles, mp 168—170°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3510 (OH), 1668 (lactam). NMR τ($CDCl_3$): 7.25 (3H, s, N-Me), 6.18 (3H, s, -OMe), 3.84 (1H, s, OH), 3.38 (2H, AB-q, J=8 cps, δ_{AB}=12 cps, aromatic protons). *Anal.* Calcd. for $C_{18}H_{23}O_3N$: C, 71.73; H, 7.69. Found: C, 71.46; H, 7.82.

Huang–Minlon Reduction of the Phenolic Keto-lactam (**31**) **(the Phenolic-lactam** (**80**))——A mixture of 10 mg of the phenolic compound (**31**), 1 ml of 85% hydrazine hydrate and 10 ml of diethylene glycol was heated at 120° for 3 hr. After cooling, 500 mg of KOH was added and the reactiom mixture was again heated at 180° for 4 hr. After cooling, 15 ml of water was added and the mixture was extracted with chloroform. The chloroform extract was washed with water, drived over $MgSO_4$ and evaporated to give 3 mg of the phenolic-lactam (**80**) as colorless needles, mp 168—170°, whose IR spectrum ($CHCl_3$) and TLC behavior were identical with those of an authentic sample.

$LiAlH_4$ Reduction of the Lactam (**32**) (***dl*-3,4-Dimethoxy-N-methylhasubanan** (**33**))——To a mixture of 70 mg of the lactam (**32**), 10 ml of dry tetrahydrofuran and 30 ml of dry ether was added 300 mg of $LiAlH_4$ and the reaction mixture was refluxed for 25 hr with stirring. After cooling, excess $LiAlH_4$ was decomposed with water and the organic layer was decanted. Removal of the solvent afforded a slightly yellow oil which

was dissolved in 3.5% HCl and washed with ether. The aqueous layer was made alkaline with 28% NH_4OH and extracted with ether. The ether extract was washed with water, dried over $MgSO_4$ and evaporated. The residual oil in benzene was chromatographed on alumina column and eluted with benzene to give 61 mg of *dl*-3,4-dimethoxy-N-methylhasubanan (**33**) as a colorless oil. Its crystalline hydrobromide was recrystallized from acetone to afford colorless needles, mp 242—250°. Yield 34 mg. NMR $\tau(CDCl_3)$: 7.80 (3H, s, N-Me), 6.20 (3H, s, -OMe), 6.14 (3H, s, -OMe), 3.29 (2H, s, aromatic protons). *Anal.* Calcd. for $C_{19}H_{27}O_2N \cdot HBr$: C, 59.69; H, 7.38. Found: C, 59.41; H, 7.42. *dl*-3,4-Dimethoxy-N-methylhasubanan (**33**) thus obtained was found to be identical with a sample of 3,4-dimethoxy-N-methylhasubanan (**34**) derived from the natural product through several steps, in terms of IR spectra ($CHCl_3$), NMR spectra ($CDCl_3$) and TLC behaviors.

Keto-nitrile (**35**)——A mixture of 16 g of 2-tetralone (**5**), 34 ml of pyrrolidine and 140 ml of dry benzene was refluxed for 5 hr while water was separated with a Dean–Stark type apparatus. Removal of the solvent and excess pyrrolidine left the crude enamine, which was dissolved in 100 ml of dry dioxane. To this solution was added 18.4 ml of iodoacetonitrile in 20 ml of dry dioxane in portions with ice cooling and the reaction mixture was refluxed for 2 hr. After cooling, 30 ml of 5% HCl and 150 ml of water were added and the mixture was stirred for 1 hr at room temperature. The solvent was removed *in vacuo* and the residue was extracted with ether. The ether extract was washed with water, dried over $MgSO_4$ and evaporated to dryness to give a crystalline solid. Recrystallization from acetone–ether gave the keto-nitrile (**35**) as colorless prisms, mp 100°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2250 (CN), 1720 (CO). NMR $\tau(CDCl_3)$: 6.19 (1H, t, $J=5$ cps, $Ar(CH_2)$-C<u>H</u>-C), 2.71 (4H, s, aromatic protons). *Anal.* Calcd. for $C_{12}H_{11}ON$: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.78; H, 6.11; N, 7.65.

Treatment of the Keto-nitrile (**35**) **with Methyl Vinyl Ketone**——A solution of 3.0 g of the keto-nitrile (**35**) and 1.7 g of methyl vinyl ketone in dry benzene was cooled to 0° and mixed with 5 drops of triethylamine. The reaction mixture was cooled for 1 hr in an ice bath and then allowed to stand at room temperature for 4 days. Then, 100 ml of chloroform was added and the organic layer was washed with 1% HCl, water and evaporated to dryness *in vacuo* to give a slightly yellow oil, which was dissolved in 5 ml of benzene and allowed to stand at room temperature over night. A crystalline solid was precipitated. Recrystallization from benzene gave 2.46 g of the diketo-nitrile (**37**) as colorless prisms, mp 120—122°. Concentration of the mother liquor left 1.61 g of a slightly yellow oil, which was chromatographed over silica gel column in chloroform and on elution of the column with the same solvent, 350 mg of the diketo-nitrile (**37**), 160 mg of the compound (**36**), 130 mg of the C-methyl compound (**38**) and 70 mg of the C-methyl compound (**39**) run out in this order. The diketo-nitrile (**37**): mp 120—122° (from benzene or methanol). Yield 2.81 g. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2260 (CN), 1720 (CO). NMR $\tau(CDCl_3)$; 7.98 (3H, s, -CO-Me), 7.79 (4H, s, -C-C<u>H</u>$_2$-C<u>H</u>$_2$-CO-). Mass Spectrum *m/e*: 255 (M^+), 157 (base peak). *Anal.* Calcd. for $C_{16}H_{17}O_2N$: C, 75.27; H, 6.71. Found: C, 74.99; H, 6.54. The compound (**36**): colorless prisms, mp 110—116° (sint.) (from ether). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3460 (OH), 2260 (CN), 1720 (CO). NMR $\tau(CDCl_3)$: 7.13 (2H s, -C-C<u>H</u>$_2$-CN), 5.62 (1H, s, OH), 2.20—2.90 (4H, m, aromatic protons). Mass Spectrum *m/e*: 201 (M^+). *Anal.* Calcd. for $C_{12}H_{11}O_2N$: C, 71.62; H, 5.51. Found: C, 71.61; H, 5.72. The C-methyl compound (**38**): colorless prisms, mp 183—186° (from ether–acetone). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3570, 3430 (OH), 2260 (CN), 1718 (CO), NMR τ ($CDCl_3$): 8.60 (3H, s, -C-Me), 7.03 (2H, s, -C-C<u>H</u>$_2$-CN), 2.60—3.00 (4H, m, aromatic protons). *Anal.* Calcd. for $C_{16}H_{17}O_2N$: C, 75.27; H, 6.72. Found: C, 75.06; H, 6.93. The C-methyl compound (**39**): colorless prisms, mp 170—172° (from ether–acetone). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3570, 3440 (OH), 2270 (CN), 1722 (CO). NMR τ ($CDCl_3$): 8.73 (3H, s, -C-Me), 7.06 (2H, s, -C-C<u>H</u>$_2$-CN), 2.70—2.85 (4H, m, aromatic protons). *Anal.* Calcd. for $C_{16}H_{17}O_2N$: C, 75.27; H, 6.71. Found: C, 74.99; H, 6.91.

Treatment of the Diketo-nitrile (**37**) **with Potassium Tertiary Butoxide** (**Keto-lactam** (**40**) **and Unsaturated Lactam** (**42**))——To a solution of 1.045 g of the compound (**37**) in 9 ml of dry benzene was added a solution of 0.678 g of potassium tertiary butoxide in tertiary butanol and the reaction mixture was allowed to stand at room temperature under nitrogen over night and then neutralized with 3.5% HCl. Removal of the solvent *in vacuo* afforded a slightly yellow residue, to which water was added and extracted with chloroform. The chloroform extract was washed with water, dried over $MgSO_4$ and evaporated to give a slightly yellow oil, which was chromatographed over silica gel column in chloroform. Elution with the same solvent gave the unsaturated lactam (**42**) in the earlier eluate and then the keto-lactam (**40**) in the following eluate. The keto-lactam (**40**) was recrystallized from acetone–chloroform to give coloress prisms, mp 218—222°. Yield 390 mg. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (NH), 1710 (CO), 1692 (lactam). NMR τ(pyridine-d_5): 7.14 (2H, AB-q, $J=16$ cps, $\delta_{AB}=19$ cps, C_8 methylene), 7.10 (2H, s, C_{15} methylene), 2.60—2.95 (4H, m, aromatic protons). *Anal.* Calcd. for $C_{16}H_{17}O_2N \cdot 1/2\ H_2O$: C, 72.70; H, 6.86. Found: 72.87; H, 6.65. The unsaturated lactam (**42**) was a slightly yellow oil. Yield 310 mg. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (NH), 1710 (CO), 1691 (lactam). NMR $\tau(CDCl_3)$: 7.98 (3H, s, -CO-Me), 7.20 (2H, AB-q, $J=16$ cps, $\delta_{AB}=18$ cps, five membered lactam methylene), 4.66 (1H, AB-q, $J=3.5$ cps, $\delta_{AB}=5$ cps, olefinic proton). Mass Sepctrum *m/e*: 255 (M^+).

Treatment of the Unstaturated Lactam (**42**) **with Acids** (**Keto-lactam** (**40**))——(a) Treatment of *p*-Toluenesulfonic Acid: To a solution of 65 mg of the unsaturated lactam (**42**) in 20 ml of benzene was added 20 mg of *p*-toluenesulfonic acid and the reactiom mixture was refluxed for 2 hr. The solvent was removed *in vacuo* and the residual brown oil was chromatographed over silica gel column in chloroform. Elution with the same

solvent gave a crystalline solid which was recrystallized from chloroform–acetone to give 20 mg of the keto-lactam (**40**) as colorless prisms, mp 220°. The keto-lactam (**40**) thus obtained was found to be identical with an authentic sample in terms of their IR spectra and TLC behaviors, and the mixed melting point was not depressed.

(b) Treatment with Formic Acid and Phosphoric Acid: A solution of 239 mg of the unsaturated lactam (**42**) in 3 ml of 100% formic acid containing 0.5 ml of 85% phosphoric acid was heated on a water bath for 2 hr, cooled, diluted with ice water and extracted with ether. The ether extract was washed with water, dried over $MgSO_4$ and evaporated. The residual oil was chromatographed on silicagel column and elution with methylene chloride gave a crystalline solid. Recrystallization from chloroform–acetone furnished 88 mg of the keto-lactam (**40**) as colorless prisms, mp 220°. The keto-lactam (**40**) thus obtained was found to be identical with an authentic sample in terms of their IR spectra and TLC behaviors, and the mixed melting point was undepressed.

Treatment of the C-Methyl Compounds (38) and (39) with Base (Keto-lactam (40))——(a) Treatment of the C-Methyl Compound (**38**) (ax. OH): A mixture of 248 mg of the C-methyl compound (38) and 165 mg of sodium in 10 ml of ethanol was refluxed for 1.5 hr. The solvent was removed *in vacuo* and the residue was acidified with 5% HCl and extracted with chloroform. The chloroform extract was washed with water, dried over $MgSO_4$ and evaporated. The residual oil in chloroform was chromatographed over silica gel column. Elution with the same solvent gave a crystalline solid which was recrystallized from acetone–ether to afford 95 mg of the keto-lactam (40) as cololess prisms, mp 218—219°. The IR spectrum and TLC behavior were identical with those of an authentic sample.

(b) Treatment of the C-Methyl Compound (**39**) (eq. OH): A solution of 67 mg of the C-methyl compound (**39**) and 75 mg of sodium in 5 ml of ethanol was refluxed for 1.5 hr and the solvent was removed *in vacuo*. To the residue, 5% HCl was added and the mixture was extracted with chloroform. The chloroform extract was washed with water, dried over $MgSO_4$ and evaporated. The residual oil was chromatographed over silicagel column in chloroform. Elution with the same solvent gave a crystalline solid which was recrystallized from acetone–ether to give 35 mg of the keto-lactam (40) as colorless prisms, mp 218—219°. The IR spectrum and TLC behavior were identical with those of an authentic sample.

Keto-lactam (40) (by the Improved Method)——To a solution of 18.5 g of the keto-nitrile (**35**) and 8.54 g of methyl vinyl ketone in 320 ml of methanol was added a solution of 2.4 g of sodium in 100 ml of methanol. The reaction mixture was allowed to stand at room temperature for 15 hr and then refluxed for 1 hr, cooled, made acidic with 5% HCl. The solvent and excess methyl vinyl ketone were removed *in vacuo*, and to the residue, water was added. The mixture was then extracted with methylene chloride and the extract was washed with water, dried over $MgSO_4$ and evaporated. The residue was chromatographed on alumina column and eluted with methylene chloride to give a crystalline solid. Recrystallization from acetone gave 18.6 g of the keto-lactam (**40**) as colorless prisms, mp 218—219°. The IR spectrum and TLC behavior were identical with those of an authentic sample, and the melting point was undepressed on admixture with an authentic sample.

Ketal-lactam (41)——A solution of 18.6 g of the keto-lactam (40), 30 ml of ethylene glycol and 500 mg of *p*-toluenesulfonic acid in 300 ml of dry benzene was refluxed for 30 hr while water was separated with a Dean–Stark type apparatus. The solvent was removed *in vacuo*, and to the residue, 5% NaOH was added and the mixture was extracted with methylene chloride. The extract was washed with water, dried over $MgSO_4$ and evaporated to give a crystalline solid. Recrystallization from benzene–ether afforded 19.13 g of the ketal-lactam (**41**) as colorless prisms, mp 184.5—185.5°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3410 (NH), 1685 (lactam). *Anal.* Calcd. for $C_{18}H_{21}O_3N$: C, 72.21; H, 7.07; N, 4.68. Found: C, 72.49; H, 7.80; N, 4.75.

N-Methyl-ketal-lactam (21)——To a solution of 35 mg of the ketal-lactam (**41**) in 15 ml of dry toluene was added 40 mg of sodium hydride and the mixed solution was refluxed on an oil bath for 3 hr, cooled, and 0.5 ml of MeI was added. The reaction mixture was refluxed for 1.5 hr and after cooling, excess sodium hydride was decomposed with water and the mixture was extracted with ether. The ether extract was washed with water, dried over $MgSO_4$ and evaporated to dryness. The residue was chromatographed over alumina column in benzene and elution with the same solvent gave a crystalline solid. Recrystallization from benzene–ether afforded 12 mg of the N-methyl-ketal-lactam (**21**) as colorless flakes, mp 133—135°. The IR spectrum and TLC behavior were identical with those of an authentic sample and the melting point was undepressed on admixture with an authentic sample.

Keto-nitrile (43)——A mixture of 4.2 g of 7,8-dimethoxy-2-tetralone (**7**), 9 ml of pyrrolidine and 150 ml of dry benzene was refluxed for 4 hr while water was separated with a Dean–Stark type apparatus. Removal of the solvent and excess pyrrolidine left the crude enamine as a brown oil, which was dissolved in 100 ml of dry acetonitrile. To this solution, 3.75 g of iodoacetonitrile was added in portions with ice cooling and the reaction mixture was refluxed for 5 hr. After cooling, 3.5% HCl was added and the mixture was heated on a water bath for 1 hr. The solvent was removed *in vacuo* and the residue was extracted with ether, washed with water, dried over $MgSO_4$ and evaporated to give a crystalline solid. Recrystallization from ether gave 2.75 g of the keto-nitrile (**43**) as colorless prisms, mp 75—76°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2270 (CN). NMR $\tau(CDCl_3)$: 6.11 (3H, s, -OMe), 6.10 (3H, s, -OMe), 3.10 (2H, s, aromatic protons). *Anal.* Calcd for $C_{14}H_{15}O_3N$: C, 68.55; H, 6.16. Found: C, 68.25; H, 6.12.

Treatment of the Keto-nitrile (43) with Methyl Vinyl Ketone——(a) To a solution of 60 mg of the keto-nitrile (**43**) and 25 mg of methyl vinyl ketone in 6 ml of dry benzene was added a solution of 5 mg of potassium tertiary butoxide in 0.3 ml of tertiary butanol and the reaction mixture was allowed to stand at room temperature for 46 hr, neutralized with 3 ml of 3.5% HCl and the solvent was removed *in vacuo*. Water was added and the mixture was extracted with ether. The ether extract was washed with water, dried over $MgSO_4$ and evaporated to give 66 mg of a slightly yellow oil which was chromatographed over silica gel column in chloroform. Elution with the same solvent gave 40 mg of crystalline solid in the earlier eluate. Recrystallization from ether afforded 30 mg of the compound (**44**) as colorless prisms, mp 135—136°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2265 (CN), 1712 (CO). NMR $\tau(CDCl_3)$: 7.97 (3H, s, -CO-Me), 6.13 (3H, s, -OMe), 6.06(3H, s, -OMe), 3.10 (2H, s, aromatic protons). *Anal.* Calcd. for $C_{18}H_{21}O_4N$: C, 68.55; H, 6.71. Found: C, 68.31; H, 6.57. Successive elution with 2% methanol in chloroform gave 30 mg of a crystalline solid, which was recrystallized from ether to give 15 mg of the C-methyl compound (**45**) and (**46**) as colorless prisms, mp 185—187°.

(b) To a solution of 90 mg of the keto-nitrile (**43**) and 45 mg of methyl vinyl ketone in 4 ml of dry methanol was added 1 ml of a solution of 1 pellet of NaOH in 20 ml of methanol and the reaction mixture was refluxed for 45 min. After cooling, acetic acid was added to neutralize and the solvent was removed *in vacuo*. The residual slightly yellow oil was dissolved in ether–chloroform (3:1) and the organic solution was washed with water, dried over $MgSO_4$ and evaporated. The residual oil was chromatographed over alumina column in ether. Elution with the same solvent gave a crystalline solid which was recrystallized from acetone–ether to afford 65 mg of the C-methyl compounds (**45**) and (**46**) as colorless prisms, 185—187°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3570 (OH), 3440 (OH), 2270 (CN), 1724 (CO). NMR $\tau(CDCl_3)$: 8.67: 8.88 (4:1, -C-Me). The mixture of the C-methyl compounds (**45**) and (**46**) was chromatographed over silica gel column in chloroform and elution with the same solvent gave the fraction which contained the C-methyl compounds (**45**) and (**46**) in the ratio of 1 to 1. Separation of the mixture (**45**) and (**46**) (1:1) was effected by the preparative thin layer chromatography. ax.-OH-Compound (**45**): colorless flakes, mp 146—148.5° (from acetone). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3590, 3460 (OH), 2260 (CN), 1720 (CO). NMR $\tau(CDCl_3)$: 8.77 (3H, s, -C-Me), 6.15 (3H, s, -OMe), 6.04 (3H, s, -OMe), 3.15 (2H, s, aromatic protons). *Anal.* Calcd. for $C_{18}H_{21}O_4N$: C, 68.55; H, 6.71. Found: C, 68.32; H, 6.80. eq.-OH-Compound: colorless flakes, mp 177—182° (from acetone). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2270 (CN), 1720 (CO). NMR τ $(CDCl_3)$: 8.67 (3H, s, -C-Me), 6.15 (3H, s, -OMe), 6.03 (3H, s, -OMe), 3.16 (2H, s, aromatic protons). *Anal.* Calcd. for $C_{18}H_{21}O_4N$: C, 68.55; H, 6.71. Found: C, 68.58; H, 6.89.

(c)(Keto-lactam (**47**)) To a solution of 2.58 g of the keto-nitrile (**43**) and 1.10 g of methyl vinyl ketone in 100 ml of methanol was added a solution of 1 pellet of NaOH in 20 ml of methanol and the reaction mixture was boiled gently on an oil bath for 30 min. The solvent was removed *in vacuo* and the residue was dissolved in chloroform. The chloroform solution was washed with 3.5% HCl, water, dried over $MgSO_4$ and evaporated to give 1.1 g of a crystalline solid, which was assigned to the keto-lactam (**47**) by comparison of the IR spectra. Concentration of the mother liquor left an oily residue, which was dissolved in a solution of 0.7 g of sodium in 100 ml of 99% ethanol, and the mixture was refluxed for 3 hr. After cooling, 3.5% HCl was added, and the solvent was removed *in vacuo* and the residue was dissolved in chloroform. The chloroform solution was washed with water, dried over $MgSO_4$ and evaporated to give a crystalline solid. Recrystallization from chloroform–methanol gave 467 mg of the keto-lactam (**47**) as colorless prisms, mp 270°. Total yield was 1.6 g. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3410 (NH), 1690 (lactam). NMR $\tau(CDCl_3)$: 6.14 (3H, s, -OMe), 6.10 (3H, s, -OMe), 3.19 (2H, s, aromatic protons), 3.35—3.55 (1H, broad s, NH). *Anal.* Calcd. for $C_{18}H_{21}O_4N$: C, 68.55; H, 6.71. Found: C, 68.69; H, 6.94.

Keto-lactam (47)——A mixture of 73 mg of the C-methyl compounds (**45**) and (**46**) and 35 mg sodium in 5 ml of 99% ethanol was refluxed gently for 4 hr, cooled, neutralized with 3.5% HCl and the solvent was removed *in vacuo* and the residue was extracted with chloroform. The extract was washed with water, dried over $MgSO_4$ and evaporated to give an oil which was chromatographed over alumina column in chloroform. Elution with the same solvent gave 50 mg of a crystalline solid. Recrystallization from chloroform–methanol afforded 30 mg of the keto-lactam (**47**) as colorless prisms, mp 270°. The IR spectrum and TLC behavior were identical with those of an authentic sample.

Ketal-lactam (48)——A mixture of 4.56 g of the keto-lactam (**47**), 30 ml of ethylene glycol, 0.8 g of *p*-toluenesulfonic acid and 300 ml of dry benzene was refluxed for 22 hr while water was separated with a Dean–Stark type apparatus. After cooling, the benzene layer was separated from the ethylene glycol layer and was washed with 3% NH_4OH, water, dried over $MgSO_4$ and evaporated. To the ethylene glycol layer was added water and the mixture was extracted with chloroform. The chloroform extract was washed with water, dried over $MgSO_4$ and evaporated. Recrystallization of the combined crude crystals from ether gave 3.6 g of the ketal-lactam (**48**) as colorless needles, mp 255—259°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3410 (NH), 1685 (lactam). NMR $\tau(CDCl_3)$: 3.50 (1H, broad s, NH), 3,23 (2H, s, aromatic protons). *Anal.* Calcd. for $C_{20}H_{25}O_5N$: C, 66.83; H, 7.01. Found: C, 66.70; H, 7.04.

Ketal-lactam (49)——To a solution of 3.74 g of the ketal-lactam (**48**) in 500 ml of dry toluene was added 2.5 g of sodium hydride (52% in mineral oil) and the reaction mixture was refluxed for 8 hr on an oil bath. After cooling, 30 ml of MeI was added and the reaction mixture was refluxed for 5 hr, cooled and excess sodium hydride was decomposed with water. The benzene layer was washed with water, dried over $MgSO_4$ and evaporated to give a crystalline solid. Recrystallization from chloroform–ether gave 3.65 g of

the ketal-lactam (**49**) as colorless flakes, mp 177°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1672 (lactam). NMR τ ($CDCl_3$): 7.21 (3H, s, N-Me), 3.25 (2H, s, aromatic protons). *Anal.* Calcd. for $C_{21}H_{27}O_5N$: C, 67.54; H, 7.29. Found: C, 67.34; H, 7.33.

Ketalization of the Keto-lactam (**30**)——A mixture of 290 mg of the keto-lactam (**30**), 10 ml of ethylene glycol, 100 mg of *p*-toluenesulfonic acid and 80 ml of dry benzene was refluxed for 30 hr while water was separated with a Dean–Stark type apparatus. After cooling, the benzene layer was washed with water, dried over $MgSO_4$ and evaporated *in vacuo* to give a crystalline solid. Recrystallization from ether gave 230 mg of the ketal-lactam (**49**) as colorless flakes, mp 177°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1672 (lactam). NMR τ($CDCl_3$): 7.21 (3H, s, N-Me), 3.25 (2H, s, aromatic protons). The ketal-lactam (**49**) thus obtained was identical with an authentic sample in terms of their IR spectra and TLC behaviors.

Diketone (**51**)——To a solution of 1 g of the keto-lactam (**20**) in 10 ml of acetic acid was added a solution of 1.2 g of bromine and 0.2 ml of 48% HBr in 5.7 ml of acetic acid with stirring at room temperature and the reaction mixture was allowed to stand at room temperature over night. Removal of the solvent *in vacuo* left the crude dibromo-ketone which without purification, was dissolved in 10 ml of acetic acid. To the acetic acid solution was added 3 g of freshly fused sodium acetate and the reaction mixture was heated at 120° on an oil bath for 6 hr. The solvent was removed *in vacuo* and 20 ml of water was added. The mixture was extracted with chloroform and the chloroform extract was washed with water, dried over $MgSO_4$ and evaporated to give a slightly yellow oil. Trituration with benzene gave a crystalline solid. Recrystallization from benzene afforded 240 mg of the diketone (**51**) as colorless prisms, mp 254—256°. Concentration of the mother liquor left a yellow oil which was dissolved in 2 ml of methanol and 10 ml of 5% HCl was added, and the mixture was refluxed for 5 hr. The solvent was removed *in vacuo* and the residual oil was diluted with water and extracted with chloroform. The chloroform extract was washed with water, dried over $MgSO_4$ and evaporated to give a crystalline solid. Recrystallization from benzene gave 65 mg of the diketone (**51**). Concentration of the mother liquor gave an oily residue which was chromatographed over silica gel column in chloroform. Elution with the same solvent afforded 45 mg of the diketone (**51**). Total yield was 350 mg. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3480 (OH), 1680 (lactam and ketone). NMR τ($CDCl_3$): 7.07 (3H, s, N-Me), 3.86 (1H, s, olefinic proton). Mass Spectrum *m/e*: 283 (M^+), 212 (base peak). *Anal.* Calcd. for $C_{17}H_{17}O_3N$: C, 72.06; H, 6.05. Found: C, 71.91; H, 6.00.

Diketal (**53**)——A solution of 85 mg of the diketone (**51**), 3 ml of ethylene glycol, 300 mg of *p*-toluenesulfonic acid and 30 ml of benzene was refluxed for 40 hr while water was separated with a Dean–Stark type apparatus. The solvent was removed *in vacuo* and 10 ml of 5% NaOH was added. The mixture was extracted with chloroform–ether (1:3) mixture and the extract was washed with water, dried over $MgSO_4$ and evaporated to give an oily residue which was chromatographed over alumina column in chloroform. Elution with the same solvent gave a crystalline solid which was recrystallized from acetone–ether to afford 95 mg of the diketal (**53**) as colorless needles, mp 255°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1673 (lactam). NMR τ ($CDCl_3$): 7.23 (3H, s, N-Me), 5.70—6.30 (8H, m, ethylene ketals). *Anal.* Calcd. for $C_{21}H_{25}O_5N$: C, 67.90; H, 6.78. Found: C, 67.94; H, 6.90.

Amine (**54**)——To a solution of 380 mg of the diketal (**53**) in 30 ml of dry tetrahydrofuran were added 60 ml of dry ether and 900 mg of $LiAlH_4$, and the reaction mixture was refluxed for 25 hr with stirring. After cooling, excess $LiAlH_4$ was decomposed with water and the organic layer was decanted. The solvent was removed and the residual oil was dissolved in ether and then extracted with 3% acetic acid. The acidic aqueous layer was made alkaline with 28% NH_4OH and extracted with ether. The ether extract was washed with water, dried over $MgSO_4$ and evaporated to give a crystalline solid. Recrystallization from ether gave 255 mg of the amine (**54**) as colorless needles, mp 125—135°. *Anal.* Calcd. for $C_{21}H_{27}O_4N$: C, 70.56; H, 7.61. Found: C, 70.27; H, 7.84.

Diketone (**52**)——A solution of 60 mg of the amine (**54**) in 5 ml of 35% HCl was allowed to stand at room temperature over night, cooled, made alkaline with 28% NH_4OH and extracted with ether. The ether extract was washed with water, dried over $MgSO_4$ and evaporated to give a crystalline solid. Recrystallization from benzene gave 30 mg of the diketone (**52**) as yellow prisms, mp 173°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3460 (OH), 1664 (CO), 1624 (double bond). NMR τ ($CDCl_3$): 7.75 (3H, s, N-Me), 3.77 (1H, s, olefinic proton). Mass Spectrum *m/e*: 269 (M^+). *Anal.* Calcd. for $C_{17}H_{19}O_2N$: C, 75.81; H, 7.11. Found: C, 75.54; H, 7.02.

Monoenolmethylation of the Diketone (**52**) (**Enol-methyl Ether** (**58**))——To a solution of 5.5 g of the diketone (**52**) in 2 ml of dry methanol was added 3 drops of BF_3·ether and the mixture was allowed to stand at room temperature for 40 hr. The solvent was removed *in vacuo* and 5% NaOH was added. The mixture was extracted with ether and the extract was washed with water, dried over $MgSO_4$ and evaporated to give 4.5 mg of a slightly yellow oil, which was chromatographed over silica gel column in chloroform. Elution with the same solvent afforded 3.5 mg of the enol-methyl ether (**58**) in the earlier eluate. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1670 (CO), 1631 (double bond). NMR τ ($CDCl_3$): 7.79 (3H, s, N-Me), 6.65 (3H, s, -OMe), 3.85 (1H, s, olefinic proton). Mass Spectrum *m/e*: 283 (M^+). The starting material (1 mg) was recovered in the following eluate. The IR spectrum and TLC behavior were identical with those of an authentic sample.

Monoenolmethylation of the Diketone (**51**) (**Compound** (**59**))——To a solution of 23 mg of the diketone (**51**) in 6 ml of dry methanol was added 0.3 ml of BF_3·ether and the reaction mixture was allowed to stand at room temperature for 20 hr. Removal of the solvent *in vacuo* gave an oil, to which NH_4OH was added

and extracted with chloroform. The chloroform extract was washed with water, dried over $MgSO_4$ and evaporated to give 26 mg of the mixture of the compounds (**59**) and (**60**) as a colorless oil. Separation of this mixture with silica gel or alumina column chromatography was not effected. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1685 (amide and CO), 1633 (double bond). NMR τ ($CDCl_3$): 6.33:6.38 (4:1, -OMe), 4.49:4.15 (4:1, olefinic proton).

Compound (50)——To a mixture of 245 mg of the compounds (**59**) and (**60**), 2 ml of dry tetrahydrofuran and 30 ml of dry ether was added 500 mg of $LiAlH_4$ and the reaction mixture was refluxed for 30 hr with stirring. After cooling, excess $LiAlH_4$ was decomposed with water and the organic layer was decanted. The solvent was removed and the residual oil was dissolved in ether–chloroform, and extracted with 3% HCl. The aqueous layer was made alkaline with 28% NH_4OH and extracted with chloroform. The chloroform extract was washed with water, dried over $MgSO_4$ and evaporated to give 230 mg of a colorless oil, which without purification was dissolved in 20 ml of chloroform. To this chloroform solution, 700 mg of activated manganese dioxide was added and the reaction mixture was stirred at room temperature for 20 hr. Removal of excess manganese dioxide by filtration and the chloroform layer was washed with water, dried over $MgSO_4$ and evaporated to give 145 mg of a yellow oil which was chromatographed over silica gel column in chloroform. Elution with the same solvent gave 80 mg of the compound (**50**) as a yellow oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1688 (CO), 1629 (double bond). NMR τ ($CDCl_3$): 7.58 (3H, s, N-Me), 6.35 (3H, s, -OMe), 4.35 (1H, s, olefinic proton). Mass Spectrum *m/e*: 283 (M^+). The hydrobromide was recrystallized from acetone to give colorless prisms, mp 254°. *Anal.* Calcd. for $C_{18}H_{21}O_2N \cdot HBr$: C, 59.35; H, 6.08; N, 3.85. Found: C, 59.59; H, 6.27; N, 3.78.

Partial Demethylation of the Ketal-lactam (49) (Phenol (63))——A mixture of 545 mg of the ketal-lactam (**49**), 10 ml of diethylene glycol, 5 g of KOH and 2 ml of 85% hydrazine hydrate was heated for 26 hr at 190°. The mixture was cooled, diluted with water, made alkaline with 28% NH_4OH and extracted with methylene chloride. The methylene chloride extract was washed with water, dried over $MgSO_4$ and evaporated to give 620 mg of a crystalline solid. Recrystallization from ether–methylene chloride gave the phenol (**63**) as colorless flakes, mp 210—225° (sint.). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500 (OH), 1669 (lactam). NMR τ ($CDCl_3$): 7.25 (3H, s, N-Me), 6.17 (3H, s, -OMe), 6.08 (4H, s, ethylene ketal), 3.89 (1H, s, OH). *Anal.* Calcd. for $C_{20}H_{25}O_5N$: C, 66.83; H, 7.01. Found: C, 66.69; H, 6.93.

Acetate (64)——A mixture of 3.10 g of the phenol (**63**), 10 ml of pyridine and 10 ml of acetic anhydride was allowed to stand at room temperature over night. Excess acetic anhydride and pyridine were removed *in vacuo* and the residue was dissolved in methylene chloride. The methylene chloride solution was washed with water, dried over $MgSO_4$ and evaporated to give 3.77 g of the acetate (64) as a colorless oil, bp 200° (2×10^{-4} mmHg). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1762 (OAc), 1671 (lactam). NMR τ ($CDCl_3$): 7.69 (3H, s, OAc), 7.20 (3H, s, N-Me), 6.08 (4H, s, ethylene ketal), 6.11 (3H, s, -OMe). Mass Spectrum *m/e*: 401 (M^+).

Keto-acetate (65)——To a solution of 3.7 g of the acetate (**64**) in 70 ml of acetone was added 70 ml of 1% HCl and the reaction mixture was heated on a water bath for 2 hr. The organic solvent was removed *in vacuo* and the residue was extracted with methylene chloride. The methylene chloride extract was washed with water, dried over $MgSO_4$ and evaporated. The residue was chromatographed over alumina column in ether and elution with the same solvent afforded a crystalline solid. Recrystallization from acetone gave 2.25 g of the keto-acetate (**65**) as colorless prisms, mp 249—251.5°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1761 (OAc), 1719 (CO), 1677 (lactam). NMR τ ($CDCl_3$): 7.65 (3H, s, OAc), 7.11 (3H, s, N-Me), 6.19 (3H, s, -OMe), 3.18 (2H, AB-q, J=9 cps, δ_{AB}=12 cps, aromatic protons). *Anal.* Calcd. for $C_{20}H_{23}O_5N$: C, 67.21; H, 6.49. Found: C, 66.96; H, 6.55.

Keto-phenol (31)——To a solution of 350 mg of the phenol (**63**) in 3 ml of acetone was added 3 ml of 3.5% HCl and the reaction mixture was refluxed for 2 hr on a water bath. The organic solvent was removed *in vacuo* and the residue was extracted with methylene chloride. The methylene chloride extract was washed with water, dried over $MgSO_4$ and evaporated. The residue in methylene chloride was chromatographed over alumina column and elution with the same solvent gave a crystalline solid. Recrystallization from chloroform-acetone afforded 205 mg of the keto-phenol (**31**) as colorless needles, mp 250°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450 (OH), 1714 (CO), 1674 (lactam). *Anal.* Calcd. for $C_{18}H_{21}O_4N$: C, 68.55; H, 6.71. Found: C, 68.84; H, 6.86. The IR spectrum and TLC behavior were identical with those of an authentic sample.

Keto-acetate (65)——A mixture of 195 mg of the keto-phenol (**31**), 1 ml of pyridine and 3 ml of acetic anhydride was allowed to stand at room temperature over night. Excess acetic anhydride and pyridine were remored *in vacuo* and the residue was disolved in methylene chloride. The methylene chloride solution was washed with water, dried over $MgSO_4$ and evaporated. The residue in methylene chloride was chromatographed over alumina column and elution with the same solvent gave a crystalline solid. Recrystallization from acetone afforded 176 mg of the keto-acetate (**65**) as colorless prisms, mp 249—251.5°. The keto-acetate (**65**) thus obtained was identified with an authentic sample in terms of their IR spectra and TLC behaviors.

Diketone (67)——To a solution of 1.083 g of the keto-acetate (**65**) in 40 ml of acetic acid was added a solution of 970 mg of bromine and a few drops of 48% HBr in 6.3 ml of acetic acid with stirring at room temperature and the reaction mixture was allowed to stand for 43 hr. Removal of the solvent *in vacuo* left the crude dibromo ketone as a yellow oil which without purificafion, was dissolved in 30 ml of acetic acid. To this solution, 4.4 g of freshly fused sodium acetate was added and the mixture was heated for 2.5 hr at 115°. The solvent was removed *in vacuo*, and the residue was mixed with water, extracted with

chloroform. The chloroform extract was washed with water, dried over $MgSO_4$ and evaporated to give 2 g of a brown oil. Trituration with acetone gave 360 mg of colorless powder (**67**). Concentration of the mother liquor gave a brown oil which was chromatographed over silica gel column in chloroform. Elution with the same solvent gave 230 mg of the same colorless powder as that obtained above. Judging from its IR and NMR spectra, the compound (**67**), was expected in this colorless powder but no further purification was tried.

***dl*-16-Oxocepharamine Acetate (68)**——A mixture of 330 mg of the above mentioned colorless powder (**67**), 2.5 ml of BF_3·ether and 10 ml of dry methanol was refluxed for 1.5 hr gently. After left on standing at room temperature over night, the solvent was removed *in vacuo* at the temperature as low as possible. The residue was diluted with NH_4OH and extracted with chloroform. The chloroform extract was washed with water, dried over $MgSO_4$ and evaporated to give 340 mg of a slightly yellow oil which was chromatographed over alumina column in chloroform. Elution with the same solvent gave a crystalline solid. Recrystallization from acetone–ether afforded 100 mg of *dl*-16-oxocepharamine acetate (**68**) as colorless prisms, mp 267°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1765 (OAc), 1684 (lactam and ketone), 1640 (double bond). NMR τ ($CDCl_3$): 7.66 (3H, s, OAc), 7.09 (3H, s, N-Me), 6.34 (3H, s, -OMe), 6.23 (3H, s, -OMe), 4.55 (1H, s, olefinic proton). Mass Spectrum *m/e*: 385 (M^+). *Anal.* Calcd. for $C_{21}H_{23}O_6N$: C, 65.44; H, 6.02. Found: C, 65.05; H, 6.23.

***dl*-Dihydrocepharamine (69)**——To a mixture of 222 mg of *dl*-16-oxocepharamine acetate (**68**), 15 ml of dry tetrahydrofuran and 50 ml of dry ether was added 500 mg of $LiAlH_4$ and the reaction mixture was refluxed for 37 hr with stirring. After cooling, excess $LiAlH_4$ was decomposed with water and the organic layer was decanted. The solvent was removed and the residual oil in ether was chromatographed over alumina column and elution with the same solvent gave 40 mg of *dl*-dihydtcepharamine (**69**) as a colorless oil which showed 2 spots on TLC. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3520, 3400 (OH), 1665 (double bond).

***dl*-Cepharamine (4)**——To a solution of 40 mg of *dl*-dihydrocepharamine (69) in 0.55 ml of DMSO were added 95 mg of DCC and 0.15 ml of 1 M solution of orthophosphoric acid in DMSO, and the reaction mixture was allowed to stand at 23° over night. To this solution were added 10 ml of water, 10 ml of 3% HCl and 10 ml of ether and the insoluble dicyclohexylurea was removed by filtration, and then the aqueous layer was washed with ether. The aqueous layer was made alkaline with NH_4OH and extracted with methylene chloride. The methylene chloride extract was washed with water, dried over $MgSO_4$ and evaporated. The residue in ether was chromatographed over alumina column and elution with the same solvent gave 14 mg of *dl*-cepharamine (**4**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1685 (CO), 1630 (double bond). NMR τ ($CDCl_3$): 7.59 (3H, s, N-Me), 6.35 (3H, s, -OMe), 6.15 (3H, s, -OMe), 4.38 (1H, s, olefinic proton). The hydrobromide was recrystallized from acetone to give colorless flakes, mp 243—246° (decomp.). Mass Spectrum *m/e*: 329 (M^+). The IR, NMR and MS spectra and TLC behavior of this sample were identical with those of cepharamine (**1**).

Oxidation of Dihydrosinomenine (β-OH) (70) with DMSO——(a) A mixture of 195 mg of dihydrosinomenine (β-OH) (**70**), 3 ml of DMSO and 2 ml of acetic anhydride was allowed to stand at room temperature for 4 hr. The mixture was poured into cooled dil. NH_4OH and extracted with methylene chloride. The methylene chloride extract was washed with water, dried over $MgSO_4$ and evaporated. The residual oil in methylene chloride was chromatographed over alumina column and elution with the same solvent gave 200 mg of sinomenine acetate (**76**) as a slightly yellow oily substance. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1765 (OAc), 1687 (CO). The hydrobromide was recrystallized from acetone to give 110 mg of colorless prisms, mp 270—271°. *Anal.* Calcd. for $C_{21}H_{25}O_5N$·HBr: C, 55.76; H, 5.80. Found: C, 55.68; H, 6.04. The IR spectrum and TLC behavior were identical with those of an authentic sample.

(b) A mixture of 99 mg of dihydrosinomenine (β-OH) (**70**), 2.5 ml of DMSO, 315 mg of DCC and 0.5 ml of 1M solution of orthophosphoric acid in DMSO was allowed to stand at room temperature over night. To this were added 25 ml of water, 49 mg of phosphoric acid and 25 ml of ether and the insoluble dicyclohexylurea was removed by filtration, and then the aqueous layer was extracted with benzene. The benzene extract was washed with water, dried over $MgSO_4$ and evaporated. The residue was chromatographed over silica gel column in chloroform and elution with the same solvent gave 52 mg of sinomenine (**61**). Recrystallization from benzene gave colorless prisms, mp 161°. The IR spectrum and TLC behavior were identical with those of an authentic sample. The melting point was undepressed on admixture with an authentic sample.

Oxidation of Dihydrosinomenine (α-OH) (71) with DMSO——To a solution of 268 mg of dihydrosinomenine (α-OH) (**71**) in 3 ml of DMSO was added 3 ml of acetic anhydride and the reaction mixture was allowed to stand at room temperature for 4 hr. The mixture was poured into ice–water, made alkaline with 28% NH_4OH and extracted with methylene chloride. The methylene chloride extract was washed with water, dried over $MgSO_4$ and evaporated. The residue was shown to be a mixture of several components from its TLC behavior. The residue in chloroform was chromatographed over silica gel column and elution with the same solvent gave 4 mg of sinomenine (**61**), whose IR spectrum was identical with that of an authentic sample. The other components were not investigated further.

Oxidation of the Model Compound (75) with DMSO——A mixture of 110 mg of the compound (**75**), 3 ml of DMSO, 315 mg of DCC and 0.5 ml of 1M solution of orthophosphoric acid in DMSO was allowed to stand at room temperature for 20 hr. To this solution were added 20 ml of water, 49 mg of phosphoric acid and 25

ml of ether and the insoluble dicyclohexylurea was removed by filtration. The aqueous layer, after washing with ether, was made alkaline with 28% NH_4OH and extracted with methylene chloride. The methylene chloride extract was washed with water, dried over $MgSO_4$ and evaporated. The residual oil was chromatographed over silica gel column in chloroform and elution with the same solvent gave an oily substance in the earlier eluate. The oil was chromatographed over alumina column in ether and elution with the same solvent afforded the compound (**50**) as colorless oil. The IR spectrum and TLC behavior were identical with those of an authentic sample.

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